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GUIDELINE

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019)

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Introduction

The Japanese Society of Hypertension (JSH) revised the Guidelines for the Management of Hypertension 2014 (JSH 2014), and published the JSH 2019. In the development of the JSH 2019, in addition to the use of the textbook description method based on the conventional guideline development strategies, clinical questions (CQs) concerning hypertension management were determined according to "Minds Manual for Guideline Development. Ver. 2.0 (2016.03.15)" established by the Medical Information Network Distribution Service (Minds) in Japan, systematic reviews (SRs) of CQs were performed to clarify evidence at present, and recommendations were formulated. In the "Introduction section", the methods used to develop the JSH 2019 are introduced.

1. OBJECTIVE OF THE JSH 2019, SUBJECTS FOR MANAGEMENT USING JSH 2019, AND JSH 2019 USERS

Hypertension is a major cause of strokes (such as cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage), heart diseases (such as coronary artery disease, cardiac hypertrophy, and heart failure), kidney diseases (such as nephrosclerosis), and macrovascular diseases. Therefore, the primary objective of the JSH 2019 is to present standard management strategies and evidence to all medical workers to provide appropriate treatment to patients with hypertension most frequently encountered by clinicians/practitioners in daily practice for the prevention of the onset/progression of hypertension complications in the brain/heart/kidney by blood pressure control. The JSH 2019 is one of data for reference while medical workers, such as attending physicians, determine therapeutic strategies by their communication with patients. It neither restricts the attending physician's right to determine prescriptions nor presents criteria for medical disputes or lawsuits. Since therapeutic strategies are individually determined based on the patient's background and complications, the attending physician who determines therapeutic strategies that differ from those in the JSH 2019 should give an adequate explanation to patients and also describe the reason for the determination of the strategies in the medical chart.

The subjects for blood pressure control using JSH 2019 consist of patients with hypertension (≥ 140/90 mmHg), people with an elevated blood pressure (130–139/80–89 mmHg), and all people with a blood pressure ≥ 120/80 mmHg in whom the cardiovascular risk increases with the blood pressure.

The JSH 2019 users include "all medical workers who examine, manage, and treat hypertensive patients, health ·

administrative personnel, and medical workers in the clinical setting." Hypertension is the most common lifestyle-related disease and difficult to treat by hypertension specialists alone. Indeed, hypertension is managed by many clinicians/practitioners. Considering such circumstances, the JSH 2019 was developed for the use of mainly clinicians/practitioners. It is also expected to be used by pharmacists who are engaged in treatment with physicians. Blood pressure control is also important for specific health checkups/health guidance, and has been increasingly performed in health promotion projects by municipalities. Therefore, the JSH 2019 is also used by team medicine members, such as health nurses, nurses, and registered dieticians, for hypertension management and health administrative personnel. In addition, "The Certified Hypertension & Cardiovascular Disease Prevention Educator System" was established in 2015. This license is given jointly by the JSH, Japanese Society of Cardiovascular Disease Prevention, and Japan Atherosclerosis Society for the prevention of cardiovascular diseases to health nurses, nurses, pharmacists, registered dietitians, physical therapists, clinical psychologists, medical psychologists, clinical technologists, and health fitness programmers who have an ability to give appropriate instructions for the improvement and prevention of lifestyle-related diseases, such as hypertension, and the management of other risk factors. The JSH 2019 is also expected to be used by people in these types of occupation.

2. CONSTITUTION OF THE GUIDELINE DEVELOPMENT COMMITTEE

At the Board of Directors of the JSH in December 2016, the guideline development chairperson (Satoshi Umemura) was selected. Under the chairperson, the basic guideline development strategies were determined. For adjustments in general contents, an executive committee consisting of 6 members including the president and vice-president of the society was organized. The secretary general (Nobuhito Hirawa) was nominated by the chairperson and accepted by the board of directors.

The guideline development committee included: (1) executive members, (2) writing members, (3) SR members, and (4) document reviewers. In addition, SR support members, liaison members, assessment members, and advisory members were also appointed.

For the selection of writing members, the guideline development chairperson devised a plan, referring to councilors' opinions, and determined writing members based on the principle that "the guidelines for hypertension management are the official guidelines of the JSH and developed on the responsibility of the entire society." and in accordance with "the Guidance on Eligibility Criteria for Participation in Clinical Practice Guideline Formulation" of the Japanese Association of Medical Science. There were 44 writing members. Due to the introduction of the CQ-SR method in the JSH 2019, SR members were recommended by the writing members, and 43 members were selected. Four SR support members were appointed. A total of 74 document reviewers were appointed for individual writing items consisting of the councilors of the JSH and special-field members recommended on a questionnaire survey. There were 2–5 document reviewers per writing item. In addition, 22 liaison members were appointed on the recommendation of 22 affiliated societies. In addition, 14 assessment members were selected from honorary members of the JSH while 5 advisory members were selected on the recommendation of such as the patient group, Japan Medical Association, and the Japan Pharmaceutical Association. The assessment members had been closely involved in the guideline formulation (JSH 2000, 2004, 2009, 2014). After the production of the final draft, we asked "Minds" to evaluate JSH2019 hypertension guideline according to the Appraisal of Guidelines for Research & Evaluation II (AGREE II).

3. GUIDELINE DEVELOPMENT STRATEGIES AND PROCEDURE

The basic principle for the development of the JSH 2019 was to establish highly transparent evidence-based consensus guidelines for clinicians/practitioners, considering the conflict of interest (COI). In addition, the JSH 2019 was developed basically according to "Minds Manual for Guideline Development. Ver. 2.0 (2016.03.15)".

The JSH 2019 uses two description methods i.e., the conventional textbook description method and recommendations formulated after SRs of clinical questions (CQs) in 17 items. In textbook description, there was not enough evidence for SRs, but 9 items about which clinicians/practitioners clinically have questions were also presented as questions (Qs), and these Qs were answered. SRs were performed mainly by several young physicians. Data on CQs in the literature were collected, and all selected items were evaluated according to the outcome as well as study design. The results were compiled (body of evidence), evaluated, and integrated. The outcomes of interventions include expected effects (benefit) and adverse events (harm). Considering their balance, "recommendations" were formulated using the Delphi method (the summarizing of opinions after repeated rounds of voting by e-mail).

Papers on many SRs will be prepared and published in Hypertens Res. Thus, see these papers for the details of SRs. SRs not published as papers and related data (such as charts) can be seen on the website of the JSH.

The development process of the JSH 2019 is as follows.

- December 25, 2016
  Executive committee meeting (guideline preparation committee meeting)
- April 14, 2017
  1st executive committee meeting
  Determination of guideline development strategies and each committee
- May 12–13, 2017
  2nd executive committee meeting, 1st guideline development committee meeting
  Confirmation and determination of guideline development strategies, committee composition, the table of contents, and CQs
- May 14, 2017
  Study meeting about the SR method
- August 19, October 19–22, and December 23, 2017
  3rd and 4th executive committee meetings and 2nd–4th guideline development committee meetings
  Evaluation of SRs and recommendations for each CQ, and parts described by a conventional method
- February-May, 2018
  Opinion exchange concerning each CQ among all writing members by e-mail
- February 12, March 24, and April 14, 2018
  5th–7th executive (expanded) committee meetings
  Evaluation of the risk score assessment method, reference values in the management of hypertension, and the blood pressure goal
- April-June, 2018
  Opinion exchange by e-mail among writing members and document reviewers for each chapter
- May 19–20, 2018
  8th executive (expanded) committee meeting, 5th guideline development committee meeting
  After evaluation of CQs, formulation of recommendations by the Delphi's method on e-mail
- July 15–16, 2018
  6th guideline development committee meeting
  Manuscript evaluation and revision
- September 13–16, 2018
  9th executive (expanded) committee meeting
- September-December, 2018
  Proofreading of the first and revised manuscripts by writing members
  Reviews by liaison members, assessment members, and advisory members and their opinion exchange
- January, 2019
  Collection of public comments, revision based on public comments, and completion of the final draft
- April, 2019
  Publication

4. ESTABLISHMENT OF THE EVIDENCE LEVEL AND RECOMMENDATION GRADE

Based on "Minds Handbook for Clinical Practice Guideline Development 2014" and "Minds Manual for Guideline Development. Ver. 2.0 (2016.03.15)", the evidence level and recommendation grade for CQs were determined.

Evidence level

A Strong: strong confidence
B Moderate: moderate confidence
C Weak: limited confidence
D Very weak: negligible confidence

Recommendation grade

1. Strong recommendation (proposal)
2. Weak recommendation (proposal)

No recommendation: no definite recommendation

(Some recommendation contents are difficult to shown using the above definition words. For such recommendations, expressions in accordance with the context are used.)

5. CONFIRMATION AND DISCLOSURE OF COI

Based on "the Guidance on Eligibility Criteria for Participation in Clinical Practice Guideline Formulation" of the Japanese Association of Medical Science, COIs during the previous 3-year period (2016–2018) were disclosed using the form of the above guidance on the website of the JSH according to each committee (writing, document review and SR committees).

Chapter 1. Epidemiology of hypertension

POINT 1

1. **Cardiovascular disease/chronic kidney disease (CKD) morbidity and mortality risks increase with blood pressure elevation above blood pressure levels of 120/80 mmHg.**
2. **The annual number of cardiovascular deaths due to hypertension in Japan is estimated to be 100000, accounting for the largest portion of all cardiovascular deaths. About 50% of cardiovascular disease deaths are estimated to be due to blood pressure> 120/80 mmHg.**
3. **Among blood pressure parameters, systolic blood pressure (SBP) more strongly predicts the**

cardiovascular disease risk. In the presence of other risk factors, this risk increases further.

4. **The number of hypertensives in Japan is estimated to be 43 million, including 31 million poorly controlled hypertensives. It is estimated that of these 31 million hypretensives, 14 million are unaware of hypertension, 4.5 million are left untreated despite disease awareness and 12.5 million are poorly controlled despite drug therapy.**
5. **The mean salt intake among the Japanese remains high. Reducing salt intake is important for lowering the blood pressure levels of the Japanese. Furthermore, the prevalence of obesity-related hypertension has increased.**
6. **In Health Japan 21 (II), a 4-mmHg decrease in the average SBP level of the Japanese within 10 years is targeted by promoting strategies for diet/physical activities/alcohol consumption. If this is achieved, the annual number of deaths from stroke will decrease by approximately10,000 and that of deaths from coronary artery disease will decrease by approximately 5000.**

1. ASSOCIATION BETWEEN HYPERTENSION AND VARIOUS DISEASES

1) Hypertension-related increase in the risk for stroke/heart disease

Hypertension is the most important risk factor for cardiovascular diseases (stroke and heart disease). In the 1960s, Japan was one of the countries with the highest mortality rate due to stroke. The mortality rate due to stroke has markedly decreased during the past 50 years, and the mortality rate from all heart diseases, including heart failure, has become higher than that due to stroke. However, the mortality/morbidity rates due to stroke are still higher than those due to acute myocardial infarction [1, 2]. The age-adjusted mortality rate due to stroke in Japan was about three times higher than that due to acute myocardial infarction [1, 2]. Several epidemiological studies have also reported that the morbidity rate from stroke was about three to four times higher than that from acute myocardial infarction [3–5]. With respect to the subtype of stroke, the morbidity rate from cerebral infarction was two to four times higher than that from intracerebral hemorrhage [3, 5, 6]. On the other hand, the morbidity rate from myocardial infarction has slightly increased primarily in urban areas [4, 7]. In the Suita Study, the morbidity rate from stroke was about two times higher than that from acute myocardial infarction, showing a reduction in the difference [8, 9].

There is a continuous, positive association between blood pressure level and risk for cardiovascular diseases [6, 10–16]. In a project to pool data from major cohort studies in Japan, EPOCH-JAPAN, a meta-analysis of 10 cohort studies (total: approximately 70,000 persons) showed that the association between blood pressure level and cardiovascular mortality risk was almost logarithmically linear in middle-aged (40–64 years) and early-phase older (65–74 years) people. The slope was stronger in younger people, and the risk was lowest in those with blood pressure levels of <120/80 mmHg (Figure 1-1) [10]. In late-phase older people (75–89 years), the cardiovascular mortality risk also increased with blood pressure level. An analysis excluding deaths during the first 3 years of follow-up to eliminate the reverse causation (a phenomenon that blood pressure decreases before death and the death rate looks higher at lower blood pressure levels) indicated a significant increase in the risk from blood pressure levels of 130/85 mmHg or higher. This association has been similarly observed when reviewing mortality due to all subtypes of stroke, cerebral infarction, intracerebral hemorrhage or coronary artery disease [10, 11, 17]. In particular, the association with mortality due to cerebral hemorrhage is stronger. Furthermore, the EPOCH-JAPAN revealed a significant association also between blood pressure level and mortality due to heart failure [10, 17].

The results of cohort studies investigating morbidity as an outcome in Japan also showed a similar association [6, 12, 13, 18]. The associations between blood pressure level and stroke/coronary artery disease morbidity risks were continuous. The risks were the lowest in blood pressure levels of <120/80 mmHg. In the Hisayama Study, the risk for lacunar infarction, a subtype of cerebral infarction, was shown to be high at blood pressure levels of 130/85 mmHg or higher [13]. The Suita Study revealed an association between SBP and the risk for new onset atrial fibrillation [19]. The Framingham Study in the United States demonstrated a continuous association between SBP and onset of heart failure [20].

Recent cohort studies have indicated the population-attributable fraction, which reflects the proportion of excess cardiovascular disease mortality/morbidity related to blood pressure level exceeding 120/80 mmHg [6, 10–13, 18]. According to EPOCH-JAPAN, blood pressure level exceeding 120/80 mmHg explained 50% of all cardiovascular disease deaths, 52% of stroke deaths and 59% of deaths from coronary artery disease. The number of excess deaths from grade I hypertension was the largest [10]. Also according to the 24-year follow-up data of NIPPON DATA 80, 43% of deaths from cardiovascular diseases (81% in middle-aged men) was attributable to blood pressure levels above 120/80 mmHg [11]. The Circulatory Risk in Communities Study (CIRCS) indicated that the portion of excess stroke morbidity from grade I hypertension has been increasing and that from grade III hypertension has been

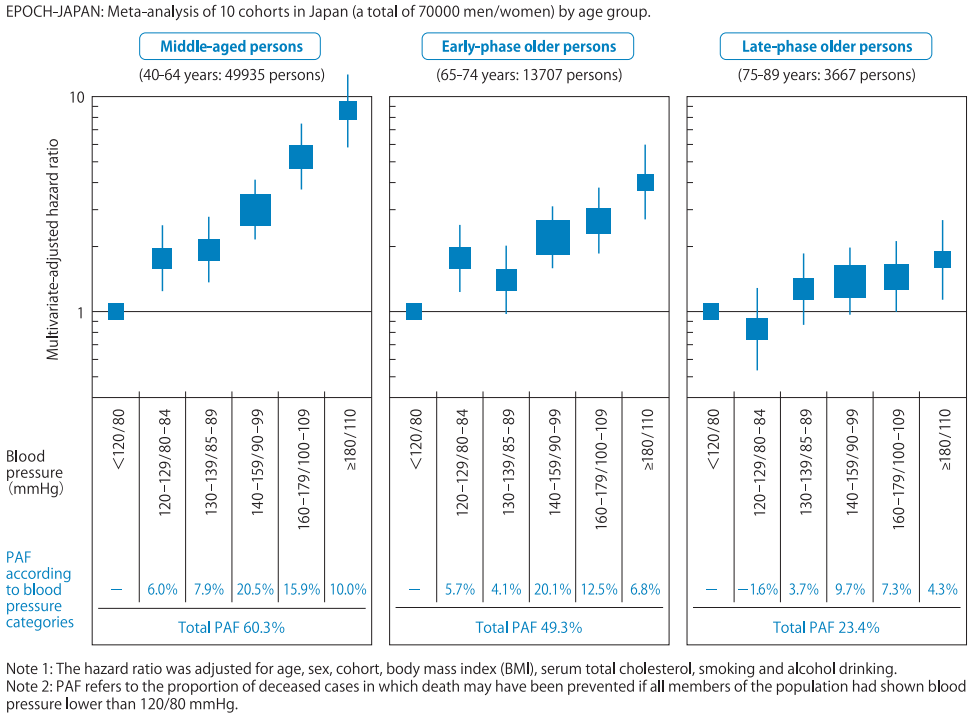


Fig. 1-1 Hazard ratio and population-attributable fraction (PAF) for cardiovascular disease mortality according to blood pressure categories (prepared from Ref. [10])

Note 1: The hazard ratio was adjusted for age, sex, cohort, body mass index (BMI), serum total cholesterol, smoking and alcohol drinking.
Note 2: PAF refers to the proportion of deceased cases in which death may have been prevented if all members of the population had shown blood pressure lower than 120/80 mmHg.

decreasing [6]. Therefore, lifestyle modification in persons with elevated blood pressure or grade I hypertension and strategies to prevent the development of hypertension are further important.

2) Hypertension and other conditions such as kidney disease/total mortality

Hypertension increases the risk for reduced estimated glomerular filtration rate (eGFR), CKD and end-stage kidney disease (ESKD) [21–24]. A cohort study in Okinawa showed that the future risk of ESKD increased by approximately 30% per 10-mmHg increase in SBP [21]. The Hisayama Study indicated that hypertension, especially mid-life hypertension, increased the risk of vascular dementia in later life (Figure 1-2a) [25]. Another study reported that middle-age hypertension increased the risk of reduction in future activities of daily living (ADL) (Figure 1-2b) [26].

Hypertension also increases the total mortality risk by various diseases described above. A meta-analysis involving 13 cohorts in Japan (total: 180000 persons; EPOCH-JAPAN) revealed that the total mortality risk increased with the blood pressure in both men and women aged 40–89 years [27]. It was estimated that blood pressure level exceeding 120/80 mmHg is responsible for approximately 20% of all-cause deaths. An estimation on the basis of the results of previous epidemiological studies showed that hypertension is the most important factor of cardiovascular death in Japan, and the annual number of deaths due to hypertension was estimated to be 100000 (Figure 1-3) [28]. According to NIPPON DATA 80, the average hypertension-related shortening of life expectancy was 2–3 years in men and women aged 40–49 [29], but the actual shortening of average life expectancy is estimated to be greater than this if we consider that this figure was not adjusted for the influence from antihypertensive therapy during the follow-up period.

3) Accumulation of risk factors, metabolic syndrome and risk for cardiovascular diseases

When other established risk factors accumulate in the presence of hypertension, the risk for cardiovascular diseases increases further [30–34]. Many cohort studies in Japan and their meta-analyses have revealed an increase in cardiovascular disease risk with the accumulation of smoking, diabetes, hypercholesterolemia or CKD in the presence of hypertension.

Metabolic syndrome is also a condition involving elevation of blood pressure as a factor. Many cohort studies in Japan have reported a metabolic syndrome-related increase in the risk for cardiovascular diseases. Cardiovascular disease morbidity and mortality risks increased 1.5- to 2.4-fold [35–37]. On the other hand, several cohort studies investigating cardiovascular disease morbidity/mortality as an end point [38–43] and the integrated analysis of 10 cohort studies including these cohorts [44] have suggested that the accumulation of metabolic risk factors is important regardless of the presence or absence of obesity. Because hypertensive patients in Japan are often free of obesity, the contribution to the population risk for cardiovascular

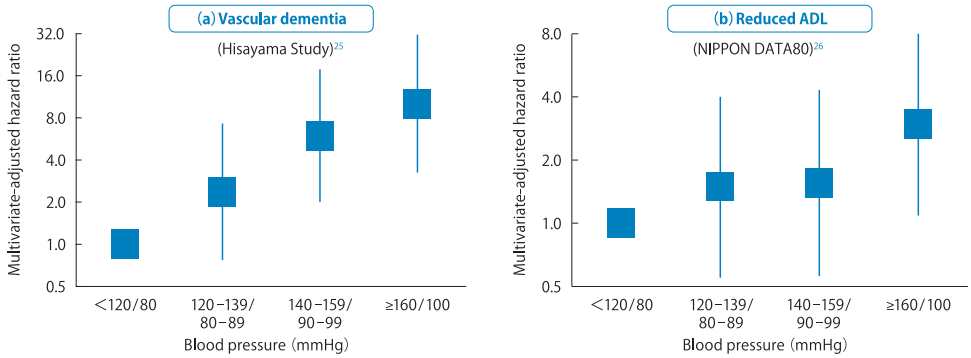


Fig. 1-2 Hazard ratio of each blood pressure level for vascular dementia (a) and reduced ADL (b). (prepared from Refs. [25, 26])

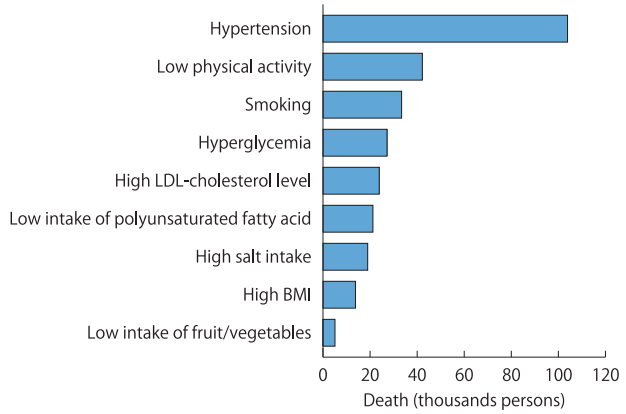


Fig. 1-3 Number of cardiovascular deaths attributable to various risk factors in Japan (prepared from Ref. 28)

diseases is higher with hypertension not associated with obesity than with hypertension associated with obesity [44, 45]. Thus, antihypertensive measures are important not only in obese individuals but also in non-obese individuals.

4) Various blood pressure parameters and cardiovascular disease risk

Large-scale meta-analyses have been carried out in Japan to identify blood pressure parameters closely associated with the risk for cardiovascular diseases among various parameters of blood pressure (including SBP, diastolic blood pressure [DBP] and pulse pressure) [46–48]. The analyses have shown that SBP most strongly predicts the future risk. In a meta-analysis involving 16 cohorts in Japan (the Japan Arteriosclerosis Longitudinal Study: JALS), SBP was the strongest predictor of stroke morbidity risk in both the middle-aged group and the older group. The prediction ability was less strong with DBP and further less strong with pulse pressure [46].

In most studies investigating the association between blood pressure and risk for cardiovascular diseases, blood pressure measured in the clinic or during health checkup was used. However, the cardiovascular disease risk-prediction ability of blood pressure measured at home and ambulatory 24-h blood pressure has been reported to be stronger than that of office blood pressure [49–54]. It has also been reported that the visit-to-visit variability in office blood pressure and the day-to-day variability in home blood pressure increase the risk for death, cardiovascular diseases, CKD and dementia [55–57].

2. CURRENT STATUS OF BLOOD PRESSURE AMONG THE NATION AND ITS CHANGES OVER TIME

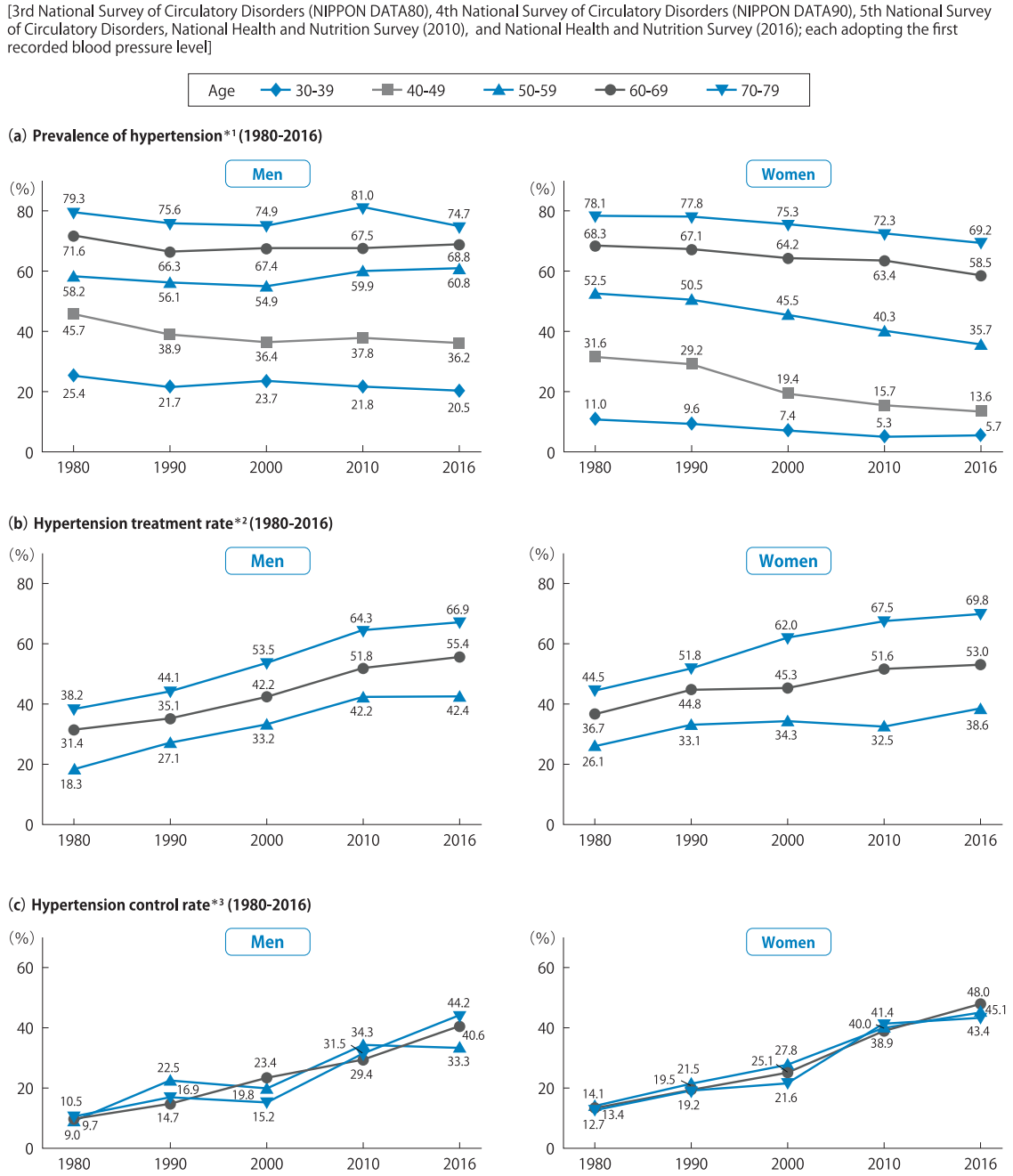
According to the National Health and Nutrition Survey 2016, the prevalence of hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg or use of antihypertensive medication) is 60% for men aged 40–74, 41% for women in the same age range, 74% for men aged 75 and over and 77% for women in the same age range [58].

According to the analysis conducted by the State about changes over time in the prevalence, treatment rate and control rate of hypertension during the 36-year period (1980–2016) on the basis of the National Surveys of Circulatory Disorders and the National Health and Nutrition Surveys, the prevalence of hypertension increased with age, exceeding 50% among men aged 50 and over and women aged 60 and over (Figure 1-4a) [59]. Although the prevalence of hypertension has been tending to decrease with age among women, there is no evident tendency of reduction among men aged 50 and over. As aging of the population further intensifies, the number of patients with hypertension can further increase in Japan.

The hypertension treatment rate (percentage of individuals receiving antihypertensive medication among hypertensives) has been rising during the past 36 years, exceeding 50% among men and women aged 60–69 and exceeding 60% among men and women aged 70–79 (Figure 1-4b) [59].

The hypertension control rate (percentage of individuals with blood pressure less than 140/90 mmHg among antihypertensive drug users) has been rising during the past 36 years, but remaining only about 40% among men and about 45% among women (Figure 1-4c) [59]. This rate is 55–60% according to some reports, but it is still not very high [60].

The average SBP, which tends to increase with age in both men and women, has decreased markedly in each age



*1: Proportion of individuals with blood pressure of 140/90 mmHg or more or taking antihypertensive drugs
*2: Proportion of individuals taking antihypertensive drugs among hypertensives
*3: Proportion of individuals with a SBP of <140 mmHg and a DBP of <90 mmHg among those taking antihypertensive drugs

Fig. 1-4 Annual changes in hypertension prevalence, treatment rate and control rate by sex and age group (1980–2016) (Source: Ref. [59])

group over the past approximately 6 decades in Japan (Figure 1-5a) [59]. The age-adjusted stroke mortality in Japan reached a peak in the 1960s and then fell sharply (1965: 361 for men and 244 for women, 2016: 36 for men and 20 for women [per 100000 population]) [61], resulting in a world top-level average life expectancy which owes much to the reduction in average blood pressure among the Japanese people. A similar tendency has been demonstrated also in other epidemiological studies in Japan [4, 62]. A reduction in average blood pressure among the entire nation in Japan seems to be attributable to progress and spread of antihypertensive drug therapy and changes in the nation's lifestyle and living environments (e.g., salt intake reduction). However, the DBP among men aged 30–59 does not show an evident reduction but is showing a movement requiring close attention (Figure 1-5b) [59].

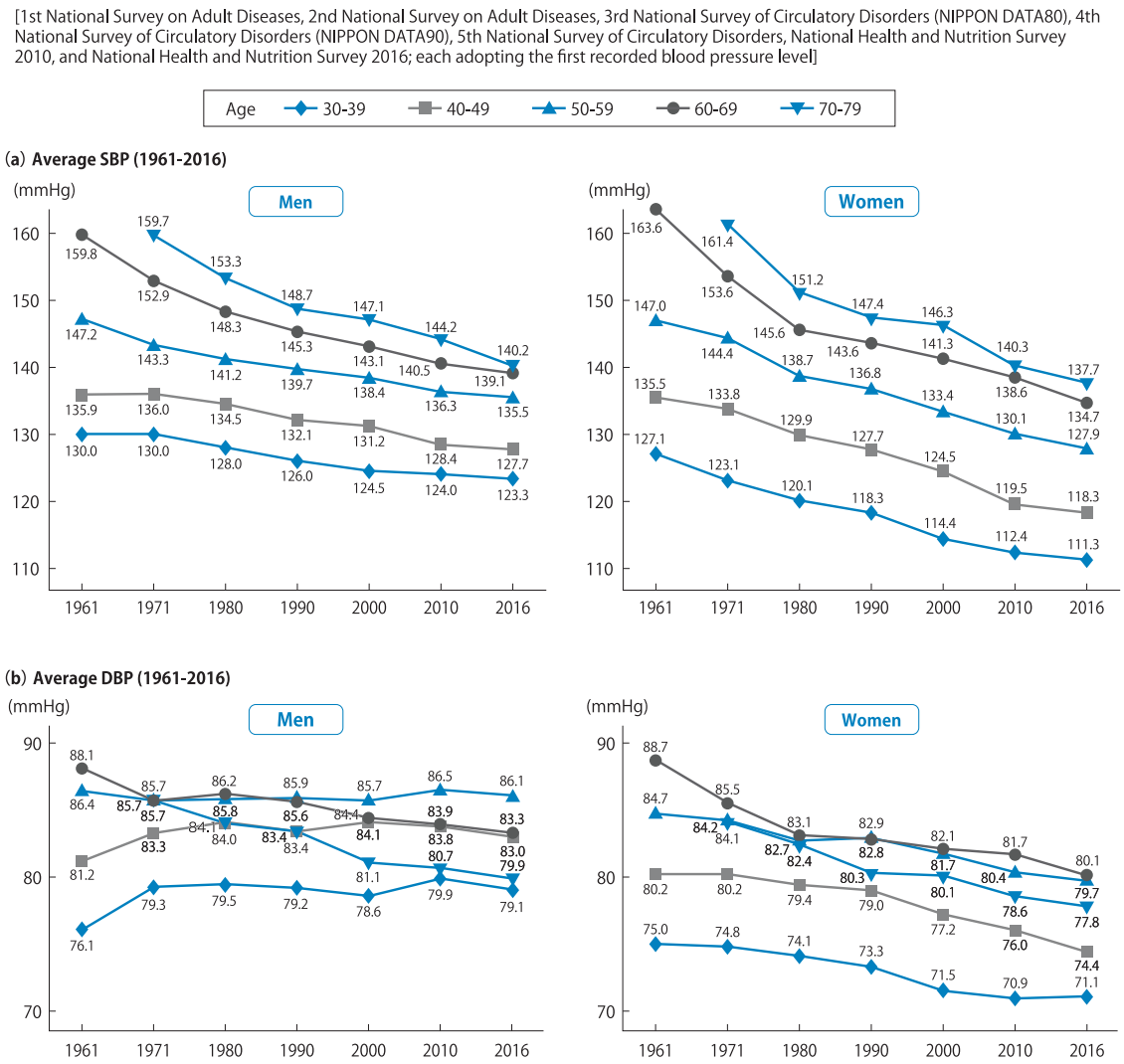


Fig. 1-5 Annual changes in average blood pressure by sex and age group (1961–2016) (Source: Ref. [59])

According to the NIPPON DATA2010, 33% of hypertensives were unaware of hypertension [63]. On the basis of these findings, the number of hypertensives in Japan is estimated to be 43 million as of 2017. Of these individuals, 31 million are estimated to be poorly controlled (140/90 mmHg or higher), 14 million of these 31 million individuals are estimated to be unaware of hypertension, 4.5 million are estimated to remain untreated despite awareness of the disease and 12.5 million are estimated to be poorly controlled despite ongoing treatment (Figure 1-6). Measures to reduce the number of poorly controlled hypertensive patients are needed.

3. CHARACTERISTICS OF HYPERTENSION IN THE JAPANESE

1) High salt intake

An excessive intake of salt was one of the possible causes for the high prevalence of hypertension and stroke in the past in Japan. A high salt intake increases blood pressure. Numerous observational or interventional studies have demonstrated that blood pressure was high in groups with a high salt intake, and that blood pressure decreased following reduced salt intake [64–66].

Few studies have strictly evaluated salt intake using 24-h urine collection in the general population. In the survey conducted in the Tohoku District in the 1950 s, the salt intake estimated by 24-h urine collection was as high as 25 g/day [67]. The mean salt intake of men and women was 12.3 and 10.9 g per day, respectively, according to the INTERMAP Study, in which salt intake was measured in men and women aged 40–59 years in four districts of Japan between 1996 and 1999 [68]. The salt intake evaluated by the weighing method in the National Health and Nutrition Survey has also been tending to decrease gradually, and the National Health and Nutrition Survey in 2016 showed that the mean daily salt intake per person was 9.9 g (men: 10.8 g,

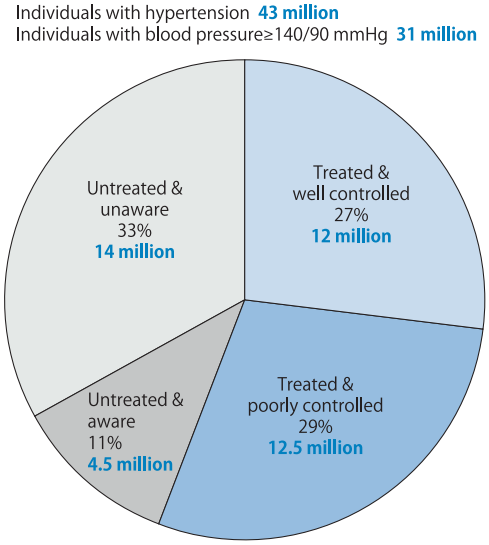


Fig. 1-6 Estimated number of hypertensives, hypertensives receiving antihypertensive drug therapy and poorly controlled hypertensives in Japan (2017)

women: 9.2 g) [58]. In the Dietary Reference Intake in Japanese (2015), the dietary goal of salt intake to be achieved in adult men and women in the next 5 years is <8.0 and <7.0 g per day, respectively [69]. Health Japan 21 (II) (2012) targeted a reduction in the average salt intake of the Japanese to 8.0 g before 2022 [70]. In the World Health Organization guidelines on sodium intake, which were published in 2012, it is recommended that salt intake should be reduced to <5 g per day in adults [71]. The current status in Japan is still far from this recommendation, indicating the need of further actions to promote salt reduction among the nation for prevention of hypertension.

2) Increases in the prevalence of obesity and metabolic syndrome

Obesity is less common in Japan than in other developed countries. However, mean body mass index (BMI, kg/m^2), which is an index of obesity, has been increasing annually in men; the proportion of obesity (BMI ≥25 kg/m^2) in men aged 20 and over was 31% [58], having increased by about twofold during the past 30 years [72, 73], according to the National Health and Nutrition Survey in 2016. On the other hand, there was no overall increase in the proportion of obesity in women aged 20 and over during the past 30 years, being 21% in 2016.

Regarding the characteristics of hypertensive Japanese, lean hypertensives with a high salt intake accounted for a high percentage in the past, but the number of obese hypertensives has recently increased, particularly among men. According to the analysis of changes over time during 3 decades from 1980 to 2010 shown in NIPPON DATA, the proportion of hypertensive men in whom obesity contributed to hypertension increased gradually over time [73]. This would reflect an increase in the prevalence of metabolic syndrome in Japan. The National Health and Nutrition Survey in 2016 showed that metabolic syndrome was strongly suspected in more than 30% of men aged over 60 years [58].

In the United States, the prevalence of obesity has markedly increased since 1990, and those with a BMI of 30 kg/m^2 or more account for more than 30% of the population [74]. In Japan, the percentage is 3 to 4%. However, it may increase with the westernization of lifestyle in the future. Strategies to prevent obesity must be promoted.

4. PUBLIC HEALTH MEASURES AGAINST HYPERTENSION

As shown by many epidemiological studies, more than half of high blood pressure-related excessive cardiovascular disease mortality/morbidity events occurred in people with mildly high blood pressure (grade I hypertension or lower) [6, 10–14, 18]. To reduce excess cardiovascular disease mortality/morbidity, high-risk strategies involving hypertensives alone are insufficient. Population strategies to lower the blood pressure distribution of the entire Japanese population are necessary (Figure 1-7) [75, 76]. The 'National Health-Promotion Project in the 21st Century' (Health Japan 21 (II)), which was announced by the Minister of Health, Labour and Welfare in 2012, targets a decrease in average SBP in Japan by 4 mmHg (men: 138 → 134 mmHg, women: 133 → 129 mmHg) within 10 years (before 2022) [70]. The goal is to lower the blood pressure distribution of the entire nation.

The establishment of target values for cardiovascular diseases in Health Japan 21 (II) is presented in Figure 1-8. A 2.3 mmHg decrease in SBP is targeted by nutritional/dietary strategies such as reducing salt intake (to 8 g per day), increasing vegetable/fruit intake (to 350 g per day) and decreasing the number of obese people. A 1.5-mmHg decrease is targeted by physical activity/exercise strategies (approximately 1500 step increase in the number of steps). A 0.12-mmHg decrease is targeted by alcohol strategies (decreasing the number of heavy drinkers). A 0.17-mmHg decrease is targeted by strategies regarding antihypertensive therapy (increasing the compliance rate by 10%). Overall, a 4-mmHg decrease in SBP is targeted [70].

In Health Japan 21 (II), the cardiovascular disease-reducing effects of target achievement were estimated using the EPOCH-JAPAN database [70]. Overall, the project

targets to decrease age-adjusted mortality for stroke (cerebrovascular disease) in men and women by 15.7 and 8.3%, respectively, and that for coronary artery disease (ischemic heart disease) by 13.7 and 10.4%, respectively, as shown in Figure 1-8. To achieve these goals, the role of blood pressure reduction is important. In brief, only a 4-mmHg decrease in average SBP in the Japanese is estimated to reduce age-adjusted mortality from stroke in men and women by 8.9 and 5.8%, respectively (the total number of deaths from stroke will decrease by approximately 10 000 per year), and that for coronary artery disease by 5.4 and 7.2%, respectively (the total number of deaths from coronary artery disease will decrease by approximately 5000 per year).

Population strategies to achieve the above targets include environmental approaches from various aspects, such as mass media-mediated public education, obligations regarding the labeling of salt content by food manufacturers, menu improvement/promotion of nutrition labeling in school lunch/food-service industries, spread of home blood pressure measurement, and utilization of IoT [64, 77, 78]. All health/medical specialists, including physicians, nurses, public health nurses, registered dieticians, pharmacists, school nurses and school dieticians must instruct all persons including hypertension-free individuals to improve their diet (salt reduction/maintenance of optimal body weight), increase physical activities and maintain moderate alcohol consumption in health care/medical practice.

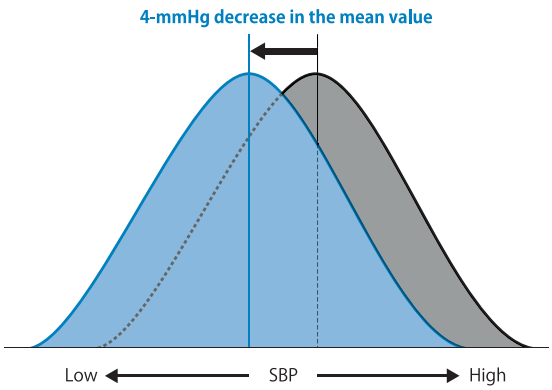


Fig. 1-7 Population strategy to shift the distribution of SBP in the Japanese to a lower level

It is necessary to promote high-risk strategies in parallel with population strategies. The Specific Health Checkups and Specific Health Guidance, started in 2008, serve as an essential element of such strategies [79]. Health insurers should take actions to facilitate detection of hypertensives by improvement in the health screening coverage, to improve the health guidance implementation rate and to reduce untreated hypertensives, treatment-discontinued hypertensive patients and poorly controlled hypertensive patients (for prevention of severe course of the disease). For this purpose, in 2015 the "Data Health Plan" involving planning and evaluation by each health insurer by analysis of health insurance claims/health screening data was started [80].

Comprehensive measures, combining the population strategies with the high-risk strategies as mentioned above, need to be taken to achieve the goals of reduction in the cardiovascular disease morbidity/mortality, optimization of healthcare expenditure and extending the healthy life expectancy of the nation (Figure 1-9) [81].

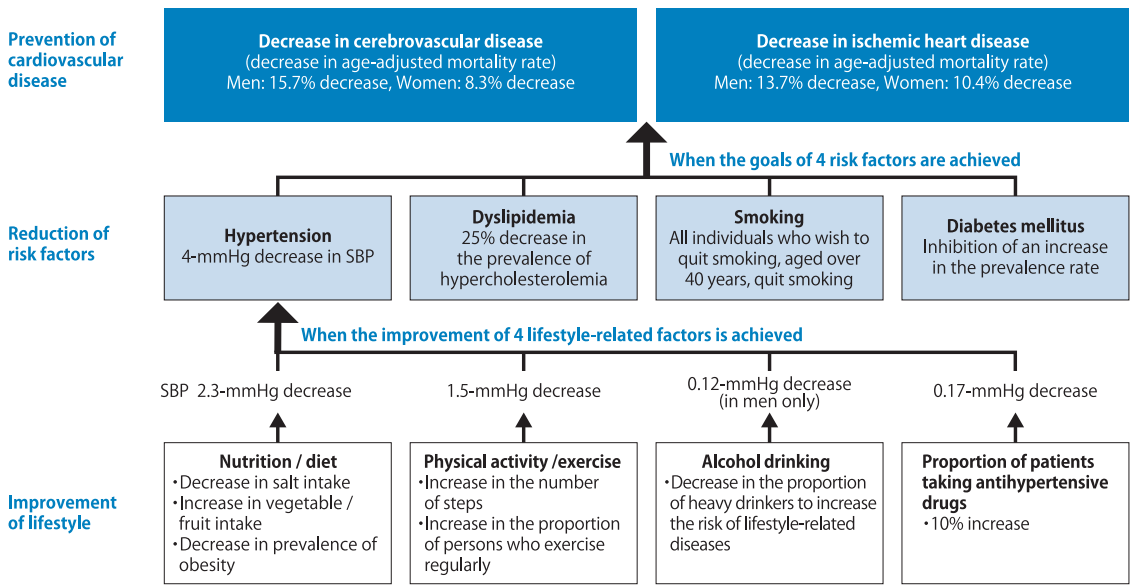


Fig. 1-8 Target establishment for cardiovascular diseases in Health Japan 21 (II) (Source: Ref. [70])

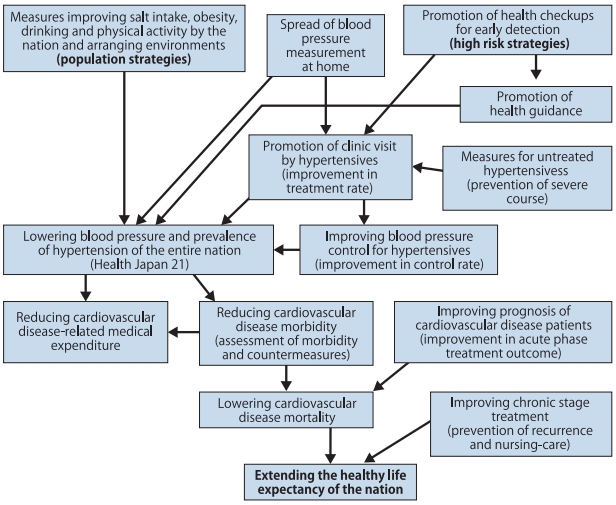


Fig. 1-9 Open issues related to hypertension and a roadmap for longer healthy life expectancy in Japan (modified from Ref. 81)

Chapter 2. Measurement and clinical evaluation of blood pressure

POINT 2A BLOOD PRESSURE MEASUREMENT/ASSESSMENT

1. **Office blood pressure should be measured by placing the forearm on a support table and maintaining the arm-cuff position at the heart level during rest in a seated position. The measurement must be performed two or more times at intervals of 1–2 min, and the mean value of two measurements that provides stable values (difference in the values: <5 mmHg) should be used. Diagnosis of hypertension should be based on office blood pressures measured on at least two different occasions.**
2. **Office blood pressure is measured by the auscultation method, which is the standard procedure, but the use of an automatic sphygmomanometer of the upper arm type is also permitted.**
3. **Home blood pressure measurement and 24-h ambulatory blood pressure (ABP) monitoring (ABPM) are useful for the diagnosis of hypertension, white coat hypertension and masked hypertension, as well as for evaluating the drug effect and its duration.**
4. **Home blood pressure should be measured with upper-arm devices. As a rule, it must be determined twice, and the mean value should be used as a blood pressure value on the occasion. When the measurement is performed only once per occasion, its value should be used as a level on the occasion. For the diagnosis of hypertension and the evaluation of responses to antihypertensive drugs, the mean of morning and evening blood pressure readings for 7 days (at least 5 days) should be used.**
5. **Criteria for hypertension differ among office blood pressure, 24-h ABP and home blood pressure. An office blood pressure of >140/90 mmHg, a home blood pressure of >135/85 mmHg and a mean 24-h ABP of >130/80 mmHg are regarded as indicators of hypertension.**
6. **When there is a discrepancy of diagnosis between office blood pressure and home blood pressure, a home blood pressure-based diagnosis should have priority.**
7. **Every blood pressure measurement should use a sphygmomanometer having undergone periodical inspection, taking into consideration its durability and past frequency of use. In addition, aneroid sphygmomanometers require immediate disposition and exchange when deterioration is suspected because errors are theoretically more likely to result in this type of sphygmomanometer following exposure to shock or changes over time.**
8. **Manufacture and export/import of mercury sphyngmomanometers will be prohibited from 2021 on. Their maintenance will also become difficult. Thus, mercury sphyngmomanometers should not be used.**

1. BLOOD PRESSURE MEASUREMENT

1) Office blood pressure measurement

Correct measurement of blood pressure is necessary for the diagnosis of hypertension. In a clinical setting (for example, an outpatient office), blood pressure is measured by the auscultation method or by using an automatic sphygmomanometer verified as to precision by an acknowledged evaluation method. Although a mercury sphygmomanometer has conventionally been used for standard blood pressure measurement by the auscultation method, manufacture and export/import of devices containing mercury (including mercury sphygmomanometers) are prohibited, for a reason of environmental pollution with mercury, from January 1, 2021 under the Minamata Convention on Mercury [82] having come into effect in 2017 and having been ratified also by Japan. It is therefore anticipated that precision control of mercury sphygmomanometers will be difficult also in Japan. As a substitute for mercury sphygmomanometers, it is recommended to use an electronically generated pressure column (quasi-mercury) sphygmomanometer (using an electronic analog column instead of a mercury column) or an aneroid sphygmomanometer for the auscultation method or to use an automatic upper-arm sphygmomanometer (see Q1).

Table 2-1 shows the standard procedure for blood pressure measurement at the outpatient office. Office blood

pressure measurement, in strict accordance with the procedure shown in Table 2-1, is known to more accurately reflect the true blood pressure compared with measurements obtained by disregarding this procedure, and is found to have a clinical value at least comparable to that of ABPM or home blood pressure measurement [83, 84]. However, blood pressure is rarely measured in accordance with such guidelines in a screening or clinical setting. In addition, the accuracy of measurement is often disregarded or ignored [85, 86].

In sphygmomanometry by the auscultation method, however, there are problems of terminal digit preference, that is, the tendency for the reading of the first digit of the mercury column height to converge at 0 (e.g., 110 mmHg, 120 mmHg), auscultation gap and examiner's hearing loss [87, 88]. At present, office blood pressure measurement is usually taken with an automatic sphygmomanometer. The Guidelines on Hypertension included in the Canadian Educational Program 2015 recommend the use of an automatic sphygmomanometer for office blood pressure

Table 2-1 Measurement of the office blood pressure

1. Device	(a) The auscultation method using a mercury or aneroid sphygmomanometer, of which the accuracy has been established, is employed. The use of an electronic sphygmomanometer of which the accuracy has been established is also possible[*1]. (b) A cuff with a bladder 13 cm wide and 22–24 cm long is used for the auscultation method. (A cuff for children is used for a brachial girth of <27 cm. When the arms are thick (arm girth ≥34 cm), a large cuff for adults is used.)
2. Measurement conditions	(a) A quiet, appropriate environment at room temperature. (b) After resting for a few minutes in a seated position on a chair with a support for a back with the legs not crossed. (c) No conversation. (d) Smoking and alcohol/caffeine consumption should be avoided before measurement.
3. Measurement methods	(a) With the forearm placed on a table, the lower end of cuff is wound at a level 2–3 cm above the elbow pit[*2] and the cuff center is maintained at the heart level (at the center of sternum or at the fourth intercostal space). (b) With the auscultation method, the cuff is rapidly inflated while palpating the radial or brachial artery, and the stethoscope is used after blood pressure has risen to 30 mmHg or more above the pulse rate disappearing level. (c) The rate of cuff deflation is 2–3 mmHg per beat or second. (d) In the auscultation method, the blood pressure at the start of the first Korotkoff sound is regarded as the systolic blood pressure, and that at the fifth Korotkoff sound[*3] as the diastolic blood pressure.
4. Frequency of measurement	Measurement is performed two or more times at 1- to 2-min intervals in one office visit. When two measurements differ markedly[*4], additional measurement is performed.
5. Evaluation	(a) The mean value of two measurements that provide stable values[*4] is adopted as the office blood pressure value. (b) Hypertension should be diagnosed on the basis of blood pressures measured on at least two different occasions.
6. Other cautions	(a) On the initial office visit, bilateral brachial blood pressure should be confirmed. On subsequent visits, the measured side (right or left) is described. (b) The cuff should not be attached over thick shirts or jackets. Furthermore, the upper arm should not be compressed by tucking up sleeves. (c) In persons with diabetes or older persons, the blood pressure should be measured after 1- and 3-min standing to confirm the presence or absence of orthostatic hypotension. (d) Examiners with sufficient audibility who have completed training for measurement should perform auscultation. (e) The pulse rate must also be measured and recorded.

[*1]: An electronically generated pressure column (quasi-mercury) sphygmomanometer is a sphygmomanometer using an electronic analog column instead of a mercury column (schematic representation given in Q1). An aneroid sphygmomanometer is a sphygmomanometer with a screw-formed needle moving in an arc-shaped manner (schematic representation given in Q1). An automated sphygmomanometer requires periodical inspection and should be used with consideration of the durability and frequency of use described in the package insert. Aneroid sphygmomanometers require immediate disposition and exchange when deterioration is suspected because errors are theoretically more likely to result in this type of sphygmomanometer following exposure to shock or changes over time.

When an automatic rolling-type sphygmomanometer is used in the waiting room, measurement should be performed under sufficient guidance and management to avoid errors.

[*2]: The cuff is wound not loosely or too tight. If wound loosely, blood pressure is overestimated. The device whose winding method is described in the package insert should be wound in the manner described in the package insert.

[*3]: Start of the fifth Korotkoff sound indicates disappearance of the Korotkoff sound. This definition is common with the European/American guidelines (ESH2018 and ACC/AHA2017).

[*4]: Differences less than approximately 5 mmHg are the criteria for judging different or stable values.

measurement in view of the fact that the accuracy of measurement by the auscultation has not been ensured [89]. Office blood pressure measurement by the auscultation method should be carried out by a well-trained examiner by the method shown in Table 2-1 adequately. If this is difficult, the use of an automatic sphygmomanometer is recommended. In terms of the accuracy of automatic sphygmomanometers, there is no significant problem when a device made by a Japanese manufacturer is used. The results of accuracy test of automatic sphygmomanometers are given in the website of the Japanese Society of Hypertension (JSH) [90].

An automatic rolling-type sphygmomanometer is used in the waiting room of the office, and the blood pressure value obtained is often adopted as an office blood pressure level. In particular, for self-measurement with the automatic rolling-type sphygmomanometer by patients, blood pressure must be measured under thorough guidance and management regarding the following points: an arm cuff should not be placed on the elbow; the arm-cuff should be maintained at the heart level; and extremely anterior tilting should be avoided.

In recent years, automated office blood pressure (AOBP) has begun to be used in Western countries. AOBP is measured many times with an automatic office sphygmomanometer while leaving the patient alone in quiet environments. AOBP has been shown to be more accurate than the manually measured blood pressure and to allow elimination of the white coat effect [91]. The results of SPRINT indicate that antihypertensive treatment with a goal set at lowering the systolic blood pressure (SBP) (measured as AOBP) to less than 120 mmHg reduced the incidence of cardiovascular events and the total mortality [92, 93]. However, because of the hurdles, such as difficulty in securing the space and the need of patient guidance, AOBP has been seldom adopted in Japan and few evaluations/analyses have been conducted concerning clinical feasibility and usefulness of AOBP measurement or the relationship between home blood pressure and AOBP.

For blood pressure measurement in adults using the auscultation method, cuffs with rubber bags 13 cm wide and 22–24 cm long are usually used. Internationally, however, cuffs with a width of ≥40% of the brachial girth and a length sufficient to cover at least 80% of the brachial girth are recommended [94].

Office blood pressure measurement requires periodical inspection of the sphygmomanometer and use of the sphygmomanometer taking into account its durability and frequency of use. In addition, aneroid sphygmomanometers require immediate disposition and exchange when deterioration is suspected because errors are theoretically more likely to result in this type of sphygmomanometer following exposure to shock or changes over time.

A problem encountered in blood pressure measurement is the presence of false hypertension related to incomplete compression of the brachial artery by an increase in arterial stiffness. The presence of incomplete compression of the brachial artery by an increase in arterial stiffness can be predicted, based on Osler's sign (case in which the brachial or radial artery is still palpable at the periphery of the cuff even when pulsation has been stopped by sufficient inflation) [95].

If pulses of the lower-limb arteries (femoral, popliteal and dorsalis pedis arteries) are weak or not palpable, blood pressure is measured in the leg to exclude peripheral artery disease. For the measurement of blood pressure in the leg, an arm cuff is applied to the lower leg, and auscultation is performed using the dorsalis pedis or posterior tibial artery, or the cuff is applied to the thigh (using a cuff with a rubber bag that is 20% wider than the femoral diameter—that is, 15–18 cm), and auscultation is performed using the popliteal artery. Currently, lower-limb blood pressure measurement at the lower leg by the cuff-oscillometric method and ankle-brachial pressure index (ABI) measurement during brachial-ankle pulse wave velocity (baPWV) measurement are commonly used.

In patients with arrhythmia (premature beats), SBP is overestimated and diastolic blood pressure (DBP) is underestimated by the auscultation method [96]. Therefore, the effects of arrhythmia must be excluded by repeating the measurement three or more times and adopting their average. In patients with atrial fibrillation, accurate sphygmomanometry is often difficult, but proportionate values of SBP and DBP can be obtained by the cuff-oscillometric method unless the patients have bradycardia [97]. In this case, the measurement must also be repeated three or more times and adopting their average [98].

In pregnant women, Korotkoff sounds (vascular murmurs) are occasionally heard at 0 mmHg. In this case, the blood pressure at the starting point of the fourth Korotkoff sound (muffling of the sound) is regarded as the diastolic pressure.

There is as yet no highly accurate or consistent method for performing indirect sphygmomanometry during exercise. In addition, there are no sufficient grounds for the evaluation of blood pressure during exercise for the general diagnosis of hypertension [96].

As blood pressure can be extremely variable, it occasionally shows marked increases even under routine measuring conditions. Therefore, a diagnosis of hypertension should be made on the basis of blood pressure measurements taken on two or more different occasions.

2) Out-of-office blood pressure measurement

Self-measurement of blood pressure at home (home blood pressure measurement) and ABPM are methods for blood

pressure measurement in an out-of-office setting. Home and ABPs are often considered to have clinical values comparable to, or greater than, that of office blood pressure. These blood pressure measurements also have value as blood pressure information differing in nature (Table 2-2) [99].

(1) Home blood pressure measurement Home blood pressure measurement is useful for improving the treatment adherence of patients and for preventing an excessive or insufficient antihypertensive effect of drugs. Measurement before taking a drug is particularly useful for assessing the duration of the drug effect (morning/evening ratio or evening/monitoring ratio) [100]. Home blood pressure measurement is also useful for the diagnosis of white coat hypertension, morning hypertension or masked hypertension and for making a diagnosis of resistant hypertension and deciding the therapeutic strategy [101]. As home blood pressure can be frequently measured over a long period, it is also useful for the evaluation of blood pressure variability over an extended period such as seasonal variations of blood pressure [102]. Home blood pressure measurement is widely prevalent in Japan [103–105]. An upper-arm-cuff device based on the cuff-oscillometric principle that has been confirmed in a population including hypertensive patients to yield differences within 5 mmHg compared with those of the auscultation method is used for home blood pressure measurement. According to the conditions presented in Table 2-3, the measurement is performed [99].

The clinical significance of home blood pressure increases by standardized measurement, as indicated for office blood pressure. On the other hand, guidance on conditions for home blood pressure measurement varies among clinicians in clinical practice; it should be standardized [106, 107]. In clinical practice, each clinician must guide the home blood pressure measurement method based on the measurement conditions described in the guidelines.

There is no definite rationale for judging which value is appropriate for use in clinical evaluation of home blood pressure (see Q2). These guidelines, as the JSH 2014 Guidelines [108], recommend measuring blood pressure twice as a rule on each occasion and adopting their mean as the blood pressure value at a given occasion. When blood pressure measurement is performed only once, the value obtained should be used as a blood pressure level on the occasion. If subjects spontaneously measure blood pressure three times, the mean of three measured values may be used as a blood pressure level on the occasion. Adherence to measurement decreases if too many measurements are requested on each occasion [109]. Therefore, four or more measurements per occasion should not be recommended. Concerning records, all values measured on one occasion should be recorded in a recording sheet, as previously described. This is aimed at avoiding "selection (report) bias, i.e., a tendency for the examiner to select and report a value he/she prefer from the different values of measurement.

To evaluate hypertension, normal blood pressure and the effects of antihypertensive drugs based on home blood pressure, the mean of the morning values and that of the evening values measured 7 days (at least 5 days) should be used.

The wrist-cuff device for blood pressure measurement is easy to use, but often provides inaccurate measurements because of the difficulty in correcting the difference in hydrostatic pressure between the heart level and wrist level,

Table 2-2 Characteristics of each type of blood pressure measurement

	Office blood pressure	Home blood pressure	ABP
Frequency of measurement	Low	High	High
Measurement standardization	Possible* [1]	Possible	Unnecessary
Reproducibility	Unfavorable	Most favorable	Favorable
White coat phenomenon	Present	Absent	Absent
Drug efficacy assessment	Possible	Optimal	Appropriate
Evaluation of the duration of drug efficacy	Impossible	Most favorable	Possible
Evaluation of short-term variability (variations at 15- to 30-min intervals)	Impossible	Impossible	Possible
Evaluation of diurnal changes (evaluation of nocturnal blood pressure)	Impossible	Possible*[2]	Possible
Evaluation of day-by-day variability	Impossible	Possible	Impossible
Evaluation of long-term variability	Possible	Most favorable	Possible

*[1] Standardized measurement increases the clinical value of office blood pressure. In clinical practice, standardized measurement is often not performed. Standardized office blood pressure measurement is strongly recommended.

*[2] Home blood pressure-measuring devices that can monitor blood pressure during sleep at night are available.

Table 2-3 Methods, conditions, and evaluation of home blood pressure measurement

1. Device	Devices based on the cuff-oscillometric method using an upper arm cuff.
2. Measurement environments	(1) A quiet, appropriate environment at room temperature[*1]. (2) After resting for 1–2 min in a seated position with the legs not crossed. (3) No conversation. (4) Smoking and alcohol/caffeine consumption should be avoided before measurement. (5) The cuff position can be maintained at the heart level.
3. Measurement conditions	(1) Essential conditions (a) Morning: within 1 h after waking up, after urination, before dosing in the morning, before breakfast, and after 1–2-min resting in a sitting position; (b) Evening (at the bedtime): after 1- to 2-min resting in a sitting position (2) Additional conditions (a) According to instructions: before dinner, before dosing in the evening, before bathing, or before alcohol consumption. Others (if necessary): in the presence of symptoms, during the daytime on holidays, during sleep at night[*2]
4. Frequency of measurement and handling of values[*3]	As a rule, measurement should be performed twice per occasion, and the mean value of two measurements should be adopted. When measurement is performed only once per occasion, the blood pressure value is used.
5. Measurement period	As long as possible
6. Recording	All values should be recorded
7. Values to be evaluated	Mean of morning values obtained for 7 days (at least 5 days). Mean of evening values obtained for 7 days (at least 5 days). All individual values.
8. Evaluation	Hypertension: mean morning or evening value ≥135/85 mmHg Normal blood pressure: mean morning and evening values <115/75 mmHg

[*1]: In particular, measurement in a non-heated room in winter increases the blood pressure level and physicians must instruct patients to measure the blood pressure at appropriate room temperature.

[*2]: Home sphygmomanometers that facilitate automatic blood pressure measurement during sleep at night are available.

[*3]: Many measurements should not be requested.

Note 1: In patients who are anxious about home blood pressure measurement, it should be avoided.

Note 2: Physicians must explain to the patients that they should not be emotionally overcome by individual values or missed measurement (unless it is frequent).

Note 3: Patients should be instructed not to discontinue antihypertensive drugs or increase/decrease the dose based on self-measurements.

Note 4: Measurement on the non-predominant arm is recommended, as a rule. If blood pressure differs between right and left sides, measurement on the predominant arm is also instructed as needed.

and because of the difficulty in completely compressing arteries due to anatomical issues with the wrist [110]. At present, therefore, a blood-pressure-measuring device with an upper-arm cuff is used for home blood pressure measurement [99]. However, for obese individuals with quite thick and short brachium, the use of a wrist-cuff device should also be considered because compression of the brachium is sometimes difficult. The accuracy of upper-arm-cuff devices for home blood pressure measurement using the cuff-oscillometric method is generally acceptable if they are the products of Japanese companies. The results of tests of the accuracy of various home blood pressure-measuring devices are provided in the website of the JSH [90]. Finger-cuff devices for blood pressure measurement are known to be inaccurate and are not recommended in the guidelines in Western countries [111, 112], although no such device for home use is available in Japan.

Since the Ohasama Study first demonstrated home blood pressure as a more reliable predictor of outcome compared with office blood pressure [50, 113], clinical data regarding the relationship between home blood pressure and the incidence of cardiovascular diseases or prognosis have been obtained [114–120]. Such favorable properties of home blood pressure are associated with the reproducibility of the mean of home blood pressure levels [121, 122].

(2) ABPM If an automatic device based on the cuff-oscillometric method [123–125] is used for noninvasive measurement of blood pressure at intervals of 15–30 min over 24 h ABPM, blood pressure information can be collected in a nonclinical setting such as a 24-h blood pressure profile or blood pressure information during specific periods (24 h, in the daytime, nighttime and early morning). In Japan, guidelines on ABPM has been published by the Japanese Circulation Society ("Guidelines for the clinical use of 24 h ambulatory blood pressure monitoring (ABPM) (JCS 2010)") [126].

Usually, blood pressure is high during waking hours and low during sleep. It has also been shown that the 24-h average of ABP is correlated more closely with the severity of hypertensive target organ damage than office blood pressure, and that it is closely associated with the regression of target organ damage mediated by antihypertensive medication [127, 128, 832]. Moreover, ABPM allows more accurate prediction of the incidence of cardiovascular diseases than office blood pressure in the general population, older population and in hypertensive patients [49, 52, 129–133].

ABPM is particularly useful for the diagnosis of white coat hypertension. It is indicated for the diagnosis of white coat hypertension, poorly controlled hypertension and resistant hypertension. The indications for ABPM are presented in Table 2-4. However, the reproducibility of the mean values of 24-h, daytime (waking hour) and nighttime (sleep) blood pressures on ABPM, as well as that of diurnal variations in blood pressure, is not always favorable, depending on activity and sleep conditions during the day. A single session of ABPM does not accurately reflect personal blood pressure information [134].

2. DIAGNOSIS OF HYPERTENSION

1) Classification of office blood pressure levels

Among most international guidelines, including those in Japan, it is common to regard patients with office blood pressure levels of 140/90 mmHg or more as having hypertension.

In the Hisayama Study in Japan, the cumulative mortality rate due to cardiovascular diseases was lowest when the SBP and DBP were <120 and <80 mmHg, respectively, and the risks of cardiovascular diseases increased significantly when the SBP was ≥140 mmHg compared with <120 mmHg, and when the DBP was ≥90 mmHg compared with <80 mmHg, including in older individuals [135, 136]. Moreover, according to the Tanno/Sobetsu Study, an 18-year prospective epidemiological study in Hokkaido, Japan, a SBP of ≥140 mmHg and a DBP of ≥90 mmHg were considered significant risk factors for cardiovascular and total mortality [137]. Similarly, in NIPPON DATA80, a significant increase in the mortality rate due to cardiovascular diseases was observed at a blood pressure of ≥140/90 mmHg [15]. In addition, according to the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for Treatment of Hypertension, a blood pressure of ≥130/80 mmHg was defined as hypertension on the basis of the meta-analysis results of the data from observational studies of the association between blood pressure level and cardiovascular diseases and from randomized controlled trials (RCTs) designed to evaluate the effects of improved lifestyles and drug therapy [111]. However, the RCTs as the rationale for such definition included few Japanese trials. Therefore, in these guidelines, a blood pressure of ≥140/90 mmHg is adopted as the criterion for grade I or higher hypertension (Table 2-5).

In JSH2014, individuals with an office blood pressure of <140/90 mmHg were regarded as showing a normal-range blood pressure. In addition, the normal blood pressure was subclassified into three groups: high-normal, normal and optimal blood pressure. However, the results of observational studies in Europe and the United States [138] and studies in Japan [139, 140] have shown that the incidences of cardiovascular diseases in individuals with a blood pressure of 120–129/80–84 mmHg and those with a blood pressure of 130–139/85–89 mmHg are higher (in the ascending order) than in those with a blood pressure of <120/80 mmHg. Furthermore, it has been shown that in the former two groups (120–139/80–89 mmHg), the chances of developing hypertension are higher than in the third group [141]. Therefore, it does not seem appropriate to regard an office blood pressure of ≥120/80 mmHg as a normal blood pressure. An office blood pressure of <120/80 mmHg is therefore expressed as normal in these guidelines (Table 2-5). The subclasses "normal blood pressure" and "high normal blood pressure" employed in JSH2014 are classified and expressed as "high normal blood pressure" and "elevated blood pressure," respectively, in these guidelines. For consistency with the goal of antihypertensive measures in these guidelines (see Chapter 3 Table 3-3), the DBP range or these two classes is set at <80 mmHg and 80–89 mmHg, respectively (Table 2-5).

Table 2-4 Indications for ABPM

1. When a home blood pressure fluctuates around 135/85 mmHg or an office blood pressure of fluctuates around 140/90 mmHg, making diagnosis of hypertension difficult.

2. When an elevated value (125–134/75–84 mmHg) is obtained on home blood pressure measurement.

3. When there is marked variability in the home blood pressure.
(a) When a definitive diagnosis of white coat hypertension is not made based on the home blood pressure level.
(b) When a definitive diagnosis of masked hypertension is not made based on the home blood pressure level.
(c) When self-measurement of blood pressure is impossible at the workplace and workplace hypertension is suspected.
(d) When a definitive diagnosis of resistant hypertension is not made based on the home blood pressure level.
(e) When the nighttime blood pressure is not measured on home blood pressure and nocturnal hypertension (non-dipper, riser) is suspected.

4. When the information on short-term variability of blood pressure is warranted.
(a) When incidental, transient hypertension or hypotension is observed.
(b) When the home and office blood pressure levels markedly change.

5. When the difference between home blood pressure and office blood pressure is extremely large.

Blood pressure classification using the office blood pressure data should be based on at least two blood pressure measurements, taken on separate occasions in the absence of antihypertensive treatment. On each occasion, blood pressure should be measured many times at intervals of 1–2 min and the mean of two stable values (difference less than 5 mmHg) should be adopted as the blood pressure value at a given occasion.

2) Classification based on out-of-office blood pressure measurement

(1) Classification based on home blood pressure In many international guidelines, including Japanese guidelines, 135/85 mmHg (Tables 2-5, 2-6) has been adopted as a criterion for hypertension on the basis of the results of meta-analysis of the data from 6470 individuals followed for a median period of 8.3 years (International Database of Home blood pressure in relation to Cardiovascular Outcome: IDHOCO) involving cross-sectional/follow-up studies in USA/Europe and Japan as well as Ohasama Study and Tsurugatani Study in Japan [112, 142–145]. Also in these guidelines, a home blood pressure of ≥135/85 mmHg was adopted as a criterion for hypertension, as is the case with JSH2014. Furthermore, since the diagnosis of hypertension on the basis of home blood pressure is more popular in Japan, these guidelines classify home blood pressure into normal, high normal and elevated blood pressures, similar to the classification of office blood pressure, on the basis of the data on untreated inhabitants collected in IDHOCO [143] and Ohasama Study [146] (Table 2-5). As described in the preceding section, classification of home blood pressure uses the mean of morning blood pressure and that of evening blood pressure each measured for 7 days (at least 5 days) (see Q2). Each of these categories of blood pressure is adopted in case in which the mean of home blood pressure in the morning or the mean of home blood pressure in the evening or both satisfy the criteria.

(2) Classification based on ABPM Many international guidelines, including those in Japan, propose to make a diagnosis of hypertension if the 24-h blood pressure measured by ABPM is ≥130/80 mmHg, the daytime blood pressure is ≥135/85 mmHg and the nighttime blood pressure is ≥120/70 mmHg on the basis of the results from cross-sectional/follow-up surveys in USA/Europe and Japan as well as their meta-analysis [126, 134, 144, 145, 147]. Also in these guidelines, similar to JSH2014, a diagnosis of hypertension is made if the mean of 24-h blood pressure is ≥130/80 mmHg, the mean of daytime blood pressure is 135/85 mmHg and the mean of nighttime blood pressure is ≥120/70 mmHg, regardless of where blood pressure is measured (Table 2-6).

3) Classification by systolic and diagnostic blood pressures

For both the classification based on office blood pressure and the classification based on out-of-office blood pressure, SBP and DBP are mutually independent risk factors, and if they belong to different blood pressure categories the individual is classified by the higher category.

The frequency of isolated systolic hypertension increases in older people because SBP increases, whereas DBP often decreases due to a reduced compliance of the large elastic arteries caused by atherosclerosis. Several studies, including the cohort studies in USA/Europe [148–150], Hisayama Study and Ohasama Study [136, 151], showed that isolated systolic hypertension was an important risk factor for cerebral or myocardial infarction in older people. Isolated systolic hypertension in older persons is classified into the burned-out type, caused by an aging-related decrease in DBP in cases of essential hypertension, and the de novo type, caused by a novel increase of SBP in old age.

4) Blood pressure measurement and procedures for hypertension diagnosis

Currently, in Japan, 77% of hypertensive patients have a sphygmomanometer for taking home blood pressure

Table 2-5 Classification of blood pressure levels in adults

Classification	Office blood pressure (mmHg)			Home blood pressure (mmHg)		
	SBP		DBP	SBP		DBP
Normal blood pressure	<120	and	<80	<115	and	<75
High normal blood pressure	120–129	and	<80	115–124	and	<75
Elevated blood pressure	130–139	and/or	80–89	125–134	and/or	75–84
Grade I hypertension	140–159	and/or	90–99	135–144	and/or	85–89
Grade II hypertension	160–179	and/or	100–109	145–159	and/or	90–99
Grade III hypertension	≥180	and/or	≥110	≥160	and/or	≥100
(Isolated) systolic hypertension	≥140	and	<90	≥135	and	<85

Table 2-6 Criteria for hypertension in different measurement methods

	SBP (mmHg)		DBP (mmHg)
Office blood pressure	≥140	and/or	≥90
Home blood pressure	≥135	and/or	≥85
ABP			
24 h	≥130	and/or	≥80
Daytime	≥135	and/or	≥85
Nighttime	≥120	and/or	≥70

measurement. Reportedly, 40% of non-hypertensive individuals possess a home sphygmomanometer [103]. In Japan, approximately 40 000 000 home sphygmomanometers may be in use, corresponding to 1 sphygmomanometer per household [104]. This value is consistent with that reported from the National Health and Nutrition Survey of Japan in 2010 [105]. On the other hand, in Japan, 72% of adult men and 63% of adult women undergo a health checkup in some form or other [152]. Therefore, individuals without a history of hypertension consult a medical facility if hypertension is shown by a health checkup or self-measurement of blood pressure/home blood pressure.

In medical facilities, office blood pressure is measured. Simultaneously, the home blood pressure measured by patients is reported to the facility, or patients begin to measure home blood pressure before the start of treatment as per physicians' recommendations (Figure 2-1). As criteria for the diagnosis of hypertension based on home blood pressure have been established, a diagnosis of hypertension is made based on patients' office and home blood pressure levels. In this case, when there is a discrepancy of decision between the two methods, a home blood pressure-based diagnosis of hypertension has priority, because the prognostic value of home blood pressure, that is, its clinical value, is higher than that of office blood pressure. Furthermore, blood pressure measurement in an out-of-office setting has already had priority over office blood pressure for the diagnosis and treatment of white coat or masked hypertension.

The JSH2014 and 2019 Guidelines differ from those in Europe and the United States in that the clinical availability, feasibility and diagnostic value of home blood pressure are highly appraised. However, ACC/AHA2017 guidelines [111] recommend that home blood pressure measurement is first conducted to evaluate the white coat effect during treatment and to identity poorly controlled masked hypertension and ABPM is then conducted for confirmation. These guidelines proposed a procedure similar to the JSH in that priority is given to diagnosis on the basis of home blood pressure.

In Japan, 40 000 000 home sphygmomanometers are in use, whereas only tens of thousands of ABPM devices are being used [104]. Actually, the clinical application of ABPM is not easy [153]. ABPM devices are expensive, and the mental/physical stress of individuals wearing them is great. In addition, there are manpower- and cost-related problems relating to the medical staff. These factors support the importance of home blood pressure measurement emphasized in the guidelines. However, ABPM has certain merits, and, if necessary, it is clinically important to perform ABPM. In these guidelines, it is recommended that ABPM should be performed, if possible, as a complementary measure for hypertension diagnosis by home/office blood pressure measurement.

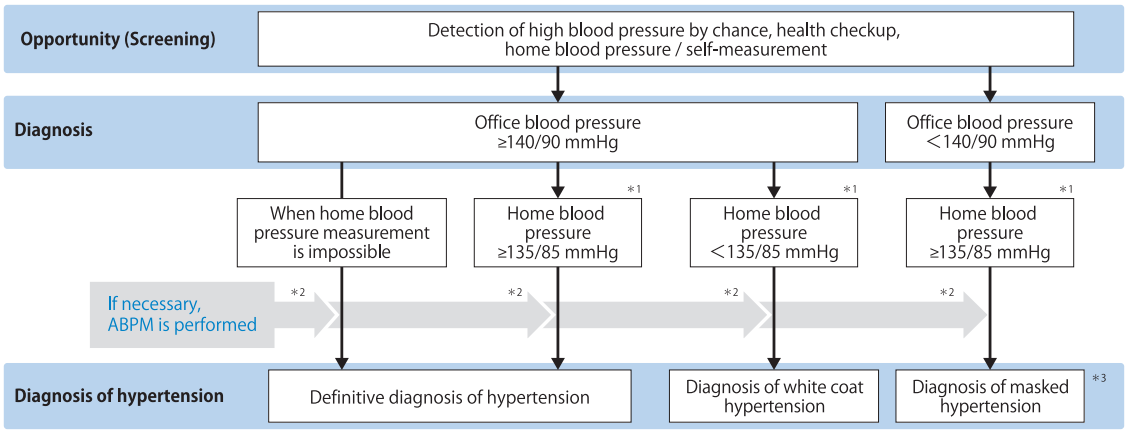
POINT 2B

[White coat hypertension]

1. **White coat hypertension is defined as cases in which the office blood pressure is ≥140 mmHg and/or 90 mmHg and the home blood pressure is <135 mmHg/85 mmHg or the 24-h mean blood pressure (measured by ABPM) is <130 mmHg/80 mmHg.**
2. **White coat hypertension is seen in 15–30% of hypertensive patients, and this percentage is higher among older persons.**
3. **Patients with white coat hypertension require careful follow-up because their risk for composite of cardiovascular events in the future is higher than in non-hypertensive individuals (individuals with normal, high normal or elevated blood pressures) (see CQ2).**

[Masked hypertension]

1. **Masked hypertension is defined as cases in which the mean office blood pressure is <140 mmHg/90 mmHg and the home blood pressure is ≥135 mmHg and/or 85 mmHg or the 24-h mean blood pressure (measured by ABPM) is ≥130 mmHg and/or 80 mmHg.**
2. **Masked hypertension includes morning hypertension (early morning blood pressure ≥135/85 mmHg), nighttime hypertension (nighttime blood pressure ≥120/70 mmHg) and daytime hypertension (daytime blood pressure ≥135/85 mmHg).**
3. **Masked hypertension is seen in 10–15% of the non-hypertensive population and in 9–23% of hypertensive patients whose office blood pressure is controlled to less than 140/90 mmHg by antihypertensive therapy.**
4. **The cardiovascular risk of untreated masked hypertension is comparable to that of sustained hypertension and may be viewed as hypertension.**



*1: When an office blood pressure-based diagnosis differs from a home blood pressure-based diagnosis, the latter should be prioritized. The blood pressure obtained by self-measurement refers to that measured using an automatic sphygmomanometer located in a public facility or at the workplace/pharmacy.
*2: Criteria for hypertension regarding ABP include a mean 24-h blood pressure of 130/80 mmHg or more, a mean daytime blood pressure of 135/85 mmHg or more and a mean nighttime blood pressure of 120/70 mmHg or more. When ABPM is possible, patients having one of the ABP levels equal to or higher than the criteria are regarded as having hypertension or masked hypertension. When all values are below the above criteria, patients are regarded as normal or having white coat hypertension.
*3: Although this diagnostic procedure is applicable for untreated hypertensive subjects, it must be considered that masked hypertension is also present in hypertensive individuals receiving treatment.

Fig. 2-1 Blood pressure measurement and procedure for hypertension diagnosis

[Diurnal variation of blood pressure]

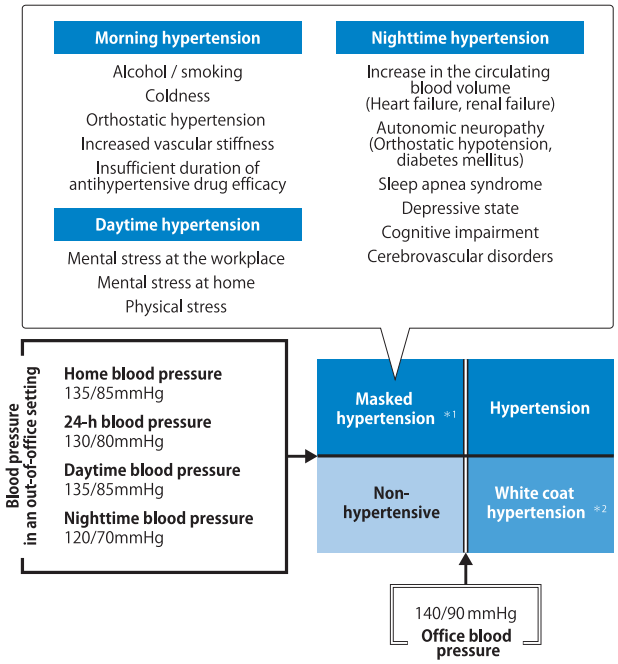
1. **During management of hypertension, care should be taken also of diurnal variation patterns of blood pressure (non-dipper, riser, dipper), nighttime blood pressure, early morning blood pressure and blood pressure at workplace.**

3. HYPERTENSION BASED ON HOME BLOOD PRESSURE AND ABPM

The office blood pressure level is not always consistent with the non-office, daily blood pressure level measured using a home sphygmomanometer or on ABPM. A rise in blood pressure related to stress in a clinical setting is called the white coat phenomenon. The intensity of the white coat phenomenon (white coat effect) is calculated by subtracting the out-of-office blood pressure level from the office blood pressure level. For the diagnosis of hypertension, the condition can be classified into four types based on office and out-of-office blood pressure levels: non-hypertensive, white coat hypertension, masked hypertension and sustained hypertension. Diagnostic procedures are presented in Figure 2-2 [154]. Although white coat hypertension and masked hypertension are diagnosed on the basis of home blood pressure or ABPM according to their definition, there is a report that the combination of home blood pressure and ABPM allows identification of white coat hypertension or masked hypertension with favorable or poor prognosis [155]. It is therefore ideal to use both of them.

1) White coat hypertension

White coat hypertension is a condition in which the blood pressure level measured in a clinical setting is at a hypertensive level but that measured in a nonclinical setting is in the non-hypertensive range (Figure 2-2) [154]. This term should be essentially used in untreated patients. White coat hypertension accounts for 15–30% of patients, with an office blood pressure of 140/90 mmHg or more, diagnosed with hypertension. The frequency increases in older persons [154]. There are many reports demonstrating that when comparing white coat hypertension with sustained hypertension, in which the blood pressure level in a nonclinical setting is also high, organ damage is mild, and the cardiovascular prognosis is also favorable [129, 154, 156]. However, this is still controversial. During preparation of these guidelines, this issue was discussed as CQ. As a result, a conclusion that this requires careful follow-up was reached, because patients with white-coat hypertension have a higher risk for cardiovascular diseases events in the future when compared with non-hypertensive individuals (see CQ2 for details). If the office blood pressure is in the range of hypertension and the out-of-office blood pressure is in the non-hypertensive range in hypertensive patients receiving treatment, the condition is described as "hypertension accompanied by white coat phenomenon or white coat effect." Similar to the diagnosis of hypertension, evaluation should first be made using the home blood pressure



*1: Masked hypertension in patients receiving treatment is described as masked hypertension during treatment. It is sometimes described as masked uncontrolled hypertension.
*2: White coat hypertension during treatment is described as hypertension accompanied by white coat phenomenon or white coat effect.

Fig. 2-2 Conditions classified as masked hypertension and its factors

and, as needed, ABPM is conducted for confirmation, to judge whether hypertension associated with the white coat effect is present.

2) Masked hypertension

Masked hypertension is a condition in which the blood pressure level measured in a clinical setting is in the non-hypertensive range, but that measured in a nonclinical setting is at a hypertensive level (Figure 2-2) [154, 157]. This term is usually used in patients taking no antihypertensive drug, but these guidelines apply the term to both untreated patients and patients diagnosed as having hypertension (including patients receiving treatment). Masked hypertension in patients receiving treatment is described as masked hypertension under treatment. In Europe and the United States, it is called "masked uncontrolled hypertension." [147, 158] Masked hypertension is defined on the basis of office and ouf-of-office blood pressure levels, but the condition varies. Morning hypertension, daytime hypertension and nighttime hypertension comprise masked hypertension, and hours during which the blood pressure level in a nonclinical setting increases differ. Masked hypertension is observed in 10–15% of the non-hypertensive general population and in 9–23% of hypertensive patients undergoing antihypertensive therapy in whom office blood pressure level is controlled at <140/90 mmHg [157]. The

Table 2-7 High risk groups for masked hypertension

- All hypertensive patients receiving antihypertensive therapy
- Elevated blood pressure (130–139/80–89 mmHg)
- Smokers
- Heavy drinkers
- Individuals exposed to much mental stress (workplace, home)
- High physical activity
- High pulse rate
- Orthostatic abnormal variation in blood pressure (orthostatic hypertension, orthostatic hypotension)
- Obesity, metabolic syndrome and diabetes mellitus
- Complication by organ failure (left ventricular hypertrophy in particular) or cardiovascular diseases

risks of organ damage and cardiovascular events in patients with masked hypertension are significantly higher than in non-hypertensive individuals or patients with white coat hypertension, being similar to those in patients with sustained hypertension. According to previous clinical studies, in patients with masked hypertension, metabolic abnormalities are more frequent than in non-hypertensive individuals, and hypertensive organ damage progresses regardless of the presence or absence of treatment for hypertension [111, 159]. In follow-up studies of untreated subjects [160], community residents [51, 161] and hypertensive patients receiving treatment [162–164], the relative risk for cardiovascular diseases in patients with masked hypertension was similar to that in patients with sustained hypertension [157]. Table 2-7 shows the high risk groups for masked hypertension. In these subjects, it is important to measure home and ABP levels regardless of the office blood pressure level. In some cases, the type of hypertension diagnosed differs between home blood pressure measurement and ABPM [155, 165], and it is necessary to check blood pressure with ABPM, as needed, in addition to home blood pressure measurement. For patients with masked hypertension receiving treatment, checking for overlooked secondary hypertension and elucidation of the cause (e.g., daily habits which require improvement) are also important, in addiction to reinforcement of treatment.

3) Morning hypertension

Patients with an office blood pressure of <140/90 mmHg and a mean home blood pressure measured early in the morning of 135/85 mmHg or more are regarded as having morning hypertension. Morning hypertension is classified into two types: non-dipper/riser and morning surge types. Both of these types may become risk factors for organ damage and cardiovascular events [166–168]. A mild morning surge is a physiological phenomenon, but an excessive morning surge becomes a risk factor. In contrast, the risk increases in a group

with the disappearance of morning surge according to a study. The disappearance of morning surge is associated with the riser type, in which the nighttime blood pressure increases, and autonomic neuropathy such as orthostatic hypotension. Factors affecting morning hypertension are shown in Figure 2-2 [168, 169]. Morning hypertension is significantly associated with the risk for all cardiovascular diseases involving brain, heart, kidneys and other organs and causes organ damage more severe than that caused by the hypertension defined on the basis of office blood pressure, thus increasing the future risk for stroke [170, 171] and the need of daily life care during late senility [115]. Early morning blood pressure can be measured with a home sphygmomanometer, but morning hypertension characterized by specifically higher early morning blood pressure than the blood pressure at other times of the day (e.g. cases in which the bedtime blood pressure is in the non-hypertensive range and early morning blood pressure is at a hypertension level or cases in which early morning blood pressure is higher by 15 mmHg or more than the bedtime blood pressure) is a risk factor independent of mean morning or evening blood pressure [115, 170–172]. In hypertensive patients receiving treatment with antihypertensive drugs, a clinically significant problem is that the hypotensive effect of medication is lowest early in the morning (immediately before intake of the drug) even when the clinical blood pressure has been controlled well.

4) Nighttime hypertension

Patients with a mean nighttime blood pressure level measured by ABPM or using a home sphygmomanometer of 120/70 mmHg or more are regarded as having nighttime hypertension. For nighttime blood pressure measurement, ABPM is used, but a home sphygmomanometer can also be used for this purpose at present [173–176]. The nighttime blood pressure measured using a home sphygmomanometer is associated with organ damage, as described for that measured by ABPM [175]. When a high nighttime blood pressure level persists after waking, it is detected as 'morning hypertension' on home blood pressure measurement. The rate of change in nighttime blood pressure is smaller than that in daytime blood pressure. An increase in mean value is more strongly associated with an increase in the risk for cardiovascular diseases and a reduction in cognitive/physical functions [177, 178]. In addition, in patients in whom the nighttime blood pressure level alone is high despite normal-range home blood pressure levels measured early in the morning/at bedtime, vascular disorder is also advanced and the risk for cardiovascular diseases is high [179].

5) Daytime hypertension (hypertension in the presence of stress)

Patients in whom the mean value of blood pressure during stress-exposed daytime hours at the workplace or at home is 135/85 mmHg or more, with favorable reproducibility, despite normal-range office/home blood pressure levels, are regarded as having daytime hypertension. Mental/physical stress influences ABP (Figure 2-2). Workplace hypertension, in which the blood pressure measured on a health checkup or in a clinical setting is normal but that measured at the workplace in the presence of stress is high, is common among obese individuals and among those with a family history of hypertension.

6) Abnormal diurnal variations of blood pressure

When the circadian rhythm of blood pressure is normal, the nighttime blood pressure decreases by 10–20% of the daytime level on waking. This normal pattern is termed a dipper. A pattern in which there is only a slight decrease in nighttime blood pressure (rate of decrease in nighttime blood pressure: 0–10%) is defined as a non-dipper, and a pattern in which there is an increase in blood pressure at night is defined as a riser. In non-dippers and risers, the risks of brain/heart/kidney damage and cardiovascular mortality are high [180–182]. When sleep time is shortened in risers, the risk for cardiovascular diseases synergistically increases [183]. In addition, non-dippers in whom there is only a slight decrease in nighttime pulse also become a risk factor for cardiovascular events, independent of blood pressure non-dippers. When both blood pressure and pulse rate show a non-dipper pattern, the risk increases markedly [184]. In addition, even when office and 24-h blood pressure levels are in the non-hypertensive range, the cardiac load or risk of cardiovascular mortality increases in patients with nighttime hypertension or non-dippers/risers [179, 182]. The factors responsible for nighttime hypertension are shown in Figure 2-2.

On the other hand, a pattern in which the nighttime blood pressure level decreases excessively (20% or more of the mean daytime blood pressure) is defined as an extreme-dipper [180, 181]. It remains controversial whether the risk of an extreme-dipper is related to an excessive decrease in nighttime blood pressure or a morning surge in blood pressure/an increase in daytime blood pressure. In older hypertensive patients with an extreme dipper pattern, asymptomatic brain disease is advanced [180, 185], and the risk of stroke is also high [129]. According to several studies, extreme dippers show a reduction in cognitive function and cerebral blood flow, as well as an increase in pulse wave velocity (PWV) [186–189]. Among young individuals with a normal 24-h blood pressure level, the risk of coronary calcium deposition in non-dippers/risers and extreme dippers is more than four times higher than that in dippers [190]. These results suggest that the impaired circadian rhythm of blood pressure/heart rate becomes a risk factor for organ damage and cardiovascular events, independent of the blood pressure level, or a predisposing factor.

In individuals working on night shifts (shift workers), blood pressure reduction is less likely to occur because the sympathetic activity does not decrease sufficiently during daytime sleep compared with nighttime sleep, often resulting in non-dipper type abnormal variations of blood pressure.

4. BLOOD PRESSURE VARIABILITY

Blood pressure variability can be assessed by frequently measurement of blood pressure. Blood pressure variability includes a beat-to-beat variation, respiration-/autonomic output-related changes in a relatively short interval, and seasonal or yearly changes. In clinical practice, short-term diurnal changes can be assessed by measurement at intervals of 10–30 min with 24-h ABPM, morning-evening differences and day-by-day variability by home blood pressure measurement, and visit-to-visit variability by office blood pressure measurement. Long-term home blood pressure measurement data reflect seasonal/annual changes as well. White coat hypertension, masked hypertension, nighttime hypertension, morning hypertension and morning surge are also classified as a phenotype of blood pressure variability.

Significant association of visit-to-visit blood pressure variability with cardiovascular disease outcomes [191–193] and prognostic significance of diurnal and day-by-day blood pressure variability measured at home and with ABPM, respectively [194–197], have been reported. However, when blood pressure variability is evaluated with considering the impact of blood pressure level, the prognostic ability of blood pressure variability for cardiovascular complications is not very high and does not exceed the importance of blood pressure level (see Q3 "Blood pressure variability evaluation method") [198–201]. Whereas, recent epidemiological studies have demonstrated the usefulness of day-by-day home blood pressure variability in the prediction of onset/progression of dementia [57, 202]. Furthermore, usefulness of seasonal variations of long-term home blood pressure measurement for the adjustment of prescribed drug dose and the prediction of cardiovascular outcome has been reported [203].

Blood pressure variability is affected largely by the setting for measurement. Of blood pressure variabilities, nighttime blood pressure dipping (vs daytime) and masked hypertension (out-of-office measurement vs office measurement) have been definitely shown to have high clinical significance (see the preceding section), whereas visit-to-visit and day-by-day blood pressure variability show no change [201, 204] or only limited change [205, 206] in response to antihypertensive drug therapy. Such blood pressure variabilities are therefore difficult to treat as an intervention-possible risk factor and currently serve only as a risk marker.

5. PULSE RATE

According to the general population-based cohort studies in Japan, the mean pulse rate is 74/min for women and 70/min for men, with the age-related differences remaining in the range of approximately ±5/min [207]. Accumulating evidence suggests that an increase in pulse rate is associated with cardiovascular morbidity and total mortality [208–210]. The Ohasama Study demonstrated an increase in cardiovascular mortality when the pulse rate by home morning blood pressure measurement exceeds 70/min [211]. The prognostic ability of pulse rate measured by 24-h ABPM is lower than that of pulse rate by office blood pressure measurement [212], but the pulse rate measured by nighttime ABPM has recently been shown significant predictive power for cardiovascular morbidity and total mortality [213]. It has also been reported that a decrease in pulse rate by drug treatment can improve the prognosis for cardiovascular diseases [214, 215]. However, there is no established evidence regarding an optimal pulse rate and an improvement of prognosis in individuals by controlling pulse rate. The definition of tachycardia at rest also varies among reports from intervention studies and observational studies, with the lower limit set from 79 to 84/min with insufficient rationale (e.g., at upper interquartile point or arbitrary defined threshold) [210]. In the current guidelines, therefore, the optimal pulse rate is not defined, but at least routine measurement of pulse rate is recommended for patients with hypertension [210].

The product of pulse rate times SBP is called "double product (rate-pressure product)" and is known as an indicator of cardiac oxygen consumption [216]. Recently, the association between double product based on home blood pressure measurement and cardiovascular death was reported [217]. However, in integrative meta-analysis of cohorts, the prognostic value of ABPM-based double product was lower than that of ABPM-based SBP [218]. Therefore, the optimal range has not been set for double product, either.

POINT 2C EXAMINATION AND DIAGNOSIS

1. **For the examination of hypertension, the overall evaluation of vascular/organ functions and cardiovascular risk in individual patients and examinations for the diagnosis of secondary hypertension should be performed by considering the cost-effectiveness.**
2. **For the overall evaluation of cardiovascular risk, factors related to metabolic syndrome and chronic kidney disease (CKD) and hypertensive target organ damage are evaluated in addition to blood pressure, including home blood pressure.**

Table 2-8 Points regarding medical history

1. History of hypertension and treatment	
Previous blood pressure level, duration of hypertension and treatment course Efficacy and side effects of antihypertensive drugs	
2. Predisposition to hypertension and pregnancy history	
Family history	Parents' histories of hypertension, diabetes and cardiovascular diseases (onset and age at onset)
Birth weight/weight gain during childhood	
Pregnancy history	Pregnancy hypertension, diabetes, proteinuria
3. Lifestyle	
Exercise	
Sleep	Sleep time, quality of sleep
Diet	Dietary contents/preferences, alcohol consumption, beverages
Smoking	
Personality/psychological state	Depressive tendency, degree of stress (workplace, home)
4. Information suggesting secondary hypertension	
Obesity	History of weight changes
Sleep apnea syndrome	Nocturnal pollakiuria, nocturnal dyspnea, headache, daytime sleepiness, depression, reduced concentration, snoring/apnea (information from patients' families)
Kidney disease	Nocturnal pollakiuria, hematuria, family history (polycystic kidney)
Drugs	Nonsteroidal anti-inflammatory drugs, Chinese traditional herbal drugs, oral contraceptives
Pheochromocytoma	Paroxysmal blood pressure increase, palpitation, sweating, headache
Primary aldosteronism/renovascular hypertension (RVHT)	Weakness, periodic paralysis of the limbs, polyuria
5. Organ disorders	
Cerebrovascular disorders	Transient ischemic attacks, muscular weakness, vertigo, headache, vision disorder
Heart disease	Dyspnea (exertional/nocturnal attacks), weight gain, edema of the lower limbs, palpitation, chest pain
Kidney disease	Polyuria, nocturnal pollakiuria, hematuria, proteinuria
Peripheral arterial disease	Intermittent claudication, coldness of the lower limbs

3. **The evaluation of target organ damage in high-risk patients such as those with diabetes mellitus, CKD or a history of cardiovascular diseases is essential if their blood pressure level is in or higher than the high normal blood pressure range.**
4. **Echocardiography (UCG), coronary artery CT, carotid ultrasonography and brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are representative, special methods of examination for evaluating target organ damage, and other recommended examinations should be performed appropriately.**
5. **If secondary hypertension is suspected from medical interview, physical examination and general laboratory tests, appropriate screening tests should be performed.**

6. EXAMINATION AND DIAGNOSIS

For the diagnosis and treatment of hypertensive patients, (1) the severity of hypertension (blood pressure level) should be evaluated, (2) essential and secondary hypertension should be differentiated, (3) the presence or absence of cardiovascular risk factors (particularly those related to diabetes mellitus, metabolic syndrome and CKD), (4) the underlying lifestyle should be clarified, (5) concurrent cardiovascular diseases and organ damage should be evaluated,

Table 2-9 Points regarding physical findings

1. Blood pressure/pulse rate	
Resting in the sitting position (blood pressure laterality and orthostatic changes in blood pressure and pulse rate on initial examination)	
2. General condition and obesity	
Height/body weight	
BMI (body weight (kg)/height $(m)^2$)	Obesity, BMI≥25 kg/m^2
Waist circumference (standing position measurement at the umbilical level)	Abdominal obesity, men: ≥85 cm, women: ≥90 cm
Dermal findings	Striated abdominal wall skin, hypertrichosis (Cushing's syndrome)
3. Facial/cervical regions	
Anemia, jaundice	
Fundic findings	
Goiter	
Carotid artery murmurs	
Dilatation of the jugular vein	
Facial appearance (endocrine disease)	
4. Thoracic region	
Heart	Apical beat and thrill on palpation (strongest point and extent of palpation), cardiac murmurs, gallop rhythms, arrhythmia on auscultation
Lung field	Rales
5. Abdomen	
Vascular murmurs and the direction of their projection, liver enlargement and tenderness, kidney enlargement (polycystic kidney)	
6. Limbs	
Arterial pulse (each superficial peripheral artery) on palpation (disappearance, attenuation, laterality), coldness, ischemic ulcers, edema	
7. Nerves	
Dyskinesia of the limbs, sensory disturbance, increased tendon reflex	

and (6) the severity of hypertension should be evaluated, considering home blood pressure.

1) History taking (Table 2-8)

The time of detecting hypertension and its circumstances (health screening, examination and self-measurement), duration, severity and course of treatment should be established. Particularly, if hypertension has been treated, the type of antihypertensive medications used and their effectiveness/the presence or absence of adverse effects should be confirmed.

As past medical histories, low birth weight or overweight in childhood and, in women, whether they have had hypertension, diabetes mellitus or proteinuria during pregnancy should be ascertained. With respect to family history, the presence or absence of hypertension, diabetes mellitus, or cardiovascular diseases and age at onset should be ascertained.

Lifestyle behaviors should be clarified in detail by asking patients about their exercise habits (frequency and intensity), sleep habits (duration and quality of sleep), dietary habits (content of meals, salt content, preference for sweets), intake of alcohol or soft drinks and smoking (amount and length of time), personality/psychological state (anxiety and depressive tendency) and severity of stress (workplace, home).

Hypertensive patients are usually symptom-free, but patients with secondary hypertension and those with complications/organ damage should be checked for the presence or absence of specific symptoms. As for signs suggestive of secondary hypertension, whether the patient has symptoms, such as nocturnal pollakiuria or nocturnal dyspnea,

early-morning headache, daytime sleepiness, depression and reduced concentration or whether there are signs of sleep apnea syndrome, such as reports of snoring and apnea by the family, should be checked, in addition to the course of body weight increases and other risk factors related to metabolic syndrome (diabetes and dyslipidemia). Moreover, a history of hematuria, proteinuria and nocturnal pollakiuria, which suggest kidney disease, and the status of use of drugs which can increase blood pressure, such as non-steroidal anti-inflammatory drugs (NSAIDs), Chinese traditional herbal drugs, oral contraceptives, immunosuppressors and molecule-targeted drugs should be confirmed. Inquiries should be made into a history of organ damage and cardiovascular diseases, thereby confirming the presence or absence of symptoms/signs, such as transient ischemic attacks, muscle weakness, dizziness, headache and visual impairment related to cerebrovascular disorders; dyspnea (exertional, nighttime), weight gain, lower limb edema, palpitation and chest pain related to heart disease; pollakiuria, oliguria, nocturia and hematuria related to kidney disease; and intermittent claudication and coldness of the lower limbs related to peripheral artery disease.

2) Examination (physical findings) (Table 2-9)

In addition to resting blood pressure and heart rate in a sitting position, left-right differences in pulse (beat) and upper arm blood pressure, upper limb-lower limb differences in pulse and blood pressure and orthostatic changes in pulse and blood pressure should be checked during initial examination.

Height and body weight are measured, and the degree of systemic obesity is evaluated by calculating the body mass index (BMI) (body weight (kg)/(height $(m)^2$). Furthermore, waist circumference is measured (in the standing position at the umbilical level) and the degree of abdominal obesity is evaluated.

Also, the presence or absence of findings suggesting secondary hypertension, sign of heart failure, atherosclerosis and cardiovascular diseases is examined. The skin is examined for abdominal striae and hirsutism; the face and neck region is examined for moon face, myxedematous face, anemia/jaundice, thyroid goiter, cervical vascular murmurs (if findings are present, the presence or absence of orbital murmurs is checked), jugular vein dilation in the sitting position and ophthalmoscopic findings; as for the chest, palpation of the apical beat and thrill (strongest point and palpation area) and auscultation for heart murmurs, gallop rhythms, arrhythmias, dorsal vessel murmurs and rales in the lung fields are performed. The abdominal region is examined for vascular murmurs/directions of their projection, a pulsating phyma on palpation, liver enlargement and kidney enlargement (polycystic kidney); the limbs are examined by palpation (disappearance, weakening and lateral difference) of arterial pulse (radial and dorsalis pedis (lower limb) arteries; if findings are present, the site of palpation is transferred to the central side in the order of the posterior tibial, popliteal and femoral arteries), cold sensation, ischemic ulcer, edema, motor disturbances, sensory disturbances, and increased or weakened tendon reflex.

Table 2-10 Clinical examination

1. General examinations (on initial consultation and a few times a year during follow-up)
On initial consultation: general examinations (blood, urine)
During follow-up (tests selected depending on the risk)
Biochemistry: creatinine (Cr), uric acid, electrolytes, lipid metabolism, glucose metabolism, liver function
Urinalysis: urinary protein, urinary sediment
eGFR is calculated from serum Cr. In case of muscular mass decrease (e.g., sarcopenia), eGFR based on cystatin is also utilized.
2. Screening tests in patients in whom secondary hypertension is suspected
The following tests are selected depending on the medical history, physical findings, general examination data and organ failure features.
Blood analysis (renin activity/active renin concentration, aldosterone, cortisol, ACTH, 2 fractions of metanephrine, 3 fractions of catecholamine, IGF-I, TSH)
Urine sample (2 fractions of metanephrine, 3 fractions of catecholamine, aldosterone)
Abdominal ultrasonography
Nighttime percutaneous oxygen partial pressure monitoring
3. Specific examinations by specialists
Tests targeting the suspected disease are selected from the following tests.
Renal artery ultrasonography, renography, hormone load test, adrenal CT (including contrast-enhanced CT), adrenal venous sampling, polysomnography (PSG)

3) Laboratory examinations (Table 2-10)

Laboratory examinations for the overall assessment of target organ damage and cardiovascular risk in individual patients and for the diagnosis of secondary hypertension are performed by always considering cost-effectiveness.

(1) General laboratory examinations General examinations that should be performed during the initial examination of hypertensive patients and a few times a year during follow-up are general urinalysis, blood cell counting, blood chemistry tests, chest X-ray and electrocardiography. For these examinations, it is also possible to use data from general mass screening and health checkups at the workplace.

On blood chemistry tests during the initial examination, general laboratory parameters are measured. During follow-up examination, creatinine (Cr), uric acid, electrolytes, fasting

triglyceride (TG), high-density lipoprotein cholesterol, total cholesterol (or low-density lipoprotein cholesterol), fasting blood sugar and hepatic function are measured in view of risk evaluation. The estimated glomerular filtration rate (eGFR) is calculated from the serum Cr, but eGFR calculated from cystatin C is also utilized if muscle mass decrease (e.g., sarcopenia) is present (see Section on CKD). Particularly in patients receiving oral-dose antihypertensive medication (diuretics, renin–angiotensin [RA] inhibitors) and older patients, sodium (Na) is additionally measured. Urinary Na/K ratio and gCr-corrected Na are useful in the evaluation of dietary profile.

(2) Evaluation of glucose tolerance and inflammatory risk factor If impaired glucose tolerance is suspected by the screening with fasting blood sugar level, the glycated hemoglobin level measurement and/or 75-g oral glucose tolerance test should be performed [219]. Although the blood level of high-sensitive C-reactive protein (CRP) is lower among the Japanese than in western and south-east Asian populations, its increase even to a minimal degree is related to coronary artery disease and silent cerebral infarction [220–222], and is a risk factor for future stroke [223].

(3) Autonomic nerve function test The frequency of orthostatic dysregulation of blood pressure, as a type of autonomic neuropathy, increases in older people and diabetics. This disorder is associated with the progression of organ damage and deterioration of long-term prognosis [224, 225]. A head-up tilting test with a tilt table is necessary for detailed examination of orthostatic hypotension. However, the standing test is used as a simple testing method in clinical practice. In this method, blood pressure 1–3 min after active standing is measured, and changes in blood pressure in comparison with that measured in a sitting (or supine) position once or twice after a 5-min rest are evaluated. Simultaneously, the pulse is recorded. When an increase in pulse is less marked than a fall in blood pressure, disorder of the pressure reflex arc is suggested. Dizziness and falls are frequently observed immediately after standing. Blood pressure immediately after standing should also be measured. Many patients with orthostatic hypotension or autonomic neuropathy show abnormal, non-dipper-type (the rate of decrease in blood pressure at night is reduced) or riser-type (the nighttime blood pressure increases) diurnal variations in blood pressure [226, 227].

(4) Examinations for secondary hypertension screening For the screening of patients suspected to have secondary hypertension on the basis of the results of medical interview, physical examinations and general laboratory investigations, the following examinations are performed: examination of the plasma renin activity (or active renin level) and hormone levels, including plasma aldosterone concentration, cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1) and three fractions of catecholamines, blood or urinary examination of two fractions of metanephrine, and abdominal ultrasonography are recommended (with respect to details such as measurement conditions, see Section 3 of Chapter 13, ENDOCRINE HYPERTENSION). Specific examinations should be selected from these examinations depending on the diseases concerned. Examination, such as nighttime pulse oximetry, may be performed for the diagnosis of sleep apnea syndrome.

Special examinations performed by experts for the definitive diagnosis of secondary hypertension include hormone load tests, adrenal gland computed tomography (including contrast-enhanced computed tomography), abdominal MRI, renal artery ultrasonography, renography, adrenal venous sampling (AVS) and polysomnography (PSG). Specific tests are selected depending on the diseases suspected.

4) Diagnosis of hypertensive organ failure

When hypertension is managed, comprehensive evaluation of organ failure caused by hypertension is also needed, in addition to evaluation of blood pressure. To this end, it is required to understand the meaning of various examinations reflecting the degree of organ failure and to conduct measurement and evaluation continuously. Such an evaluation of target organ damage should be conducted in high-risk patients with diabetes mellitus or a history of cardiovascular events whose blood pressure is in or higher than the high-normal range, in addition to patients with hypertension.

(1) Brain and fundus Asymptomatic cerebrovascular disorders (silent cerebral infarcts, cerebral white matter lesions, asymptomatic cerebral hemorrhage and cerebral microbleeds) are strong risk factors for stroke and dementia, and are related to depression and falls in elderly people [228, 229]. MRI is superior to computed tomography for the evaluation of these asymptomatic cerebrovascular disorders. However, during routine clinical practice, neither CT nor MRI is used for screening of organ failure in hypertensive patients.

At present, asymptomatic cerebrovascular disorders are often detected during thorough brain checkup. Asymptomatic brain/neck vascular lesions can advance into symptomatic cerebrovascular disorders and asymptomatic cerebrovascular disorders are closely associated with hypertension and involve a high risk for progression into symptomatic cerebrovascular disorders, thus indicating the importance of antihypertensive treatment [230].

In elderly hypertensive patients, the evaluation of cognitive impairment with the mini-mental state examination (MMSE)

or Hasegawa dementia scale and evaluation of depression on the basis of the Geriatric Depression Scale (GDS) or Beck Depression Inventory (BDI) are also useful for estimation of the risk of future occurrence of dementia and cardiovascular disease and prediction of outcome [231, 232].

Ophthalmoscopy is used as a general screening method. In particular, ophthalmoscopy is essential when hypertension is complicated by diabetes mellitus. Arterial stenosis is the first sign of hypertension's influence on retinal vessels. It is followed by atherosclerosis, and the severity of condition is evaluated on the basis of its cross-reaction with blood pillar reflex or veins. This involves problems related to universality and reproducibility, and contradictory reports describe the association between mild fundus lesions and onset of cardiovascular disease [233, 234]. However, soft exudate/papilledema is seen also in patients with hypertensive encephalopathy (a hypertensive emergency) or malignant hypertension, and fundus bleeding suggests severe hypertension and is associated also with the cardiovascular risk [233, 234]. Immediate actions, including referral to hypertension specialists, are needed when any of these findings is obtained.

(2) Heart Electrocardiography (ECG) is one of the general examinations. Usually, left ventricular hypertrophy is diagnosed on the basis of high ECG potentials (e.g., Sokolow–Lyon voltage criteria, Cornell voltage criteria), but "strain pattern" also is a risk for onset of cardiovascular disease [235]. However, care should be taken of the fact that high potentials may be shown even in the absence of left ventricular hypertrophy in young patients and slim patients.

Improvement in findings from ECG or UCG following antihypertensive treatment reflects improved prognosis and is an indicator for evaluation of antihypertensive efficacy [235]. The European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Hypertension Treatment Guidelines 2018 list ECG and UCG findings as indicators useful in determining the appropriateness of antihypertensive treatment [236]. In Japan, there are no UCG-based diagnostic criteria for left ventricular hypertrophy, but the left ventricular myocardial weight index among healthy Japanese has been shown [237, 238].

The blood levels of brain natriuretic peptide (BNP), which was isolated and identified in Japan, or N-terminal pro-BNP increase markedly in patients with symptomatic heart failure due to left ventricular systolic and diastolic dysfunction (caution: increase is smaller in obese patients), and they have been widely used clinically for the diagnosis of this condition and for evaluation of therapeutic effects [239]. Clinically, they are useful for the screening of hypertensive patients with dyspnea for heart failure.

For the noninvasive screening of hypertensive patients with chest pain for coronary artery disease, ECG (at rest/during exercise), UCG, cardiac nuclear medicine test, coronary artery CT and coronary artery catheterization should be performed in accordance with the guidelines regarding the Noninvasive Diagnosis of Coronary Artery Lesions, which were established by the Japanese Circulation Society [240].

(3) Kidney eGFR and proteinuria (qualitative) are used as general examinations for evaluation of renal dysfunction [241]. Because urinary protein (+/-) examined by the test paper method corresponds to a urinary albumin level of approximately 30 mg/gCr, urinary protein should be measured as needed [241]. CKD is a condition in which 0.15 g/gCr or more proteinuria (30 mg/gCr or more microalbuminuria) or GFR<60 mL/min/1.73m^2 or both persists for 3 months or longer [241]. The severity of CKD evaluated using these two indicators correlates significantly with CKD progression, progression to terminal-stage renal failure, cardiovascular death and total mortality [241]. Recent studies revealed an association between microalbuminuria and prognosis not only in diabetic patients but also in hypertensive patients [242–245].

(4) Blood vessels Evaluation of angiopathy, including atherosclerosis, can be roughly divided into two types: morphological evaluation and functional evaluation.

i) Carotid ultrasonography

Carotid artery intima-media thickness (IMT) is an indicator for morphological evaluation of angiopathy and is an independent indicator for prediction of outcome [246]. IMT≥1.1 mm is abnormal (IMT-C10: Measuring the IMT on the distal wall 10 mm proximal to the common carotid artery-carotid sinus junction) [247, 248], If asymptomatic carotid artery stenosis (diameter stenosis rate 50% or more = moderate stenosis, 70% or more = severe stenosis) has been detected, antihypertensive treatment and other methods of risk control should be considered positively [230].

According to recent meta-analyses, IMT does not markedly improve the evaluation with the use of existing risk models (Framingham risk score) [249], and it is considered as unsuitable as an indicator for evaluation of exacerbation/improvement of the risk following changes in condition or treatment [250, 251].

ii) ABI

ABI is the ratio of the ankle SBP to the brachial SBP (the higher of the right or left brachial SBP) [252]. ABI measurement with the Doppler method is recommended in the AHA2012 Guidelines on ABI Measurement and Evaluation [252], whereas ABI measurement with a simple oscillometric method is used in Japan [253]. There is a good

correlation between ABI values measured with these two methods [254].

ABI≤0.90 reflects complication by peripheral artery disease [252, 253], and ABI≤0.90 and between 0.91 and 1.00 involves a higher risk for onset of cardiovascular disease (≥1.40 is also a risk but the frequency is low) [252, 253]. ABI measurement should be considered in high-risk patients [255].

iii) PWV

PWV is an indicator of arterial stiffness, and carotid-femoral PWV (cfPWV) and baPWV have been used [253]. cfPWV and baPWV have been reported to be independent indicators of prognosis in the meta-analyses based on individual participants data (IPD) summarized from published data [256, 257].

Both cfPWV and baPWV have been shown to improve the evaluation results of existing risk models, with the improvement of the prognostic ability larger when baPWV was used in the low-risk group [257]. cfPWV may be useful when measured in cases at moderate or higher risk [256]. baPWV may be applicable to risk assessment also in low-risk cases, but there is a need of verifying the medico-economic efficiency of its measurement, and its measurement may be useful in patients aged 50 and over or patients having risk factors other than blood pressure.

The cut-off level is cfPWV > 10 m/sec [236] and baPWV≥18 m/sec (reproduced with simplification from Ref. [258]). However, it should be borne in mind that the cut-off level does not divide the risk into two categories and that the relationship of PWVs to onset of cardiovascular disease is linear.

The cardio–ankle vascular index (CAVI) is an indicator of arterial elasticity determined from pulse wave velocity and upper-arm blood pressure and not dependent on blood pressure at the time of measurement [253, 259]. CAVI is higher in the presence of cardiovascular disease, and its cut-off level 9.0 has been proposed [253, 259]. CAVI also rises in the presence of risk factors for cardiovascular disease and decreases in response to treatment [253, 259]. In an observational study of 1080 patients with hypertension complicated by abnormal glucose or lipid metabolism, CAVI was reported as a significant indicator of predicting the onset of cardiovascular disease [260].

iv) Pulse wave analysis

Central blood pressure is most frequently used for pulse wave analysis [253]. Because sex and cardiovascular risk factors affect the central blood pressure, brachial SBP cannot replace central blood pressure, and a meta-analysis has shown that the ability of predicting outcome is higher with central blood pressure than with brachial SBP [261]. International criteria levels of central blood pressure were reported recently [262]. A recent domestic multicenter study also confirmed the usefulness of central blood pressure as a prognostic indicator [263].

v) Endothelial function test

The endothelial function test aimed at evaluating the endothelial dysfunction (an early sign of atherosclerosis) has been covered by health insurance in Japan [253]. Flow-mediated vasodilation (FMD) and reactive hyperemia peripheral arterial tonometry (RH-PAT) are used for this test [253], but they reflect different conditions [264]. Both FMD and RH-PAT have been reported to be independent prognostic factors by a meta-analysis [265], and standard values of FMD by age and sex among Japanese people have been reported [266].

vi) Aortic aneurysm

Dilatation of the aorta on plain chest X-ray is a finding suggesting thoracic aortic aneurysm or aortic dissension, and the presence of a palpable pulsatile mass in the abdomen suggests abdominal aortic aneurysm or aortic dissection. If any of these abnormalities is detected, CT or MRI should be considered. Abdominal ultrasonography is useful in screening of abdominal aortic aneurysm, but its indications have not been definitely defined [255].

Table 2-11 summarizes the characteristics of each indicator [267]. Of the indicators with high abilities of predicting the outcome (indicators whose usefulness has been confirmed in meta-analysis), ECG, eGFR, proteinuria (qualitative) and ophthalmoscopy may be shown as general examination to be used for evaluation of organ failure. Although there is no clear-cut definition of intervals for measurement of the indicators of organ failure, it is necessary to conduct evaluations at intervals of 1–2 years because organ failure progresses with aging. For indicators largely affected by blood pressure (e.g., pulse wave velocity, pulse wave analysis), it seems essential to conduct evaluation upon stabilization of blood pressure after the start of antihypertensive treatment.

CQ1 IS ANTIHYPERTENSIVE TREATMENT BASED ON HOME BLOOD PRESSURE RECOMMENDED RATHER THAN THAT BASED ON OFFICE BLOOD PRESSURE IN ADULTS WITH ESSENTIAL HYPERTENSION?

►Antihypertensive treatment based on home blood pressure is strongly recommended.

Recommendation Grade 1 Evidence Level B

Evidence summarization

We included 12 RCTs, comparing antihypertensive treatment based on home blood pressure with antihypertensive treatment based on office blood pressure, with the reduction in mean of 24-h or daytime ABP level as an outcome. High heterogeneity was observed among these trials. We then conducted meta-analysis after excluding 3 trials in which the same target blood pressure for both home and office blood pressure was employed (this factor possibly responsible for heterogeneity), the heterogeneity disappeared, and the degree of reduction in

Table 2-11 Indicators of organ damages

Examination	Outcome predicting ability[*1]	Simplicity	Cost	Reproducibility	Cut-off level	Indicator improvement after treatment its relation to prognosis
1) Brain/fundus oculi						
MR angiography	Possible	–	High	Good	Asymptomatic cerebral infarction, cerebral white matter lesion, or asymptomatic cerebral hemorrhage	Unknown
Cognitive function test	Possible	Fair	Low	Good	Mini-mental state examination≤26, Hasegawa dementia scale≤25	Unknown
Evaluation of depression	Possible	Fair	Low	Good	GDS≥10, Beck depression inventory (BDI)>10	Unknown
Funduscopy (mild)	Possible	Fair (experience needed for reading)	Low	Fair	Arterial narrowing, blood pillar reflex, cross-reaction with vein	Unknown
Funduscopy (severe)	Good	Fair (experience needed for reading)	Low	Good	Retinal hemorrhage, microaneurysm, cotton-wool patch, papilledema	Unknown
2) Heart						
Electrocardiogram	Good	Good	Low	Good	Sokolow-Lyon: SV1+RV5>35 mm or RV5 or V6≥26 mm, Cornell Voltage: SV3+RaVL>28 mm (male), 20 mm (female) Strain pattern	Indicator improvement leads to better prognosis.
Echocardiogram	Good	Fair	Moderate	Good	No cut-off level set	Indicator improvement leads to better prognosis.
3) Kidney						
eGFR	Good	Good	Low	Good	eGFR<60 mL/min/1.73m^2	Indicator improvement leads to better prognosis.
Proteinuria (qualitative)	Good	Good	Low	Good	+ or higher	Indicator improvement leads to better prognosis.
Proteinuria (microalbuminuria is covered by insurance only in cases of diabetic nephropathy)	Good	Good	Low	Fair	0.15 g/gCr or more	Indicator improvement leads to better prognosis.
4) Blood vessel						
Carotid ultrasound imaging	Good	Fair	Moderate	Good	IMT≥1.1 mm	Poor improvement
ABI	Good	Oscillometric method is good; Doppler is fair	Moderate	Good	ABI≤0.90	Poor improvement
Carotid-femoral artery pulse wave velocity (cfPWV)	Good	Fair	Moderate	Good	>10 m/sec	Unknown
baPWV	Good	Good	Moderate	Good	≥18 m/sec	Unknown
CAVI	Good [267]	Good	Moderate	Good	≥9.0	Unknown
Central blood pressure	Good	Oscillometric method is good, tonometry is fair	Moderate	Good	Standard level established, but no cut-off level set.	Unknown
Flow-mediated vasodilatation (FMD)	Good	Fair	Moderate	Good	-	Unknown
RH-PAT	Good	Fair	Moderate	Good	-	Unknown

[*1]: Good = Tests confirmed to be useful in meta-analysis

ambulatory SBP/DBP following antihypertensive treatment based on home blood pressure was larger by −3.64 mmHg (95% confidence internal [CI] −5.04 to −2.23) for systolic pressure and −2.16 mmHg (95% CI −3.18 to −1.14) for diastolic pressure than that following antihypertensive treatment based on office blood pressure. A similar result was obtained also when the analysis was confined to 5 trials with the 24-h ABP level as an outcome. No RCT evaluating the incidence of cardiovascular diseases or mortality was identified.

Commentary

A number of studies have shown that home blood pressure is more reliable and reproducibly than office blood pressure [122, 268] and is more closely associated with cardiovascular diseases and target organ damage [50, 113, 143, 156, 269]. On the basis of such evidence, the Guidelines on Hypertension Treatment 2014 (JSH2014) states clearly: "If the office blood pressure differs from the home blood pressure, priority should be given to diagnosis based on the home blood pressure." [108] However, a part of clinicians have a view that office blood pressure suffices [106]. To resolve such a difference in awareness/view, it is essential to compare antihypertensive treatment based on home blood pressure with conventional antihypertensive treatment based on office blood pressure and to demonstrate clearly whether the prognosis and hypertension control will be improved by the use of home blood pressure as an indicator.

With such a background, we recently conducted systematic review (SR) by setting this CQ during preparation of JSH2019 [270]. The following three outcomes were set for this review: 1) reduction in the incidence of cardiovascular diseases, 2) reduction in cardiovascular mortality, 3) reduction in mean 24-h ABP levels.

1) **Reduction in the incidence of cardiovascular diseases**
2) **Reduction in cardiovascular mortality**
   No RCT corresponding to outcome 1) or 2) was identified.
3) **Reduction in mean 24-h ABP levels**

Twelve RCTs were included (Table CQ1-1) [271–282]. For the trials in which mean 24-h ABP levels had not been evaluated, mean daytime ABP level was used as a surrogate outcome. Meta-analysis of the 12 trials revealed high inter-trial heterogeneity (Figure CQ1-1, $I^2 = 75\%$). When the analysis excluded 3 trials employing the same target blood pressure for both home and office blood pressure (this factor possibly responsible for heterogeneity), the heterogeneity disappeared, and the degree of reduction in ABP following antihypertensive treatment based on home blood pressure was larger by 3.64 mmHg (95% CI −5.04 to −2.23) for systolic pressure and 2.16 mmHg (95% CI −3.18 to −1.14) for diastolic pressure than that following antihypertensive treatment based on office blood pressure (Figure CQ1-2). This difference in antihypertensive efficacy remained unchanged regardless of the presence or absence of home blood pressure data server transfer or healthcare professional's telemonitoring. Similar results were observed also when the analysis was confined to 5 trials after exclusion of 4 trials having employed the daytime blood pressure as an outcome (inter-group difference in reduction of 24-h ABP levels: −4.08 mmHg in terms of SBP and −2.64 mmHg in terms of DBP).

Conclusions

Antihypertensive treatment based on home blood pressure has been shown to be more useful in reducing mean 24-h ABP levels than treatment based on office blood pressure. All of the three trials, employing the same target blood pressure for both home and office blood pressure (a factor possibly responsible for heterogeneity) [271, 281, 282], had been carried out before wide spread of the knowledge about difference between home and office blood pressures. The results of a recent study clarifying the blood pressure level leading to the same incidence of cardiovascular diseases also demonstrated the validity of home blood pressure which was about 5 mmHg lower than the office blood pressure [143]. Therefore, antihypertensive treatment with the target reduction in home blood pressure to a level 5 mmHg lower than the office blood pressure shown in these guidelines may be useful in reducing mean 24-h ABP levels.

On the other hand, no RCT adopting the reduction in the incidence or mortality of cardiovascular diseases was identified. Thus, there is no evidence directly confirming that antihypertensive treatment based on home blood pressure can reduce the incidence or mortality of cardiovascular diseases compared with antihypertensive treatment based on office blood pressure. However, according to the meta-analysis of observational studies using mean 24-h ABP data among Asian subjects [283], the difference in antihypertensive efficacy by 3.64 mmHg (systolic pressure) and 2.16 mmHg (diastolic pressure) obtained from the above-mentioned meta-analysis of trials (having adopted reduction in mean ABP levels as the outcome) is suggested to be associated with a reduction of the risk for cardiovascular diseases by 16.6 and 16.2%, respectively. Furthermore, in the HOMED-BP Study conducted in Japan, involving patients with essential hypertension, the home blood pressure during antihypertensive treatment was reported to be closely associated with the risk for onset of or death from cardiovascular diseases than office blood pressure [54, 269]. This suggests that antihypertensive treatment

Table CQ1-1 RCTs included

Author/Year of publication	Subject	Intervention outlined	Control outlined
Broege 2001 [271]	40 hypertensive patients	Home blood pressure data collected by nurse over telephone at intervals of 2 weeks and used for switching the medication. Physician provides treatment based on home blood pressure, with a goal set at reducing maximum blood pressure level to <150/90 mmHg.	Visiting the clinic at intervals of 2 weeks to receive adjustment of medication. Treatment provided to maintain maximum blood pressure level <150/90 mmHg.
Fuchs 2012 [272]	121 patients receiving antihypertensive treatment and with poorly controlled blood pressure	Pharmacist gives guidance on the basis of blood pressure data (to half of the subjects). As a rule, switching of antihypertensive drug is avoided, and guidance on improvement of habits is provided. The goal of antihypertensive treatment not specified.	Conventional clinical care + pharmacist guidance (for half of all cases) provided. As a rule, switching of antihypertensive drug is avoided, and guidance on improvement of habits is provided. The goal of antihypertensive treatment not specified.
Godwin 2010 [273]	552 patients aged over 18 and diagnosed with hypertension or receiving antihypertensive treatment and with poorly controlled blood pressure	Home blood pressure measured. As needed, physician checks the blood pressure. Goal set at <135/85 mmHg.	Conventional clinical care; Canadian guidelines used as an indicator; goal set at office blood pressure <140/90 mmHg.
Hanley 2015 [274]	55 patients with a history of stroke/TIA (51 patients included in analysis)	Physician can access the home blood pressure data transferred and provides treatment based on such data. Goal of antihypertensive treatment not specified. Telemonitoring performed.	Conventional clinical care; the goal of antihypertensive treatment not specified.
Madsen 2008 [275]	236 new patients with hypertension aged 20–80 or receiving antihypertensive treatment and poorly controlled as to blood pressure	Physician and patient can access the home blood pressure data at Web or via PDA cellphone. Medication switched on the basis of such data. Goal at home blood pressure <135/85 mmHg. Telemonitoring performed.	Conventional clinical care; goal set at office blood pressure <140/90 mmHg.
McKinstry 2013 [276]	401 patients aged over 18 with office blood pressure >145/85 mmHg (359 patients included in analysis)	Healthcare professionals and patient can access the home blood pressure data. Goal set at <135/85 mmHg. Telemonitoring performed.	Conventional clinical care; goal set at <140/90 mmHg on the basis of British Hypertension Society's guidelines.
Neumann 2011 [277]	60 patients aged 18–80 with poorly controlled blood pressure and receiving no ARB (57 patients included in analysis)	Blood pressure data transmitted via cellphone. Physician is informed in case of failure to satisfy the antihypertensive criteria or excessive blood pressure fall, to begin discussion with patient over therapeutic strategy. Physician always access the home blood pressure data, and patient is given the home blood pressure data once a month. Goal set at home blood pressure <135/85 mmHg (<130/80 mmHg in cases complicated by diabetes or renal dysfunction). Telemonitoring performed.	Patients advised to call or visit physician upon poor reduction in blood pressure or appearance of adverse reactions and to measure blood pressure at home once daily. Goal of antihypertensive treatment not specified.
Parati 2009 [278]	298 patients with mild or moderate hypertension or poorly controlled blood pressure	Physician can access the transferred home blood pressure data and provides treatment on the basis of such data. Goal set at <135/85 mmHg. Telemonitoring performed.	Conventional clinical care (blood pressure measured by physician; goal set at office blood pressure <140/90 mmHg)
Rinfret 2009 [279]	223 hypertensive patients with high ABP levels	Self-measured blood pressure data and self-assessed adherence data are combined with prescription data and reported to physician/pharmacist/nurse. If blood pressure is poorly controlled, nurse checks the patient and submits a report to physician/pharmacist. Goal of antihypertensive treatment not specified. Telemonitoring performed.	Conventional clinical care; goal of antihypertensive treatment not specified.
Rogers 2001 [280]	121 patients poorly controlled blood pressure and considering to switch the antihypertensive drug	Home blood pressure data transferred and processed centrally, followed by weekly report to physician/pharmacist/nurse. Drug dose level adjusted on the basis of such a report. Goal of antihypertensive treatment not specified. Telemonitoring performed.	Conventional clinical care (in accordance with JNC6 guideline)
Staessen 2004 [281]	400 patients with office DBP ≥95 mmHg	Decision made by blinded physician at the coordination center on the basis of blood pressure data. Medication adjusted on the basis of home DBP. Medication adjust to maintain diastolic pressure in the 80–89 mmHg range.	Treatment based on office DBP. Medication adjusted to maintain DBP in the 80–89 mmHg range.
Verberk 2007 [282]	430 patients aged over 18, with SBP 139–200 mmHg and DBP 90–120 mmHg	Steps of treatment are taken semi-automatically on the basis of home blood pressure data. Home/ office blood pressure is controlled to 120–140/80–90 mmHg.	Physician takes the steps of treatment semi-automatically on the basis of home blood pressure data. Randomly measured blood pressure is controlled to 120–140/80–90 mmHg.

Studies including patients with essential hypertension were extracted.

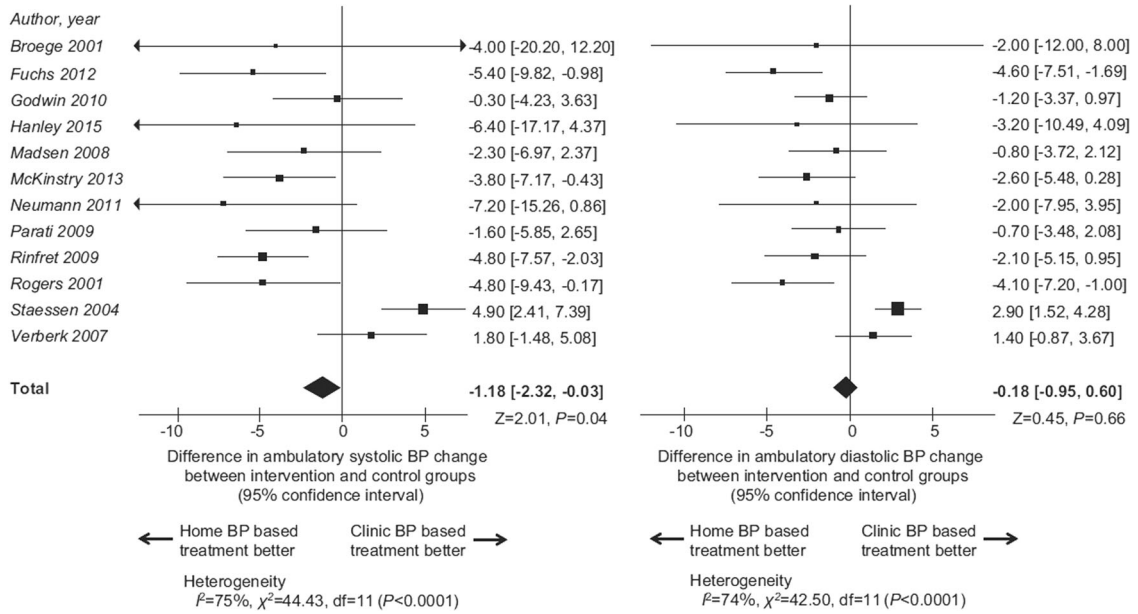


Fig. CQ1-1 Results of meta-analysis of all 12 RCTs (Source: Ref. [270])

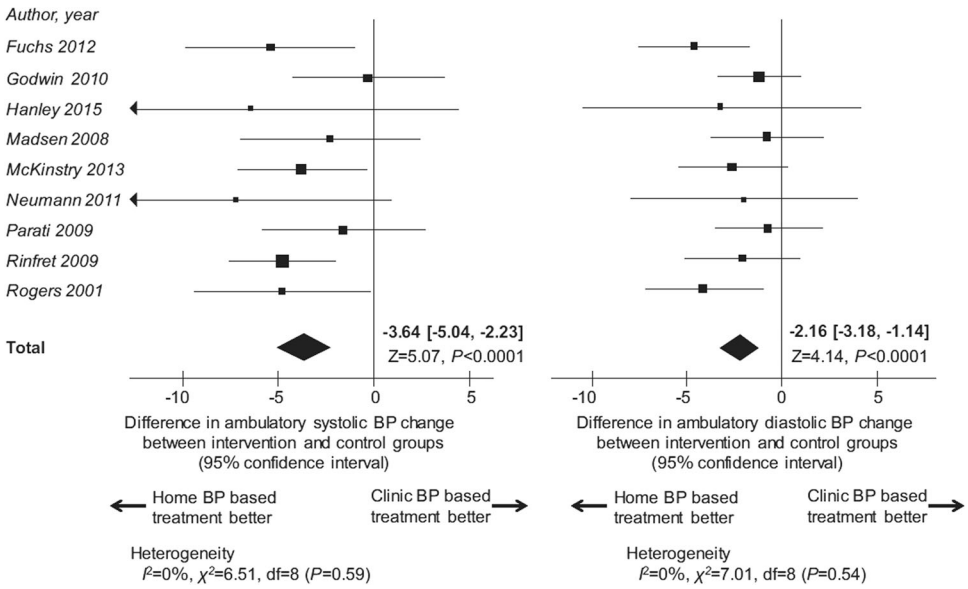


Fig. CQ1-2 Results of meta-analysis excluding 3 RCTs having adopted the same goal of antihypertensive treatment. We excluded three studies [271, 281, 282] employing the same target BP for both home and office readings. (Source: Ref. [270])

aimed at achieving the goal of home blood pressure reduction proposed in these guidelines is useful also in reducing the incidence and mortality of cardiovascular diseases.

After completion of this SR, a report was published concerning the results of TASMINH4 Study in the United Kingdom designed to evaluate the degree of blood pressure reduction in the group managed on the basis of office blood pressure, the group managed on the basis of home blood pressure and the group undergoing home blood pressure telemonitoring [284]. Its primary outcome was the office blood pressure measured with an automated sphygmomanometer, but the goal of home blood pressure reduction was set at a level 5 mmHg lower than that of office blood pressure reduction [284]. In that study, SBP was lower by 3.5 mmHg in the home blood pressure-based management group and by 4.7 mmHg in the home blood pressure telemonitoring group than in the office blood pressure-based management group, thus supporting the results of our SR [284].

For the reasons given above, this CQ strongly recommends implementation of antihypertensive treatment based

on home blood pressure. However, it is essential to set the goal of treatment in line with the goal of blood pressure reduction recommended in the present guideline. It is additional required that home blood pressure measurement is conducted appropriately in accordance with the present guideline.

LITERATURE SEARCH

Two SR members independently conducted literature search with PubMed and Cochrane Library to extract papers concerned with this CQ.

CQ2 IS FOLLOW-UP NEEDED FOR PATIENTS WITH WHITE COAT HYPERTENSION?

►Patients with white coat hypertension have a higher risk for composite of cardiovascular events than non-hypertensive individuals. Furthermore, a high risk for progression of white coat hypertension to sustained hypertension has been reported. Therefore, careful follow-up is needed for patients with white coat hypertension.

Recommendation Grade 2 Evidence Level C

Evidence summarization

Among antihypertensive drug-naïve individuals, those having white coat hypertension have a higher future risk for composite of cardiovascular events than those without hypertension. The risk for developing sustained hypertension is also significantly higher in individuals with white coat hypertension than in non-hypertensive individuals.

Commentary

Patients with white coat hypertension have hypertensive office blood pressure and non-hypertensive out-of-office blood pressure. According to previous studies, organ damage is milder and the cardiovascular prognosis is more favorable in patients with white coat hypertension than in patients with sustained hypertension whose blood pressure is high also when measured outside the office. In addition, it has also been reported that white coat hypertension in some cases progresses to sustained hypertension, contributing in the long run to a high risk for cardiovascular events. We conducted SR within the framework of this CQ [285]. The term "white coat hypertension" is used for treatment-naïve patients with hypertension in the narrower sense of the term. According to guidelines and statements in Europe and the USA, ABPM is primarily recommended for evaluation of out-of-office blood pressure, whereas importance has been emphasized to home blood pressure in Japan. This SR therefore adopted the following two policies: (1) Any of ABPM or home blood pressure may be used for evaluation of out-of-office blood pressure; and (2) White coat hypertension received antihypertensive treatment were excluded. Because the features of cardiovascular prognosis differ between Japan and western countries, the following five events based on classification of stroke and cardiovascular events were set for this SR: 1) Onset of cardiovascular diseases (composite endpoints consisted of cardiac events and stroke) or its death, 2) Onset of stroke events or its death, 3) Onset of cardiac events or its death, 4) All-cause mortality, and 5) Deterioration to sustained hypertension.

Two SR members independently conducted literature search with PubMed, Cochrane Library and Ichushi-Web. Eleven papers fitting the outcomes for this CQ and enabling meta-analysis were extracted.

1) Onset of cardiovascular diseases (composite endpoints consisted of cardiac events and stroke) or its death

Seven papers corresponding to this outcome were identified [129, 157, 286–290]. Meta-analysis of these papers revealed a significant risk for onset of cardiovascular diseases in the white coat hypertension group compared with normotension group (relative risk [RR] 1.33, 95% CI 1.10–1.62, $P = 0.003$). Open issues, such as insufficient adjustment of confounding factors and small sample size, were identified. The greatest difficulty lay in the difference of definition for white coat hypertension and "normotension" among individual studies. However, also when meta-analysis was confined to 5 papers in which white coat hypertension and "normotesion" had been classified in accordance with the definition given in JSH2014 [84, 157, 286–288], the white coat hypertension had a significantly higher risk for onset of cardiovascular diseases than normotension group (RR 1.28, 95% CI 1.06–1.53).

2) Onset of stroke events or its death

Seven papers related to this outcome were extracted. Excluding papers which had used redundant databases, two papers were finally adopted for meta-analysis [157, 286]. The analysis revealed a tendency for higher risk for onset of or death from stroke in the white coat hypertension group than normotesion group, although this difference was not statistically significant (RR 1.44, 95% CI 0.95–2.18, $P = 0.09$).

3) Onset of cardiac events or its death

The two papers identical to those adopted for the outcome "onset of cardiac events or its death" were subjected to meta-analysis of this outcome [157, 286]. The risk for onset of or death from cardiac disease in the white coat hypertension group was comparable to that in normotension group (RR 1.10, 95% CI 0.81–1.50). The risk between the two groups was not statistically significant even when a paper involving hypertensive patients receiving treatment

and not adjusted as to the fact of ongoing treatment was included in the analysis [291].

4) All-cause mortality

Five papers pertaining to this outcome were extracted [157, 286, 288–290]. The risk for total death in the white coat hypertension group was comparable to that in the normotension group (RR 1.15, 95% CI 0.93–1.43). Of the extracted papers, only one demonstrated that white coat hypertension was a risk for total death compared with non-hypertensive condition [289]. In this paper, however, white coat hypertension was defined as blood pressure <140/90 mmHg when measured by a nurse and <160/95 mmHg when measured by a physician.

5) Progression to sustained hypertension

Three studies reporting this outcome were identified [292–294]. All three of these studies reported a higher risk for progression to sustained hypertension in the white coat hypertension group than in normotension group, and a similar result was obtained from meta-analysis (RR 2.85, 95% CI 2.32–3.49).

Conclusions

This SR revealed that among antihypertensive drug-naïve individuals, the risk for progression to sustained hypertension was significantly higher in the white coat hypertension group than in normotension group. Regarding the onset of events, the risk for onset of and death from cardiovascular diseases was significantly higher in the white coat hypertension group than in normotension group, whereas the risk for total death and that for onset of or death from cardiac disease were statistically comparable between the two groups. The risk for onset of and death from stroke tended to be higher in the white coat hypertension group than in normotension group, but this difference was not significant. The incidence of stroke and its contribution of blood pressure is greater in Japanese people than in western people. However, it remains unknown whether the white coat hypertension itself has a risk for events or the risk for events is high as a result of progression of white coat hypertension to sustained hypertension. Therefore, for Japanese patients with white coat hypertension, careful follow-up may be necessary, thereby taking into account not only occurrence of events but also the high probability of progression to sustained hypertension.

During this SR, we adopted both ABPM and home blood pressure as out-of-office blood pressure data for diagnosis of white coat hypertension, but the papers adopted for the SR almost evaluated out-of-office blood pressure using the ABPM data. However, there is a report (although a report of a single cohort study) demonstrating that the risk for stroke differs between "complete white coat hypertension" (both home blood pressure and ABPM are normotension) and "partial white coat hypertension" (only one of them is normonetsion) [156], suggesting the need of paying attention also to the difference in out-of-office blood pressure.

This SR involves the following limitations: (1) the definition of white coat hypertension and/or outcome differed among studies; (2) the definition of sustained hypertension at the baseline included ongoing antihypertensive drug treatment in some studies, possibly underestimating the risk of white coat hypertension because the patients receiving such treatment may include cases of white coat hypertension; (3) the method for measuring office blood pressure used for diagnosis of white coat hypertension was not uniform; and (4) the influence of antihypertensive medication during the follow-up period was not considered in all studies.

Accurate diagnosis of white coat hypertension using a combination of precisely measured office blood pressure with home blood pressure and ABPM is important in the evaluation of the risk of subjects for cardiovascular diseases. Because the evidence level of each study matching this CQ is low, it can only be said that "the prognosis is poor at a high probability" as an answer to the question "Is the prognosis poor for patients with white coat hypertension compared with normotensiveindividuals?"

Home blood pressure or ABPM is the clinical information which should be collected during diagnosis/treatment of hypertension and they can contribute also to improvement in patient adherence to hypertension management. Therefore, identification of patients with white coat hypertension and their careful follow-up may be highly beneficial for both patients and healthcare providers.

Q1 WHICH SPHYGMOMANOMETERS ARE RECOMMENDED INSTEAD OF MERCURY SPHYGMOMANOMETERS?

- Manufacture and export/import of mercury sphygmomanometers (Figure Q1-1a) will be prohibited from 2021. Maintenance of this type of sphygmomanometer will also be difficult on and after that year. Thus, use of mercury sphygmomanometers should be avoided.
- At medical facilities, electronic upper-arm sphygmomanometers for medical use, formally accredited and distributed in Japan, are recommended.
- Electronically generated pressure column (EPC) sphygmomanometers (Figure Q1-1b) in which a mercury-free electronic pressure display that enables manual auscultatory measurement is provided through the simulation of a falling mercury column, can be used for measurement in approximately the same manner as mercury

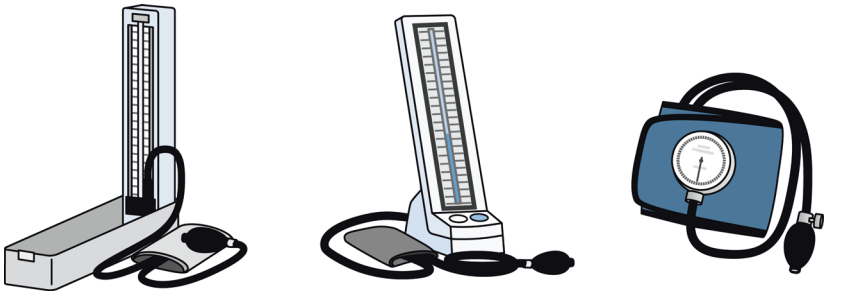


Fig. Q1-1 Schematic representation of mercury sphygmomanometer, electronically generated pressure column sphygmomanometer and aneroid sphygmomanometer

sphygmomanometers. As a successor to mercury sphygmomanometers, use of EPC sphygmomanometer is recommended particularly when comparison with mercury sphygmomanometer readings is required (e.g., epidemiological studies).

- Aneroid sphygmomanometers (Figure Q1-1c) based on mechanical pressure gauge are not recommended because they are structurally susceptible to influence from shock and deterioration over time, leading to erroneous readings. If deterioration is suspected, this type of sphygmomanometer should be immediately exchanged with a new one.
- When a sphygmomanometer is purchased, it is advisable to check the status of clinical evaluation by a third party by referring to the website of the JSH. During use, whether the device is being measured correctly in each subject should be checked.
- Routine inspection (confirming normal functioning during routine use) and periodical inspection/maintenance (detailed inspection conducted periodically) are essential for sphygmomanometers.

Table Q1-1 Shortcomings of mercury sphygmomanometers

1) Because the mercury column scale is adjusted with high purity mercury, readings can be erroneous if mercury purity is reduced by contamination with impurities or other factors.
2) The circuit is usually sealed but leak or evaporation of mercury can be occurred by some reasons.
3) During measurement, the mercury column ascends and descends precisely reflecting the change in pressure inside the upper arm cuff, but precision of such motions can be reduced by impurities or contamination in the mercury column.
4) If handled inappropriately, the liquid mercury in the column can be separated.
5) Like electronic sphygmomanometers, deterioration of rubber tubes over time is unavoidable.*
6) If the rubber in the pressure rubber ball falls off and obstructs the tube lumen, normal air feeding and discharging can be impaired.*
7) Systematic deviation (drift) of readings may result from device deterioration, and such drift is often overlooked.

*Applicable also to electronically generated pressure column sphygmomanometers.

COMMENTARY

1) Minamata Convention on Mercury

Mercury is a bioaccumulative toxic substance [295, 296]. To protect human health and environment from the toxicity of mercury, the Minamata Convention on Mercury came into effect in 2017 [297, 298]. Under this convention, manufacture and export/import of mercury-containing products, including mercury sphygmomanometers, will be prohibited from 2021 on. This section summarizes the latest findings as to this topic and describes sphygmomanometers to be used instead of mercury sphygmomanometers.

2) Problems with mercury sphygmomanometers

Mercury sphygmomanometers (Figure Q1-1a) have a long history of use as a standard device for blood pressure measurement, but they involve many shortcomings as shown in Table Q1-1 [297] and cannot be expected to remain accurate throughout the period of their use. In the Law for Securing the Quality, Efficacy and Safety of Drugs and Medical Devices [Drugs and Medical Devices Law (Drug/Medical Device Law)] of Japan, mercury sphygmomanometers are classified as general medical devices (Class I) which can be distributed after a report to the regulatory authority, without necessitating specific approval. There is no legal assurance about maintenance of this kind of device after it is sold. Furthermore, maintenance of the device will become difficult under the Minamata Convention of Mercury. For these reasons, mercury sphygmomanometers should not be used any more.

3) Electronic sphygmomanometers: Semiconductor pressure sensor

Currently available electronic sphygmomanometers of both automated and manual types use a semiconductor pressure sensor (pressure transducer) for measurement of the air

pressure in the cuff. The semiconductor pressure sensor is highly precise, low in cost and easy to manipulate, and therefore indispensable for an electronic sphygmomanometer (automated sphygmomanometer) that automatically reads the blood pressure. This type of sphygmomanometer does not require experience or high skill for blood pressure measurement, is free of biases dependent on examiners and allows simultaneous measurement of pulse rate. Since the measured values are automatically recorded in the built-in memory, erroneous self-recordings of blood pressure by patients can be prevented [299]. Furthermore, the electronic sensor works stably for a long period of time and, even when it goes out of order, complete deactivation is seen much more frequently than indication of wrong blood pressure levels [300]. Therefore, the probability for systematic drift of blood pressure readings due to deterioration (as seen with mercury sphygmomanometers and aneroid sphygmomanometers) is low with electronic sphygmomanometers [300]. Some types of electronic sphygmomanometers designed for reading of blood pressure levels by the examiner (manual sphygmomanometers) are equipped with the function of displaying the inner cuff pressure digitally or reading the level also automatically.

4) Aneroid sphygmomanometers

Aneroid sphygmomanometers based on mechanical pressure gauge in the narrower sense of the term are designed to measure the air pressure in the cuff on the basis of the degree of deflection of the plate spring (Figure Q1-1c). Aneroid sphygmomanometer is low in cost, has a long history of use, and is still being used commonly in many countries, particularly in developing countries. In some developed countries, aneroid sphygmomanometers are sometimes used as disposable devices for the purpose of reducing the cost needed for management. However, caution is needed when this type of sphygmomanometer is used because the blood pressure readings can be inaccurate depending on examiners for the following reasons: (1) more susceptible to physical shock than the other types of sphygmomanometer; and (2) certain level of skill is required for measurement, as is the case with the mercury sphygmomanometer [299, 301]. If an aneroid sphygmomanometer is used, it should be checked more frequently than electronic sphygmomanometers. Same as mercury sphygmomanometers, the aneroid sphygmomanometers of any mechanical designs, including plate spring, are classified as general medical devices (Class I) in Drug/Medical Device Law of Japan.

5) Electronically generated pressure column sphygmomanometers

Of the sphygmomanometers using a semiconductor pressure sensor, electronically generated pressure column (EPC) sphygmomanometers (also called pseudo-mercury, mercury image or mercury-free sphygmomanometers) are a type in which real-time bar graph corresponding to the inner arm-cuff air pressure is displayed on the portrait liquid crystal display (LCD) screen as an imitation of liquid mercury column (Figure Q1-1b). Examiners can detect the Korotkoff sounds by the stethoscope to determine blood pressure level according to the displayed bar graph. This is a type of electronic sphygmomanometer but is not classified to automated sphygmomanometers because blood pressure is not read automatically. With many types of EPC sphygmomanometer, cuff inflation and deflation are done manually. EPC sphygmomanometers allow blood pressure measurement with an approximately same technique as the mercury sphygmomanometers and are without shortcomings arising from the use of metal mercury. However, because the semiconductor pressure sensor precisely reflects the air pressure inside the cuff, the bar graph can move minutely, making reading of the blood pressure difficult, if the pressure is displayed without processing the sensor-related information. To which extent the pressure changes and the frequency of measurement are reflected in the movement of the bar graph on liquid crystal display varies among individual devices, resulting in differences in convenience for use.

6) Sites for blood pressure measurement

Blood pressure should be measured with an upper arm-cuff sphygmomanometer by the standard method (e.g., setting the cuff at the heart level of the non-predominant arm) [268].

Compared with the upper arm-cuff device, the wrist-cuff sphygmomanometer is more compact in size and easier to carry, but it has a shortcoming with correction of hydrostatic pressure [268]. For example, even a 5 cm difference in the height from the right atrium of the heart can cause a 3.5 mmHg or more blood pressure difference, possibly giving an unfavorable influence on clinical decision making. The radial artery and the ulnar artery are surrounded by the radius, ulna and long tendon tissue in the vicinity of the wrist. The arteries cannot be always obstructed sufficiently even when a sufficient pressure exceeding the normal arterial pressure is applied in the wrist cuff [110, 268]. Furthermore, flexion and overextension of the wrist can affect blood pressure readings [110, 268]. Therefore, the currently available wrist-cuff sphygmomanometers are not appropriate for deciding the therapeutic strategy in clinical practice.

Finger cuff sphygmomanometers yield blood pressure values physiologically different from those obtained with upper-arm devices. When blood pressure at the finger is measured, vasospasm in a cold environment and the hydrostatic pressure difference from the heart are

unavoidable [268]. In the 1990s, another simpler device for blood pressure measurement based on PWV or pulse transit time was devised [302] and markedly temporarily also in Japan. In recent years, some devices for noninvasive and continuous blood pressure measurement on the basis of PWV were commercialized. However, they involve large errors and are difficult for use in accurate blood pressure measurement in clinical practice.

7) Standards for sphygmomanometers

Sphygmomanometers are manufactured in accordance with the standards in each country/region and are marketed under approval (or certification or just notification) of the governmental agency. In Japan, Japanese Industrial Standard (JIS) corresponds to the former and private third-party certification organizations commissioned by the Pharmaceutical and Medical Device Agency (PMDA) or PMDA itself corresponds to the latter. The protocols for testing of the blood pressure measuring accuracy of automated sphygmomanometers, used upon approval or certification, include the International Protocol of the ESH-IP 2010 [303] and the International Standardization Organization (ISO) 81060-2 provided by the ISO [304]. Usually, in addition to fulfill other criteria, the measuring accuracy of a device must be proven in accordance with one of the testing protocols for the approval or certification.

The Association for the Advancement of Medical Instrumentation (AAMI, USA) and the American National Standards Institute (ANSI) revised the ANSI/AAMI Standards and adopted the ISO 81060-2 (2013) [304]. The ESH-IP was merged into the ISO standard when the standard was revised in 2018. Therefore, ISO 81060-2:2018 [304] is promised to be predominantly used in each step of clinical evaluation before approval/certification and post-marketing clinical evaluation. ISO does not refer to mercury sphygmomanometers at all even in its 2013 version. Thus, transition from mercury sphygmomanometers to electronic sphygmomanometers has been completed also in the international standards.

Sphygmomanometers should be checked to correctly measure blood pressure according to subject's physique and characteristics (e.g., pregnant woman, child, or individual in late senility). As far as the physique is concerned, rules on arm circumference are established during the process of clinical evaluation, but general condition is not usually taken into consideration. Pregnant women and children are categorized as a special population in the international standards, and a test specific to each population is needed; however, sphygmomanometers have actually been used clinically without paying much attention to such condition. To overcome this problem, third party organizations, independent of manufacturers and distributors, have been testing sphygmomanometers with a clinical evaluation protocol for the special population or the general population to ensure the reliability of the sphygmomanometer. The validation results have been published in scientific journals and have been summarized and disclosed on websites such as dabl® Educational Trust [305] and Medaval™ [306]. To fulfill the responsibility as a professional society in the world's largest sphygmomanometer producing country, the JSH has been making public the information on clinical evaluation of sphygmomanometers marketed in Japan and the address for contact on its website in line with the above-mentioned scientific activities [90].

8) Maintenance/inspection of sphygmomanometers being used

Sphygmomanometers sold in Japan can be viewed as remaining accurate for the durable period and the frequency of use specified by their manufacturer (see the instructions for each device; e.g., 5 years and about 30,000 times for the device use, and 1 year for the cuff). However, it is important to conduct maintenance/inspection, including routine check of normal functioning of a given sphygmomanometer (routine inspection) and periodical detailed inspection (periodical inspection).

Examples of detailed inspection of sphygmomanometers includes the following: (1) the pressure level indicated is always zero in the absence of pressure; (2) the pressure indicated does not fall by 2 mmHg or more when the device is left standing for 3 min without air deflating after pressurization to 200 mmHg; (3) when the air is deflated at the full speed, the pressure indicated returns to zero immediately (in about a second); (4) if a sphygmomanometer is linked to another sphygmomanometer whose accurate pressure indication has been confirmed, the pressure indicated following pressurization to 200, 150 and 100 mmHg is consistent between the two devices. Inspection of the electronic circuits is also recommended. However, manual manipulation of pressure is difficult with some of automated sphygmomanometers. Thus, if periodical inspection is difficult by the medical facility oneself, it should be performed by an appropriate agent providing maintenance/inspection services. Aneroid sphygmomanometers are structurally susceptible to influence from shock and aging, leading to erroneous readings. If deterioration is suspected, this type of sphygmomanometer should be immediately exchanged with a new one.

Conclusions

SPHYGMOMANOMETERS REPLACING THE MERCURY SPHYGMOMANOMETERS

Upper arm-cuff electronic sphygmomanometers formally accredited and marketed in Japan is usually recommended

as substitutes for mercury sphygmomanometers. Furthermore, electronic sphygmomanometers for medical use are classified as controlled medical devices (Class II) under the Drug/Medical Device Law, and they are required to undergo maintenance/inspection as specific maintenance/control-requiring medical devices. Therefore, upper-arm electronic sphygmomanometers for medical use are recommended for continued use at medical facilities. In a previous study, switching of a mercury sphygmomanometer to a certified oscillometric electronic sphygmomanometer for medical use resulted in a change of the therapeutic strategy in only about 5% of all cases [307]. Other criteria for selection of substitute sphygmomanometers include device size/weight, whether cuff inflation/deflation is automated, whether only deflation is automated (because inflation with a pump consumes electricity, only inflation is manually operated in some types of sphygmomanometers used at wards), how the inside-cuff air pressure measured by the semiconductor pressure sensor is displayed, and whether an outside power source is needed. Other essential differences seen among devices are whether they are able to measure systolic and diastolic pressures automatically or the examiner has to read the pressure level manually. For telemedicine in which the subject/patient cannot be directly touched by the physician, the blood pressure values can be collected with the use of an automated sphygmomanometer which reads the pressure level automatically.

For epidemiological or other studies in which maintaining consistency in blood pressure readings to the past measured by mercury sphygmomanometer is required, an EPC sphygmomanometer is recommended because it provides the smallest differences in readings compared to mercury sphygmomanometers [300].

Before purchase and use of each type of sphygmomanometer, the status of third party evaluation should be checked at the appropriate website such as that of JSH. Furthermore, electronic sphygmomanometers of both automated and manual types should be originally checked as to whether measurement is being conducted appropriately in each subject, same as the check needed for mercury sphygmomanometers. For example, several cuff sizes corresponding to the arm circumference are available for some types of sphygmomanometers and, if an inappropriate cuff is used, there may be a 10 mmHg or larger error of pressure reading [308]. In patients with arrhythmia, reliability of automatically measured blood pressure is usually not ensured. In the presence of arrhythmia, blood pressure is unstable and it is required under the current guidelines to conduct blood pressure measurement three times or more, regardless of the method employed (auscultation or oscillometric method), to eliminate the influence from arrhythmia as far as possible. In cases in which automated measurement appears difficult, blood pressure should be measured at least once by a skillful examiner based on the auscultation method with the use of an EPC sphygmomanometer.

Q2 HOW MANY TIMES AND HOW MANY DAYS SHOULD HOME BLOOD PRESSURE BE MEASURED?

- It should be measured within 1 h after waking up in the morning, after urination in the morning, before dosing in the morning, before breakfast and at the bedtime in the evening (each after sitting still for 1–2 min).
- Measurement should be done twice at each occasion, and the mean of two measurements should be adopted as the blood pressure level for a given occasion. If measurement is done only once on a given occasion, the level obtained is adopted.
- All blood pressure levels measured at a given occasion should be entered into the recording form without selection.
- Hypertensive patients should continue measurement throughout the life as long as self-measurement is possible.
- For the diagnosis of hypertension and the evaluation of responses to antihypertensive treatment, the mean of 7-day measurement in the morning (for at least 5 days) and that in the evening should be used.
- If the mean home blood pressure in the morning or the mean blood pressure in the evening or both satisfy the criteria for home blood pressure-based diagnosis of hypertension, a home blood pressure-based diagnosis of hypertension is made.
- If both the mean home blood pressure in the morning and the mean home blood pressure in the evening have satisfies the goal of antihypertensive treatment, it can be judged that the goal of home blood pressure has been achieved by antihypertensive treatment.

COMMENTARY

Like office blood pressure, home blood pressure become more valuable clinically if measured in a standardized manner. At present, however, the conditions for measuring home blood pressure guided to patients vary among clinicians [106], and it is necessary to provide uniform guidance on such conditions. During clinical practice, it is strongly recommended that each clinician guides the patients as to the home blood pressure measuring method on the basis of the conditions shown in these guidelines.

ABPM collects blood pressure data related to time (a relationship by the function of time) in a continuous manner at intervals of 15–30 min during a particular day. Setting the conditions for measurement by ABPM does not fit the nature of ABPM. On the other hand, home blood pressure measurement can be characterized by high reproducibility and stability and is based on the assumption that

measurement is done continuously under the conditions as constant as possible [121, 122].

1) When should measurement be done?

Home blood pressure varies greatly under the influence of various environmental factors [309]. The self-measured blood pressure is greatly affected also by the time of a day when measurement is done [310]. Therefore, for home blood pressure measurement, measurement in the morning and in the evening (a method which can be continued for a long period of time under certain conditions) has been usually adopted in many studies and described in the guidelines in many countries.

In these guidelines, blood pressure measurement in the morning is recommended to be conducted within 1 h after waking up. A more strict setting of the conditions for measurement may be "conducting measurement immediately after waking" or "measurement within 10 min after waking." However, what is most important in home blood pressure measurement is continuation of self-measurement of blood pressure. If the timing for measurement is set too strictly, adherence to the measuring practice may decrease. However, since changes in blood pressure by various environmental factors may occur within 1 h after waking, it is necessary to set the conditions similar to those shown in Table 2-3. For shift workers, the period within 1 h after waking is not always the morning. For such workers, it is necessary to specify the time of measurement while leaving the condition "within 1 h after waking" undeleted. For patients taking medication, a major purpose of home blood pressure measurement is evaluation of responses to the antihypertensive drugs used. Home blood pressure before drug intake in the morning is the blood pressure during the period reflecting the trough efficacy of medication, and measuring this blood pressure means evaluation of the continuity of drug efficacy and is therefore indispensable [311, 312].

Setting the conditions for home blood pressure measurement in the evening is often difficult because of inter-individual or intra-individual diversity of lifestyle. Particularly for workers and housewives, setting strict conditions of measurement (e.g., before supper, before bathing or before alcohol consumption) may reduce the adherence to measurement. For this reason, these guidelines set only a condition similar to "at bedtime." The timing "at bedtime," however, usually includes the occasion after bathing, after alcohol consumption and, in some cases, after drug intake. All of these three occasions work in the direction of reducing blood pressure [313–315].

We should therefore take into consideration that the home blood pressure measured in the evening under such a condition is lower than the home blood pressure measured in the morning. Usually, the SBP is lower by only about several mmHg, but the Ohasama Study reported the evening SBP of hypertensive patients to be lower by 10–20 mmHg than that measured in the morning [316]. According to the reports from Europe, there is no difference between and morning and evening home blood pressures. Or many reports from Europe indicate that the home blood pressure in the evening is higher than that in the morning [317, 318]. This discrepancy may be attributable to the difference in the timing of blood pressure measurement (often measured at dinner time in Europe and at bedtime in Japan). It may also be associated with the difference in the habits (e.g., bathing) between Japanese and Europeans. Blood pressure in the evening corresponds to the blood pressure at 12–16 h after drug intake from the viewpoint of the efficacy of antihypertensive drugs taken once daily in the morning and this may be close to the peak efficacy. The morning/evening ratio, which compares the drug efficacy based on evening home blood pressure (close to the peak efficacy) with the drug efficacy before drug intake in the morning (trough efficacy), has been used for continuous evaluation of drug efficacy [311, 312]. For these reasons, these guidelines recommend additional measurement of blood pressure before supper, before drug intake in the evening, before bathing and before alcohol consumption (Table 2-3).

2) How many times should measurement be done?

Regarding home blood pressure evaluation, there is no definite evidence as to how many times measurement should be done at an occasion and which of the values obtained at an occasion should be adopted. The JSH2009 Guidelines [319] and the Home Blood Pressure Measurement Guide (2003 [320], 2012 [268]) set a range of measuring frequency, i.e. "once or more times (1–3 times) at an occasion." Later, many clinicians and hypertension researchers demanded adoption of a uniform frequency of measurement in guidelines. Blood pressure can change largely during a short period, and home blood pressure is not an exception. In many cases, the blood pressure level measured first at a given occasion is higher than the subsequent levels of the same occasion. On the other hand, there are also reports that the second measurement on a given occasion yielded a higher blood pressure level in 10% or more of the occasions analyzed [321, 322]. From the clinical viewpoint that the examiner may feel anxious if measurement is done only once on an occasion and that the examiner tends to conduct measurement many times regardless of high or low blood pressure level recorded at the first measurement, these guidelines recommend measuring blood pressure twice as a rule on an occasion and adopting their mean as the blood pressure level on a given occasion, similar to the recommendation in the JSH2014 Guidelines [108]. If measurement has been done only once, it is acceptable to adopt that value as the blood pressures on a given occasion. If the examiner has voluntarily conducted

measurement 3 times, the mean of three measurements may be adopted for that occasion. Because measurement is conducted too many times on a given occasion, the measurement continuation rate can decrease [109]. For this reason, it is not recommended to carry out measurement 4 times or more on a given occasion. As far as recording is concerned, it is recommended to enter all blood pressure levels measured on a given occasion into the recording form, similar to the conventional practice.

3) How many days should measurement be done?

A characteristic of home blood pressure lies in the availability of abundant blood pressure information covering a long period of time. Blood pressure self-measurement at home is useful as health information for improvement of habits and health management and is expected to improve the adherence to intake of antihypertensive drugs [323, 324]. For hypertensive patients, therefore, there is no need to specify the duration of measurement and it is advisable to continue measurement throughout the life as long as self-measurement is possible.

However, setting the duration of measurement is indispensable if home blood pressure is used for diagnosing and treating hypertension. The duration of measurement varies depending on the purpose. During clinical practice in Japan, it is superior in terms of convenience if the mean of 2 weeks or 4 weeks is counted as one unit. On the other hand, care should be taken of the possibility that requiring patients to conduct measurement every day reduce their adherence to measurement [325].

According to guidelines in Europe and the USA, measurement should be done at the time of new diagnosis, at the start of antihypertensive drug treatment, upon change in drug dose level, type and dosing time, and during 7 days (at least 3 days [112, 144] or 4 days [145]) before the next planned clinic visit. Regarding the method for clinicopharmacological evaluation of responses to antihypertensive drug treatment, evaluation based on the mean of 5-day or longer data has been shown to be necessary by the results of evaluation of reproducibility of home blood pressure and placebo effects collected from a total of 214 subjects of the Ohasama Study (treatment-naïve hypertensive patients and outpatients visiting hypertension clinics) [326].

These guidelines, therefore, recommend using the mean of 7 days (at least 5 days) for diagnosis of hypertension and evaluation of responses to antihypertensive drug therapy. This recommendation is similar to that given in the JSH2014.

As described in the Section "1) When should measurement be done?", the home blood pressure in the morning and that in the evening can vary depending on environmental factors and physiological conditions, and their clinical significance is also considered to vary. Therefore, the data on blood pressure in the morning and that in the evening should be processed for analysis separately.

Combining these results together, these guidelines recommend using the mean of 7-day measurement (at least 5-day measurement) of blood pressure in the morning and that in the evening for diagnosis of hypertension and evaluation of responses to antihypertensive treatment on the basis of home blood pressure.

Because home blood pressure levels in the morning and that in the evening have the potential of predicting the outcome in both the antihypertensive drug user group and the non-user group [171, 327, 328], these guidelines recommend making a home blood pressure-based diagnosis of hypertension in cases in which the mean home blood pressure in the morning or the mean home blood pressure in the evening or both satisfy the criteria for home blood pressure-based diagnosis of hypertension. Similarly, if both the mean home blood pressure in the morning and the mean home blood pressure in the evening have satisfies the goal of antihypertensive treatment, it can be judged that the goal of home blood pressure has been achieved by antihypertensive treatment.

Q3 BLOOD PRESSURE VARIABILITY EVALUATION METHOD

- Variability in blood pressure involves diverse periodical features, ranging from beat-to-beat variability to yearly changes, and the components of variability possible to assess vary depending on the method used for blood pressure measurement.
- The influence at the level of blood pressure should be taken into consideration for accurate evaluation of blood pressure variability.
- Although an association between blood pressure variability and cardiovascular outcome has been reported, few methods are established for markedly altering only the variability in blood pressure, and it is difficult to achieve evident suppression of day-by-day or visit-to-visit blood pressure variability with the use of antihypertensive medication alone.
- What is first essential is to evaluate and control the blood pressure level sufficiently by accurate blood pressure measurement and this should be followed by assessment of various indicators of blood pressure variability to take actions needed.

COMMENTARY

1) Blood pressure variability

Blood pressure variability involves diverse periodical features, ranging from beat-to-beat change to yearly changes.

Table Q3-1 Blood pressure measuring methods and blood pressure variability

	Intraarterial pressure measurement[*1]	ABPM	Home blood pressure	Office blood pressure
Beat-to-beat blood pressure variability	○	x	x	x
Mayer's wave[*2]	○	x	x	x
Blood pressure variability per 15-30 min	○	○	x	x
Diurnal variability	○	○ (poor reproducibility)	△[*3]	x
Morning-evening difference	○	○	○	x
Nighttime dipping	○	○ [176]	○[*3]	x
Morning hypertension	○	○	○	x
Weekly variability	x	x	○	x
Monthly cycle	x	x	○	△
Visit-to-visit variability	x	x	△	○
Seasonal variability	x	x	○	△
White coat hypertension (phenomenon)	○	○	○	x

[*1]: Not conducted in routine clinical practice.

[*2]: Fluctuating components of approximately 10 sec cycle. Known to reflect variability in autonomic nerve output originating from baro-/chemoreceptor reflex.

[*3]: Can be assessed with recently marketed home blood pressure devices that measure nocturnal blood pressure during sleep [176].

Changes following growth or aging are also large waves of variability. These features are combined with irregular and accidental changes to determine blood pressure variability in individuals (Table Q3-1). In clinical practice, short-term to diurnal variability is assessed primarily by ABPM, whereas variability between morning and evening and day-by-day variability are assessed primarily by measurement of home blood pressure. Visit-to-visit variability is primarily assessed by measurement of office blood pressure. Long-term measurement of home blood pressure reflects seasonal and yearly changes as well. As indicators of variability, various calculation methods have been proposed, including classical standard deviation (SD), maximum minus minimum difference (MMD) and methods using complex mathematical equations. The conditions for blood pressure measurement also are a large factor affecting the blood pressure variability.

2) Indicators of blood pressure variability

Study reports on blood pressure variability often used SD as an indicator of variability. However, cautious is needed of the fact that SD correlates strongly with blood pressure level. The reported positive correlation between SD and sympathetic nerve activity [329] and the reduction in SD following antihypertensive treatment [330] are diminished when the coefficient of variability (CV) (calculated by dividing SD by the blood pressure level) is used [329, 330].

Regarding short-term blood pressure variability, the use of average real variability (ARV) yielded by averaging of the absolute difference between two neighboring blood pressure readings has been proposed [331]. For example, if blood pressure measurement at intervals of 30 min yields SBP 120, 140 and 130 mmHg, the ARV is calculated as $(20 + 10)/2 = 15$ mmHg. ARV is also affected by the blood pressure level, but the difference in intervals of measurement can be taken into consideration if weighting is incorporated into the analysis, reflecting the sequence of multiple sessions of blood pressure measurement.

Because the relationship of the increased blood pressure level to the increased SD is not completely linear, the influence from the blood pressure level due to biased blood pressure distribution remains in the CV. For this reason, variability independent of the mean (VIM; also called "SD independent of the mean [SDIM]") [332] was proposed as an indicator of variability almost completely independent of blood pressure level [192, 206, 333]. VIM can be evaluated as an indicator of blood pressure variability not affected by the blood pressure level at all. However, since VIM differs according to populations analyzed, direct comparison of VIM among populations is impractical. Furthermore, since the correlation among indicators of variability is high [332, 334] and VIM is calculated as a modified form of the blood pressure-SD proportional relationship (an equation employed for calculation of CV), using the simply calculable CV as an indicator of variability instead of VIM is acceptable in many clinical settings. Other than these

indicators, usefulness of residual SD (RSD; also called "root mean square error [RSME]") have also been assessed.

3) Short-term variability in ABPM [176]

Short-term variability in ABPM reflects target organ damage [194, 335]. The Ohasama Study reported the association of its SD with the cardiovascular outcome for the first time in the world [336]. In the meta-analysis of 8 cohorts, the SD of nighttime blood pressure was a strong predictor of both cardiovascular death and cardiovascular disease onset (P≤0.0082), but the predictive power of the SD of daytime blood pressure was not stronger than that of blood pressure level [337]. According to the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO), the SD and ARV of 24-h systolic ABPM data significant predicted stroke and cardiovascular events, such as coronary artery disease ($P \leq 0.03$), when they were used separately. However, the significance of these variability indicators disappeared almost completely when the blood pressure level was incorporated into the model [196]. This difference is probably because SD and ARV are strong influenced by blood pressure level.

4) Dipper and morning hypertension

As described in Chapter 2.3. "6) Abnormal variability of diurnal blood pressure," ABPM allows assessment of the degree of nighttime blood pressure dipping in comparison to the daytime blood pressure level. This daytime-nighttime difference is an indicator differing from the visit-to-visit change in office blood pressure [338]. According to the IDACO, the daytime/nighttime blood pressure ratio determined by ABPM was a significant predictor of cardiovascular mortality independent of blood pressure [339]. However, the association with the onset of cardiovascular diseases was modest [339]. The risk for cardiovascular death is higher in non-dippers (small nighttime dipping) than in dippers [182, 340].

Early morning blood pressure elevation (morning surge) has been noted as a high-risk disease type [166, 167]. As described in Chapter 2.3. 3) "Morning hypertension," there are many reports on morning surge, but there are also reports stating that the concept "blood pressure is low at night and high in the morning" resembles the concept "nighttime blood pressure dipping/dipper," and that this represents a low-risk condition if a definition close to dipper is applied to this concept [341, 342]. According to the IDACO, a risk for total death and onset of cardiovascular diseases was noted in the subjects whose morning surge intensity was ranked in the top 10% range, whereas no such risk was noted when the difference was less than 20 mmHg [343]. Studies reporting a high risk of morning surge tended to be based on comparison of data among short segments of the daytime and the nighttime, rather than the data from the entire daytime (morning) or the entire nighttime. Therefore, the risk noted in those studies might reflect the blood pressure variability during short periods of time (lasting for several tens of minutes to one hour) rather than during the entire daytime or nighttime.

5) Day-by-day variability of home blood pressure

Home blood pressure is optimal for analysis of day-by-day variability in blood pressure. Because the conditions for self-measurement of home blood pressure can be settled easily, reliability of home blood pressure measurement data is high. Regarding the relationship between home blood pressure variability and organ damage, a three-year follow-up study of Home Blood Pressure for Diabetic Nephropathy (HBP-DN) revealed an association of renal dysfunction with the SD of home blood pressure [344]. In addition, an association between gross albuminuria and CV of home blood pressure in patients with type 2 diabetes mellitus has been reported [345]. Whereas, none of SD, CV and ARV predicted the progression of renal dysfunction [346] and the pulse wave velocity had no association with the diurnal variability of home blood pressure [347].

Numerous reports demonstrated a significant association between day-by day variability and cardiovascular outcome [195, 197, 348]. However, in a Belgian study, VIM based on the home blood pressure in the broader sense of the term (observer/examiner measured blood pressure at each participant's home) was not associated with any of total mortality or onset of cardiovascular diseases [198], and the degree of VIM's contribution to the model of prediction of cardiovascular outcome remained less than 1% on the whole (although it was significant in some cases) during the Ohasama Study [199]. In the International Database of Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO), which was a home blood pressure-based meta-analysis project [200], both the SBP and the DBP of the study population divided uniformly into 10 groups according to CV were found to have a significant cardiovascular risk only in the highest CV group, with its threshold level being 11.0% for SBP and 12.8% for DBP. However, this value corresponds to an SD of approximately 15/11 mmHg if the blood pressure is 135/85 mmHg. This indicates that if the home blood pressure daily measured by one of the subjects shows a normal distribution, 95% (approximately ±2SD) of all values remain in the range 105–165/63–107 mmHg and 5 out of 100 values are off this range, thus demonstrating a remarkably wide distribution of home blood pressure level of an individual. If such a large variability is observed in the results of measurement, check of the measuring conditions and determination of underlying illness should first be considered.

It has been reported that medication alters day-by-day variability of blood pressure, such as a report that the use of Ca channel blockers (CCBs) or diuretics suppressed the day-by-day variability in patients after transient ischemic attack [349], and that the day-by-day variability in home blood pressure was reduced more markedly by concomitant use of Olmesartan and amlodipine than by concomitant use of diuretics [350]. In the Hypertension Objective Treatment based on Measurement by Electrical Device of Blood Pressure (HOMED-BP), however, the day-by-day variability of home blood pressure was not affected by any first-line drug of CCBs, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) [204]. Furthermore, in the HOMED-BP, the day-by-day variability of baseline home blood pressure in the morning did not predict outcome. VIM in the evening was barely significant ($P = 0.043$), but the day-by-day variability of home blood pressure recorded in the morning or evening during monotherapy using any of the 3 first-line antihypertensive drugs had no association with cardiovascular outcome, thus allowing a conclusion that reducing the blood pressure is more important than any other thing when improving the outcome [204].

6) Visit-to-visit variability

The visit-to-visit variability is expressed as variability in office blood pressure and has been reported to be associated with cardiovascular outcome [333, 351, 352]. However, there are many points requiring precaution when interpreting this finding, i.e., lack of sufficient adjustment of the confounding factors during analysis, analysis covering only the high-risk group, and emphasis of the highest risk group only by dividing the indicators of variability into segments instead of analyzing them as continuous values. The Third National Health and Nutrition Examination Survey (NHANES III) in the United States demonstrated SD and CV as significant predictors of total death even after multivariate adjustment, but it revealed no cardiovascular risk [353]. In a large-scale placebo-controlled randomized comparative study Systolic Hypertension in Europe (Syst-Eur), there was a 10.5 mmHg difference in SBP level between the active drug treatment group and the placebo group, but VIMs in the two groups were identical and VIM had no association with total death or onset of cardiovascular diseases after adjustment for confounding factors [201].

Regarding changes in the visit-to-visit variability following antihypertensive treatment, it has been reported that antihypertensive drugs other than CCBs increased the visit-to-visit variability [192], that CCBs and ARB reduced the visit-to-visit variability [354] and that the visit-to-visit variability was reduced more by the addition of diuretics to CCBs than by the addition of β-blockers [205]. In Syst-Eur, in contrast, the changes in variability in the antihypertensive treatment group (primarily using CCBs) did not differ from that in the placebo group [201]. Thus, differences in the influence of antihypertensive drugs on visit-to-visit variability have not yet been fully validated.

7) White coat hypertension and masked hypertension

White coat hypertension and masked hypertension, which are diagnosed on the basis of a combination of office/screening blood pressure and out-of-office blood pressure, are indicators of blood pressure variability whose clinical significance has been established most. The cardiovascular risk of white coat hypertension is controversial [288, 355, 356] as described in detail in CQ2 "Is follow-up needed for patients with white coat hypertension?". Periodical follow-up by home blood pressure measurement or ABPM is at least necessary for patients with white coat hypertension [294]. The risk involved in masked hypertension was high and comparable to that of persistent hypertension for both treatment-receiving patients and treatment-naïve patients also in the IDHOCO [288]. For such patients with masked hypertension, control of out-of-office blood pressure is more important and treatment with long-acting antihypertensive drugs is necessary. Reference should be made to Chapter 2.3. "1) White coat hypertension, 2) Masked hypertension."

8) Seasonal variability of home blood pressure

If home blood pressure is measured for a long period of time, detailed assessment of monthly to yearly changes is possible [357, 358]. When seasonal variability of home blood pressure was analyzed among patients of HOMED-BP in whom no change in prescription was made during one year, the morning home blood pressure in this group was 6.7/2.9 mmHg higher during winter than during summer, with the peak recorded in mid- to late-January [203]. This cycle of change was 2–3 weeks earlier than the change in atmospheric temperature. However, in the study at Aizumisato Town of Fukushima Prefecture, the cycle of room temperature was close to that of atmospheric temperature [357], suggesting an association with daylight hours, activity level and annual cycle of some hormones [359]. Furthermore, the seasonal variability was greater in older people, men, and residents in areas south of Kanto [203].

If the dosing method and dose level of antihypertensive drugs are adjusted to the seasonal variability at an early stage, the summer – winter difference in home blood pressure can be suppressed [360]. Among the patients covered by HOMED-BP, the cardiovascular risk was significantly higher in the group showing greater blood pressure dipping in the summer (the high variability group) and the group showing home blood pressure elevation in the

summer/reduction in the winter (the reversed group) than in the low to medium variability group, suggesting the usefulness of antihypertensive treatment with seasonal variability taken into consideration [360].

9) Cognitive function and blood pressure variability

Visit-to-visit variability during youth is associated with the hippocampal area at middle age [361] and the visit-to-visit variability at advanced age is known to be a predictor of cognitive impairment [362] and onset of dementia [363]. Also in analysis of ABPM data, a significant association of the increase in SD (weighted by the frequency of measurement) with cognitive impairment was shown in a cross-sectional study [364]. Concerning the relationship between cognitive function and day-by-day variability in blood pressure, the Ohasama Study revealed that day-by-day variability and blood pressure level independently predicted cognitive impairment in the future [202]. Also in the Hisayama Study, both the home blood pressure-based hypertension and high day-by-day CV independently predicted cerebrovascular dementia, and the risk for onset of Alzheimer's disease was high in individuals with 7.6% or higher CV of SBP regardless of home blood pressure level [57]. Association of blood pressure variability with the risk for non-cardiovascular diseases, such as dementia, is one of the open issues to be studied hereafter.

10) Pulse rate variability

Like blood pressure, pulse rate also shows variability. In the Ohasama Study, an association was noted between daytime ABPM-based pulse rate variability and cardiovascular death, but the analysis using nighttime ABPM data revealed no such association [336]. ABPM-based pulse rate variability is poorly reproducible [365]. The correlation of home blood pressure-based pulse rate variability with ABPM-based pulse rate variability is low [366] and pulse rate variability is considered to differ markedly depending on the method of blood pressure measurement, although its clinical significance is unclear.

Conclusions

Variability in blood pressure revealed by comparison of blood pressure data collected under different conditions, such as white coat hypertension/masked hypertension (revealed by comparison between office and out-of-office blood pressures), nighttime blood pressure dipping/hypertension, morning – evening differences in blood pressure and morning surge (reflecting blood pressure difference between active hours and nighttime sleep or bedtime/awakening process), is closely associated with the cardiovascular risk. On the contrary, day-by-day variability and visit-to-visit variability based on measurement under similar conditions tend to have less association with the outcome than the blood pressure level. There are few interventional methods that markedly alter the variability, and it is difficult to definitely suppress the day-by-day or visit-to-visit blood pressure variability with the use of antihypertensive drugs. Healthcare professionals and patients/subjects are first required to conduct sufficient evaluation/control of blood pressure level on the basis of accurate blood pressure measurement and then to assess various indicators of blood pressure variability so that appropriate actions can be taken. However, blood pressure variability may be viewed as having certain significance as a marker reflecting the blood pressure measuring conditions, drug intake status and living environments in individuals.

Chapter 3 Principles of hypertension management and treatment

POINT 3A

1. **Antihypertensive treatment should be performed to prevent death and reduction in the quality of life (QOL) due to the occurrence/progression/recurrence of cardiovascular diseases.**
2. **Antihypertensive treatment consists of non-pharmacological therapy (including lifestyle modifications) and pharmacological therapy.**
3. **During the initial examination of a hypertensive patient, confirmation of persistently high blood pressure should be made, associated with evaluation of the blood pressure level, ruling out of secondary hypertension and checking for presence/absence of factors affecting the prognosis (risk factors, organ dameges, cardiovascular diseases).**
4. **Individuals with blood pressure ≥130/80 mmHg (elevated blood pressure level or higher categories) should be stratified into three risk groups (high risk, moderate risk and low risk) according to the blood pressure level and other factors affecting the prognosis.**
5. **In high-risk patients, absolute risk is high and antihypertensive treatment can markedly reduce the absolute risk. However, since the reduction in relative risk achieved by antihypertensive treatment does not depend on the patient's background risk level, the necessity of antihypertensive treatment is suggested also in low- and moderate-risk patients.**
6. **Lifestyle modifications should be attempted in all individuals with blood pressure ≥120/80 mmHg (high-**

normal blood pressure level or higher categories). In high-risk individuals with elevated blood pressure level and patients with hypertension (≥140/90 mmHg), lifestyle modifications/non-pharmacological therapy should be performed actively, and antihypertensive treatment should be started as needed.

7. **For high-risk patients, antihypertensive treatment should be started early, in addition to the attempt of lifestyle modifications. In low- and moderate-risk patients, emphasis should be placed on lifestyle modifications and, while evaluating individual features, the need of pharmacological therapy should be considered during the course of such attempts.**

1. OBJECTIVES OF TREATMENT

The objectives of antihypertensive treatment are to prevent the occurrence/progression/recurrence of cardiovascular diseases related to persistent high blood pressure, reduce mortality and help individuals with high blood pressure lead their lives as normally as do healthy people. According to a meta-analysis of antihypertensive treatment data, a 10 mmHg decrease in systolic blood pressure (SBP) and a 5 mmHg decrease in diastolic blood pressure (DBP) reduce the risks of major cardiovascular events by approximately 20%, stroke by 30–40%, coronary artery disease by approximately 20%, heart failure by approximately 40% and total death by 10–15% [367–369]. The extent of reduction in the relative risk for cardiovascular diseases achieved by such antihypertensive treatment does not basically differ among subjects who have different ages, sex or presence/absence of associated diseases [369–378]. The effect of antihypertensive treatment in preventing decline in renal function is not constant [369, 379].

Even when the relative risk is reduced to the same extent by antihypertensive treatment, the reduction in absolute risk (risk difference) is greater in high-risk patients than in low-risk patients. For this reason, clinical studies often focused on high-risk patients [150, 380]. In low-risk and moderate-risk patients from the juvenile group and the middle-aged group, the reduction in absolute risk is small and the effect of treatment in preventing cardiovascular diseases is less likely to appear in short time. Evidence concerning low-risk or moderate-risk hypertension is limited, since clinical studies require a larger number of subjects and a longer period of observation. However, even in low-risk and moderate-risk subjects, antihypertensive treatment reduced the relative risk for cardiovascular diseases [369–371, 378], thus suggesting the need of antihypertensive treatment. Therefore, also in low-risk and moderate-risk individuals such as individuals with elevated blood pressure level and young patients with hypertension, a treatment plan should be devised appropriately by predicting the responses to treatment on the basis of the evidence from high-risk patients. For antihypertensive treatment of low-risk hypertension, lifestyle modifications/non-pharmacological therapy should be applied as a rule, and cost-effectiveness should be considered before applying pharmacological therapy.

2. TARGETS FOR ANTIHYPERTENSIVE TREATMENT

Antihypertensive treatment should be indicated for individuals with high blood pressure of all ages. The HYVET study [381] involving patients aged over 80 years showed that antihypertensive pharmacological therapy decreased stroke-related mortality, cardiovascular morbidity, such as heart failure, and total mortality. All individuals with blood pressure level ≥120/80 mmHg require some measures targeting their blood pressure level. If the risk for cardiovascular diseases is low, lifestyle modifications should be primarily performed. If the risk is higher, pharmacological therapy should be considered.

Basically, pharmacological therapy is not performed in those with white coat hypertension, and the possibility that the condition may progress to hypertension in the future should be informed. Physicians must instruct patients to measure home blood pressure and improve their lifestyle. Scheduled follow-up should be performed (see Chapter 2 “Measurement and clinical evaluation of blood pressure”).

3. LIFESTYLE MODIFICATIONS, NON-PHARMACOLOGICAL THERAPY AND PHARMACOLOGICAL THERAPY

Antihypertensive treatment can be roughly categolized as non-pharmacological therapy or pharmacological therapy. Non-pharmacological therapy includes, diet therapy (focusing on salt reduction), lifestyle modifications (e.g., exercise, alcohol restriction, alleviation of obesity) and therapeutic interventions such as continuous positive airway pressure (CPAP) (for sleep apnea syndrome) and renal artery intervension or adrenal tumor resection (for secondary hypertension). Lifestyle modifications are recommended not only for patients with hypertension but also for all individuals other than those with normal blood pressure. Because lifestyle modifications can reduce blood pressure significantly, they are important as measures to be taken for individuals in whom pharmacological therapy is not started (e.g., individuals with high-normal blood pressure, and low-risk or moderate-risk individuals with elevated blood pressure). Furthermore, lifestyle modifications enhance the potency of antihypertensive drugs and are therefore useful in improving the blood pressure control of patients receiving pharmacological therapy. Furthermore, since lifestyle

modifications are effective as a means of preventing the onset of hypertension and suppressing the progression of hypertension, they are adopted also as a population strategy in the health promotion programs targeting specific populations (including individuals with normal blood pressure or high-normal blood pressure) or population of the entire society. In the present guidelines, lifestyle improvement promotion by primarily information delivery) are distinguished from the lifestyle modifications/non-pharmacological therapy (involving planned intervention into lifestyles by communication by healthcare professionals such as physicians, nurses, public health nurses, pharmacists and registered dieticians).

For individuals with normal blood pressure, it is recommended to acquire an appropriate lifestyle or to continue such a lifestyle. Guidance for lifestyle modifications should be given to individuals with high-normal blood pressure and low-risk or moderate-risk individuals with elevated blood pressure and, if improvement is not seen, the guidance should be given repeatedly. For high-risk individuals with elevated blood pressure and patients with hypertension, intervention into their lifestyles is made in a well-planned and scheduled manner by healthcare professionals and its efficacy needs to be evaluated. These steps should be taken continuously and repeatedly, if improvement is not seen, the intervention should be reinforced.

4. RISK STRATIFICATION FOR PROGNOSIS ASSESSMENT AND MANAGEMENT PLANS

1) Cardiovascular diseases, organ damages, and risk factors

Hypertension is a major risk factor for cardiovascular diseases. In particular, the attributable risk of hypertension for stroke is high. (see Chapter 1 "Epidemiology of Hypertension"). Not only hypertension but also risk factors other than hypertension, the degree of organ damages, such as hypertension-associated organ damages, and the history of cardiovascular diseases are closely associated with the prognosis of hypertensive patients (Table 3-1) [30–32, 382, 383]. Therefore, in hypertension treatment, it is important to evaluate the blood pressure level, risk factors for cardiovascular diseases and the presence or absence of organ damages/cardiovascular diseases.

According to the evidence available in Japan, risk factors for cardiovascular diseases other than blood pressure level include age, sex (man), smoking, diabetes mellitus, dyslipidemia, chronic kidney disease (CKD) (proteinuria, reduction in estimated glomerular filtration rate [eGFR]) and obesity [30–37, 384–386]. These risk factors have been referred to also in previously published guidelines. The presence of atrial fibrillation as an associated disease also contributes greatly to the onset of stroke [16, 386].

Table 3-1 Factors affecting the prognosis of cardiovascular diseases

a. Risk factors for cardiovascular diseases other than blood pressure
Advanced age (65 years or older)
Sex (man)
Smoking
Dyslipidemia[*1]
Hypo-HDL-cholesterolemia (<40 mg/dL)
Hyper-LDL-cholesterolemia (≥140 mg/dL)
Hypertriglyceridemia (≥150 mg/dL)
Obesity (BMI ≥25 kg/m^2) (especially visceral fat-type obesity)
Family history of juvenile cardiovascular diseases (49 years or younger)
Diabetes mellitus
Fasting blood glucose ≥126 mg/dL
2-h post-loading blood glucose ≥200 mg/dL
Casual blood glucose ≥200 mg/dL
HbA1c ≥6.5% (NGSP)
b. Organ damages/cardiovascular diseases
Brain
Cerebral hemorrhage/cerebral infarction
Transient ischemic attacks
Heart
Left ventricular hypertrophy (electrocardiography and echocardiography)
Angina pectoris, *myocardial infarction*, or after coronary intervension
Heart failure
Nonvalvular atrial fibrillation[*2]
Kidney
Proteinuria
Low eGFR[*3] (<60 mL/min/1.73 m^2)
CKD
Blood vessels
Macrovascular disease
Peripheral artery disease (low ABI [≤0.9])
Atherosclerotic plaque
Increased pulse wave velocity (baPWV≥18 m/sec, cfPWV>10 mg/sec)
Increased CAVI (≥9)
Eyeground
Hypertensive retinopathy

Italic: Factors affecting the prognosis used for risk stratification

*1: When the triglyceride level is 400 mg/dL or more or when blood is collected after meals, non-HDL- cholesterol (total cholesterol – HDL-cholesterol) is used. Its criterion is LDL-cholesterol + 30 mg/dL.

*2: Nonvalvular atrial fibrillation is listed as a hypertensive organ damage.

*3: The eGFR is calculated using the following formula with serum creatinine (eGFRcreat). When the muscular volume is extremely small, the following formula with serum cystatin (eGFRcys) is more appropriate.

$$\text{eGFRcreat}\ (\text{mL/min/1.73 m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}\ (\text{women: } \times 0.739)$$

$$\text{eGFRcys}\ (\text{mL/min/1.73 m}^2) = (104 \times \text{Cys}^{-1.019} \times 0.996^{\text{age}}(\text{women: } \times 0.929)) - 8.$$

Concerning organ damages, various indicators determined by physician's examination or laboratory examinateons are available. Of these indicators, left ventricular hypertrophy (ECG) [387–390], proteinuria (including albuminuria in diabetic patients) [391–393] and reduction in eGFR [33, 34, 394] are recommended for use in routine practice because they are simple to evaluate, and because definite evidence for their influence on prognosis has been collected from Japanese cohorts and their evaluation is feasible

Table 3-2 Stratification of the risk of cardiovascular diseases based on office blood pressure

Risk Category / Classification of blood pressure	Elevated blood pressure 130-139/80-89 mmHg	Grade Ⅰ hypertension 140-159/90-99 mmHg	Grade Ⅱ hypertension 160-179/100-109 mmHg	Grade Ⅲ hypertension ≥180/≥110 mmHg
Category Ⅰ No prognostic factor	Low risk	Low risk	Moderate risk	High risk
Category Ⅱ At least one of age (≥65), sex (man), dyslipidemia and smoking	Moderate risk	Moderate risk	High risk	High risk
Category Ⅲ At least one of cardiovascular diseases, nonvalvular atrial fibrillation, diabetes mellitus and CKD with proteinuria, or 3 or more of Category Ⅱ risk factors	High risk	High risk	High risk	High risk

Risk of cardiovascular diseases was stratified by combination of prognostic factors with reference to the absolute risk yielded from the JALS score and the Hisayama score. The prognostic factors used for stratification are blood pressure, age (≥65), sex (man), dyslipidemia, smoking, history of cardiovascular diseases (cerebral hemorrhage, cerebral infarction, myocardial infarction), nonvalvular atrial fibrillation, diabetes mellitus and CKD with proteinuria.

during routine clinical practice (including general practitioners). Other indicators of organ damages, such as increased arterial stiffness (increased pulse wave velocity), obstructive atherosclerosis and carotid artery plaques/stenosis, could also be evaluated as needed for futher evaluation of risk assessment (see Chapter 6 "Hypertension associated with organ damages"). As indicators of cardiovascular diseases, it is recommended to utilize stroke (cerebral hemorrhage, cerebral infarction), ischemic heart disease (myocardial infarction, angina pectoris, history of coronary artery intervension) and heart failure whose diagnosis can be confirmed.

2) Evaluation of absolute risk for onset of cardiovascular diseases and stratification of cardiovascular disease risk in Japan

In the European/American guidelines, the overall risk for cardiovascular diseases is based on the absolute risk assessed from the results of cohort studies in Europe and the USA (Atherosclerotic Cardiovascular diseases [ASCVD] Risk Score [395, 396], Systematic Coronary Risk Estimation [SCORE] [397, 398]). In these countries and areas for cardiovascular risk assessments, the influence on coronary artery disease is greater than that on stroke. In Japan, on the contrary, stroke occurs more frequently, it is thus, necessary to conduct assessment of the overall risk for cardiovascular diseases in a way specified to Japan.

Basic principles of the present guidelines when conducing assessment of the risk for cardiovascular diseases are: (1) evidence in Japan is used; (2) the absolute risk is calculated from risk factors; and (3) risk stratification is conducted with reference to the calculated absolute risk. The factors affecting the prognosis used for risk stratification are cardiovascular diseases, advanced age (65 and over), sex (man), smoking, dyslipidemia, diabetes mellitus, brain hemorrhage, brain infarction, myocardial infarction, nonvalvular atrial fibrillation and proteinuria (Table 3-1, blue color). Obesity and eGFR are not employed for risk stratification because they were not detected as significant for predicting composite cardiovascular events in the JALS [386] or the Hisayama Study [399].

The following principles are applied: a) Patients having history of cardiovascular diseases are rated as having high risk (secondary prevention); b) patients having atrial fibrillation are also rated as having high risk; c) patients having CKD with proteinuria or having diabetes mellitus are rated as having high risk on the basis of the evidence in Japan. Patients with end-stage kidney disease (ESKD) have high risk but they are not discussed here because the hypertension management in such patients differs from that in patients with other disease (see Chapter "End-stage kidney disease"). d) In the other patients, the absolute risk for composite cardiovascular events is obtained by calculation of the risk scores using the risk factors based on the JALS [386] and the Hisayama Study [399] and is utilized as reference information for risk assessment. e) Because calculation of the absolute risk using the risk score described above in d) is not always easy for clinicians during routine clinical practice, a table of risk stratification that reflects a) through d) is prepared for classification of cardiovascular risk into three categories (high risk, moderate risk and low risk) (Table 3-2).

In this risk stratification table, Risk I corresponds to cases where no factor affecting the prognosis other than blood pressure is present (women younger than 65 and without diabetes mellitus, dyslipidemia, smoking, nonvalvular atrial fibrillation, proteinuria positive CKD and cardiovascular diseases). Risk II corresponds to men aged 65 and over having dyslipidemia and/or smoking but without cardiovascular diseases, nonvalvular atrial fibrillation, diabetes

mellitus and proteinuria positive CKD. Risk III corresponds to patients having at least one of history of cardiovascular diseases, nonvalvular atrial fibrillation, diabetes mellitus and proteinuria positive CKD and patients having three or more of the risk factors listed for Risk II. Each of these three risk categories is subdivided into low risk, moderate risk and high risk with the office blood pressure taken into consideration.

Regarding each column of this risk stratification table, risk levels have been confirmed with the actual data of JALS that there is no large discrepancy between the cardiovascular disease risk level determined by the definition of stratification and the cardiovascular disease risk level calculated from the risk score [386]. However, because both the absolute risk calculation and the risk stratification on the basis of risk scores include some hypotheses, the attending physician makes a final judgment about the risk of each patient, taking into account the blood pressure level and the presence/absence of other factors affecting the prognosis.

Because age contributes greatly to the absolute risk, the absolute risk in juvenile and middle-aged patients is not always high even when they have some risk factors [386, 399]. Therefore, in low-risk or moderate-risk patients, it is necessary to conduct risk assessment again about 3–5 years later. Furthermore, in low-risk or moderate-risk patients, assessment of not only the risk for onset in 5 or 10 years but also the life-time risk for onset [400, 401]. The relative risk may also be useful from the viewpoint of improving the patient's awareness of lifestyle modifications in these subjects. Sincehe evidence on life-time risk calculation available in Japan is limited, its detail is not described in the present guidelines.

5. PLANNING OF HYPERTENSION MANAGEMENT AT THE INITIAL EXAMINATION

The plan of hypertension management to be devised at the initial examination should include: 1) confirmation of blood pressure being persistently high and evaluation of its level, 2) ruling out of secondary hypertension, 3) evaluation of factors affecting the prognosis, such as risk factors, concomitant organ damages and cardiovascular diseases, 4) guidance for lifestyle modification, 5) evaluation of the necessity of pharmacological therapy and 6) setting of the target levels of blood pressure control. These steps should be taken in sequence or, if needed, in parallel.

1) Confirmation of blood pressure being persistently high and evaluation of its level

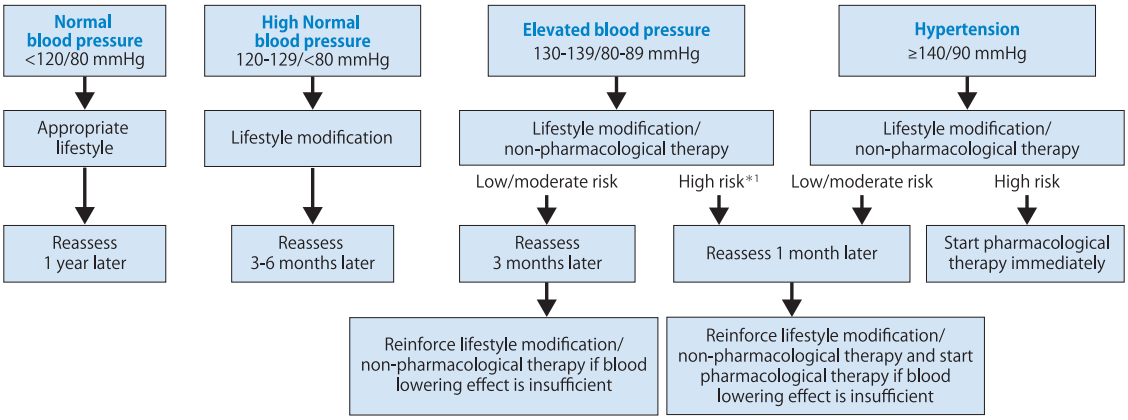
When the office blood pressure at the first examination is high during routine clinical practice (excluding management of hypertensive emergency or urgency), it is necessary to confirm whether the blood pressure is persistently high by conducting blood pressure measurement at the clinic on another day or utilizing the recent health screening blood pressure data or home blood pressure measurement. When home blood pressure data are utilized, the presence/absence of white coat hypertension, white coat phenomenon and masked hypertension is also checked. In cases where white coat hypertension or masked hypertension is suspected or a large variation in blood pressure is predicted, evaluation by 24-h ambulatory blood pressure monitoring (ABPM) should also be considered. Although office blood pressure is used for risk assessment and planning of hypertension management, it is reasonable to place emphasis on home blood pressure or ABPM data during the decision making process if there is a large discrepancy between the office blood pressure and the home blood pressure or ABPM data [132, 402–404]. However, as far as cardiovascular morbidity or mortality is concerned, sufficient evidence based on comparison is not available as to which of office blood pressure or home blood pressure/ABPM data is more beneficial (see CQ1). Studies are awaited. For accurate assessment of home blood pressure, it is also useful to use a home sphygmomanometer automatically recording the measured blood pressure levels in the memory or a home sphygmomanometer recoding the measured levels via the Internet.

2) Ruling out of secondary hypertension

Secondary hypertension is defined to be hypertension attributable to some particular causes. Secondary hypertension often encountered includes renal parenchymal hypertension, primary aldosteronism (PA), renovascular hypertension (RVHT) and sleep apnea syndrome. When any secondary hypertension is suspected on the basis of diseases history, findings of physical examination and laboratory test data, the further screening for specific forms of secondary hypertension is recommended. As needed, the patient is referred to hypertension specialist/other specialists for cardiovascular diseases, endocrine diseases, renal diseases or additional tests needed for diagnosis are conducted. Details are given in Chapter 13 "Secondary Hypertension."

3) Evaluation of factors affecting the prognosis such as risk factors, concomitant organ damages and cardiovascular diseases

The presence of risk factors for cardiovascular diseases other than hypertension and organ damages/cardiovascular diseases should be checked (see Section 4 of this chapter). In patients at elevated blood pressure level or hypertension level, the risk for cardiovascular diseases should be stratified on the basis of office blood pressure, risk factors and organ damages/cardiovascular diseases. A plan of hypertension management (Figure 3-1) should be devised according to the office blood pressure level and the risk for cardiovascular diseases.



*1: Among the individuals with elevated blood pressure, those rated at high risk are treated in the same manner as those rated at moderate risk if they are older people aged 75 years or over, or have bilateral carotid artery stenosis, cerebral main artery occlusion, unevaluated cerebrovascular damages, proteinuria negative CKD or nonvalvular atrial fibrillation. The necessity of pharmacological therapy is considered depending on the subsequent course in individual cases.

Fig. 3-1 Planning of hypertension management corresponding to the blood pressure level at the initial examination

4) Guidance for lifestyle modification

Lifestyle modification is recommended for all individuals other than those with normal blood pressure. Blood pressure should be evaluated again after a certain period of time after the guidance, to consider the necessity of reinforced guidance for lifestyle modification (non-pharmacological therapy) or pharmacological therapy according to the blood pressure level and risk.

5) Evaluation of the necessity of pharmacological therapy

The target levels of blood pressure control and the timing of starting antihypertensive treatment should be decided, taking into consideration the principles for target level setting (see Chapter 3. 6. Target levels of blood pressure control, Table 3-3) and the features of individual patients. Concrete explanation should be given about the therapeutic strategy to each patient, so that treatment may be started after deepening the patient's understanding and sharing of the strategy with the patient.

Figure 3-1 is a plan of hypertension management at the initial examination for an individual not yet having developed cardiovascular diseases. For individuals at normal blood pressure level (<120/80 mmHg), continuation of an appropriate lifestyle should be recommended. Attempts of lifestyle modification should be made for 3–6 months in individuals at high-normal blood pressure level (<120–129/80 mmHg) and for approximately 3 months in low-risk or moderate-risk individuals at elevated blood pressure level (130–139/80–89 mmHg) and, if improvement is not seen during that period, stronger actions for lifestyle modification (reinforced lifestyle modifications/non-pharmacological therapy) should be taken. For high-risk individuals at elevated blood pressure level (130–139/80–89 mmHg) and low-risk or moderate-risk individuals at hypertension level (≥140/90 mmHg), well-planned intervention into lifestyle (lifestyle modifications/non-pharmacological therapy) should be made from the beginning and reassessment is made approximately one month later (if improvement is not seen, stronger non-pharmacological therapy and start of antihypertensive pharmacological therapy should be considered). Of the high-risk individuals at elevated blood pressure level belonging to the late senile generation (age ≥75), having bilateral carotid artery stenosis or cerebral main artery occlusion or having cardiovascular diseases (not evaluated as to carotid artery stenosis and cerebral main artery occlusion) or nonvalvular atrial fibrillation, the actions similar to those for low-risk or moderate-risk individuals should be initially taken, followed by evaluation of the necessity of antihypertensive treatment and the timing of the start of such treatment during the course of the actions in individual cases.

For high-risk individuals at hypertension level (≥140/90 mmHg), antihypertensive treatment (pharmacological therapy) should be started not later than the start of well-planned intervention into lifestyle (lifestyle modification/non-pharmacological therapy). During the acute stage of antihypertensive pharmacological therapy, close attention should be paid to appearance of adverse events and the speed of blood pressure reduction in individual cases while attempting to achieve the target levels of blood pressure control.

Patients with history of cardiovascular diseases are at high risk and are required well-planned intervention into lifestyle (lifestyle modifications/non-pharmacological therapy) regardless of their current blood pressure level. For such individuals, antihypertensive pharmacological therapy should be started early, with reference to the target levels of blood pressure control set for each disease. In addition,

treatment for secondary prevention corresponding to specific cardiovascular diseases should be performed (e.g., lipid therapy, diabetes therapy, cessation of smoking, antithrombosis therapy) in addition to the approach to blood pressure.

POINT 3B

1. **For prevention of cardiovascular diseases, guidance on lifestyle modifications should be provided regardless of blood pressure level. The target levels of blood pressure control are <140/90 mmHg in individuals older than 75 years or having cerebrovascular disease (bilateral carotid artery stenosis and/or cerebral main artery occlusion present or not yet evaluated) or CKD (proteinuria negative) and <130/80 mmHg in individuals younger than 75 or having cerebrovascular disease (without bilateral carotid artery stenosis and cerebral main artery occlusion), coronary artery disease or CKD (proteinuria positive), diabetes mellitus or using antithrombotic drugs.**
2. **Antihypertensive treatment is provided primarily by means of once daily drug treatment, as a rule, while taking care to avoid adverse reactions and concomitantly using other appropriate antihypertensive drugs to elevate the hypotensive effects. If the target is set at lowering blood pressure by 20/10 mmHg or more, concomitant medication should be considered at the beginning of antihypertensive treatment.**
3. **Tolerability of antihypertensive treatment (potential of adverse reactions or adverse events such as reduced organ perfusion arising from excessive hypotensive effects) varies depending on the condition and the magnitude or rate of blood pressure reduction in individual cases. Care needs to be taken of the process of achieving the goal of antihypertensive treatment as well as the tolerability of antihypertensive treatment after achievement of the goal.**
4. **Home blood pressure measurement is useful not only in diagnosing white coat hypertension and masked hypertension but also in improving the judgment of hypotensive effects and the patient's adherence and concordance.**
5. **Reducing the number of tablets to be taken at a time and the frequency of drug intake is useful in improving adherence and blood pressure control.**
6. **Sufficient communication, information supply and attention to QOL and adverse reactions are useful in improving adherence and blood pressure control and in preventing cardiovascular diseases.**
7. **Before treatment, its strategy should be decided after establishing physician–patient concordance encompassing all of epidemiological/clinical study data, patient's clinical background, pharmacological activity of antihypertensive drugs, healthcare expenditure and cost-effectiveness.**

6. TARGET LEVELS OF BLOOD PRESSURE CONTROL (TABLE 3-3)

In a meta-analysis of 61 prospective studies designed to evaluate the relationship between blood pressure and cardiovascular mortality [405], the risk for death from stroke or ischemic heart disease became higher as the blood pressure rose in a wide range of age from 40s to 80s, and this relationship was seen not only in the blood pressure range corresponding to hypertension but also in the range less than 140/90 mmHg (down to about 115/75 mmHg). Therefore, to promote health of the nation, lifestyle modifications as described in Chapter 4 are recommended regardless of blood pressure level. In the Japanese Society of Hypertension (JSH) 2014 guideline, the target levels of blood pressure control for low-risk individuals younger than 75 were set at <140/90 mmHg because no definite association with improved prognosis was seen when blood pressure was reduced to less than 130 mmHg in interventional studies of complication-free hypertensive patients such as OSLO [406], AUSTRALIAN [407], MRC [408] and FEVER [409]. In subsequent studies SPRINT [92] (target set at <120 mmHg) and Cardio-Sis [410] (target at 130 mmHg), strict blood pressure control reduced the cardiovascular events, but all of these studies involved patients having risk factors or complication. In HOPE-3 [411] which involves hypertensive patients possessing risk factors, the mean blood pressure achieved in the intervention group was 128/76 mmHg, but the cardiovascular events were not significantly suppressed. However, a meta-analysis of several of these studies revealed a significantly lower risk for coronary artery disease morbidity or mortality in the group with SBP controlled to less than 130 mmHg than in the group controlled to 130–139 mmHg [369]. In Japan, the risk for cardiovascular diseases is low in individuals aged less than 75, without risk factors and having blood pressure less than 140/90 mmHg, and there is not adequate evidence for improved prognosis following antihypertensive treatment in this group. Therefore, for adults younger than 75, the target level of blood pressure control is set at less than 130/80 mmHg (a range known to involve a low risk for cardiovascular diseases). However, for treatment-naïve adults with office blood pressure 130–139/80–89 mmHg, blood pressure should be lowered by means of starting or reinforcing lifestyle modifications in low-risk or moderate-risk patients and by adding initiation of antihypertensive treatment in high-risk patients. For patients having started antihypertensive treatment, lifestyle modifications should be reinforced if the risk is low or moderate and reinforcement

Table 3-3 Target levels of blood pressure control

	Office blood pressure (mmHg)	Home blood pressure (mmHg)
Adults younger than 75[*1]	<130/80	<125/75
Patients with cerebrovascular disease (without bilateral carotid artery stenosis and cerebral main artery occlusion)		
Patients with coronary artery disease		
Patients with CKD (proteinuria positive)[*2]		
Diabetic patients		
Patients using antithrombotic drugs		
Older patients aged 75 and over[*3]	<140/90	<135/85
Patients with cerebrovascular disease (bilateral carotid artery stenosis or cerebral main artery occlusion present or unevaluated)		
Patients with CKD (proteinuria positive)[*2]		

[*1]: Among treatment-naïve individuals with office blood pressure 130–139/80–89 mmHg, lifestyle modification is started or reinforced for low-risk or moderate-risk cases, and measures including start of antihypertensive treatment are taken for high-risk cases (if their blood pressure is not reduced by lifestyle modification lasting for approximately 1 month or longer) with a final target set at less than 130/80 mmHg. If antihypertensive treatment has already been started and blood pressure is 130–139/80–89 mmHg, lifestyle modification is reinforced for low-risk or moderate-risk cases and measures including reinforced antihypertensive treatment are taken for high-risk cases, with a final target set at less than 130/80 mmHg.

[*2]: Proteinuria is judged as positive if protein level in random urine sample is 0.15 g/gCr or more.

[*3]: In case where the goal of antihypertensive treatment is usually set at less than 130/80 mmHg considering comorbidities or other factors, achieving the goal of less than 130/80 mmHg should be attempted even in older patients (aged 75 and over) if tolerable.

Care needs to be taken of the risk for excessive hypotensive effects both during and after the process of achieving the goal of antihypertensive treatment. The judgment of excessive hypotensive effects should take into account the features of individual cases since it can vary depending on not only the achieved level of blood pressure but also the magnitude or rate of blood pressure reduction and the condition of individual cases.

of antihypertensive treatment should be additionally made if the risk is high, towards the final goal of blood pressure less than 130/80 mmHg.

In older people, care needs to be taken of possible occurrence of events, such as renal dysfunction, when blood pressure is controlled to less than 130 mmHg [412], and the target level of blood pressure control for older people aged 75 and over able to visit outpatient clinics without assistance is usually set at less than 140/90 mmHg. Furthermore, since older people often have organ damage, antihypertensive treatment should be performed carefully, with close attention paid to symptoms and changes in laboratory test data arising from blood pressure reduction and impaired blood flow through major organs (see Chapter 8 "Hypertension in older persons").

Past interventional studies using home blood pressure as an indicator did not yield sufficient evidence, and the target of home blood pressure control should be set at lowering both SBP and DBP by 5 mmHg from the office blood pressure level on the basis of the results of observational studies such as Ohasama Study [146, 413] and HOMED-BP [54, 269].

In patients with diabetes mellitus, coronary artery disease or proteinuria positive CKD who are known to have high risk for cardiovascular diseases, the target of blood pressure control should be set at less than 130/80 mmHg. In patients with cerebrovascular disease in whom bilateral carotid artery stenosis and/or cerebral main artery occlusion is present or has not yet been evaluated and in proteinuria negative CKD patients, the target should be set at less than 140/90 mmHg, while it should be set at less than 130/80 mmHg in patients with cerebrovascular disease without bilateral carotid artery stenosis and cerebral main artery occlusion and patients using antithrombotic drugs (see Chapter 6 "Hypertension Associated with Organ Damage" and Chapter 7 "Hypertension Complicated by Other Diseases").

To date, no clinical study aimed at determining the lower limit of the target levels of blood pressure control has been carried out. According to the results of studies comparing the occurrence of cardiovascular events or adverse events with the stratification of blood pressure levels achieved by intervention, low-risk or high-risk patients with hypertension showed an increased mortality or incidence of stroke and renal impairment following blood pressure control to less than 120 mmHg (see Q4). A similar tendency was noted also in patients with hypertension complicated by diabetes mellitus, CKD, cerebrovascular disease or coronary artery disease. In VALISH [412], which involved older subjects, the composite endpoints including renal failure increased in the group with blood pressure controlled to less than 130 mmHg. When analysis is made on the basis

Table 3-4 Methods for the medical staff and patient to establish a partnership and continue concordance-based medical practice

- Talking with the patient about the risk of hypertension and benefits of treatment
- Providing information on hypertension treatment verbally, in writing and using video materials
- Determining the patient's life-matched therapeutic strategy based on the patient's agreement and subjective selection
- Decreasing the frequency of dosing and number of tablets to be taken by simplifying the regimen (use of a fixed-dose combination, one-package dispensing)
- Promoting self-measurement/recording of home blood pressure with a feedback of assessment of the results
- Establishing a treatment-supporting system involving the medical staff (physician, nurse, pharmacist, dietitian), patient and his/her family
- Talking with the patient about medical expenses or the cost incurring upon suspension of treatment
- Talking with the patient about reasons for missing doses, particularly paying attention to adverse effects/anxiety/problems and changing the drug if necessary

of achieved blood pressure levels, the possibility of reverse causality cannot be ruled out, but no prospective study involving inter-group comparison except for SPRINT has demonstrated the benefit of blood pressure control to such low levels. Therefore, care needs to be taken of possible induction of cardiovascular events or other adverse events when blood pressure is reduced to less than 120 mmHg in non-older people and to less than 130 mmHg in older people.

7. SELECTION OF TREATMENTS

Several genetic and environmental factors are involved in the etiology and progression of essential hypertension. Therefore, treatment always includes the correction of lifestyle (non-drug therapy), which comprises the greater portion of environmental factors. However, few patients achieve the target of blood pressure control by lifestyle modifications alone, and drug therapy is necessary in most cases. In individual patients, the risk should be stratified by comprehensively evaluating the blood pressure level, risk factors for cardiovascular diseases and presence of cardiovascular diseases, and a treatment plan must be established according to the risk stratification (Figure 3-1).

1) Lifestyle modifications

Hypertension is a lifestyle-related disease. Lifestyle modifications may prevent hypertension and exhibit blood pressure-decreasing effects [414–416]. For promotion of health, lifestyle modifications should be recommended to all people regardless of blood pressure level. In particular, when other lifestyle-related diseases, such as dyslipidemia, diabetes mellitus, metabolic syndrome and obesity, are concomitantly present, lifestyle modifications are very important as a treatment method, and it is possible to simultaneously reduce these risk factors with safety at a low cost. To maintain the blood pressure-decreasing effects of lifestyle modifications, it is necessary for both physicians and patients to continue efforts over a long period [417].

Although many hypertensive patients fail to achieve the target of blood pressure control by lifestyle modifications alone, it is possible to decrease the number and doses of antihypertensive drugs by enhancing their effects. Therefore, even after the start of antihypertensive drug therapy, the importance of lifestyle modifications does not change [418, 419]. The contents of lifestyle improvement are described in Chapter 4.

2) Antihypertensive drug therapy

Many patients with hypertension require drug therapy. Major antihypertensive drugs that are currently used include Ca channel blockers (CCBs), renin–angiotensin system inhibitors (angiotensin II receptor blockers [ARBs] and angiotensin converting enzyme [ACE] inhibitors), diuretics (thiazide, loop diuretics and mineralocorticoid receptor [MR] antagonists) and β-blockers. In accordance with the condition, α-blockers and central sympathetic nerve inhibitors (methyldopa, clonidine and guanabenz) are additionally administered. The action mechanisms and adverse effects of respective antihypertensive drugs are characteristic. On the basis of evidence on prognosis improvement from large-scale clinical studies, diuretics, CCBs, ACE inhibitors and ARBs are selected as first-line drugs (Chapter 5).

For the administration of antihypertensive drugs, (1) a drug to be administered once a day should be selected; (2) when a −20/−10 mmHg or greater decrease in blood pressure is targeted, combination therapy should be considered in the initial phase; (3) to enhance the depressor effects of drugs without adverse effects, drugs should be combined appropriately; (4) if a drug shows only a weak depressor effect or is poorly tolerated (e.g., difficulty in drug intake continuation for a reason of adverse reactions), it must be switched to another drug with a different action mechanism; and (5) positive indication should be considered in accordance with concomitant diseases or conditions, and antihypertensive drugs should be selected, considering contraindications/careful administration and interactions with combined drugs other than antihypertensive drugs.

8. OTHER POINTS REQUIRING ATTENTION

1) Long-term treatment (continued treatment)

The objective of long-term treatment is to prevent cardiovascular diseases and target organ damage by maintaining a

target blood pressure level over a long period and comprehensively managing risk factors other than blood pressure.

As hypertension does not cause any marked symptoms, and as treatment continues over a long period, some patients may stop visiting medical facilities. A blood pressure decrease by antihypertensive drugs is misunderstood as the cure for hypertension, and treatment is discontinued in some cases [420]. Attending physicians should perform patient-involved treatment by sufficiently explaining the condition of hypertension, treatment methods, expected effects of treatment and adverse effects of antihypertensive drugs that may occur, by close communication with patients. In addition, it is important to make efforts/devise measures so that patients may observe lifestyle modifications and continue hospital visits and taking drugs. A good physician (clinic/hospital)–patient relationship must be maintained, and much attention should be paid so that antihypertensive treatment may not affect the patient's daily living or social activities. The sufficiency of communication with the physician and the degree of patient satisfaction with the medical staff markedly affect the patient's QOL [421].

2) Attention to the QOL

Hypertensive patients' QOL is objectively and comprehensively evaluated on the basis of generalized comfort, physical symptoms, sexual activity, working efficiency, emotional state, intellectual functions, satisfaction with their lives, and social activities [422]. Although the influence of hypertension on the QOL is less marked than that of other serious diseases, the QOL is impaired by being conscious of hypertension [423, 424]. Problems with emotional responses, home life, social activities, sleep and heart and digestive functions appear with increases in blood pressure [425]. Furthermore, the QOL reduces with age, and there are marked individual differences among older persons [426].

Although treatment for hypertension improves the QOL [427–429], the adverse effects of antihypertensive drugs reduce it [430]. Mental interventions, such as deepening the patient's understanding of hypertension, alleviating negative emotions (e.g., anxiety and depression) and avoiding aggressive behaviors (e.g., competition and hostility), can reduce blood pressure and improve the QOL, accompanied by reduction of the risk for stroke [431]. As treatment for hypertension continues over a long period, it is important to maintain a favorable QOL for the continuation of treatment.

3) Adherence/concordance

The term 'compliance' (meaning obedience/acceptance) has been used to express the patient taking a drug and continuing treatment according to the physician's instructions. However, this means simply obeying regulations/orders and does not reflect what hypertension treatment should be. The entity 'adherence' (meaning continue/attachment) or 'concordance' (meaning agreement/harmony) was introduced [432, 433]. Adherence refers to the patient understanding the disease and necessity of treatment and continuing treatment spontaneously and positively, which is more desirable. In addition, the term concordance involves continuing to determine a therapeutic strategy based on an agreement by discussion on an equal footing between the patient (as a member of the team) and healthcare staff (physicians and others) on the assumption that the patient has sufficient knowledge of the disease and treatment. If the physician continues treatment from force of habit without sufficiently understanding the risk of hypertension or advantages and disadvantages of antihypertensive treatment (i.e., inertia), it may prevent the establishment of concordance. A supporting system by the medical staff, as a team, should be established in addition to favorable communication between the physician (hospital) and the patient. Table 3-4 shows the ways by which to approach such adherence-/concordance-based medical practice.

Adherence to antihypertensive treatment is related to favorable/unfavorable blood pressure control and the development/prognosis of cardiovascular diseases [434–439]. Factors associated with poor adherence to antihypertensive treatment include 1) youth, 2) sex (woman), 3) complex prescription such as polypharmacy, 4) difficulty accessing a medical facility, 5) mild hypertension and 6) mental problems such as depression and anxiety [440, 441]. To achieve favorable adherence/concordance, it is necessary for the physician and the patient to understand the condition of hypertension, the objective of treatment (prevention of target organ damage and cardiovascular diseases), treatment methods (lifestyle modifications and drug therapy), expected effects and adverse effects of treatment, and health expenditure [442–445]. In addition, self-monitoring of home blood pressure and guidance about medication by pharmacists improve adherence to antihypertensive treatment [446, 447]. The appearance of adverse effects related to antihypertensive drugs affects adherence to antihypertensive treatment [448]. Of antihypertensive drugs, diuretics are more likely to lead to poor adherence, but adherence can be improved if diuretics are prescribed as fixed-dose combinations [449]. When the number of tablets to be taken and frequency of dosing are smaller, adherence improves [425, 450]. In this sense, the use of a fixed-dose combination decreases the number of tablets to be taken and reduces drug expenses, improving adherence/concordance [451]. Generic drugs approved by drug elution and biological equivalence tests (changes in the blood concentration of a drug after administration) may also improve adherence as drug expenses can be reduced.

In the future, it is desired that adherence to drug therapy is evaluated accurately by measurement of blood and urine

levels of the drug used [452–454]. If out-of-office blood pressure and status of drug intake are monitored via Internet and cell phone lines, drug intake adherence management is expected to be improved [455, 456].

POINT 3C

[Blood pressure management in hypertensive patients taking antithrombotic drugs]

1. **As hypertension is a risk factor for intracranial hemorrhage during therapy with antithrombotic drugs (antiplatelet drugs and anticoagulants), strict blood pressure control should be performed in patients taking these drugs.**

4) Blood pressure management in hypertensive patients taking antithrombotic drugs

Recently, antiplatelet drugs have been increasingly used for the secondary prevention of atherosclerotic diseases (transient cerebral ischemic attacks, cerebral infarction, coronary artery disease, carotid artery disease, and peripheral arterial disease), and oral anticoagulants for the prevention of cardiogenic cerebral embolism/deep venous thrombosis. Treatment with these antithrombotic drugs increases the incidence of hemorrhagic complications, especially intracranial hemorrhage [457, 458]. After percutaneous coronary intervention with a drug-eluting stent, combination therapy with two antiplatelet drugs (dual antiplatelet therapy [DAPT]), such as aspirin and a thienopyridine family drug, is administered for a long period. To treat atherosclerotic disease with atrial fibrillation, an antiplatelet drug is often combined with an oral anticoagulant. Such combination therapy with antiplatelet and anticoagulant drugs (dual therapy and triple therapy) further increases the risk of hemorrhage [458–462].

As hypertension is a risk factor for intracranial hemorrhage during treatment with antithrombotic drugs, strict blood pressure management is important. In the subanalysis of JCAD (a registry study on coronary artery disease), the risk for onset of intracranial hemorrhage associated with SBP elevation was higher in the combination therapy group (DAPT, dual therapy or triple therapy) than in the antiplatelet monotherapy group [463]. The PROGRESS sub-analysis involving patients taking antithrombotic drugs showed that the mean blood pressure in the antihypertensive drug group was 8.9/4.0 mmHg lower than that in the placebo group, and that the incidence of intracranial hemorrhage decreased by 46% [464]. In the BAT prospective observational study involving Japanese patients taking antiplatelet drugs and/or warfarin, there was a correlation between the blood pressure level during therapy and incidence of intracranial hemorrhage, and the cutoff value of blood pressure for predicting the onset of intracranial hemorrhage was 130/81 mmHg [465]. In SPS3 designed to compare the antihypertensive effects between the target SBP<130 mmHg group and the target SBP 130–149 mmHg group of patients with lacunar infarction receiving aspirin alone or aspirin + clopidogrel, the overall incidence of stroke was 19% lower in the former group than in the latter group, with the incidence of cerebral hemorrhage lower by 63% (statistically significantly) in the former group [466]. Although evidence on the target level of blood pressure control to prevent hemorrhagic complications during therapy with antithrombotic drugs is not sufficient, blood pressure control should be further promoted carefully, considering a target level of 130/80 mmHg, if possible, aiming at <130/80 mmHg, while monitoring ischemic symptoms/findings of important organs, such as the brain, heart and kidney, in order to prevent intracranial hemorrhage in hypertensive patients taking antithrombotic drugs (with respect to patients with cerebral infarction, see Chapter 6 "1. Cerebrovascular disease"; with respect to patients with atrial fibrillation, see Chapter 6 2. "4) Atrial fibrillation").

5) Cost-effectiveness of antihypertensive treatment

As hypertension treatment requires a long period of time, causing large economic burdens on both patients and the society, economic aspects must be considered during clinical practice (e.g., considering the adoption of genetic drugs). Furthermore, it is necessary to consider cost-effectiveness as well, from the public medical or social point of view. The most frequently adopted method for cost-effectiveness analysis of healthcare technology uses QALY (quality-adjusted life year) as an indicator of effectiveness [467]. In cost-effectiveness analyses, the results are commonly expressed using the incremental cost-effectiveness ratio (ICER)—that is, an additional cost required for target therapy in comparison with control therapy to obtain specific effects. When the ICER per QALY is less than 50,000 to 100000 dollars in the United States, 20,000 to 30,000 pounds in England and 5000000 yen in Japan, the target therapy is usually regarded as cost-effective. Therefore, cost reduction is not always needed to make a judgment on the cost-effectiveness [468, 469]. The score of expenses varies from the viewpoint or perspective adopted for a given analysis, but "payer's perspective" is often adopted. Expenses include not only those for antihypertensive drugs but also all related expenses such as those for consultations, examinations and treatment for hypertension-related cardiovascular complications.

Regarding cost-effectiveness of antihypertensive drugs, all of the 14 antihypertensive drugs were judged to be cost-effective when compared with the untreated group or the

placebo group in a systematic review (SR) of 76 English papers published until August 2016 (cost reduction: ~ 19,945 dollars/QALY). In 9 of the papers comparing CCBs with ARBs, ARBs were considered to be cost-effective compared to CCBs, while the remaining 2 papers revealed an inverse result. Thus, the results of cost-effectiveness analysis varied depending on the premises/assumptions adopted for the analysis. Of the 8 papers comparing ARBs with ACE inhibitors or β-blockers, all demonstrated that ARBs were cost-effective [470].

When NICE (UK) conducted cost-effectiveness analysis to prepare the Hypertension Guidelines made public in 2011, comparison among diuretics, ACE inhibitors/ARBs, β-blockers, CCBs and no treatment revealed the lowest cost with diuretics. In that analysis, CCBs were judged to be cost-effective, with ICER being 1960 pounds/QALY in men and 1580 pounds/QALY in women [145]. In the economic evaluation conducted in the USA before introduction of the Hypertension Guidelines 2014, antihypertensive drug treatment was estimated on the whole to suppress cardiovascular events and cardiovascular death and to improve QALY, accompanied by reduction of healthcare expenditure [471].

Two papers have been published concerning cost-effectiveness of strict antihypertensive treatment based on the SPRINT results. One of them estimated the cost-effectiveness of strict antihypertensive treatment to be 23,777 dollars/QALY (thus cost-effective). Even when it was assumed that the incidence of adverse events from the standard therapy rose 3-fold and the incidence of serious adverse events from the strict therapy was three times the incidence from the standard therapy, the strict therapy was considered to be cost-effective [472]. In the second paper, the cost-effectiveness of the strict therapy was estimated to be 28,000 dollars/QALY (cost-effective). Even when the adherence from the 5th year on was assumed to be lower than before, the strict therapy was estimated to be cost-effective [473]. However, since the expenses of healthcare (including drug prices) differ between Japan and foreign countries, we should consider that the results of overseas analyses are not directly applicable to Japan.

The results of domestic analyses are presented below. Compared to the diagnosis of hypertension solely based on office blood pressure, the diagnosis additionally using home blood pressure measurement [474] can rule out white coat hypertension, resulting in favorable cost-effectiveness. In the analysis model on the prognosis of patients with essential hypertension [475], cost-effectiveness was analyzed on 4 treatment methods, i.e. treatment with ARBs (partially combined with CCBs), ARBs (partially combined with diuretics), CCBs (partially combined with ARB) and diuretics (partially combined with ARB). When the hypotensive effect was the same, there was no difference in cost or life year between any two of these four methods in patients without diabetes mellitus at the start of treatment, while treatment with ARB (partially combined with CCBs) had the lowest cost and the highest efficacy in patients with diabetes mellitus at the start of treatment [476]. When cost-effectiveness was analyzed on 4 treatment methods (uncombined ARB treatment, uncombined CCB treatment, ARB + CCB treatment and no antihypertensive drug) [477], reflecting the differences in antihypertensive efficacy among these treatment methods, QALY in men without diabetes mellitus was highest in the ARB + CCB treatment group, followed by the uncombined ARB treatment group and the uncombined CCB group, and lowest in the no antihypertensive drug group. Cost was lowest in the no antihypertensive drug group, followed by the uncombined CCB group and the ARB + CCB group, and highest in the uncombined ARB group. ICER of combined ARB + CCB treatment relative to the untreated group was 200000 yen/QALY, allowing a conclusion that the combined ARB + CCB treatment was cost-effective [478].

Taken together, these results suggest that antihypertensive therapy primarily using ARB, ACE inhibitors, CCBs and diuretics (drugs often used in Japan) and placing emphasis on home blood pressure is favorable in terms of cost-effectiveness. It is necessary to conduct cost-effectiveness analysis of hypertension management conducted in accordance with the present guidelines.

CQ3 WILL STRICT ANTIHYPERTENSIVE THERAPY REDUCE CARDIOVASCULAR EVENTS AND MORTALITY AS COMPARED TO CONVENTIONAL ANTIHYPERTENSIVE THERAPY?

►JSH2019 recommends the target level of less than 130/80 mmHg for the purpose of reducing cardiovascular events. In individual cases, care needs to be taken of tolerability including appearance of adverse reactions.

Recommendation Grade 2 Evidence Level B

Evidence Summarization

The risk for cardiovascular composite events, fatal/non-fatal myocardial infarction and fatal/non-fatal stroke was significantly lower in the strict antihypertensive therapy group than in the conventional antihypertensive therapy group. In the sub-analysis of the relationship between the target level of blood pressure control and the outcome, strict antihypertensive therapy with the target set at less than 130/80 mmHg significantly reduced the risk for cardiovascular composite events and fatal/non-fatal stroke, without increasing the adverse events. However, we considered that there is no adequate evidence supporting the recommendation of target level less than 120 mm Hg at the present,

since there are only few randomized controlled trials (RCTs) setting the target level at less than SBP 120 mmHg there are concerns of tolerability, such as increase in adverse reactions. We therefore recommend to set the target level of SBP less than 130 mmHg.

Commentary

Regarding RCTs aimed at evaluating the target level of blood pressure control, we conduct hand search of references with PubMed, Cochran Library, Ichushi-Web, papers on SR/meta-analysis [369, 479–487] and references cited in those papers. Nineteen papers on RCTs designed to compare the magnitude of blood pressure reduction from the baseline between the strict treatment group and the conventional treatment group and involving a 6-month or longer follow-up period (55529 subjects in total) [92, 269, 410, 466, 488–502] were adopted for analysis. The subjects of these RCTs were often high-risk patients with hypertension complicated by diabetes mellitus, kidney disease or lacunar infarction. RCTs involving patients on maintenance dialysis, patients at the acute stage of stroke and pediatric patients were excluded from the analysis. The target level of blood pressure control for the strict treatment group and that for the conventional treatment group set in each RCT were adopted without modification. The outcomes analyzed were cardiovascular composite events (including fatal/non-fatal myocardial infarction, fatal/non-fatal stroke, fatal/non-fatal heart failure, cardiovascular death, acute coronary syndrome, obstructive arterial disease and aortic aneurysm), total death, fatal/non-fatal myocardial infarction, fatal/non-fatal stroke and adverse events [503].

1) Cardiovascular composite events

The risk for cardiovascular composite events was significantly lower in the strict treatment group (mean target level of blood pressure control 131.4/76.5 mmHg) than in the conventional treatment group (140.3/80.7 mmHg) (14 studies, Figure CQ3-1) [92, 269, 410, 466, 488, 490, 491, 493, 497–502]. Also in analysis of the subgroup (target level less than 130 mmHg), excluding RCTs with the target level for the strict treatment group set at less than SBP 150 mmHg or less than 140/90 mmHg, the risk for cardiovascular composite events was significantly lower in the strict treatment group (mean target level 127.5/75.8 mmHg) than in the conventional treatment group (136.7/80.2 mmHg) (9 studies) [92, 269, 410, 466, 488, 493, 497, 499, 500].

2) Total death

The risk for total death did not differ between the strict treatment group (mean target level of blood pressure control 130.5/77.1 mmHg) and the conventional treatment group (138.8/81.5 mmHg) (19 studies) [92, 269, 410, 466, 488–502]. Also in subgroup analysis, excluding RCTs with the target level for the strict treatment group set at less than SBP 150 mmHg or less than 140/90 mmHg, the risk for total death did not differ between the strict treatment group (mean target level 127.3/76.5 mmHg) and the conventional treatment group (135.9/81.0 mmHg) (13 studies) [92, 269, 410, 466, 488, 492–497, 499, 500].

3) Fatal/non-fatal myocardial infarction

The risk for myocardial infarction was significantly lower in the strict treatment group (mean target level of blood pressure control 132.8/76.5 mmHg) than in the conventional treatment group (141.6/80.4 mmHg) (12 studies) [92, 269, 410, 466, 488, 490, 491, 493, 498, 500–502]. In subgroup analysis, excluding RCTs with the target level for the strict treatment group set at less than SBP 150 mmHg or less than 140/90 mmHg, the risk for myocardial infarction

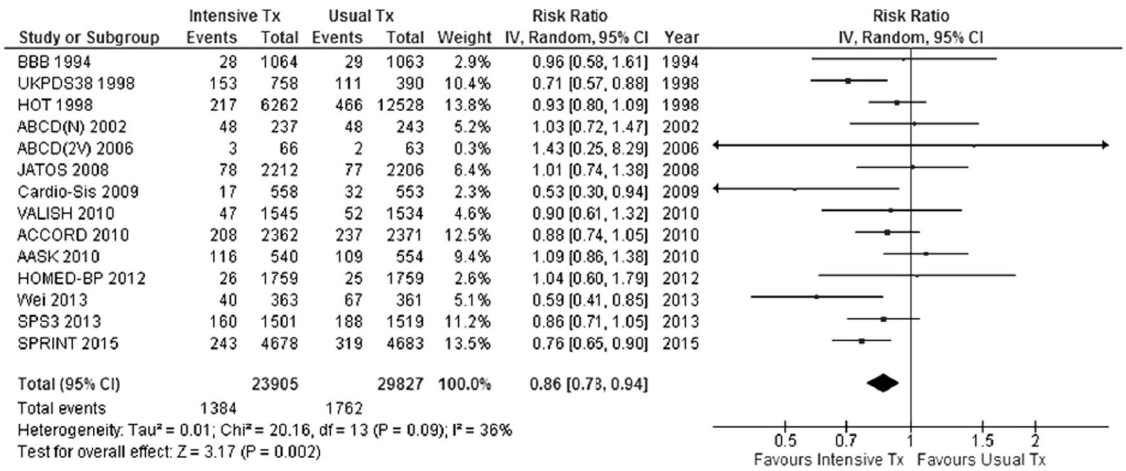


Fig. CQ3-1 Reduction in cardiovascular composite event risk following strict treatment

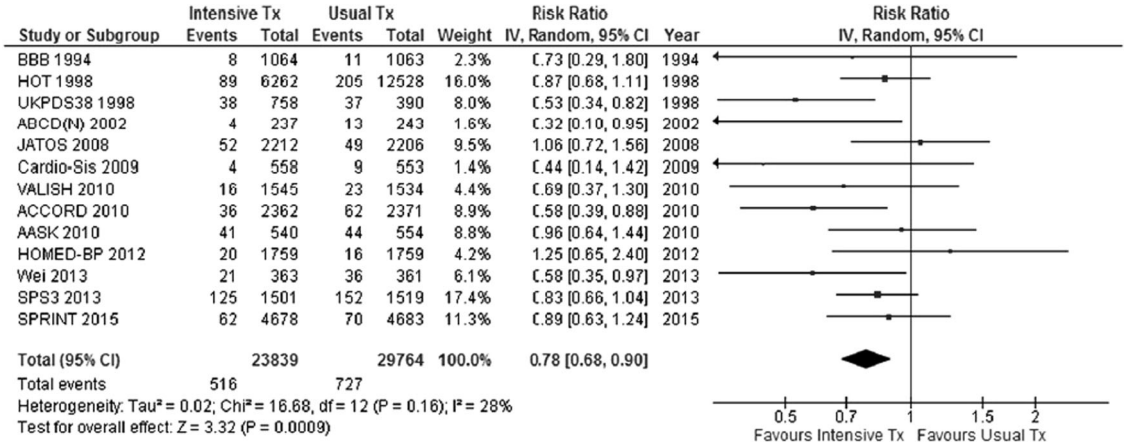


Fig. CQ3-2 Reduction in stroke risk following strict treatment. Blood pressure achieved: Strict treatment group 132.4/76.7 mm Hg, Conventional treatment group 141.5/80.8 mm Hg. IV: Inverse variance, Random: Random effect model (Source: Ref. [503])

did not differ between the strict treatment group (mean target level 128.8/75.5 mmHg) and the conventional treatment group (137.9/79.4 mmHg) (7 studies) [92, 269, 410, 466, 488, 493, 500].

4) Fatal/non-fatal stroke

The risk for stroke was significantly lower in the strict treatment group (mean target level of blood pressure control 132.4/76.7 mmHg) than in the conventional treatment group (141.5/80.8 mmHg) (13 studies, Figure CQ3-2) [92, 269, 410, 466, 488, 490, 491, 493, 498–502]. Also in subgroup analysis, excluding RCTs with the target level for the strict treatment group set at less than SBP 150 mmHg or less than 140/90 mmHg, the risk for stroke was significantly lower in the strict treatment group (mean target level 128.7/75.9 mmHg) than in the conventional treatment group (138.3/80.2 mmHg) (8 studies) [92, 269, 410, 466, 488, 493, 499, 500].

5) Adverse events

The risk for adverse events tended to be higher in the strict treatment group (mean target level of blood pressure control 129.4/74.7 mmHg) than in the conventional treatment group (138.2/77.4 mmHg) although the difference was not significant (7 studies, Figure CQ3-3) [92, 410, 466, 496, 498, 500, 501]. Also in subgroup analysis, excluding RCTs with the target level for the strict treatment group set at less than SBP 150 mmHg or less than 140/90 mmHg, the risk for adverse events tended to be higher in the strict treatment group (mean achieved level 126.7/74.6 mmHg) than in the conventional treatment group (135.9/77.5 mmHg) although the difference was not significant (5 studies) [92, 410, 466, 496, 500].

LITERATURE SEARCH

Hand search was conducted on the papers identified by PubMed, Cochrane Library and Ichushi-Web (as of March 31, 2018) and the papers cited in SR/meta-analysis papers [369, 479–487].

Q4 WHICH BLOOD PRESSURE LEVELS ARE CALLED "EXCESSIVE BLOOD PRESSURE FALL" DURING ANTIHYPERTENSIVE TREATMENT?

- If blood pressure has been reduced to less than SBP 120 mmHg, care needs to be taken of excessive blood pressure fall, i.e., adverse events arising from blood pressure fall.
- During initial treatment, blood pressure should be reduced first to SBP 130 mmHg and, if no sign or finding of hypotension is seen, the blood pressure should be further reduced to 120 mmHg. If done so, excessive blood pressure fall is unlikely to occur.
- In older patients, care needs to be taken of the possibility of excessive blood pressure fall if blood pressure has been reduced to less than SBP 130 mmHg.

COMMENTARY

1) Collection of evidence related to excessive blood pressure fall

To demonstrate that the blood pressure level resulting in antihypertensive treatment falls under the category of excessive blood pressure fall, it is needed to evaluate the balance between the benefit arising from reduction of blood pressure to a given level and the disadvantages arising from anticipated adverse events. However, since no prospective

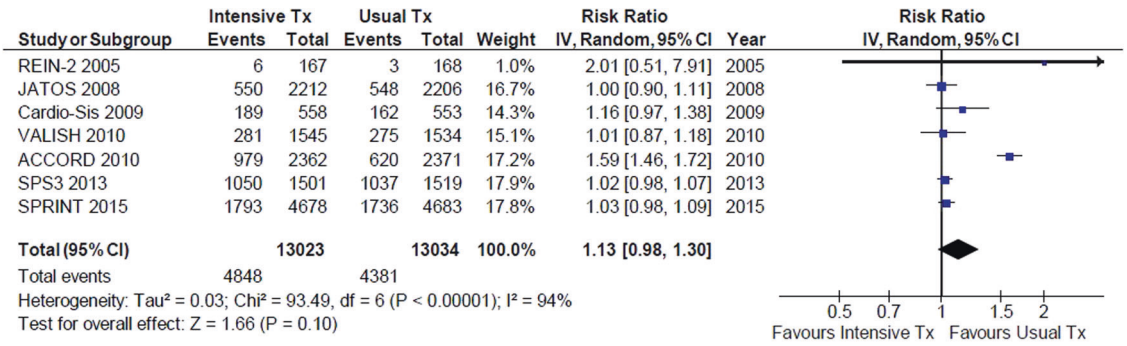


Fig. CQ3-3 Relationship between strict treatment and adverse events. Blood pressure achieved: Strict treatment group 129.4/74.7 mmHg, Conventional treatment group 138.2/77.4 mmHg. IV: Inverse variance, Random: Random effect model

interventional study has been conducted to verify excessive blood pressure fall, we must refer to the results of retrospective interventional/observational studies conducted for other purposes. Furthermore, the blood pressure levels falling under the category of excessive blood pressure fall can vary depending on background variables/complications such as age, diabetes mellitus and coronary artery disease. To extract a conventional view from the limited evidence under the influence of these confounding factors, we processed and evaluated the available information in the following way.

(1) Selection of clinical studies to be evaluated The evaluation covers studies in which antihypertensive treatment was performed in subjects, because excessive blood pressure fall does not occur unless intervention into blood pressure is made. These studies were combined with studies involving prospective follow-up of subjects during antihypertensive treatment. The evaluation excluded cross-sectional surveys and cohort studies including subjects for whom antihypertensive treatment was not always performed.

(2) Evaluation of blood pressure SBP is used for evaluation of blood pressure levels. This is because more efforts are usually required to control SBP than DBP, and the relationship to the risk for cardiovascular events is higher for SBP [46, 47, 504]. Another reason is that when reduction in organ blood flow is regarded as a shortcoming of excessive blood pressure fall, emphasis is placed on maintenance of SBP than DBP except for the heart. The J-curve phenomenon of coronary artery disease and DBP is not discussed here because it is discussed in CQ7.

The data adopted are the results of comparison among the groups having reached a conventional range of blood pressure following antihypertensive treatment in evaluation of the blood pressure reached or the blood pressure recorded during treatment. That is, the results of stratified analysis according to the level of reached blood pressure following antihypertensive treatment, the results of cohort studies in patients receiving antihypertensive treatment and the results of outcome comparison based on the reached blood pressure level in registry studies are adopted as the data. However, even when the strict antihypertensive treatment group with a target set at SBP <120 mmHg has achieved the averaged blood pressure of <120 mmHg as a result of treatment, the blood pressure may be >120 mmHg in some subjects of this group. Also, in the conventional treatment group with a target set at SBP <140 mmHg, some subjects may show blood pressure reduction to <120 mmHg and may suffer disadvantages arising from excessive blood pressure fall. In view of such possibilities, the results of comparison stratified according to a conventional range of blood pressure reached are adopted, the mean of the blood pressure reached in each group is not considered, and the results of comparison of groups having some overlaps in the distribution range of blood pressure reached are not adopted.

(3) Outcome evaluation As mentioned above, evaluation of excessive blood pressure fall is conducted on the basis of balance between benefits and adverse events. To make clear the advantages/disadvantages of this approach, hard endpoints with high seriousness level, such as stroke, myocardial infarction, death and renal failure, are evaluated as adverse events.

(4) Literature search On December 20, 2017, literature search of PubMed was conducted using the algorithm given below, resulting in identification of 25 papers satisfying the above-mentioned conditions [412, 505–528].

"achieved blood pressure" OR "on-treatment blood pressure".

2) Criterion blood pressure level for judging "excessive blood pressure fall"

The results of clinical studies extracted with these criteria are listed in Table Q4-1. On the basis of these results, the

Table Q4-1 Results of studies on the relationship between achieved blood pressure and occurrence of various events in hypertensive patients having received antihypertensive treatment

Author/Year	Subject	Age (years)	Antihypertensive drug	No. of subjects	SBP achieved	Outcome evaluated	Analysis results	Remarks
Cruickshank 1987 [505]	HT	17−77	β-blocker	902	102−138, 139−149, 150−223	Death from MI	≤138, n.s.	Clatterbridge Hospital
Cruickshank 1987 [506]	HT	17−77	β-blocker	902	102−136, 137−148, 149−215	Death from ST	≥age 60, ≤136, ST death↑	Clatterbridge Hospital
Samuelsson 1987 [507]	HT requiring treatment	47−54	β-blocker, diuretic	686	<143, 143−151, 152−159, >159	CAD	<143, CAD↑	Goeteborg primary prevention study
Kaplan 1999 [508]	HT being treated with antihypertensive drug	33−79	Not specified	MI 718 Non-MI 2136	<140, 140−159, 160−179, ≥180	MI	Both MI and non-MI, <140 MI↓	Case control study
Teramoto 2012 [509]	HT	50−79	ARB	14,721	<130, 130−139, 140−159, 160−179, ≥180	Composite EP (ST, CAD, sudden death)	<130, n.s.	OMEGA sub-analysis
Teramoto 2015 [510]	HV without CVD history	50−79	ARB	13,052	<130, 130–139, ≥140	ST, CAD, sudden death	<130, n.s.	OMEGA sub-analysis
Teramukai 2016 [511]	HT without CVD history	50–79	ARB	13,052	<130, 135–139, 140–159, ≥160	Composite EP (ST, CAD, sudden death)	<130, n.s.	OMEGA sub-analysis
Qin 2017 [512]	Grade I HT	45–75	ACE inhibitor	3187	<120, 120–139, ≥140	Composite EP (ST, MI, CV death), total death	<120. ST, total death, composite EP↑	CSPPT sub-analysis
Ogihara 2009 [513]	High-risk HT	20–84	ARB, CCB	4553	<130, 130–139, 140–149, 150–159, ≥160	Composite EP (ST, CAD, HF, sCr elevation, DA, PAD)	<130, n.s.	CASE-J sub-analysis
Sleight 2009 [514]	High-risk HT	≥55	ACE inhibitor, ARB	25,558	≤130, 130–142, 142–154, >154	Composite EP (ST, MI, HF hospitalization, CV death)	≤130, n.s.; 121, MI↑; 112, CV death, composite EP↑, ST n.s.	ONTARGET sub-analysis
Okin 2012 [515]	HT with left ventricular hypertrophy	55–80	ARB, β-blocker	9193	≤130, 131–141, ≥142	ST, MI, CV death, total death	≤130, total death↑	LIFE sub-analysis
Böhm 2017 [516]	High-risk HT	≥55	ACE inhibitor, ARB	30,937	<120, 120–139, 140–159, ≥160	ST, MI, HF, CV death, total death	<120, CV death, total death↑	ONTARGET, TRANSCEND sub-analysis
Weber 2013 [517]	High-risk HT	≥60	ACE inhibitor + (diuretic or CCB)	10,705	110–119, 120–129, 130–139, ≥140	ST, MI, CAD, CV death, total death, sCr elevation	<130, sCr elevation↑; <120, MI, CAD, total death↑	ACCOMPLISH sub-analysis
Staessen 1989 [518]	HT	≥60	Diuretic	352	100–144, 146–158, 160–236	Total death	100–144, total death↑	EWPHE active drug group sub-analysis
Myers 2016 [519]	HT treated with antihypertensive drug	≥66	Not specified	6183	<110, 110–119, 120–129, …, 150–159, ≥160	Composite EP (ST, MI, HF, CV death)	<110, composite EP↑	Stratification according to CHAP, AOBP
Yano 2017 [412]	ISH (≥160/<90 mmHg)	70–84	ARB	3035	<130, 130–145, ≥145	Composite EP (ST, MI, HF, renal event, total death)	<130, composite EP↑(particularly pressure fall>40)	VALISH sub-analysis
Nilsson 2011 [520]	Diabetes, being treated with antihypertensive drug	35–75	Not specified	12,751	100–109, 110–119, 120–129, 130–139, ≥140	ST, CAD	100–109, CAD↑, ST n.s.	Review, Registry
Berl 2005 [521]	Diabetic nephropathy	30–70	ARB, CCB	1590	≤120, >120	ST, MI, HF, CV death, total death	≤120, CV death, total death, HF↑	IDNT
Li 2018 [522]	CKD (eGFR 30–60 mL/min/1.73m^2)	Mean 61.2	ACE inhibitor	3230	≤130, 131–135, 136–140, 141–145, >145	Composite EP (ST, MI, CV death), total death, renal EP (eGFR↓≥30%, ESKD)	≤130, ST, renal EP n.s.	CSPPT sub-analysis
Odden 2016 [523]	Lacunar infarction, antihypertensive treatment	≥30	Not specified	2747	<124, ≥124 Non-linear regression analysis	Composite EP (ST, MI, CV death, total death, CV hospitalization)	<124, composite EP↓; 120–128, ST lowest	SPS3 sub-analysis
Messerli 2006 [524]	HT, CAD	≥50	CCB, β-blocker	22,576	<110, 110–119, 120–129, …, 150–159, ≥160	Composite EP (ST, MI, total death)	<120, composite EP↑	INVEST sub-analysis
Coca 2008 [525]	HT, CAD	≥50	CCB, β-blocker	22,576	<140, ≥140	ST	<140, ST↓	INVEST sub-analysis
Cooper-DeH off 2010 [526]	HT, CAD, diabetes	≥50	CCB, β-blocker	6400	<110, 110–114, 115–119, 120–124, 125–129	Composite EP (ST, MI, total death)	<130, n.s.; <110, total death↑.	INVEST sub-analysis
Verdecchia 2015 [527]	HT, CAD	≥55	ACE inhibitor, ARB	19,102	Non-linear regression analysis	ST, MI	118, ST↓; MI n.s.	ONTARGE sub-analysis
Vidal-Petiot 2016 [528]	HT, stable CAD	Mean 65.2	Not specified	22,672	<120, 120–129, 130–139, 140–149, ≥150	ST, MI, HF, CV death, total death	<120, MI, HF, CV death, total death↑	CLATIFY (Registry)

ARB: angiotensin II receptor blocker, CAD: coronary artery disease, CCB: Ca channel blocker, CVD: cardiovascular disease, CV death: death from cardiovascular disease, DA: aortic dissection, EP: endpoint, ESKD: end-stage kidney disease, HF: heart failure, HT: hypertension, ISH: isolated systolic hypertension, MI: myocardial infarction, n.s.: no significant difference, PAD: peripheral artery disease, sCr: serum creatinine, ST: stroke

blood pressure levels shown below in (1) through (4) fall under the category of excessive blood pressure fall in hypertensive patients having diverse background variables, i.e., the blood pressure levels requiring carefulness as to possible occurrence of adverse events due to blood pressure fall.

In many clinical studies, the blood pressure levels achieved were evaluated by averaging the blood pressure levels recorded during the intervention period. Also during clinical practice, it is appropriate to evaluate the possibility of excessive blood pressure fall by checking blood pressure levels recorded during frequent visits by the patient.

(1) Low-risk hypertensive patients During initial treatment, blood pressure is reduced to SBP 130 mmHg. If no dysfunction is seen in the organs of the circulatory system, such as the brain, heart and kidneys, further blood pressure reduction to SBP 120 mmHg can be done safely. Care is needed about the possibility of excessive blood pressure fall if SBP has been reduced to less than SBP 120 mmHg.

(2) High-risk hypertensive patients Also, in high-risk hypertensive patients, blood pressure is reduced to SBP 130 mmHg during initial treatment. In the LIFE, which studies patients with hypertension associated with left ventricular hypertrophy, the mortality rose at SBP ≤130 mmHg, but this increase in mortality is estimated to have been associated with progression of heart failure. Then, blood pressure can be reduced to 120 mmHg, while paying closer attention to possible reduction in circulatory system organ function associated with blood pressure reduction than required in low-risk hypertensive patients. SBP less than 120 mmHg may fall under the category of excessive blood pressure fall in high-risk hypertensive patients.

(3) Older people Although paying attention to inter-individual differences becomes more important as the age gets higher (e.g., 75 and over), it is usually possible to reduce blood pressure safely to SBP 130 mmHg. When blood pressure is to be reduced by 40 mmHg or more, adequate care needs to be taken of reduction in circulatory system organs during the course of blood pressure reduction. In case where blood pressure is reduced to less than SBP 130 mmHg, care is needed for occurrence of adverse events arising from excessive blood pressure fall.

(4) Diabetes mellitus, CKD, cerebrovascular disease, coronary artery disease In all of these cases, blood pressure can be reduced safely to SBP 120 mmHg, although attention to possible reduction in organ blood flow and function is needed. Care is needed of the possibility of excessive blood pressure fall if blood pressure is reduced to less than 120 mmHg.

3) Evidence and problems with clinical practice related to excessive blood pressure fall

To clarify the blood pressure levels that fall under the category of excessive blood pressure fall, we evaluated the results of outcome comparison according to the blood pressure levels reached as a result of antihypertensive treatment. However, since these finding were derived from retrospective analyses, we cannot rule out the possibility of reversed causal relationship. That is, we cannot rule out that serious events, such as death, occurred in the presence of poor general condition (e.g., heart failure and frail condition) combined with hypotension, rather than the events caused by blood pressure reduction as a result of antihypertensive treatment. Therefore, when the extent of blood pressure fall is evaluated in individual patients during clinical practice, assessment is needed not only about blood pressure level but also the general condition (including complications of the non-circulatory system organs). In cases where blood pressure has been controlled to SBP less than 130 mmHg or less than 120 mmHg and no symptom or sign of hypotension is noted, there is no need to reduce the antihypertensive treatment.

Because the occurrence of adverse events is affected not only by the level of blood pressure reached but also by the magnitude or speed of blood pressure fall, close attention needs to be paid to reduction in circulatory system organ function during antihypertensive treatment. This is particularly important in older patients.

Chapter 4. Lifestyle modifications

POINT 4

1. **Lifestyle modifications are important for the management of hypertension, both before and after the initiation of antihypertensive drug therapy.**
2. **Salt reduction: The target of salt reduction is <6 g per day.**
3. **Dietary pattern: Fruit/vegetable intake should be increased, and cholesterol/saturated fatty acid intake should be reduced. Intake of polyunsaturated fatty acid and low fat dairy products should also be increased.**
4. **Maintaining a proper body weight: Body mass index (BMI) ([body weight (kg)]/ [height (m)] ^{2}) should be kept <25.**
5. **Exercise: Mild aerobic exercise (dynamic and static muscular load exercise) should be performed (at least 30 min/day or 180 min/week).**
6. **Reduction of alcohol intake: Alcohol intake should be restricted to ≤20–30 mL ethanol/day (man) or ≤10–20 mL ethanol/day (woman).**

Table 4-1 Points of lifestyle modifications

1. Salt reduction to <6 g per day
2. Increased intake of vegetables/fruit*; reduced intake of saturated fatty acids and cholesterol;
increased intake of polyunsaturated fatty acids and low fat dairy products
3. Maintaining proper body weight: BMI ([body weight (kg)]÷[height (m)]^2): <25
4. Exercise therapy: Mild aerobic exercise (dynamic/static muscle load exercise) for at least 30 min/day or 180 min/week
5. Reduction of alcohol intake: ≤20–30 mL ethanol per day in men and ≤10–20 mL ethanol per day in women
6. Smoking cessation

Combined lifestyle modifications are more effective.

*Increased intake of vegetables/fruit is not recommended for patients with renal dysfunction requiring restriction of potassium intake. Fruit intake should not exceed about 80 kcal/day in patients who need to restrict their energy intake, such as obese and diabetic patients.

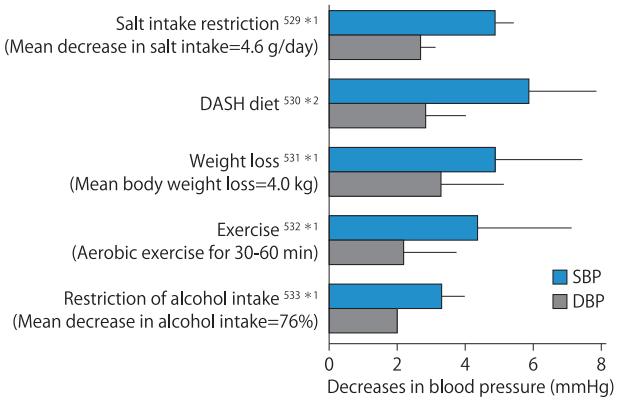
7. **Quitting smoking: Treatment/guidance for smoking cessation should be provided, and passive smoking must be avoided.**
8. **Others: Exposure to cold should be avoided. Emotional stress should be managed.**
9. **Comprehensive lifestyle modifications are more effective.**

GENERAL

Lifestyle modifications are expected to exert antihypertensive effects and are important also from the viewpoint of prevention of hypertension. All hypertensive patients receiving antihypertensive drug therapy should also receive education and guidance regarding lifestyle modifications, which are expected to reinforce the antihypertensive effects and can lead to dose reduction of medication. It is essential to guide infants and children to have appropriate lifestyles. Table 4-1 shows the aspects of lifestyles to be modified. As illustrated in Figure 4-1 [529–533], the degree of blood pressure reduction achieved by modification of individual aspects is not always large, but comprehensive modifications are more effective, and multidisciplinary guidance, including guidance by dieticians and physical therapists, is necessary.

1. SALT REDUCTION

Observational studies including the INTERSALT have indicated the association between excessive salt intake and an increase in blood pressure [64]. In addition, many interventional studies, such as the DASH-Sodium and TONE, have also shown the hypotensive effects of salt



*1 Meta-analysis, *2 Randomized controlled trial
See "2) Nutrients and dietary patterns" for details of DASH diet.

Fig. 4-1 Decreases in blood pressure levels by lifestyle modifications

reduction [415, 530]. Because salt reduced with a goal set at <6 g/day is expected to be effective in reducing blood pressure and suppressing cardiovascular events, these guidelines adopt the salt reduction goal of <6 g/day. Validity of the salt reduction goal <6 g/day is described in CQ4. Regarding the goal of salt reduction, the American College of Cardiology (ACC)/American Heart Association (AHA) Hypertension Treatment Guidelines 2017 presented a goal of 1500 mg sodium/day (equivalent to 3.8 g salt/day), stating that even when this goal is not achieved, blood pressure may be reduced if the daily salt intake is reduced at least by 1000 mg (equivalent to 2.5 g salt) [111]. On the other hand, the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Hypertension Treatment Guidelines 2018 proposed a goal of reducing salt intake to <5 g/day [534], and the World Health Organization (WHO) Guidelines (for the general population) strongly recommended a salt intake less than 5 g per day [535]. Thus, although ACC/AHA2017 proposed a severer goal of salt reduction, the other representative guidelines proposed a goal of salt reduction close to the goal set in this guideline.

Although salt intake by Japanese has been tending to decrease gradually, it is still high (10.8 g/day by men and 9.1 g/day by women according to the National Health and Nutrition Survey in 2017) [536]. The high awareness of the necessity of salt reduction among hypertensive patients has not always led to corresponding daily practice [537], and it is therefore important to assess the salt intake level in individual patients when guiding them towards salt reduction. Table 4-2 shows the method of evaluation of salt intake level [538]. During clinical practice and at health checkup facilities, it is essential to evaluate the daily urinary salt excretion estimated from urinary sodium level and to propose a feasible method of salt reduction with the use of a simple questionnaire such as the food intake frequency questionnaire. However, because the estimate based on a

Table 4-2 Guidelines for evaluation of salt intake

Primary users	Evaluation method	Recommend ability
Special facilities for hypertension treatment	Measurement of sodium (Na) excretion in 24-h pooled urine, weighting or a 24-h recollection dietary survey by a registered dietician.	These methods are highly reliable and recommendable, but are complicated. Recommended if the cooperation of patients and ability of facilities are secured.
Medical facilities in general	Measurement of Na and creatinine (Cr) in spot urine[*1] and second urine after waking, survey regarding the frequency of meals, and dietary history method.	Although the reliability is slightly lower than 24-h urine pooling, the method is simple and is recommended as a practical evaluation procedure.
Patients themselves	Estimation in early morning urine (nighttime urine) using an electronic salt sensor installed with a calculation formula.	Although the reliability is low, the method is recommendable. It is convenient and can be performed by the patients themselves.

[*1] The following formula for estimation of 24-h urinary sodium excretion using spot urine:

24-h urinary Na excretion (mEq/day)=21.98 × [spot urine Na (mEq/L)÷spot urine Cr (mg/dL)÷10 × estimated Cr excretion in 24-h urine]$^{0.392}$

Estimated Cr excretion in 24-h urine (mg/day)=body weight (kg) × 14.89+height (cm) × 16.14–age × 2.043–2244.45

spot urine sample is not highly reliable, it is necessary to repeat measurement while providing guidance to individuals and to judge the efficacy by evaluation of a trend. Sensitivity to salt is high in older people, patients with compromised renal function and patients with complication by metabolic syndrome. For these groups, salt reduction is considered to be more effective, but when guiding salt reduction in frail older people and patients on chronic hemodialysis, it is necessary to adjust the daily salt intake depending on physique, nutritional state and physical activity level, rather than adhering to the above-mentioned goal of <6 g/day.

In Japan, a large proportion of salt is taken from processed foods, and to promote salt reduction at a national level it is necessary to launch educational campaigns for understanding of the nutrient compositions labeled on food products as well as to promote development and marketing of low salt food. Presently, in Japan, the Na but not the salt content is required to be included in the nutritional information on processed foods, and the salt content has to be calculated by multiplying the Na content by 2.54. However, it has been decided to make it mandatory to label processed foods with the salt content by 2020. This regulation is expected to make it easier for consumers to understand the salt content of foods. Furthermore, the Japanese Society of Hypertension (JSH) Salt Reduction Committee has been introducing on its website the low salt foods judged as comparable in taste to common food products while passing the check as to the labeled ingredients, for the purpose of assisting salt reduction efforts [539]. If low salt foods are improved, their utilization may be advised not only to hypertensive patients but also to normotensive individuals from the viewpoint of prevention of hypertension. In Japan, salt intake by infants and children is also high [540]. The attempt of salt reduction in school lunch has also been started, and it is an important task to take measures for promotion of salt reduction also in educational settings.

2. NUTRIENTS AND DIETARY PATTERNS

Because potassium antagonizes the hypertensive activity of sodium, intake of potassium rich foods, such as vegetables and fruits, is expected to manifest hypotensive effects. In a meta-analysis of 23 studies involving a total of 1213 hypertensive patients, focusing on the relationship between potassium replenishment and blood pressure, blood pressure reduction following potassium replenishment (4.25/2.53 mmHg on average) was significant, and a dose-response relationship was noted between potassium intake (<50 mmol/day, 50–99 mmol/day, ≥100 mmol/day) and the magnitude of blood pressure reduction [541]. In another meta-analysis focusing on the relationship between potassium intake and stroke, the risk for stroke was lowest when the potassium intake was 90 mmol (ca. 3500 mg)/day [542]. The WHO Guidelines on Potassium Intake recommends at least 90 mmol potassium intake per day for the purpose of reducing blood pressure and suppressing the risk for cardiovascular diseases [535]. Regarding potassium intake by Japanese (age 20 and over), the National Health and Nutrition Survey in 2017 reported 2382 mg for men and 2256 mg for women [536]. In view of the target of daily potassium intake (3000 mg or more) proposed in the "Dietary Nutrient Intake Standards for Japanese 2015" (Ministry of Health, Labour and Welfare) [543], more active potassium intake is recommended. However, for obese individuals and diabetic patients, intake of fruits needs to be kept within the range of proper energy intake. According to the Diabetes Management 2016, fruit intake should not exceed about 1 Unit (80 kcal) per day (one piece of banana, about a half of apple) [544]. For patients with chronic kidney disease (CKD), potassium intake needs to be

restricted (≤2000 mg/day at stage 3b and ≤1500 mg/day at stage 4 or higher) [545], and appropriate guidance about vegetable/fruit intake is needed. Recently, usefulness of the urinary sodium/potassium ratio as an indicator of the cardiovascular risk was reported, and it was suggested that the sodium/potassium ratio determined from frequent measurements of spot urine samples can serve as a simple and highly reliable indicator [546]. In Japan where salt intake is high but potassium intake is low, we may consider it important to provide guidance on salt reduction plus active intake of potassium.

Reports are available on the hypotensive efficacy of dietary patterns rather than individual nutrients taken from foods. Among others, sufficient evidence has been reported on DASH (Dietary Approach to Stop Hypertension), which is rich in vegetables, fruits and low fat dairy products and poor in saturated fatty acids and cholesterol, and its combination with salt reduction program (DASH-sodium diet) [414, 530]. In addition, hypotensive efficacy has been reported with the dietary patterns rich in olive oil and polyunsaturated fatty acid, such as Mediterranean diet and Nordic diet, as well as the dietary style rich in seafood, grains, vegetables, fruits and beans and poor in meat [547]. The traditional Japanese dietary pattern is close to these dietary patterns and will provide a necessary dietary style if combined with a salt reduction program.

3. MAINTAINING A PROPER BODY WEIGHT

In Japan, individuals are judged as obese if the BMI ([body weight (kg)]/[height (m)]^2) is ≥25 kg/m^2 [548]. According to the National Health and Nutrition Survey in 2017, the percentage of obese individuals was higher than 25% in all age groups of men over 20 years. Among others, the percentage of obese individuals was 30% or higher at age 30–69. In women, on the other hand, the percentage of slim individuals is high at low ages and the percentage of obese individuals increases with age, recording 20% or more at age 50 and over [536].

There is definite evidence for the association between obesity and increased incidence of hypertension. Their causal relationship has been shown in many cohort studies in Japan [549–551] and overseas [552–559]. It has been estimated that the risk for onset of hypertension is 1.5–2.5 at BMI 25.0–29.9 kg/m^2 (if risk at BMI<20 kg/m^2 is 1). High BMI [552–554, 556, 557, 559] and weight gain over time [549, 558] are significant risk factors for onset of hypertension. According to NIPPON DATA, the degree of obesity's contribution to hypertension rose from 11 to 27% in men and from 19 to 26% in women during the 30-year period (1980–2010) [560]. This change reflects an increased prevalence of metabolic syndrome, and the results of sub-analysis indicate that hypertension and elevated blood pressure are the most frequent factors constituting the metabolic syndrome. It is particularly noteworthy that the incidence of hypertension is higher in individuals with greater weight gain during the period from youth to middle/advanced age. The prevalence of metabolic syndrome among the citizens aged 40 and over was 26% for men and 10% for women [35]. Furthermore, cohort studies demonstrated a 1.5- to 2.4-fold risk for onset of or death from cardiovascular diseases in the metabolic syndrome group compared with the group without metabolic syndrome [35–37]. Of the obese children in latter years of elementary school and junior high school, 3–5% had hypertension, and the prevalence of hypertension among these children became higher as obesity progresses [561]. Because pediatric hypertension and obesity can often lead to adulthood hypertension and obesity [562], early corrective actions are needed.

Regarding the hypotensive effects of weight reduction, it has been estimated in a meta-analysis that a 1.0 kg weight reduction lowers systolic blood pressure (SBP) by about 1.1 mmHg and diastolic blood pressure (DBP) by about 0.9 mmHg [563]. A recent meta-analysis also revealed significant blood pressure reduction (−4.5/−3.2 mmHg) following a 4 kg weight reduction [531]. A study of obese Japanese also demonstrated significant blood pressure reduction was achieved by 3% or more weight reduction [564], suggesting that overall lifestyle improvement and weight reduction by means of salt reduction, exercise and diet therapy should be first attempted in the management of obese hypertensive patients. Because obesity can be complicated not only by hypertension but also by abnormal glucose/lipid/uric acid metabolism, coronary artery disease, cerebral infarction, fatty liver/liver cancer, abnormal menstruation, pregnancy-associated complications, sleep apnea syndrome, obesity-related hypoventilation syndrome, orthopedic disease and obesity-related nephropathy [548], these conditions need to be taken into account during management of obese hypertensive patients. Among others, obesity-related kidney disease [565, 566] is directly associated with hypertension, and intense obesity can cause proteinuria and renal dysfunction. Thus, obesity itself can serve as a factor causing aggravation of renal function [567]. Also in Japan, 10-year follow-up of 123764 inhabitants having received local health screening at age 40 and over identified obesity as a risk factor for onset of proteinuria in both men and women and as a risk factor for estimated glomerular filtration rate (GFR) reduction in women [22]. Body weight control is importance because aggravation of renal function can make hypertension severer.

In addition to BMI, which is calculated from body weight, judgment of visceral fat volume (a factor constituting the metabolic syndrome) is important. The waist circumference corresponding to a visceral fat volume of 100 cm^2 as measured by horizontal abdominal CT scan at the umbilical level has been reported to be 85 cm in men and 90 cm in women [568]. In recent years, a method for judging

visceral fat volume with relatively high accuracy without exposure to radiation has been developed, such as the abdominal BIA method using bioelectrical impedance analysis (BIA) [569, 570] and the dual impedance method [571]. In the near future, abdominal visceral fat will be adopted as another test item for general health checkup, in addition to abdominal circumference measurement. Like obesity, excessive visceral fat accumulation is considered to cause blood pressure elevation by abnormal glucose/lipid metabolism and increased fat tissue angiotensinogen expression [572] as well as via insulin resistance. Furthermore, it can cause progression of atherosclerosis and increase of thromboembolism by hypoadiponectinemia [573] and increase in plasminogen activator inhibitor [574]. It is considered that within the accumulated visceral fat, infiltration of immunocompetent cells takes place and increase in inflammatory cytokines (TNF-α, IL-6, saturated fatty acid) and chemokine (MCP-1) occurs, resulting in formation of a base for various metabolic abnormalities. Individuals showing an increase in visceral fat requires guidance as to daily living towards reduction of visceral fat even when obesity with BMI ≥25 kg/m^2 is absent.

Obesity and visceral fat accumulation syndrome correlate closely with various lifestyle-related diseases, and alleviation of obesity and visceral fat by weight reduction is useful in improving each factor associated with lifestyle-related diseases. However, there is no definite evidence supporting that such measures lead to achievement of the final goal of treatment, i.e., reduction in the incidence of or mortality from cardiovascular diseases. However, in studies involving intervention with salt reduction programs or exercise therapy, these measures may manifest weight reducing effects in addition to the effects in improving the target parameters of intervention, leading to reduction of the morbidity and mortality.

For hypertension associated with obesity, Ca channel blockers (CCBs), angiotensin II receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, low-dose thiazide diuretics and β-blockers are used as major antihypertensive drugs. It is necessary to use ARBs and ACE inhibitors (drugs that alleviate abnormal glucose metabolism and insulin resistance likely to complicate obesity) in such patients, but little evidence is available concerning differences in efficacy among antihypertensive drugs in the absence of a clinical study involving only obese hypertensive patients. However, since many large-scale clinical studies on antihypertensive drugs involve obese subjects as about 30% of all subjects, reference should be made to the data from such studies for the time being. The goal of antihypertensive treatment in obese hypertensive patients should be initially set equal as the goal of antihypertensive treatment in general. Concerning body weight control in people during late senility (aged 75 and over), it needs to be borne in mind that body weight cannot be used as an indicator because there are cases showing excessive visceral fat in the abdominal region despite weight loss caused by sarcopenia-associated skeletal muscle mass reduction. In patients with sarcopenia associated with hypertension, reduction in physical activity level and weight loss are associated with the subsequent frail tendency and it is recommended to maintain a proper body weight by mild resistance exercise and nutritional therapy [575].

In patients with intense obesity (BMI ≥35 kg/m^2 in Japan) complicated by disease attributable to intense obesity (e.g., hypertension, diabetes mellitus and sleep apnea syndrome), improvement in blood pressure control following surgery for obesity (Roux-en-Y) has been reported [576].

4. EXERCISE THERAPY

The hypotensive effects of aerobic persistent dynamic exercise has been established by many meta-analyses [532, 577]. The ACC/AHC 2013 Guidelines on Lifestyle Management to Reduce Cardiovascular Risk states, on the basis of the results of meta-analyses reported in from 2001 to 2008, that exercise therapy is expected to lower SBP by 2–5 mmHg and DBP by 1–4 mmHg [578]. Reports of meta-analysis have been published, demonstrating that an increase in physical activity resulted not only in blood pressure reduction but also in reduction of body weight, bodily fat and waist circumference [579], improvement in insulin sensitivity [579], suppression of the onset of type 2 diabetes mellitus [579], improvement in serum lipid profile, maintenance of skeletal muscle mass (prevention of sarcopenia), prevention and alleviation of articular disease [580], increase in physical performance by increased oxygen uptake, primary prophylaxis of mental health disturbance [581] and prevention of dementia [579]. Furthermore, reduction in physical activity increases the incidence of cardiovascular diseases, and maintenance or increase of physical performance by continued exercise lowers the prevalence of various chronic diseases [582] and death rate [583]. Therefore, appropriate exercise therapy is strongly recommended as one of the means for lifestyle modification in hypertensive patients.

Aerobic persisting dynamic exercise like rapid walking, step exercise, slow jogging and running has been recommended for prevention and treatment of lifestyle-related diseases such as hypertension, dyslipidemia, abnormal glucose metabolism and obesity [577, 578]. The recommended intensity of exercise is about 40–60% of maximum oxygen uptake [578]. This corresponds to the Borg scale score 12 to 13 (“slightly hard”). In practice, the recommendation by the American College of Sports Medicine (ACSM)/AHA for general population (aged 18–65) also

describes the intensity to be about 40–60% of maximum oxygen uptake. However, there is a report that mixture of high intensity exercise and moderate intensity exercise is more useful in reducing the incidence of cardiovascular diseases [584]. Thus, no final conclusion has been reached yet about the intensity of effective exercise. However, exercise with high intensity (75%VO_{2max}) is dangerous since blood pressure increases markedly during such exercise in hypertensive patients, resulting in activation of the endogenous hypertensor system (sympathetic nerve system and renin–angiotensin system) after the exercise [585]. If safety is considered, the intensity of exercise should be set at moderate or less in hypertensive patients.

Blood pressure begins to decrease about 4–5 mmHg immediately after transient exercise and the hypotensive effect remains to be seen for about 22 h [586]. Furthermore, there is a report that the magnitude of blood pressure reduction after acute exercise correlated with that after chronic exercise [587]. For this reason, it has been recommended that exercise should be performed periodically (for 30 straight minutes or more every day, if possible) [588]. The ACSM/AHS recommendation to the general population states that each session of exercise should last for at least 10 min and that exercise should be done for 40 min or more in total per day [584]. Rather than persisting dynamic exercise alone, its combination with supplementary exercise (resistance exercise and/or stretching) is useful because it is effective as a means of maintaining skeletal muscle mass, preventing osteoporosis, lower back pain and knee pain [580] and improving the range of motion (ROM) and function of joints. Reports are available on several meta-analyses demonstrating significant hypotensive effects of resistance exercise alone [589, 590]. However, its evidence level is low because the variation in the absolute value of hypotensive effects was large among studies.

The WHO positioned shortage of physical activity as the fourth leading risk factor (6%) for global death, and set forth the exercise guidelines for each age group in the Global Recommendations on Physical Activity for Health (2010) [591]. In Japan, on the basis of such WHO recommendations, the "Physical Activity Criteria for Health 2013" was recommended [592]. According to that guidance, individuals with health checkup data within the criterion range are recommended to perform physical activity of any intensity for 40 min or more every day at age 65 and over and to perform physical activity of 3 Mets or higher intensity for 60 min or more every day at age 18–64.

Exercise therapy is advised for patients with grade II or less severe hypertension without cardiovascular diseases (patients with grade III or severer hypertension should perform exercise therapy after blood pressure has been lowered). High-risk patients, such as those having complication by cardiovascular diseases, should receive prior medical check, to set an appropriate exercise load level and to take actions such as restriction or prohibition of exercise as needed. Although exercise should not be restricted simply because of advanced age, prior medical check is indispensable when older patients perform exercise therapy [579].

Primarily in the United States, the view "Exercise is Medicine (EIM)" has been proposed and applied clinically. This does not simply involve exercise therapy but recommends safety management of physical activity and exercise, exercise therapy and exercise programs as healthcare, with a goal set at achieving and improving health management by cooperation among healthcare staff members (physicians, affiliated healthcare professionals and exercise leaders). It is necessary to introduce the concept EIM to Japan and to promote exercise as a healthcare program more actively.

5. REDUCTION OF ALCOHOL INTAKE

Habitual alcohol consumption can lead to an increase in blood pressure [533, 593, 594]. Heavy drinking induces hypertension, and can also cause stroke, alcoholic cardiomyopathy, atrial fibrillation and nocturnal sleep apnea, as well as cancer, increasing the mortality rate. However, many epidemiological studies indicated a J-shaped or U-shaped relationship between the volume of alcohol and the risk for cardiovascular diseases, demonstrating that the risk for myocardial infarction was lower in moderate drinkers than in nondinkers [594–598]. Regarding cerebrovascular disease, it has been shown that hemorrhagic stroke increases linearly as alcohol intake increases and a J-shaped relationship is noted between ischemic stroke and alcohol intake [594, 599]. It has been reported that the risk for CKD is also lower in drinkers than in nondinkers [600, 601]. The relationship between the volume of alcohol and the overall mortality was shown to be J-shape [594, 602, 603], but a recent meta-analysis did not confirm the reduction in mortality among moderate drinkers [598].

A single intake of alcohol causes a decrease in blood pressure that is sustained for several hours [604], but chronic alcohol consumption increases blood pressure. It has been reported that restriction of alcohol intake is followed by a decrease in blood pressure in 1–2 weeks [605, 606]. A meta-analysis of clinical studies also showed the hypotensive effects of alcohol restriction although the reduction in blood pressure was only 3/2 mmHg [533]. Studies using ambulatory blood pressure monitoring (ABPM) revealed that alcohol restriction increased the nighttime blood pressure despite reduction in morning and daytime blood pressure and resulted in a small change in mean 24-h blood pressure [607, 608]. In management of hypertension, drinking, in terms of ethanol intake, should be restricted to 20–30 mL (equivalent to 180 mL of *sake*, 500 mL of beer, 90 mL of *shochu*, a double

whisky and 2 glasses of wine)/day or less in men and to 10–20 mL per day or less in women.

6. SMOKING CESSATION

Although smoking is an established risk for cardiovascular diseases, the relationship between smoking and blood pressure remained unclarified for a long period of time. It has recently shown that smoking a cigarette causes an increase in blood pressure persisting for 15 min or more [609]. Acute effects of smoking include stimulation of sympathetic nerve activity, increases in oxidative stress and vasoconstriction [610], and atherosclerosis has been reported as a chronic effect of smoking [611]. These effects are considered to be closely involved in the onset of hypertension.

Several cross-sectional studies demonstrated a relationship between habitual smoking and hypertension [612–614], while there are also reports that blood pressure is lower in smokers [615, 616]. Furthermore, it has been reported that blood pressure increases after smoking cessation [617–619], and weight gain after smoking cessation may be associated with such a change. During blood pressure management after smoking cessation, care needs to be taken of weight gain due to changes in dietary style.

Meanwhile, two prospective cohort studies revealed association of smoking with the onset of hypertension. When more than 28,000 American women without hypertension were followed for about 10 years, the incidence of hypertension was high among smokers and significantly high among smokers consuming 15 cigarettes or more per day [620]. When about 13,000 men without hypertension were followed for 14.5 years, the incidence of hypertension was significantly higher in individuals having a history of smoking than in nonsmokers [621]. The risk for onset of hypertension was higher in individuals with SBP less than 120 mmHg or DBP less than 80 mmHg. Smoking increases the risk for cardiovascular diseases not only by inducing hypertension but also directly without being mediated by hypertension. Still more, it serves as an independent risk factor for cancer and respiratory disease as well. Therefore, smoking cessation is very important.

The influence of smoking is considered to reach surrounding people as well, and several reports have been published concerning the relationship between passive smoking and hypertension. There is a report that passive smokers have higher 24-h blood pressure and a higher prevalence of masked hypertension [622]. Recent cross-sectional studies in China and Korea demonstrated a higher prevalence of hypertension among women due to passive smoking at home [623–626]. Like in Japan, the percentage of smokers among women is low in China and Korea but the percentage of smokers among men is high in these countries, leading to identification of passive smoking by women at home as a social issue. Whether passive smoking is responsible for hypertension needs to be proven by prospective cohort studies. Regarding the influence of electronic tobacco on blood pressure, no report is available and this is an open issue.

When providing guidance for smoking cessation, "Guidelines on Smoking Cessation" [627] and "Standard Manual for Treatment with Smoking Cessation" [628], prepared by joint research groups involving professional societies, deserve reference. As needed, use of drugs assisting smoking cessation should be considered. If certain requirements are satisfied, the guidance for smoking cessation is covered by health insurance.

7. OTHER LIFESTYLE MODIFICATIONS

Exposure to cold increases blood pressure, which, consequently, is increased during winter. The cardiovascular mortality rate during winter is greater when protective measures against the cold are inadequate [629]. Therefore, the homes of hypertensive patients should be adequately heated in winter, with particular attention to heating of the toilet, bathroom and dressing room, which is often disregarded in Japan. In 2013, the results from a 3-year follow-up study of coldness-caused blood pressure elevation were reported, demonstrating an inverse correlation between atmospheric temperature and blood pressure and the need of particular care on cold days and for men, slim people and drinkers during hypertension management [630].

Regarding the relationship between emotional stress and blood pressure, a recent meta-analysis indicated that the incidence of hypertension is increased two fold or more by mental/social stress [532, 631]. Hypertensive patients experience two-fold or more stress compared with normotensive individuals [631]. Effectiveness of Yoga, meditation and biofeedback in stress control was suggested, but the evidence was not strong [588, 632–634].

The influence of sleep disorder on health has been pointed out by epidemiological studies [635–637] and several review papers on such studies have been published [638, 639]. Sleep disorder stimulates the activity of the sympathetic nerve system and the hypothalamus– pituitary–adrenal system and alters the metabolism, diurnal variation, inflammation, etc., resulting in long-term impacts expressed as onset of hypertension, dyslipidemia, cardiovascular diseases, diabetes mellitus and weight gain. There is also a report about a difference between men and women, demonstrating that the blood pressure elevation due to moderate or severer sleep apnea syndrome was evident in men but absent in women [640]. According to a report, a combination of several factors, such as short sleeping hours, shift working and insufficient holidays, is involved in new onset of metabolic syndrome, including hypertension [641].

The style of bathing (water temperature, bathroom temperature, whether soaking in hot tub, duration and

frequency of bathing) differs greatly among countries. From Japan, it has been reported that the central blood pressure decreased following bathing [642] and that the diurnal variation of blood pressure was enlarged by bathing or drinking, resulting in lower blood pressure after supper and at bedtime [315].

Reports are available about the relationship of constipation to the onset of cardiovascular diseases and chronic renal failure [643, 644]. As straining to defecate increases the blood pressure, guidance for the prevention of constipation should be given, and, if necessary, laxatives should be administered.

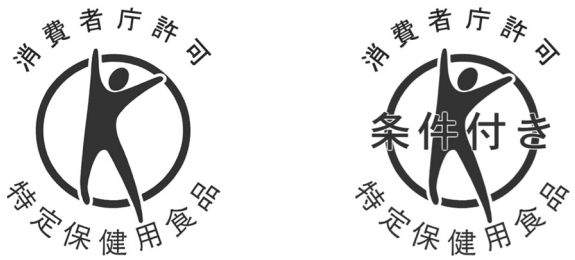
Regarding the relationship between sexual intercourse and hypertension, problems in one's sex life related to antihypertensive medication have been reported, but there is no consensus of view about this topic and further studies are needed [645]. Meanwhile, recent studies demonstrated that the influence of blood pressure on woman sex life was not large [646, 647]. Considering that sexual intercourse increases blood pressure in men, hypertensive patients with cardiovascular diseases should refrain from vigorous sexual activity.

8. COMBINED MODIFICATIONS OF LIFESTYLE AND OTHER FACTORS

Influence of single lifestyle correction on blood pressure has been reported and studies on correction of composite lifestyles have also been conducted. Many of such studies were designed to evaluate the efficacy of intervention into exercise and diet. In normotensive women, intervention for exercise and diet resulted in alleviation of marked blood pressure elevation immediately after exercise, accompanied by improvement in pulse wave velocity (PWV) and alleviation of plasma nitric oxide (NO) level elevation [648].

The DASH [414] and DASH-Sodium [530] studies suggested that combined improvements in diet facilitate a marked decrease in blood pressure. Also, the TONE study [649] showed that a combination of salt reduction and weight loss is more likely to reduce blood pressure and prevent cardiovascular diseases even when they are performed less rigorously. A more marked decrease in blood pressure has been reported to be achieved by a combination of salt intake reduction, weight loss, exercise, restriction of alcohol intake and a DASH diet [650]. Therefore, lifestyle modifications should be started in childhood to prevent lifestyle-related diseases, including hypertension.

Several studies have been carried out concerning the relationship between presence/absence of awareness of hypertension and improvement in lifestyle, demonstrating a tendency for selection of salt intake reduction in by individuals aware of hypertension although unsatisfactory aspects as to weight control were additionally shown [651, 652].



Food for specified health uses (FOSHU) (including Reduction of disease risk FOSHU / standardized FOSHU) (left) and Qualified FOSHU (right)

Fig. 4-2 Foods for specified health uses

It was recently suggested that measures against lifestyle-based diseases on the basis of cognitive behavioral therapy are important [653]. Concerning treatment of hypertension, the nation-wide plan of promoting actions by extensively disseminating the awareness that onset/progression of illness can be prevented does not seem to have been sufficiently achieved. To achieve this, improvement/reform in both patients and healthcare providers may be required. For patients, improvement in lifestyle and adherence to drug intake are required [111, 236]. For healthcare providers, overcoming the clinical inertia is required. Composite attempts in accordance with guidelines are needed. Thus, establishment of a guidance strategy, including cognitive behavioral therapy by a multidisciplinary team is essential.

9. FOODS FOR SPECIFIED HEALTH USES (FOSHUS)

FOSHU refers to foods to be ingested for specified health purposes, permitted according to Clause 1, Article 26, of the Health Promotion Act or approved according to Clause 1, Article 29, of the same act (Commissioner of the Consumer Affairs Agency), carrying a label describing that consumption of the food contained in the package may achieve the health purpose. Food with health function that is not substantiated by scientific evidence that meets the level of FOSHU, or food with certain effectiveness but without the established mechanism of the effective element for the function, will be approved as qualified FOSHU. They are expressed with marks shown in Figure 4-2. The hypotensive effects of foods considered effective for blood pressure control are often based on an ACE-inhibiting activity, but the indicated 'recommended daily intake' should be strictly observed when consuming these foods. In addition, physicians must instruct pregnant women and patients with renal dysfunction to pay attention to the recommended daily intake. Patients must also be informed that the intake of FOSHU cannot be a substitute for antihypertensive medication. A warning to consult a physician should be given to patients already on antihypertensive medication if they wish to use such foods. In July 2015, the labeling system for "functionality labeled foods" (based on a prior report to the

regulatory authority) was started, but these guidelines do not recommend such foods.

Information on FOSHU is available on the homepage of the Consumer Affairs Agency [654] or the National Institute of Health and Nutrition [655].

CQ4 IS THE SALT REDUCTION GOAL LESS THAN 6 G/DAY RECOMMENDED FOR HYPERTENSIVE PATIENTS?

►Setting a salt reduction goal at less than 6 g/day for hypertensive patients is strongly recommended.

Recommendation Grade 1 Evidence Level A

EVIDENCE SUMMARIZATION

In a meta-analysis of 185 interventional studies designed to evaluate the hypotensive effect of salt reduction, salt reduction (reduction of mean urinary salt excretion from 11.8 g/day to 3.9 g/day) lowered the blood pressure of hypertensive patients by 5.51/2.88 mmHg, and sub-analysis confined to Asian patients also revealed a blood pressure reduction by 7.75/2.68 mmHg. Also in other meta-analyses, effectiveness in lowering blood pressure was shown following salt reduction to less than 6 g/day.

In the combined analysis of the data from 4 studies, including PURE Study, a J-shaped relationship was observed between the salt intake level and the cardiovascular events and total death. Problems in the study method (e.g., use of estimated values based on a single spot urine sample) were pointed out about these studies, although the study results do not rule out the possibility that excessive salt reduction is hazardous. On the other hand, in a study evaluating long-term prognosis by multiple measurements of 24-h pooled urine samples at the start of observation, a linear relationship was noted between salt reduction level and total death. Taken together, these results suggest that salt reduction with a goal set at less than 6 g/day is useful.

COMMENTARY

Association of excessive salt intake with blood pressure elevation has been pointed out since many years ago in observational studies such as INTERSALT [64]. The hypotensive effect of salt reduction has been demonstrated in interventional studies, including DASD-Sodium [530] and TONE [415]. In a meta-analysis of 185 interventional studies designed to evaluate the hypotensive effect of salt reduction, salt reduction (reduction of mean urinary salt excretion from 11.8 g/day to 3.9 g/day) lowered the blood pressure of hypertensive patients by 5.51/2.88 mmHg, and sub-analysis confined to Asian patients (9 studies) also revealed a blood pressure reduction by 7.75/2.68 mmHg [656]. In a meta-analysis of 8 interventional studies of a hypertensive population, including prehypertension cases, analysis was conducted by dividing the salt intake level into 4 categories: low (<5.3 g/day), relatively low (5.3–9.2 g/day), relatively high (9.3–14.5 g/day) and high (>14.5 g/day). In that analysis, blood pressure showed a dose-dependent change, with 6.87/3.61 mmHg reduction recorded following salt reduction to 4.5–8.2 g/day (Figure CQ4-1) [657]. Also in other meta-analyses, effectiveness in lowering blood pressure was shown following salt reduction to less than 6 g/day [658, 659]. On the basis of these reports, the Evidence-Based Nutrition Practice Guidelines for the Management of Hypertension in Adults prepared by the Evidence Analysis Library® (USA) proposed a view that salt reduction to 3.8–5.1 g/day lowers blood pressure by 12/6 mmHg at maximum [660]. Thus, salt reduction with a goal set at less than 6 g/day for hypertensive patients is supported by adequate evidence.

Salt reduction with a goal set at less than 6 g/day is expected to suppress the onset of or death from cardiovascular events by hypotensive effects, but no long-term interventional study evaluating the direct relationship of salt intake level to cardiovascular events, cardiovascular death or total death has been reported. In the combined analysis of the data from 4 studies, including PURE Study based on the values estimated from a single spot urine sample, a J-shaped relationship was observed between the salt intake level and the cardiovascular events and total death, and a significant increase of combined primary endpoints (total death, myocardial infarction, stroke and heart failure) was noted in the group with sodium intake less than 3 g/day (equivalent to about 7.6 g salt/day) compared with the group with sodium intake 4–5 g/day (equivalent to 10.2–12.7 g salt/day) [661]. However, in a prospective observational study based on the salt intake level calculated with the Food Frequency Questionnaire (FFQ) in subjects at high cardiovascular risk (83% = hypertensive patients), a reduction in total death was noted in the salt reduction group (less than 5.8 g salt/day), and the incidence of cardiovascular events (stroke, myocardial infarction, cardiovascular death) rose by 72% in the group with a larger salt intake at one year later [662]. In a meta-analysis of the data from 14 cohort studies and 5 interventional studies, the incidence of stroke, death from stroke and death from coronary artery disease was higher in the group with salt intake ≥5.1 g/day than in the group with salt intake <5.1 g/day [659]. Furthermore, a linear relationship between salt intake level and total death was noted in the survey of salt intake level (evaluated using 24-h pooled urine samples 3–7 times during the interventional study lasting for 1.5–4 years) and total death during the follow-up period (23–26 years) among prehypertensive cases [663]. One possible factor resulting in such contradictory results in observational studies is the large bias in the low value range or the high value range of urinary

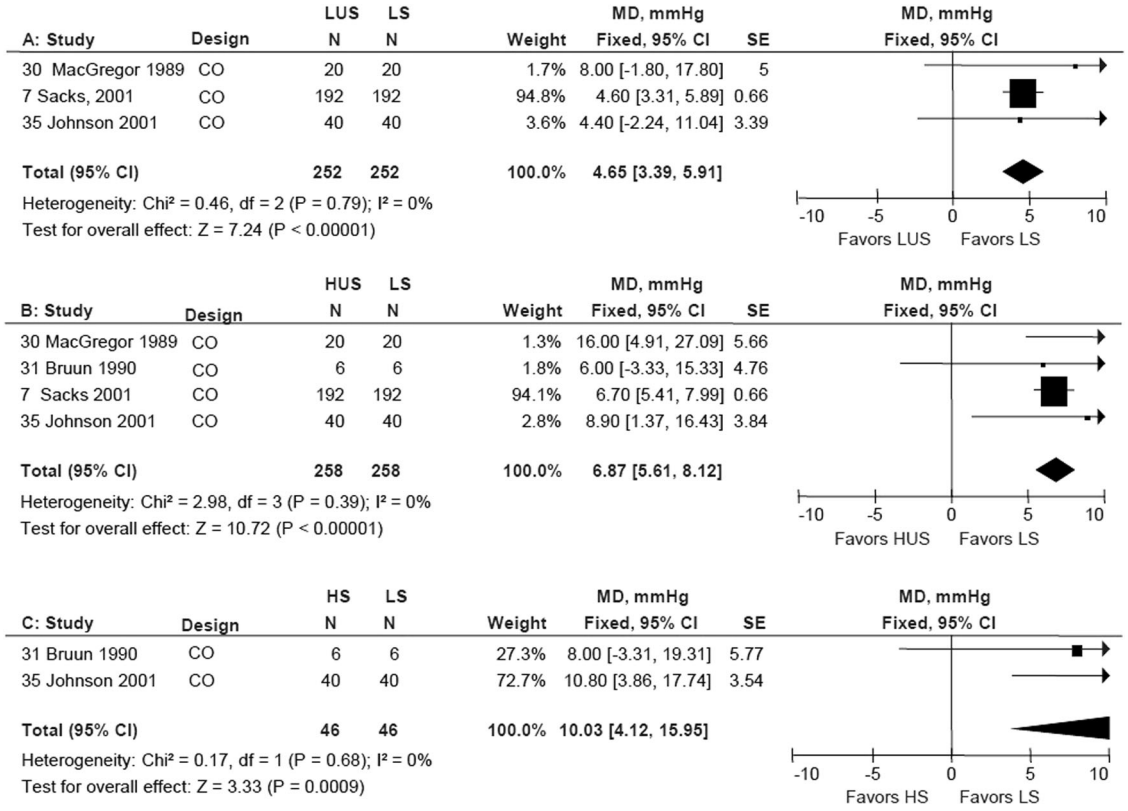


Fig. CQ4-1 Meta-analysis of interventional studies on salt reduction and blood pressure (systolic pressure) reduction in hypertensive patients [657]. A: Salt intake level "relatively low" vs "low", B: Salt intake level "relatively high" vs "low", C: Salt intake level "high" vs "low". Low: Na<2070 mg (salt<5.3 g), relatively low: Na 2070–3657 mg (5.3–9.2 g), relatively high: Na 3657–5700 mg (9.3–14.5 g), high: Na>5700 mg (salt>14.5 g). CO: cross-over, Fixed: fixed effect model. (Source: Ref. 657) Reproduced by permission of Oxford University Press on behalf of the American Society for Nutrition)

salt excretion determined by Kawasaki Method using spot urine samples (employed in PURE Study) or the possibility of so-called "reverse causation" in observational studies based on single measurement [664, 665]. Because there is no long-term interventional study using the salt intake level evaluated with 24-h pooled urine as an indicator, the evidence available is not adequate for the relationship between salt intake level and suppression of events. However, adequate evidence is available for the view that salt reduction with a goal set at <6 g/day is effective in lowering blood pressure in hypertensive patients. Therefore, it is recommended to adopt the salt reduction goal of <6 g/day because this is expected to suppress the onset of cardiovascular events as well as cardiovascular death by hypotensive effects.

LITERATURE SEARCH

In addition to the papers quoted in the JSH2014, other papers related to CQ were identified by the literature search with PubMed (including Cochrane Database of systematic review [SR]) for the period between January 2013 and June 2017.

No new SR was conducted because the risk for biases was considered to be small according to the results of the bias evaluation conducted during the adopted SR.

Q5 ARE HYPOTENSIVE EFFECTS POSSESSED BY FOODS FOR SPECIFIED HEALTH USES (FOSHUS)?

- FOSHUs related to hypertension contain peptide, Tochu (Eucommia) leaf glycoside, acetic acid, ☒-aminobutyric acid and flavonoid as functional components.
- Regarding the clinical studies needed before application for registration of FOSHUs, the duration of studies required is shorter and the sample size required is smaller than those required for application for approval of antihypertensive drugs.
- FOSHUs contain components with hypotensive effects but sufficient hypotensive effects are difficult to expect of FOSHUs.
- Explanation about FOSHUs should be given that they do not serve as a substitute for hypotensive drugs and

not guiding the patients to have excessive expectation of their hypotensive effects, and their intake should not be actively recommended.

COMMENTARY

Under the system on foods with health function, it is permitted to describe the function of some particular nutritional components of food products specified by the government in the product's label if such products are expected to achieve health-related purposes (useful in maintaining or promoting health) and satisfy the standards set by the government. Foods with health function include "foods for specified health uses" (FOSHUs) approved individually by the Consumer Affairs Agency, "foods with nutritional function" self-accredited by the manufacturer/distributor in accordance with the Food Labeling Standards and "function-labeled foods" registered by a report to the regulatory authority (begun in April 2015).

"Foods with nutritional function" are utilized for replenishing specific nutrients and their label describes the function of nutrients contained and precautions. One such product related to blood pressure is "Potassium," whose label provides the following information: (1) information about nutritional function ("a nutrient needed to maintain normal blood pressure"), and (2) precautions ("Observe the recommended daily intake level, because excessive intake of this product does not accelerate illness healing or promote health" and "Avoid intake of this product if your renal function is compromised").

"Function-labeled foods" are products whose functionality based on scientific evidence is described in the label at the responsibility of the manufacturer/distributor. This type of food needs to be registered with the Commissioner of Consumer Affairs Agency before marketing by reporting the information on its safety and the evidence for functionality, but this type does not under the approval process based on clinical study data or the like. This category of foods with health function was introduced to increase alternatives for food products providing easily understandable information on functionality in the label and to enable selection of products by consumers without misunderstanding of the function of products, because acquisition of approval to FOSHUs is difficult. However, there is controversy over objective reliability of these products, and their intake for the purpose of hypotensive effects is not recommendable.

The label for FOSHUs related to hypertension provides the following information about functionality: (1) "This product contains xxx and is a food suitable for individuals whose blood pressure is relatively high"; (2) "This product is not intended for therapeutic use. Consult your physician if you are receiving treatment of hypertension"; and (3) "Recommended daily intake level." To date, slightly less than 100 products have been approved as FOSHUs, containing peptide, Tochu leaf glycoside, acetic acid, γ-aminobutyric, and flavonoids as functional components.

Peptide includes sardine peptide (valyl-tyrosine), wakame seaweed peptide (phenyl-alanyl-tyrosine, valyl-tyrosine, isoleucyl-tyrosine), royal jelly peptide (valyl-tyrosine, isoleucyl-tyrosine, isoleucyl-valyl-tyrosine), casein dodecapeptide, sesame peptide (leucyl-valyl-tyrosine) and lactotripeptide (isoleucyl-prolyl-proline, valyl-prolyl-proline). Because these peptides inhibit ACE and can cause cough, although rarely, during prolonged use, their label includes a precaution about the need of consulting a physician.

Geniposidic acid, which is a Tochu leaf glycoside, is considered to exhibit hypotensive effects by acting as an agonist for the parasympathetic nerves.

Acetic acid reduces the vascular resistance and, according to some reports, has ACE inhibitory activity.

γ-Aminobutyric acid is known to lower blood pressure by the mechanism of suppressing vasopressin secretion or suppressing noradrenaline release from ganglia.

Hyperoside (an Enryu Tea extract called flavonoid or polyphenol), isoquercitrin and cocoa flavonol lower blood pressure by stimulation of NO formation, ACE inhibitory activity or activation of eNOS by antioxidative activity.

The application for approval of foods containing these functionality-related components as FOSHUs needs to be submitted with the following data: (1) data about the health-related purposes of the nutrients contained in the foods for specified health uses and the medical and nutritional data supporting their recommended amounts of daily intake (2) data on safety of the nutrients contained in the foods for specified health uses. The data submitted are required to consist of data in vitro, data in vivo in animals and data from studies in humans. The studies in humans should include a long-term intake study of the product under application conducted at the recommended daily intake level determined on the basis of the prior dose determination study. The tests/studies involve volunteers outside the applicant and are assigned to third party institutions, as a rule. The study design should be placebo-controlled double-blind comparative study. However, the minimum intake period required is about 12 weeks, not long enough to call the study "a long-term study."

Regarding the sample size (number of subjects), the current regulations state: "It is necessary to set the testing method and the subjects sufficient to check for statistically significant differences." However, there is an additional statement in the regulations, saying: "Because the type and magnitude of activity vary depending on the nature of the information to be labeled and the components involved, it is difficult to uniformly set the number of subjects required

corresponding to the type and method of test. It is therefore required to secure the number of subjects necessary for a given test corresponding to the extent of the product's activity. If the thus set number of subjects is not large enough to allow valid statistical test of significance, the data collected will be treated as reported cases."

Under such regulations, the applications submitted for approval of FOSHUs may be composed of applications based on well-designed study data and applications not based on well-designed study data, and it will be difficult to make a definite conclusion about the hypotensive effects of such products because of the presence of confounding factors possibly affecting the hypotensive effects (e.g., the amount of the active ingredient contained and user's background variables). Although the functionality-related components are expected to manifest hypotensive effects, we cannot say definitely whether the products will actually manifest hypotensive effects if we consider the sample size and the test period in comparison to those for the tests conducted during development of antihypertensive drugs.

Therefore, explanation about FOSHUs should be given that they do not serve as a substitute for hypotensive drugs and not guiding the patients to have excessive expectation of their hypotensive effects, and their intake should not be actively recommended.

Chapter 5. Antihypertensive treatment

POINT 5A

1. **The preventive effects of antihypertensive drugs on cardiovascular diseases are determined by the degree to which blood pressure decreases rather than their class.**
2. **Among main antihypertensive drugs, such as Ca channel blockers (CCBs), angiotensin II receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, low-dose diuretics and β-blockers, appropriate antihypertensive drugs should be selected based on compelling indications, contraindications and conditions that require the careful use of drugs and the presence or absence of complications.**
3. **In hypertensive patients without compelling indications, the initial antihypertensive drug should be selected from CCBs, ARBs, ACE inhibitors and diuretics.**
4. **Antihypertensive drugs should be administered once a day, in principle, but it is important to control the blood pressure over 24 h. Twice-a-day administration is necessary in some cases.**
5. **A gradual reduction in blood pressure is necessary in hypertensive patients in general, but the target control level should be achieved within several weeks in high-risk patients such as those with grade III hypertension and multiple risk factors.**
6. **To achieve the target of blood pressure control, lifestyle modifications and intensified non-drug therapy should be performed. If blood pressure control is poor, two or three drugs should be combined.**
7. **Combination therapy with different classes of antihypertensive drugs exhibits potent antihypertensive effects, and is useful for achieving the target of blood pressure control.**
8. **Among the combinations of two drugs, those of an ARB/ACE inhibitor (ARB or ACE inhibitor) + CCB, ARB/ACE inhibitor + diuretic and CCB + diuretic are recommended.**
9. **Simplification of the prescription using fixed-combination drugs is useful for improving adherence and controlling blood pressure.**

1. BASIC PRINCIPLES FOR THE SELECTION OF ANTIHYPERTENSIVE DRUGS

As blood pressure increases, it is more difficult to control it at the target level by lifestyle modifications alone, and treatment with antihypertensive drugs becomes necessary. The occurrence of cardiovascular diseases can be prevented by reducing the blood pressure with antihypertensive drugs. A meta-analysis of large-scale clinical studies has shown that this effect is proportional to the degree of decrease in blood pressure rather than the class of antihypertensive drug [367, 666]. The antihypertensive drug with the greatest antihypertensive effect and efficacy for various associated conditions should be selected for each hypertensive patient.

1) First-line drugs

Five classes of antihypertensive drugs including CCBs, ARBs, ACE inhibitors, diuretics and β-blockers (including αβ-blockers) have been shown to prevent the occurrence of cardiovascular diseases [236, 367]. For each class of the drug, there are compelling indications, contraindications and conditions that require the careful use of drugs. When these conditions are present, condition-matched antihypertensive drugs should be selected (Tables 5-1, 5-2). In hypertensive patients without specific conditions, the initial antihypertensive drug should be selected from CCBs, ARBs, ACE inhibitors and diuretics.

There is evidence that β-blockers alone or in combination with other drugs are less useful than other drugs with respect to diabetes mellitus-inducing actions [667, 668] and

Table 5-1 Conditions for which major antihypertensive drugs are indicated

	CCBs	ARBs / ACE inhibitors	Thiazide diuretics	β-blockers
Left ventricular hypertrophy	●	●		
Heart failure with reduced ejection fraction		●*1	●	●*1
Tachycardia	● (Non-dihydropyridines)			●
Angina pectoris	●			●*2
Post myocardial infarction		●		●
Proteinuria /CKD with microalbuminuria		●		

*1 Administration should be started at a low dose, and the dose should be gradually increased carefully.

*2 Caution is needed in patients with coronary spastic angina.

Table 5-2 Contraindications for major antihypertensive drugs and conditions requiring careful administration

	Contraindications	Careful administration
CCBs	Bradycardia (non-dihydropyridines)	Heart failure
ARB	Pregnancy	Renal artery stenosis*1 Hyperkalemia
ACE inhibitors	Pregnancy Angioneurotic edema Apheresis with a specific type of membrane/hemodialysis*2	Renal artery stenosis*1 Hyperkalemia
Thiazide diuretics	Condition in which the body fluid levels of sodium and potassium are markedly decreased	Gout Pregnancy Impaired glucose tolerance
β-blocker	Asthma Marked bradycardia Untreated pheochromocytoma	Impaired glucose tolerance Obstructive pulmonary disease Peripheral artery disease

*1 As a rule, ARBs/ACE inhibitors are contraindicated for patients with bilateral renal artery stenosis.

*2 See Section 5 of Chapter 5, "3) ACE inhibitors".

preventive effects on organ damage/cardiovascular diseases especially in older patients [669–673]. Furthermore, the vascular function-improving effects of β-blockers are less marked than those of ACE inhibitors or ARBs [673]. These are primarily based on the results of conventional β-blockers represented by atenolol. No randomized controlled trial (RCT) with β-blockers, such as carvedilol and bisoprolol, has evaluated cerebrovascular mortality, all-cause mortality, hypotension, or bradycardia as an outcome. A meta-analysis showed the antihypertensive actions of bisoprolol in comparison with a placebo, but such actions of carvedilol were not always observed (see CQ6). Another meta-analysis found that the preventive effects of β-blockers on cardiovascular events in patients aged <60 years were similar to those of other classes of drugs [674].

As diuretics, thiazide-type diuretics, such as thiazide diuretics and thiazide analogues, are routinely used. They are effective for salt-sensitive hypertension, including hypertension in older persons [675]. There is evidence on their preventive effects on stroke in the Japanese [676–679]. These drugs are also appropriate for combination therapy with an ARB or an ACE inhibitor. In the COPE Study, diuretics were significantly more useful than β-blockers for combination therapy with a CCB [679]. Thiazide diuretics increase the blood glucose level [680], but the incidence of such metabolic adverse effects decreases at a low dose.

Therefore, CCBs, ARBs, ACE inhibitors or low-dose diuretics should be selected as first-line drugs in hypertensive patients without compelling indications.

2) Use of antihypertensive drugs

The ultimate objective of antihypertensive treatment is to prevent cardiovascular diseases. Once antihypertensive drug therapy has been started, the realization of the target control level should always be borne in mind. However, the reality is unsatisfactory, as various investigations have found that the target is achieved in only approximately 50% of those taking antihypertensive medication [681, 682]. The rate at which the target of blood pressure control can be achieved using a single drug is <40%, being not high [683]. The use of antihypertensive drugs to achieve the target level of blood pressure is shown in Figure 5-1. Antihypertensive drug therapy should be started with a single drug at a low dose. If adverse effects appear or little antihypertensive effect is noted, the drug should be replaced by another class of drug. If the antihiypertensive effect is still insufficient, the dose should be increased or a different class of antihypertensive drug at a low dose should be used concomitantly. In this case, combination

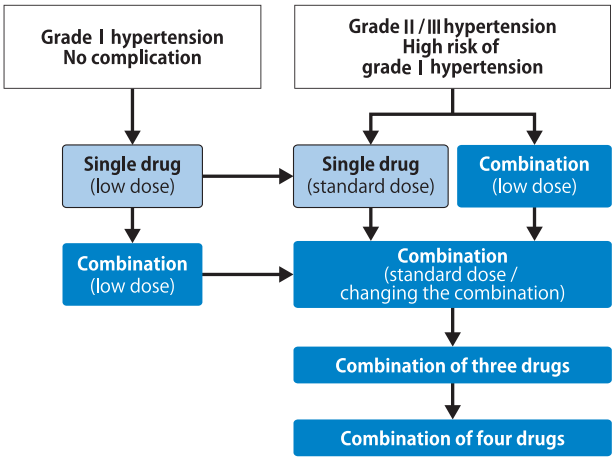
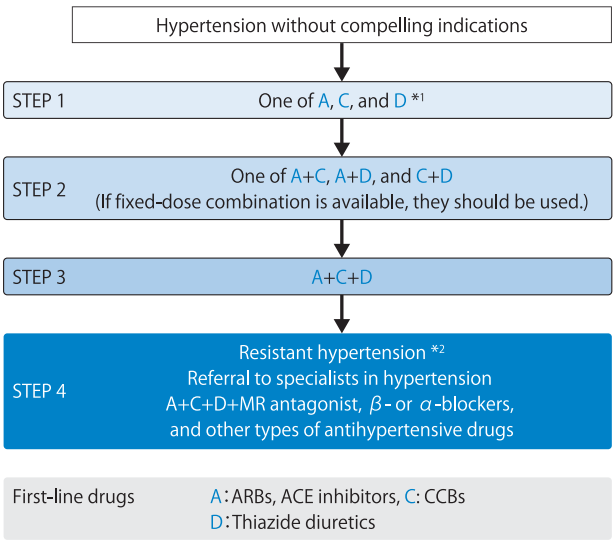


Fig. 5-1 Use of antihypertensive drugs to achieve the target level of blood pressure control



*1 In older patients, administration should be started at half of the standard dose, and the dose should be increased at 1–3-month intervals.
*2 See Section 6 of Chapter 5, 'Strategies for resistant or poorly controlled hypertension'.

Fig. 5-2 Procedures of antihypertensive treatment in the absence of compelling indications

therapy with a different class of antihypertensive drug at a low dose shows more marked antihypertensive effects compared with doubling the dose of the antihypertensive drug [684, 685]. In patients with grade II or severer hypertension (≥160/100 mmHg), antihypertensive medication may be started with a single drug at a standard dose or with a combination of two drugs at low doses [236, 686]. However, fixed-combination antihypertensive drugs as first-line drugs are not covered by health insurance. An increase in the dose of antihypertensive drugs other than ACE inhibitors and ARBs increases the frequency of adverse effects [687]. If the target control level cannot be achieved by combination therapy with two drugs, a combination of three drugs should be introduced. If necessary, four drugs may be used in combination.

The procedures of antihypertensive therapy for hypertension in the absence of compelling indications are shown in Figure 5-2. If a condition for which antihypertensive therapy should be indicated is present, a single, condition-matched antihypertensive drug or combination therapy with other classes of antihypertensive drug may be considered. To facilitate long-term adherence, antihypertensive drugs with once-a-day administration are desirable. Many clinical studies have suggested the importance of 24-h blood pressure control by also paying attention to the out-of-office blood pressure. The effects of many antihypertensive drugs commercially available today do not persist for 24 h if used clinically. If the trough blood pressure measured at home or over 24 h is high, the time of administration may be tentatively changed from morning to evening, the dose split into morning and evening or an additional dose taken in the evening or before going to bed [688, 689]. Recently, the results of a meta-analysis showed that the oral administration of an antihypertensive drug at night reduced the risk of cardiovascular diseases [690].

A gradual rate of blood pressure reduction that achieves the target level in a few months is necessary, because it causes fewer adverse effects. In particular, in older patients in whom the ability to regulate blood pressure is reduced, a rapid decrease should be avoided. However, with patients at a high risk of cardiovascular diseases, there are results indicating that the difference in the rate of blood pressure reduction during the first 1–3 months after commencing treatment affected the subsequent occurrence of disease; [691] therefore, in these cases, the attainment of the target level within several weeks is recommended.

3) Drug interactions

Interactions between antihypertensive drugs may enhance the antihypertensive effect or offset adverse effects in some combinations, but may aggravate adverse effects in others [692]. Particular attention is necessary with regard to the enhancement of the cardioinhibitory effect by a combination of a β-blocker and a non-dihydropyridine (non-DHP) CCB, aggravation of hyperkalemia by a combination of an ARB/ACE inhibitor and an mineralocorticoid receptor (MR) antagonist and an increase in the frequency of withdrawal syndrome by a combination of a central sympatholytic drug and a β-blocker. Interactions between antihypertensive drugs and drugs for the treatment of other diseases include the attenuation of the antihypertensive effects of diuretics, β-blockers, ACE inhibitors and ARBs by nonsteroidal anti-inflammatory drugs, enhancement of the antihypertensive effects of CCBs and β-blockers by histamine H_2-receptor blockers, an increase in the blood digoxin concentration by a combination of digoxin and a

non- DHP CCB, and interactions between DHP CCBs and antifungal/antimicrobial drugs. Furthermore, the antihypertensive effects of DHP CCBs may be reduced when they are combined with rifampicin, phenobarbital, or carbamazepine. The concomitant use of an ARB or an ACE inhibitor with a nonsteroidal anti-inflammatory drug or a diuretic may cause acute renal insufficiency or an excessive decrease in blood pressure, particularly in older patients, with poor water intake-/vomiting-/ diarrhea-/excessive sweating-related dehydration or under restriction of salt intake. A well-known example of food–drug interaction is an increase in the blood concentration of DHP CCBs after their administration following the consumption of grapefruit or grapefruit juice.

Some patients taking sympathetic drugs, antidepressants, anesthetics or antitumor drugs that increase blood pressure as an adverse effect require treatment with antihypertensive drugs (see Section 7 of Chapter 13, Drug-induced hypertension).

4) Dose reduction and withdrawal of antihypertensive drugs

Blood pressure shows seasonal fluctuations [693], and a temporary decrease in the dose or withdrawal may be considered in patients who show a decrease in blood pressure in summer. Conversely, because of the increase in blood pressure in winter, dose elevation or the readministration of the antihypertensive drug becomes necessary in many patients. Even if a normal blood pressure has been maintained for 1 year or more by antihypertensive medication, blood pressure often increases to a hypertensive level usually within 6 months of a reduction in dose or withdrawal of the drug. The percentage of patients in whom blood pressure could be maintained after the withdrawal of antihypertensive medication varies widely among studies from 3 to 74%. The characteristics of patients in whom a normal blood pressure could be maintained even after withdrawal include having grade I hypertension before treatment, a young age, normal body weight, low salt intake, being a nondrinker, using only one antihypertensive drug and having no organ damage [694]. Therefore, withdrawal of antihypertensive medication may be attempted exclusively in patients with grade I hypertension without organ damage or complications on the condition that an appropriate lifestyle is maintained and blood pressure is monitored periodically. However, it cannot be recommended for other hypertensive patients.

2. COMBINATION THERAPY

To achieve the target level of blood pressure control, combination therapy with two or three drugs is performed in many patients. A meta-analysis showed that the antihypertensive effects of a combination of different classes of antihypertensive drug were more marked than those of the double-dose administration of the same drug [684]. Evidence that strict management of blood pressure by combination therapy contributes to the further prevention of cardiovascular events based on large-scale clinical studies is being accumulated, but there is little evidence regarding whether combination therapy decreases the all-cause and cardiovascular mortality rates in comparison with monotherapy; this issue remains to be clarified [695]. The usefulness of combinations of drugs that cancel out each other's adverse effects, such as that of a diuretic and an ACE inhibitor or ARB, is also supported from the point of view of pharmacological actions. Several studies have suggested that combination therapy with an ARB/ACE inhibitor and a CCB [696] and that with an ARB/ACE inhibitor and a diuretic [697] are more useful than that with a β-blocker and a diuretic. Currently, the following combinations are recommended among first-line drugs: (1) an ACE inhibitor or ARB + a CCB, (2) an ACE inhibitor or ARB + a diuretic, and (3) a CCB + a diuretic (Figure 5-3).

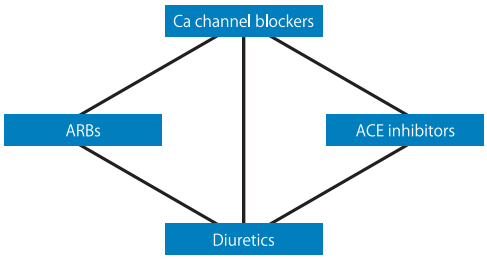


Fig. 5-3 Combination of two drugs

1) Merits of combination therapy

In the RENAAL Study, combination therapy with a CCB and an ARB inhibited progression to end-stage kidney disease (ESKD) [698]. In Japan, several studies have also demonstrated that the enhancement of antihypertensive effects and reduction of proteinuria by combination therapy with an ACE inhibitor or ARB at a standard dose and a CCB are more marked than those by high-dose ARB therapy, and that the incidence of events in the combination therapy group is significantly lower among patients with a history of cardiovascular diseases [699–702]. Furthermore, combination therapy with an ACE inhibitor and a diuretic decreases the incidence of diabetic complications, that of coronary events, cardiovascular mortality rate and total mortality rate in diabetics in comparison with placebo treatment [703].

In patients aged ≥80 years, this combination therapy significantly decreases the stroke-related and total mortality rates [381]. The PROGRESS Study [676], which was conducted as a recurrent stroke inhibition study, showed the

preventive effects of combination therapy with an ACE inhibitor and a diuretic on recurrent stroke.

Thus, a large number of clinical studies have found that antihypertensive treatment with combination regimens decreases the number of events.

2) Combinations of antihypertensive drugs in combination therapy

(1) An ARB/ACE inhibitor + a CCB In the COLM study, in which combination therapy with an ARB and a CCB was investigated in Japan, the antihypertensive effects of this therapy and its preventive effects on cardiovascular events were similar to those of combination therapy with an ARB and a diuretic, and the incidence of adverse events was lower in the former group [704]. In the ASCOT Study, a combination of an ACE inhibitor and a CCB exhibited more potent antihypertensive effects than that of a β-blocker and a diuretic, and prevented cardiovascular events [696]. In type 2 diabetics with albuminuria treated with this combination, a decrease in the estimated glomerular filtration rate (eGFR) was less marked than in those receiving combination therapy with an ACE inhibitor and a diuretic [705]. Furthermore, a meta-analysis of several RCTs, including the above study, showed that combination therapy with an ARB/ACE inhibitor and a CCB more potently protected eGFR/creatinine clearance compared with that with an ARB/ACE inhibitor and a diuretic, exhibiting more marked renoprotective effects [706]. Based on the results of these studies, an ACE inhibitor or ARB should be combined with a CCB in a high-risk group regarding cardiovascular events or late-phase older patients and with a diuretic in those with fluid retention.

(2) An ARB/ACE inhibitor + a diuretic A meta-analysis showed that the 24-h antihypertensive actions of combination therapy with an ARB/ACE inhibitor and a diuretic were similar to those of that with an ARB/ACE inhibitor and a CCB [707]. According to the results of sub-analysis, combination therapy with an ARB and a diuretic more potently reduced the 24-h blood pressure under unrestricted activities compared with a combination of an ARB and a CCB in men, older patients, non-obese patients, and non-diabetics [707]. In the VALUE Study involving high-risk hypertensive patients [691], the preventive effects of combination therapy with a CCB and a diuretic on complicated cardiovascular events were similar to those of that with an ARB and a diuretic.

(3) A CCB + a diuretic A meta-analysis of four RCTs [409, 679, 691, 708] regarding the effects of combination therapy with a CCB and a diuretic showed that this combination significantly decreased the incidences of myocardial infarction and stroke in comparison with combination therapy with a CCB and other drugs, and that the total and cardiovascular mortality rates were similar [709]. In the INVEST Study [710], a non-DHP CCB was used in patients with coronary artery disease, and the preventive effects of combination therapy with a CCB and an ACE inhibitor on total mortality, nonfatal myocardial infarction and nonfatal stroke were similar to those of that with a β-blocker and a diuretic.

(4) An ACE inhibitor + an ARB A meta-analysis showed that combination therapy with an ACE inhibitor and an ARB more markedly decreased the urinary protein level than monotherapy [711], delaying progression to ESKD [712]. However, according to several studies, in the ACE inhibitor + ARB group, the introduction of dialysis was more frequent than in the monotherapy group, with a 2-fold increase in the creatinine level and an increase in the mortality rate [713, 714]. Generally, this combination is not recommended. When selecting this combination, treatment should be started at a low dose, and careful follow-up is needed.

(5) A CCB + a diuretic + an ARB/ACE inhibitor (3-drug combination) If the antihypertensive effects of two-drug therapy are not sufficient, combination therapy with three drugs, that is, an ACE inhibitor/ARB, a CCB and a diuretic, should be performed. Combination therapy with a CCB, a diuretic, and an ARB more markedly reduces the office and 24-h blood pressures compared with any 2-drug combination regimen among these drugs. Furthermore, it was reported that adverse events were similar to those related to 2-drug combination therapy [715].

(6) Combinations with other drugs An MR antagonist is frequently combined with a CCB, a diuretic, and a β-blocker. There is evidence that MR antagonists improve the prognosis of heart failure patients, as demonstrated for ACE inhibitors, ARBs, and β-blockers. In guidelines for the management of heart failure, it is recommended that an MR antagonist should be administered [716, 717]. Therefore, in patients with heart failure, an ACE inhibitor or ARB should be combined with a β-blocker, a diuretic, and an MR antagonist. When combining an ACE inhibitor or ARB with an aldosterone/MR antagonist, the renal function and serum potassium level must be carefully examined. If the target blood pressure is not reached under 3-drug combination therapy, the additional administration of the following drugs must be considered: (1) MR antagonists, (2) β-blockers, (3) α-blockers, (4) renin inhibitors and (5) others (non-DHP CCBs, central sympatholytic drugs or hydralazine) (see Section 6 of Chapter 5, Strategies for resistant hypertension and poorly controlled hypertension).

3. FIXED-COMBINATION DRUGS

A reduction in the number of tablets to be taken and simplification of the prescription by the use of fixed-combination drugs is advantageous for improving adherence [451]. The ADVANCE Study [703], which compared the effects of a fixed-combination drug of an ACE inhibitor and a diuretic with those of a placebo in diabetics, indicated the usefulness of the fixed-combination drug. Adherence was similar between the fixed-combination drug and placebo. A meta-analysis showed that fixed-combination drugs exhibited more potent antihypertensive effects than combination therapy with respective drugs by improving adherence, and that these drugs improved the rate at which the target level of blood pressure control is achieved [718]. On the other hand, a meta-analysis of RCTs regarding the antihypertensive actions of combination therapy with respective drugs and a fixed-combination drug demonstrated that there were no differences in the antihypertensive actions or adverse events between the two groups [719]. The dose of a fixed-combination drug is fixed, and initial administration may cause an excessive decrease in blood pressure. Therefore, initially, a single drug or a combination of two drugs should be administered, and, after fixing the dose/doses, it should be switched to a fixed-combination drug. Before switching to a 3-drug combination drug, the doses should be fixed by combination therapy with 3 drugs, as indicated for 2-drug combination drugs.

In Japan, fixed-combination drugs of an ARB and a diuretic (two-drug combination), those of an ARB and a CCB, and those of an ARB, a CCB, and a diuretic (three-drug combination) are currently available. The price of a fixed-combination drug is less expensive than the total price of respective drugs, and this is a medicoeconomical merit.

4. GENERIC PRODUCTS

Generic products contain the same active ingredient as contained in an original drug. They were inspected/approved based on the results of "specification and study methods" involving an elution study, a "safety study" and a "biological equivalence study" in which changes in the blood concentration after standard-dose administration were compared with those for the original drug in healthy adult volunteers. When applying approval for manufacturing, a clinical study involving patients with hypertension is not obligatory, but drugs inspected/approved based on the results of the above studies become commercially available as generic products. In particular, the active ingredient, additives, and manufacturing method of authorized generic products are equivalent to those of an original drug, and such products should be used to provide medical practice that can be continued by reducing drug expenditure.

5. CHARACTERISTICS AND MAJOR ADVERSE EFFECTS OF VARIOUS ANTIHYPERTENSIVE DRUGS

1) CCBs

CCBs bind to Ca channels on the cell membrane, inhibiting the intracellular influx of Ca ions. They are classified into 3 types: dihydropyridines (DHPs), benzothiazepines (BTZs), and phenylalkylamines based on their chemical structures. In Japan, DHPs and BTZs are used as antihypertensive drugs. In particular, the former is primarily selected due to its potent hypotensive effects. A phenylalkylamine preparation, verapamil, is included in first-line antihypertensive drugs in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111], but it is not indicated as an antihypertensive drug in Japan.

CCBs bind to voltage-dependent Ca channels, inhibiting the intracellular influx of Ca ions and exhibiting antihypertensive actions [720]. Ca channels are classified into two types: high- and low-voltage-activated types. As the former, the N (neural) type, which exists in the nerve terminal, is known in addition to the L (long-lasting) type characterized by a slow rate of inactivation. As the latter, the T (transient) type is known, as the rate of inactivation is fast. These subtypes of Ca channel exhibit various physiological functions due to differences in the electrophysiological properties and mode of in vivo distribution. Furthermore, some drugs have characteristic effects by actions on the N and T types in addition to the L type.

The primary pharmacological actions of CCBs are as follows: (1) coronary and peripheral vasodilation, (2) suppression of the cardiac contractile force and (3) suppression of the conduction system. DHP CCBs rapidly and potently dilate blood vessels, showing little inhibitory effects on cardiac contractility or the conduction system at clinical doses.

Nifedipine was first developed as an L-type CCB. This drug shows potent fast-acting hypotensive actions, but it may increase myocardial oxygen consumption by the activation of the sympathetic nerves or renin–angiotensin (RA) system related to a decrease in the blood pressure. Concerning short-acting nifedipine, the duration of potent hypotensive actions is short; therefore, the blood pressure may change, and a study suggested that this drug may exacerbate ischemic coronary heart disease [721]. Therefore, when administering nifedipine, a sustained-release preparation should be used. Actually, sustained-release nifedipine CR is still frequently selected as an antihypertensive drug to be administered once a day. Previously, the contents of nifedipine capsules had been sublingually administered to patients with hypertensive urgency/emergency in past days. However, this method

induces reflex tachycardia, cerebral infarction or myocardial ischemia related to excessive blood-pressure fall; therefore, it is not recommended [722].

Among L-type CCBs that are currently used as antihypertensive drugs, long-acting preparations are primarily selected. In particular, the half-life of amlodipine in blood and duration of action are long, and its effects slowly appear; therefore, this drug may not induce reflex sympathetic or RA-system activation, and its usefulness is highly evaluated. Amlodipine is the most commonly used as an antihypertensive drug. Long-acting DHP CCBs exhibit substantial hypotensive effects over 24 h, preventing left ventricular hypertrophy or the progression of arteriosclerosis [723, 724]. Antihypertensive therapy with CCBs exhibits central blood pressure-decreasing effects, which cannot be detected based on brachial blood pressure, and blood pressure variability-reducing effects. These effects are advantageous from the viewpoint of the quality of blood pressure control, and are evaluated as characterizing CCBs [206, 725]. In addition, it was confirmed that long-acting DHP CCBs did not affect glucose/lipid/electrolyte metabolism, and that there was no increase in the incidence of malignant tumors or myocardial infarction [726]. DHP CCBs exhibit potent hypotensive actions, but maintain organ blood flow; therefore, they are positively indicated for patients with organ damage or older patients, and used as a first-line drug in many patients. In particular, DHP CCBs are recommended for patients with chronic cerebrovascular disorder, left ventricular hypertrophy, or angina pectoris.

DHP CCBs that antagonize N- or T-type Ca channels in addition to L-type Ca channels are also used. As an L-/N-type CCB, cilnidipine is selected. As L-/T-type CCBs, efonidipine, azelnidipine, and nilvadipine are selected. As an L-/T-/N-type CCB, benidipine is selected [727]. As the characteristics of L-/N-type CCBs, they may reduce sympathetic nerve activity by the suppression of noradrenaline release from the sympathetic nerve terminal, and there is no increase in the heart rate or plasma epinephrine level, differing from L-type CCBs [728]. Furthermore, it is suggested that the proteinuria-reducing effects of cilnidipine combined with an RA-system inhibitor may be more marked than those of amlodipine, but such effects are not significant in diabetics; the long-term renal prognosis remains to be clarified [699, 729]. CCBs that inhibit T- or N-type Ca channels may exhibit secondary actions, differing from amlodipine, but there is little evidence based on large-scale clinical studies in accordance with the ICH-GCP in comparison with amlodipine.

The adverse effects of DHP CCBs include hypotension related to marked vasodilation, palpitations, headache, hot flushes, facial flushes, edema, gingival growth and constipation. DHP CCBs are metabolized by cytochrome P450 (CYP3A4) [730]. Therefore, macrolide antibiotics, azole antifungal drugs, tacrolimus, HIV protease inhibitors, cimetidine, cyclosporine, and grapefruit juice, which are metabolized by this enzyme, delay the metabolism of DHP CCBs, enhancing their hypotensive effects. On the other hand, rifampicin, phenobarbital, and carbamazepine induce CYP3A4, reducing the hypotensive effects of CCBs.

As a BTZ CCB, diltiazem alone is commercially available. The peripheral vasodilative actions of diltiazem are less marked than those of DHP CCBs, but this drug potently inhibits the conduction system, especially atrioventricular node conduction, increasing coronary blood flow. Therefore, the incidences of vasodilation-related edema, which is observed as an adverse effect of DHP CCBs, and reflex sympathicotonia-related adverse events are low. Diltiazem is indicated for patients with angina pectoris, vasospastic angina, or essential hypertension (mild to moderate). As the duration of action for diltiazem tablets is short, sustained-release diltiazem capsules are recommended. Diltiazem is contraindicated for patients with congestive heart failure, grade II or higher atrioventricular block, or sick sinus syndrome. Furthermore, sufficient caution is necessary regarding its use in older patients with latent heart disease or its concomitant use with digitalis or β-blockers.

2) ARBs

In Japan, seven types of ARBs are commercially available. ARBs are the second most common antihypertensive drugs in Japan, following CCBs. ARBs are used alone or in combination with CCBs or diuretics and for the treatment of grades I-III hypertension. As their action mechanism, they produce a hypotensive effect by specifically binding to angiotensin II (AII) type 1 (AT1) receptors and strongly inhibiting strong AII-mediated vasoconstriction, body fluid retention and sympathetic activity. On the other hand, at the tissue level, non- ACE-mediated AII production systems, such as the chymase system, are present. ARBs also inhibit the actions of AII at the receptor level. The administration of ARBs may increase the blood AII level by a feedback mechanism and stimulate AII type 2 (AT2) receptors, which antagonize the cardiovascular actions of AT1 receptors [731]. Furthermore, a study reported their antagonistic actions on the ACE-AII-AT1 receptor system by the activation of the ACE2-angiotensin (1–7)-Mas system [732].

The organ-protecting actions of ARBs were also observed, and these drugs have been used as a first-line drug in patients with cardiac/renal/cerebral complications or diabetes mellitus. However, their organ-protecting actions are primarily derived from hypotensive actions [359, 712, 733]. Furthermore, the effects of ARBs are primarily based on class effects [734], but evidence regarding the uric acid-reducing lowering effects of losartan is being accumulated [735]. Recently, fixed-combination drugs, such as ARB + CCB, ARB + diuretic, and ARB + CCB +

diuretic preparations, have been increasingly prescribed as combination therapy with ARBs. The simplification of prescriptions using fixed-combination drugs, with caution regarding excessive blood-pressure fall, may improve adherence, contributing to good blood pressure control. However, caution is needed when combining several RA system inhibitors [736].

The adverse effects of ARBs are infrequent regardless of the dose, and these are highly tolerable antihypertensive drugs [687]. However, administration to pregnant or breast-feeding women is contraindicated, and ARBs should be carefully administered to patients with severe liver dysfunction. ARBs must not be used in patients with bilateral renal artery stenosis or those with one kidney and unilateral renal artery stenosis, in principle, because of the risk of a rapid reduction in renal function. A decrease in body fluid volume and Na deficiency are also quasi-contraindications. In older patients or those with chronic kidney disease (CKD) (especially in those with an eGFR of <30 mL/min/1.73 m^2), renal function may deteriorate to provoke acute kidney injury (AKI), and administration should be carefully started at a low dose. The eGFR and serum potassium level should be measured within 2 weeks to 1 month after the start of administration. Subsequent monitoring is also necessary. If adverse effects, such as kidney dysfunction and hyperkalemia, appear, the dose of the drug should be promptly decreased, or administration must be discontinued, or the drug should be switched to a CCB, and the physician should consult a doctor who specializes in diagnosing and treating kidney disease or hypertension [736].

3) ACE inhibitors

ACE inhibitors inhibit the RA system, which is a strong pressor system, in blood and tissue, and simultaneously stimulate the kallikrein– kinin–prostaglandin system, which is a depressor system. This may also be involved in hypotensive effects. The hypotensive effect of an ACE inhibitor is nearly the same as, or slightly weaker than, that of an ARB. However, according to a systematic review (SR) by the Cochrane Library, the cardiovascular event- and all-cause mortality risk-reducing effects of the former in hypertensive patients were similar to those of the latter [737]. ACE inhibitors activate the fibrinolytic system, inhibiting the coagulation system. The Blood Pressure Lowering Treatment Trialists'Collaboration (BPLTTC) meta-analysis showed that ACE inhibitors significantly reduced the risk of coronary artery disease [666]. Another meta-analysis indicated that ACE inhibitors reduced the risks of myocardial infarction and all-cause mortality in diabetics [738]. Furthermore, other meta-analyses showed that both ACE inhibitors and ARBs inhibited progression to ESKD in patients with CKD or diabetic kidney disease [712], and that they prevented cardiovascular events in CKD patients [739]. In addition, ACE inhibitors reduced the all-cause mortality rate in CKD patients [739].

The adverse effects of ACE inhibitors include dry cough due to the enhancement of bradykinin activity. Dry cough is frequent in East Asians, including Japanese [740]. The maximum doses of ACE inhibitors in Japan were established as lower than in Europe and the United States. This also contributes to their hypotensive effects. On the other hand, the induction of a cough prevents aspiration pneumonia [741]. As an important adverse effect, angioneurotic edema may occur. A study reported that combination therapy with a DPP-4 inhibitor, a drug for type 2 diabetes mellitus, increased the incidence of angioneurotic edema [742]. As shock or anaphylactoid symptoms may occur, an ACE inhibitor is contraindicated for patients undergoing apheresis with an adsorber consisting of dextran sulfate-fixed cellulose, tryptophan-fixed polyvinyl alcohol or polyethylene-telephthalate and those receiving hemodialysis with acrylonitrile–sodium methallylsulfonate membrane. Furthermore, cilazapril may excessively reduce the blood pressure in patients with liver cirrhosis, and it should be avoided. As many ACE inhibitors are excreted by the kidney, their administration should be started at a low dose in patients with kidney damage. Other adverse effects and cautions are the same as those of ARBs.

4) Direct renin inhibitors (DRIs)

Among DRIs, only aliskiren is currently available in Japan. Hypertension is an indication to be covered by health insurance. DRIs belong to RA system inhibitors in a wide sense. Their inhibitory actions on the RA system are common with those of ARBs and ACE inhibitors. However, they inhibit renin enzyme activity, differing from ARBs and ACE inhibitors, and plasma renin activity (PRA) reduces, but the plasma concentration of renin increases. The half-life of aliskiren is long (40 h), with good tissue transfer. This drug exhibits stable hypotensive effects for many hours when administered once a day, and is well tolerated [743, 744]. Aliskiren is particularly indicated when neither an ARB nor ACE inhibitor can be used because of the adverse effects despite a condition for which an RA system inhibitor should be positively indicated. The hypotensive and adverse effects of DRIs are similar to those of ARBs and ACE inhibitors [745], and their albuminuria-reducing effects in diabetics with albuminuria are also similar to those of ARBs [746].

A study reported that combination therapy with an RA system inhibitor enhanced the proteinuria-reducing effects [747]. However, in the ALTITUDE Study, in which the efficacy of combination therapy with aliskiren was compared with that of conventional treatment involving RA system inhibitors in high-risk patients with type 2 diabetes

mellitus, there was no further decrease in the incidence of complicated cardiovascular/renal events, and the incidences of hyperkalemia and hypotension increased [748]. Therefore, DRIs are contraindicated for diabetics receiving an ARB or an ACE inhibitor (excluding patients in whom blood pressure control is markedly poor despite other antihypertensive treatments with an ARB or ACE inhibitor). Furthermore, as a rule, combination therapy with a DRI and another RA system inhibitor (ARB, ACE inhibitor) is contraindicated for hypertensive patients with CKD, with an eGFR of <60 mL/min/1.73 m^2.

Serious adverse effects include vascular edema, anaphylaxis, hyperkalemia and kidney dysfunction. Combination therapy with itraconazole or cyclosporine and administration to pregnant women are contraindicated. In addition, as a rule, administration to patients with bilateral or unilateral renal artery stenosis is also contraindicated, as described for other RA system inhibitors (ARBs and ACE inhibitors), because the renal function may rapidly decrease.

5) Diuretics

In Japanese, salt-sensitive hypertension is frequent. In antihypertensive treatment, salt reduction is important, but a diuretic at a low dose may be used in hypertensive patients in whom salt restriction is difficult. In large-scale clinical studies, such as the SPRINT study, the proportion of patients taking a diuretic was high [92], and even diuretic therapy alone prevented cardiovascular events [726, 749]. Furthermore, diuretics are inexpensive. As antihypertensive drugs, thiazide-type diuretics are commonly used. With respect to kidney function, they are selected in patients with an eGFR of ≥30 mL/min/1.73m^2. They decrease the circulating blood volume by inhibiting Na reabsorption in the renal distal tubules, but exhibit hypotensive effects by reducing peripheral vascular resistance in the long term. Thiazide-type diuretics are classified into thiazide diuretics and thiazide-like diuretics. It is controversial whether the clinical efficacy differs between thiazide diuretics and thiazide-like diuretics [750, 751]. However, evidence is limited. In the Japanese Society of Hypertension (JSH) 2019 Guidelines, the two types of drugs are regarded as thiazide-type diuretics.

To patients with severe kidney dysfunction/ESKD (eGFR <30 mL/min/1.73m^2), loop diuretics are initially administered. Loop diuretics exhibit diuretic actions by inhibiting NaCl reabsorption in the ascending limbs of the loop of Henle. They show more marked diuretic effects but less potent hypotensive effects compared with thiazide-type diuretics. If the efficacy is insufficient, marked diuretic effects may be obtained by combining a loop diuretic with a thiazide-type diuretic [736].

Diuretics may be particularly effective in hypertensive patients with increased salt sensitivity, such as older patients, patients with low renin hypertension, hypertensive patients with CKD, those with diabetes mellitus and those with insulin resistance. They are also useful for decreasing blood pressure in hypertensive patients in whom salt restriction is difficult, those with an excessive body fluid volume related to edema or patients with resistant hypertension. Furthermore, their preventive effects on heart failure are marked [92, 752]. Recently, ARB + diuretic fixed-combination drugs have been prescribed, but the ACCOMPLISH, GUARD, and J-CORE studies, in which combination therapy with an RA system inhibitor and a diuretic was compared with that with an RA system inhibitor and a CCB, showed that the latter more markedly ameliorated blood pressure changes, maintaining the eGFR and preventing cardiovascular/renal events [350, 705, 753–755], whereas the former more potently reduced albuminuria/proteinuria [350, 705, 753–755].

The administration of thiazide-type diuretics should be started at a low dose (concerning fixed-combination drugs, there is a dose corresponding to 1/4, but, generally, a half dose is used), and thus the appearance of adverse effects can be prevented and hypotensive effects can be obtained [756]. Furthermore, hypotensive effects are enhanced by combining a diuretic with other classes of antihypertensive drugs, but combination therapy with β-blockers should be avoided, because it affects glucose/lipid metabolism. According to several studies, combination therapy with RA system inhibitors markedly reduced proteinuria [705, 753, 754]. However, kidney dysfunction (decrease in eGFR), an excessive decrease in blood pressure in summer related to seasonal blood pressure changes, hyponatremia and hypokalemia must be considered.

The adverse effects of diuretics include electrolyte abnormalities, such as hyponatremia (caution is needed in older small women and older patients under salt restriction therapy) [757], hypokalemia and hypomagnesemia, in addition to adverse effects on the metabolic system, such as hyperuricemia, hypertriglyceridemia and impaired glucose tolerance. The incidence of hyponatremia related to thiaziade-type diuretics is higher than that related to loop diuretics, and the rate of severe-status patients is higher [758, 759]. A study indicated the involvement of *SLCO2A1* (prostaglandin transport protein) gene mutations in hyponatremia [760]. In the SHEP study, diuretic-induced hypokalemia led to the loss of prognosis-improving effects [761]. The ALLHAT study also demonstrated that hypokalemia was associated with an increase in the mortality rate regardless of diuretic administration [762]. The prevention of hypokalemia is important to reduce the mortality rate in hypertensive patients [763]. To prevent hypokalemia, combination therapy with an ACE inhibitor or ARB or that with a K preparation or MR antagonist should be

conducted, and guidance for the consumption of citrus fruits containing a high level of K is recommended. As serious adverse effects, photodermatosis and thrombocytopenia are observed, although their incidences are low.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were approved as drugs for treatment of diabetes mellitus. Although they are not classified as diuretics, clinical studies, including large-scale ones, suggested their sodium diuretic effects, hypotensive effects, and preventive effects on cardiovascular/renal events [764]. In addition, the significance of SGLT2 inhibitors in the treatment of hypertension complicated by diabetes mellitus has been emphasized [236], as described in the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension, which were recently revised.

6) β-Blockers (including αβ-blockers)

β-Blockers lower the blood pressure by reducing cardiac output by a decrease in the heart rate and a reduction in cardiac contractility related to blockade of myocardial β_1-receptors, suppressing renin production in the kidney and inhibiting central sympathetic outflow. Their properties vary: β_1-receptor selectivity, presence or absence of intrinsic sympathomimetic actions, hydrophilic/lipophilic properties, and duration of action. Although peripheral vascular resistance increases shortly after the initiation of treatment, it returns to its original level after long-term treatment. β-Blockers are not included in first-line drugs in the JSH2014 and the JSH 2019 Guidelines, but they are classified as main antihypertensive drugs. Indications for the use of β-blockers are hypertension in young patients showing sympathetic hyperactivity, effort angina, after myocardial infarction, hypertension complicated by tachycardia, hypertension with a high cardiac output, including that caused by hyperthyroidism, high renin hypertension and aortic dissection [111, 534]. It should be noted that β-blockers are not uniform, and they are classified into 3 types: β_1-selective, non-selective, and α-receptor-blocking drugs [111, 534]. In the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, the use of respective drugs is described [111]. In hypertensive patients, long-acting β_1-selective drugs are frequently used [111, 765, 766]. The hypotensive effects of αβ-blockers in hypertensive patients are not marked. In particular, carvedilol is selected for heart failure patients with systolic dysfunction regardless of the presence or absence of hypertension [767]. β-Blockers are used as basic drugs in the treatment of heart failure with reduced ejection fraction regardless of the presence or absence of hypertension. In Japan, carvedilol and bisoprolol are covered by health insurance based on evidence [768]. With respect to their use in heart failure patients, administration should be started at a low dose, and the dose should be gradually increased, as described in the Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure [768].

A meta-analysis showed that the preventive effects of β-blockers on cardiovascular events were similar to those of other antihypertensive drugs, whereas their preventive effects on stroke in older patients were less potent than those of other antihypertensive drugs [769]. In addition to the weak hypotensive effects of β-blockers, this supports the reason why β-blockers are not included in standard first-line drugs, as described in guidelines in Europe and the United States. In a large-scale clinical study of high-risk hypertensive patients with multiple risk factors (ASCOT-BPLA), a combination of a β-blocker and a diuretic was found to be inferior to that of a CCB and an ACE inhibitor in preventing the occurrence of heart disease events [696]. β-Blockers exert adverse effects on glucose and lipid metabolism when used alone or in combination with diuretics [679, 770, 771]. Therefore, they must be carefully administered to older patients or when hypertension is complicated by other diseases such as diabetes mellitus and impaired glucose tolerance. However, some studies have reported that αβ-blockers, which have vasodilative actions by α-blockage, and lipophilic β_1-blockers, particularly carvedilol, showed no metabolic adverse effect on their concomitant use with RA system inhibitors, and that the incidence of diabetes mellitus was lower than in patients taking hydrophilic β-blockers. A clinical study to evaluate the long-term outcome is necessary [772, 773]. However, currently, there is no evidence regarding the usefulness of calvedilol or an lipophilic β_1-selective drug, bisoprolol, in hypertensive adults for whom β-blockers are not positively indicated (see CQ6).

β-Blockers are contraindicated or carefully used for patients with obstructive pulmonary disease, such as bronchial asthma, bradycardia, grade II or severer AV block, Raynaud's phenomenon, or pheochromocytoma (when a β-blocker is not combined with an α-blocker, or other than αβ-blockers). As β-blockers may induce coronary vasospasm, a β-blocker should be combined with a CCB in patients with vasospastic angina pectoris. As its sudden discontinuation may induce withdrawal symptoms such as angina pectoris and hypertensive attacks, its dose should be gradually reduced before withdrawal [774]. Caution is needed in its concomitant use with verapamil or diltiazem, because it is most likely to induce bradycardia and heart failure.

7) α-Blockers

α-Blockers selectively block α_1-receptors on the smooth muscle cells of the sympathetic nerve terminal, reducing the blood pressure by peripheral vasodilative actions. They do

not inhibit suppressive α_2-receptors on the sympathetic nerve terminals side and rarely cause reflex tachycardia, especially when they are the long-acting type. They are used for blood pressure control in patients with pheochromocytoma. They are administered before sleep for the treatment of morning hypertension [775]. They are indicated for hypertensive patients with urination disorder complicated by prostatic hypertrophy. As first-dose phenomena, they may cause dizziness, palpitation and syncope due to orthostatic hypotension. Therefore, their administration should be started at a low dose with gradual increases.

8) MR antagonists

MR antagonists, such as spironolactone (SPL) and eplerenone (EPL), act on MRs in the distal kidney tubule and conjugated collecting kidney tubule, promoting sodium excretion without the loss of potassium (K) and exhibiting antihypertensive effects. They may be effective for low renin hypertension. In patients with resistant hypertension, additional administration at a low to moderate dose (SPL: 25 to 50 mg/day) may further decrease blood pressure [776, 777]. Furthermore, MR antagonists are generally used for medical therapy for primary aldosteronism (PA) [778].

As aldosterone affects the cardiovascular system, MR antagonists have an organ-protecting effect, and many large-scale clinical studies have indicated that MR antagonists improve the prognosis of heart failure or that after myocardial infarction [779, 780]. The effects of EPL administration (initial dose: 25 mg (once a day), maximum dose: 50 mg) on chronic heart failure have been shown [781], but every-two-days administration at 25 mg should be started in patients with moderate renal dysfunction (creatinine clearance: 30 to <50 mL/min), and the dose may be increased to 25 mg to be administered once a day at maximum. EPL has also been confirmed to reduce proteinuria [782, 783]. However, great care should be taken when combining it with an RA system inhibitors or in the presence of kidney dysfunction/heart failure because EPL may induce hyperkalemia. Furthermore, EPL is contraindicated for patients receiving K preparations, diabetic nephropathy patients with albuminuria or proteinuria, and patients with moderate or severe kidney damage (creatinine clearance: <50 mL/min). After all, EPL can be administered to patients with normal kidney function other than those with diabetic nephropathy to decrease blood pressure and reduce proteinuria. This restriction does not apply to SPL, but hyperkalemia must also be considered. SPL induces adverse effects, such as gynecomastia, impotence and menorrhalgia, whereas EPL causes few adverse like these effects.

In the spring of 2019, the manufacturing and the use of a new non-steroidal MR antagonist, Esaxerenone, were approved. This drug must not be combined with K preparations, as indicated for EPL. It could be carefully administered to diabetics with albuminuria or proteinuria and patients with moderate renal dysfunction (eGFR: 30 to 59 mL/min/1.73 m^2). Needless to say, we should pay attention to hyperkalemia.

9) Centrally acting sympatholytic drugs

Methyldopa, clonidine, and guanabenz are used. When the goal of antihypertensive therapy is not reached despite the use of an RA system inhibitor, a CCB, and a thiazide diuretic, the addition of a centrally acting sympatholytic drug or vasodilator following the administration of an MR antagonist, a β-blocker, and an α-blocker is considered [784–787].

A meta-analysis of RCTs involving patients with essential hypertension showed that methyldopa exhibited significantly more marked hypotensive effects compared with a placebo [787]. However, the appearance of dizziness as an adverse effect must be considered. Methyldopa is indicated for patients with renal dysfunction. It can be safely used from the first trimester of pregnancy or in patients with pregnancy-induced hypertension after Week 20 of pregnancy [788].

Clonidine and guanabenz inhibit sympathetic activities by stimulating α_2-receptors in the rostral ventrolateral area of the medulla oblongata, which is the sympathetic center, thus reducing blood pressure. They are administered before sleep for the treatment of morning hypertension. On the other hand, adverse effects, such as sleepiness, thirst, malaise and impotence, are frequent. Sudden discontinuation may induce withdrawal symptoms. As sodium/water retention is observed, the concomitant use of a diuretic is sometimes necessary. Clonidine and guanfacine are selected to treat attention deficit hyperactivity disorder (ADHD) in children and adults, but they may induce hypotension and bradycardia; therefore, caution is needed [789].

10) Classic vasodilators

Hydralazine dilates blood vessels by directly acting on the vascular smooth muscle [784]. As it acts quickly, it is used for the treatment of hypertensive emergencies. It can be safely used from the first trimester of pregnancy or in patients with pregnancy-induced hypertension after Week 20 of pregnancy. As adverse effects, angina pectoris, headache, palpitation, tachycardia and edema are observed. Fulminant hepatitis has also been reported, and this drug is contraindicated for patients with liver damage. Systemic lupus erythematosus-like symptoms may appear when classic vasodilators are used continuously.

POINT 5B

[STRATEGIES FOR RESISTANT HYPERTENSION AND POORLY CONTROLLED HYPERTENSION]

1. **In patients with resistant hypertension or poorly controlled hypertension, responsible factors, such as**

lifestyle-related factors, including excessive salt consumption, obesity and alcohol consumption, poor adherence, white coat hypertension/ white coat phenomenon, the inappropriate selection of antihypertensive drugs and their doses, sleep apnea syndrome, secondary hypertension, such as PA, kidney dysfunction and others, and an increase in the body fluid volume, mental stress, and attenuation of hypotensive effects related to the use of other drugs, should be considered.

2. **After making an inquiry and communicating with the patient, lifestyle modifications and guidance for drug therapy should be performed. In antihypertensive treatment, multiple drugs differing in the action mechanism, including diuretics, should be combined. A sufficient dose of antihypertensive drugs should be used, and the frequency and time of dosing must be carefully adjusted.**
3. **MR antagonists are useful for reducing blood pressure as an additive drug for resistant hypertension.**
4. **Organ damage may be present, and the proportion of high-risk patients is high. In addition, the incidence of cardiovascular diseases is high. Furthermore, incidence of secondary hypertension is high. Therefore, consultation with a hypertension specialist should be needed at an appropriate time.**

6. STRATEGIES FOR RESISTANT HYPERTENSION AND POORLY CONTROLLED HYPERTENSION

1) Definition and prevalence

In many hypertensive patients, blood pressure is not adequately controlled even with the taking of antihypertensive drugs. Patients in whom blood pressure does not decrease to the target level despite the use of three different antihypertensive drugs, including a diuretic, are regarded as having resistant hypertension [790]. Those in whom therapy with four or more antihypertensive drugs decreases blood pressure to the target level may also be regarded as having controlled resistant hypertension. However, in a strict sense, resistant hypertension refers to a condition in which therapy with three antihypertensive drugs, including a diuretic, at appropriate doses in combination with sufficient lifestyle modifications does not decrease blood pressure to the target level [791]. Furthermore, patients who do not meet the definition despite poor blood pressure control with 2-3 antihypertensive drugs or those in whom no diuretic is used should also be regarded as having poorly controlled hypertension. It may be practical to perform strategies similar to those for resistant hypertension in this poorly controlled hypertension. Even in patients with poorly controlled or resistant hypertension, a sufficient decrease in blood pressure may be achieved by correcting factors presented in Table 5-3. Hypertensive patients in whom blood pressure does not decrease to the target level despite the use of ≥5 drugs are regarded as having refractory hypertension [792–794]. Patients with resistant or refractory hypertension include a high proportion of those with organ damage and high-risk patients regarding cardiovascular diseases, and the physician should refer the patient to a hypertension specialist at an appropriate time [790, 792, 795].

The incidence of resistant hypertension varies among diagnostic criteria, target blood pressure levels and study populations. In clinical practice, it is reportedly approximately 2 to 3%, but may exceed 50% at outpatient nephrology or hypertension clinics [796]. A meta-analysis involving 961035 hypertensive patients receiving treatment indicated that those with resistant hypertension accounted for 13.7% in 20 observational studies and 16.3% in 4 RCTs [797]. In Japan, the J-HOME Study involving clinicians/practitioners showed that home or office blood pressure control was poor in 13% of patients taking three or more antihypertensive drugs [101]. However, the incidence of resistant hypertension meeting the strict definition described above may be lower, but the actual number is unclear. Furthermore, the incidence of resistant hypertension in patients in whom a blood pressure level of <140/90 mmHg is not achieved has been reported. However, if a lower target level is established in the future, the incidence of resistant hypertension may increase; it may be difficult to simply compare annual changes. The incidence of refractory hypertension ranged from 0.5 to 1.7% [792–794] according to cohort studies involving hypertensive patients in Europe, the United States, and East Asia.

2) Factors for resistance to treatment and approaches to them

In patients with resistant or poorly controlled hypertension, it is important to consider etiological factors and establish an appropriate approach. There are many factors for poor control, including failure in correct blood pressure measurement due to the use of a small cuff on a large arm or pseudohypertension (see Section 1 of Chapter 2, "1) Measurement of office blood pressure"), blood pressure measurement-associated problems, such as white coat hypertension/white coat phenomenon, poor drug adherence, lifestyle-related problems, such as excessive salt consumption, obesity and excessive alcohol consumption, patient conditions, such as sleep apnea syndrome and an excessive body fluid volume, combinations and doses of antihypertensive drugs, problems regarding the duration of drug efficacy, the consumption of drugs/foods that increase blood pressure or attenuate the actions of antihypertensive drugs and secondary hypertension (Table 5-3). Of these, white coat hypertension/white coat phenomenon [798], poor drug adherence [799] and sleep apnea syndrome [800] are frequently observed, and the incidence of secondary hypertension is also high.

Table 5-3 Factors and strategies for resistant or poorly controlled hypertension in hypertension treatment

Factors	Strategies
Problems with blood pressure measurement	
Use of an inappropriately small cuff	Use of a cuff with a width of 40% of the brachial girth and a length sufficient to cover at least 80% of the brachial girth
Pseudohypertension	Attention to marked atherosclerosis
White coat hypertension/white coat phenomenon	Confirmation by home blood pressure and/or ABPM
Problems regarding medication management (poor adherence)	Relieving patient's concern about medications by sufficient explanation and education Changing the drug if adverse effects are observed Considering psychological factors if drug maladjustment is repeated Considering economic problems Considering the dosing schedule matched with the patient's lifestyle Increasing physician's enthusiasm
Lifestyle problems	
Excessive salt intake	Explanation of the significance and necessity of salt reduction Repeated guidance in cooperation with a registered dietitian
Obesity (excessive caloric intake and lack of exercise)	Repeated guidance on restriction of energy intake and exercise
Excessive alcohol consumption	Guidance to restrict alcohol intake at ≤20–30 mL ethanol per day
Sleep apnea syndrome	Appropriate treatments such as continuous positive airway pressure (CPAP)
Volume overload	
Inappropriate use of diuretics	In combinations of three or more drugs, one should be a diuretic. Select a loop diuretic in patients with advanced kidney dysfunction (eGFR: <30 mL/min/1.73m^2). Attempt to maintain the effect of diuretics
Progression of nephropathy	Guidance in salt intake restriction and use of diuretics according to the above principles
Inappropriate combinations/doses of antihypertensive drugs	Combinations of antihypertensive drugs that have different action mechanisms, including a diuretic, at sufficient doses
Insufficient duration of drug efficacy	Use of antihypertensive drugs at night or in the evening in patients with morning/nighttime hypertension
Drugs/foods that may increase blood pressure	When non-steroidal anti-inflammatory drugs, adrenocorticosteroids, *Kampo* formulas containing licorice, glycyrrhizin preparations, oral contraceptives, cyclosporine, erythropoietin, antidepressants or moleculy-targeted drugs are used concomitantly, discontinue them or reduce the dose if possible. Select antihypertensive drugs considering the pressor mechanisms of the other drugs and drug interactions
Secondary hypertension	Screening tests should be conducted while monitoring of characteristic symptoms/findings. The patient should be referred to a hypertension specialist

Furthermore, physicians' problems including the inappropriate use of antihypertensive drugs are also involved in treatment resistance in many cases [801, 802]. A state in which health care professionals do not comply with the necessity of enhancing antihypertensive treatment according to guidelines is termed "clinical inertia". In an essential definition, patients with poor blood pressure control after approaching these factors are regarded as having resistant or refractory hypertension. Therefore, patients in whom sufficient approaches are not performed are sometimes regarded as false resistant or refractory hypertension.

In patients with apparent, white coat phenomenon-related resistant or poorly controlled hypertension, it may not be necessary to intensify antihypertensive treatment if home or 24-h blood pressure is controlled. In patients with white coat hypertension-type resistant hypertension, organ damage is less marked than in those with true resistant hypertension, and the prognosis is not poor [798, 803].

Patient drug adherence is also important. Adherence is poor in 23 to 65% of patients with resistant hypertension [804].

A survey regarding blood pressure control and its factors indicated that the attitude of physicians to treatment was the most important factor [801]. In addition, if the patient does not accept antihypertensive treatment because of insufficient explanations, or if the physician is not aware of the adverse effects of antihypertensive drugs, adherence tends to be unsatisfactory. To improve blood pressure control, a

Table 5-4 Drug therapy for resistant or poorly controlled hypertension

When the target level of blood pressure cannot be achieved using three drugs, a CCB, an ARB/ACE inhibitor and a diuretic,

1. Increasing the dose or changing the frequency of administration (to twice a day or once at night)
2. Additional administration of an MR antagonist (the serum potassium level should be monitored)
3. Additional administration of a sympatholytic drug (αβ-,β- or α-blockers)
4. Additional combination therapies
   a. Addition of a centrally acting sympatholytic drug
   b. Addition of a vasodilator (e.g. hydralazine)
   c. Concomitant use of dihydropyridine and non-dihydropyridine CCBs
   d. Concomitant use of either two of the following ARBs, ACE inhibitors and DRIs
   (the serum potassium level and kidney function should be monitored
   e. Concomitant use of thiazide and loop diuretics
5. Consultation with a hypertension specialist at an appropriate time

positive attitude of the physician to treatment, efforts to improve the patient's understanding of hypertension treatment, encouragement to modify lifestyle and the selection of appropriate antihypertensive drugs are important. The patient's economic and psychological problems must also be considered. A meta-analysis showed that approaches to prevent "clinical inertia", such as adequate information provision from the patient to the physician, 24-h ambulatory blood pressure monitoring (ABPM)/home blood pressure measurement, and education of the medical staff, improved blood pressure control [802].

The resistance of hypertension is often in the condition of the volume-overload that results from excessive salt intake, no use or inadequate use of diuretics and the presence of renal insufficiency. In this condition, the appropriate use of diuretics is effective. Even in resistant hypertension patients taking diuretics, a strict salt restriction is useful for decreasing blood pressure [805].

If sufficient blood pressure control cannot be achieved, the presence or absence of the factors mentioned in Table 5-3 must be evaluated. If there is no sign of secondary hypertension or no problem with blood pressure measurement or drug adherance, but the control of blood pressure is insufficient even on treatment using three or more drugs, lifestyle guidance including salt restriction should be performed again.

Suggested adjustment of antihypertensive drug therapy is summarized in Table 5-4. If no diuretic has been used, its use should be started, and, if a diuretic is used, its dose and type should be optimized. With respect to the adequate doses of diuretics, see Chapter 5 "5) Diuretics". While monitoring the influence on electrolytes and metabolism, the use of a diuretic at a dose higher than the recommended dose can be considered. In patients with an eGFR of ≥30 mL/min/1.73 m^2, thiazide-type diuretics should be selected. When selecting trichlormethiazide, administration should be started at 1 mg per day. If blood pressure control is insufficient, the dose can be increased to 2 mg per day. In patients with an eGFR of <30 mL/min/1.73 m^2, loop diuretics should be selected. Among loop diuretics, furosemide has a short duration of action, and thus it must be administered several times a day. The use of a diuretic with a longer duration of action may be recommended.

Concerning antihypertensive drugs other than diuretics, several antihypertensive drugs differing in the action mechanism should be combined. When selecting these drugs, drugs to be positively indicated should be predominantly adopted, but a combination of a CCB and an ARB or ACE inhibitor may be primarily used. Furthermore, it is important to use a sufficient dose for blood pressure control. If a sufficient decrease in blood pressure cannot be achieved by combination therapy with three drugs, a CCB, an ARB or ACE inhibitor and a diuretic, the pharmacological therapy should be intensified or modified. Increasing their doses, switching the frequency of dosing from once in the morning to twice in the morning and evening or once in the evening, and addition of another antihypertensive drug may be effective for blood pressure control. In patients with resistant hypertension, if the duration of action of an antihypertensive drug is insufficient, a period of poor blood pressure control is likely to occur. To control blood pressure at the target level over 24 h, diurnal changes in blood pressure should be evaluated by morning and evening measurement of home blood pressure or 24-h ABPM, and not only the type of antihypertensive drugs but also the time of administration should be adjusted. A study showed that the administration of antihypertensive drugs before sleep decreased 24-h and nighttime blood pressures in patients with resistant hypertension, improving the proportion of patients in whom the target of blood pressure control is achieved [806].

Concerning combination therapy, it has been indicated that a sufficient decrease in blood pressure can be achieved by the additional administration of an MR antagonist; its use as an additive drug is recommended [776, 777, 807] (see CQ 5). Furthermore, combination therapy with sympatholytic drugs, such as αβ-, α- and β-blockers, should be considered. In patients with poor blood pressure control despite this therapy, central sympatholytic drugs, such as a-methyldopa, and vasodilators, such as hydralazine, become candidates. As a rule, the concomitant use of drugs of the same class should be avoided, but combination therapy with DHP and non-DHP CCBs, that with an ARB and an ACE or DRI and that with thiazide-type and loop diuretics are sometimes selected. For such combination therapies or

high-dose administration, adverse effects and an excessive decrease in blood pressure may occur, and thus caution is needed. Consultation with a hypertension specialist at an appropriate time is recommended for patients who require multiple antihypertensive drugs.

3) Renal denervation

Renal denervation (RDN) is the recently developed endovascular catheter technology to lower blood pressure. Via femoral artery access, both renal arteries are cannulated in sequence to generate high-frequency energy on the vascular wall and to ablate the renal nerves localized in the adventitia of renal arteries. In 2009, RDN was first applied in humans for the treatment of resistant hypertension. Then, several studies reported that RDN markedly reduced office and 24-h blood pressures in comparison with treatment with antihypertensive drugs, suggesting its clinical usefulness [808–810]. However, a single-blind comparative study published in 2014 (SYMPLICITY-3 study) [811] indicated that hypotensive effects were similar between the RDN and sham (control) groups, although there was no problem regarding the safety. The efficacy of this procedure was reviewed. A clinical study that had been conducted in Japan was discontinued because the target number of patients was not reached. The results showed that office and 24-h blood pressures in the RDN group were slightly lower than in the drug therapy group, although there were no statistical significant differences [812]. The results of the SYMPLICITY-3 study suggested that the presence or absence of the effects of this treatment depends on the treatment procedure, site of cauterization, and patient factors [813, 814]. Thereafter, with advances in the development of instruments, ultrasonic instruments with high frequency were introduced, and clinical studies involving strict criteria for patient selection were conducted. A blind comparative study involving untreated patients with mild or moderate hypertension indicated that office and 24-h blood pressures in the RDN group were significantly lower than in the sham group [815–817]. Many issues regarding this treatment remain to be resolved: there are problems regarding long-term hypotensive effects or safety; this treatment is not effective in all patients; and success or failure in RDN is confirmed based on blood pressure assessment alone. However, RDN may be useful as a non-pharmaceutical procedure for hypertension treatment in patients with mild hypertension in addition to those with resistant hypertension.

CQ5. IS THE ADMINISTRATION OF MR ANTAGONISTS TO PATIENTS WITH RESISTANT HYPERTENSION RECOMMENDED?

►MR antagonists should be used as an additional drug to further decrease blood pressure in patients with resistant hypertension.

Recommendation grade: 2, Evidence level: B

SUMMARY OF EVIDENCE

A meta-analysis of 4 RCTs showed that the additional administration of Spironolactone (SPL) at 25 to 50 mg/day significantly reduced office and out-of-office blood pressures in patients with resistant hypertension in comparison with a placebo and doxazosin or bisoprolol. However, in these trials, the follow-up period was short, and the patient background was not uniform. The long-term preventive effects of SPL on cardiovascular diseases and its influence on the onset of adverse events are unclear. Furthermore, other MR antagonists, such as Eplerenone (EPL), may also be useful for the treatment of resistant hypertension, as demonstrated for spironolactone. However, there is no sufficient report, and their usefulness must be examined in the future.

INTERPRETATION

Resistant hypertension refers to a condition in which blood pressure does not decrease to the target level despite the administration of 3 antihypertensive drugs (CCB, ACE inhibitor/ARB, thiazide-type diuretic), including a diuretic, at adequate doses by lifestyle modifications [791]. With respect to the etiology of resistant hypertension, the involvement of aldosterone [818] was indicated. Concerning the antihypertensive effects of additionally administered MR antagonists, various studies have reported that the additional administration of MR antagonists is useful for reducing blood pressure regardless of the presence or absence of PA [819, 820]. If the benefit of MR antagonist can be demonstrated in treating those who have been resistant to 3 antihypertensive drugs and have completed the screening for PA, this information may be very useful for drug selection in patients with resistant hypertension.

Prior to the preparation of the present guidelines, articles involving the administration of MR antagonists to patients with resistant hypertension and examining its influence on blood pressure were extracted from the PubMed, Cochrane Library, and Ichushi-Web to investigate the usefulness of additionally administered MR antagonists in patients with resistant hypertension. Focusing on 8 RCTs or trials involving meta-analysis, 4 trials [807, 821–823] were finally selected as candidates for meta-analysis. When investigating this CQ, we adopted two articles published by Liu et al. [777] and Zhao et al. [776], who conducted a meta-analysis of the 4 trials, considering that their evidence grade is high. The number of studies with EPL or new MR antagonists was limited, and their evidence grade may not be satisfactory; therefore, we excluded them in the present study.

The results of meta-analysis in the present study showed that the additional administration of SPL significantly reduced systolic and diastolic office blood pressures by 15.73 and 6.21 mmHg, respectively, and systolic and diastolic out-of-office blood pressures (home or ABPM) by 8.70 and 4.12 mmHg, respectively, in comparison with a placebo or control drug. The incidence of adverse events, such as hyperkalemia (≥5.0 mmol/L) and renal failure in the SPL group, was slightly higher than in the control group, but there was no significant difference. A study analyzing 6 RCTs (involving kidney damage or dialysis patients) adopted on secondary evaluation also indicated that hyperkalemia (≥5.0 mmol/L) occurred in only 15 (2.9%) of 524 patients, and that 3 (0.6%) dropped out due to this adverse event. It may be prevented by closely monitoring the serum potassium level and kidney function before spironolactone administration or during the administration period. The additional administration of spironolactone should be considered in patients with resistant hypertension on the assumption that monitoring of adverse effects, such as gynecomastia/impotence and menorrhalgia, may be sufficiently performed, considering its inexpensiveness, availability, and potent hypotensive effects.

Thus, the additional administration of SPL at 25 to 50 mg/day to patients with resistant hypertension may be useful for further decreasing blood pressure. However, in these trials, the follow-up period was short, and the patient background was not uniform. The long-term preventive effects of SPL on cardiovascular events and its influence on the onset of adverse events are unclear. Neither studies of MR antagonists for resistant hypertension in Japan nor international studies regarding the effects of EPL or new MR antagonists on resistant hypertension have been sufficiently reported. Therefore, their usefulness must be examined in the future.

LITERATURE SEARCHING

We searched the literature before June 2017 by combining the following search terms: “mineralcorticoid receptor antagonists”, “hypertension”, “resistant”, “Practice”, “Guidelines”, “Randomized Controlled Trial”, and “Meta-Analysis” on the PubMed, Cochrane Library, and Ichushi-Web. Based on the results of searching, we extracted articles regarding this CQ. As a result, 140 documents were hit, and 8 of these were identified as ones to be analyzed in a meta-analysis. Excluding 4, the other 4 documents were analyzed in a meta-analysis. Of these 4 documents, one involved patients with type 2 diabetes mellitus, and another involved stage 2 or 3 CKD patients with resistant hypertension. Finally, we adopted two articles involving a meta-analysis of the 4 documents.

CQ6. CAN A B-BLOCKER, CARVEDILOL OR BISOPROLOL, BE RECOMMENDED AS A FIRST-LINE DRUG FOR HYPERTENSIVE PATIENTS WITHOUT COMPELLING INDICATIONS?

►Neither carvedilol nor bisoprolol, which are β-blockers, should be recommended as a first-line drug for hypertensive patients without compelling indications.

Recommendation grade: 2, Evidence level: D

SUMMARY OF EVIDENCE

None of the 8 RCTs evaluated the cardiovascular mortality rate, all-cause mortality, hypotension, or bradycardia as an outcome. A meta-analysis of 8 RCTs showed that bisoprolol significantly reduced blood pressure at 5 mg/day (mean difference in systolic blood pressure (SBP): −5.75 mmHg, 95% confidence interval [CI]: −6.38 to −5.13), 10 mg/day (−6.96 mmHg, 95%CI: −11.06 to −2.56), and 20 mg/day (−7.60 mmHg, 95%CI: −12.64 to −2.56) compared with a placebo, whereas the blood pressure-lowering effects of carvedilol were not uniform. A meta-analysis of 2 RCTs regarding carvedilol found no increase in the incidence of other adverse events as compared with placebo. Among studies regarding blood pressure-lowering effects and other adverse events, there was no bias in publication.

INTERPRETATION

The JSH2014 Guidelines described that the initial antihypertensive drug for hypertensive patients without compelling indications should be selected from CCBs, ARBs, ACE inhibitors, and diuretics. β-Blockers were not included in first-line drugs. As β-blockers, atenolol and propranolol have been primarily used, but, currently, carvedilol and bisoprolol, which became available following these drugs, are more frequently selected as main drugs. On the other hand, atenolol has been primarily used as evidence regarding β-blockers, and carvedilol and bisoprolol do not have established evidences regarding β-blockers. We examined whether carvedilol and bisoprolol can be recommended as a first-line drug for hypertensive patients without compelling indications [824].

Concerning antihypertensive effects, there were 2 RCTs of carvedilol using a placebo [825, 826]. The administration of carvedilol at 50 mg/day significantly reduced blood pressure in comparison with the placebo (mean difference in SBP: −8.33 mmHg, 95%CI: −12.90 to −3.77), but there were no differences in the effects between 12.5 [826] or 25 mg/day [825, 826] of carvedilol and the placebo (Figure CQ6-1). There were 6 RCTs regarding the blood pressure-lowering effects of bisoprolol [827–832]. A meta-analysis showed that bisoprolol significantly reduced blood

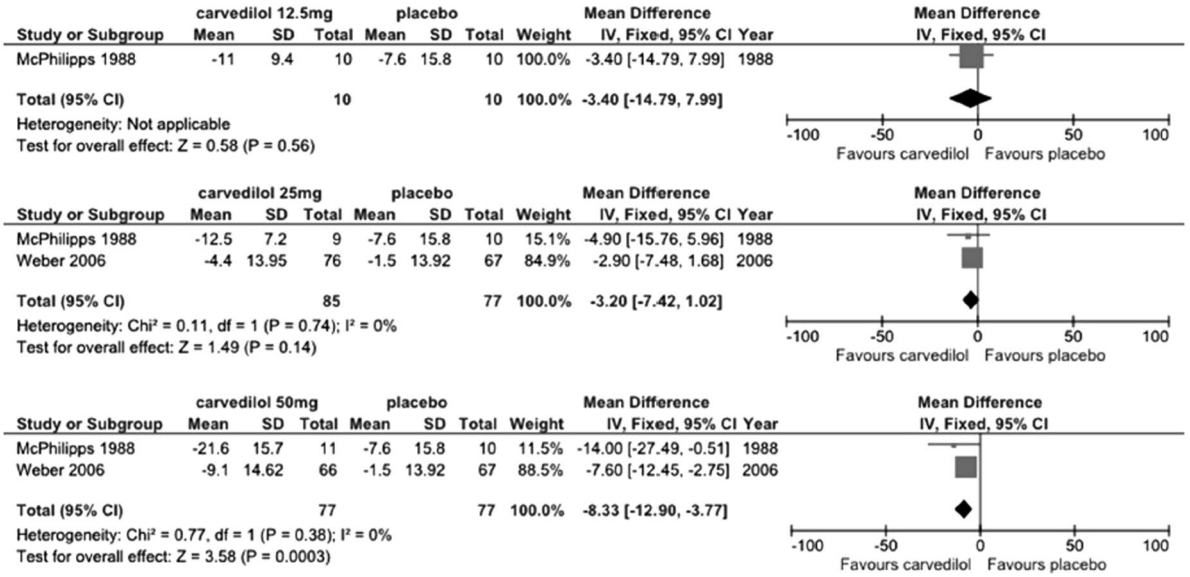


Fig. CQ6-1 SBP-reducing effects of carvedilol (vs. placebo). Fixed: Fixed effect model, IV: Inverse variance. (Source: Ref. [824])

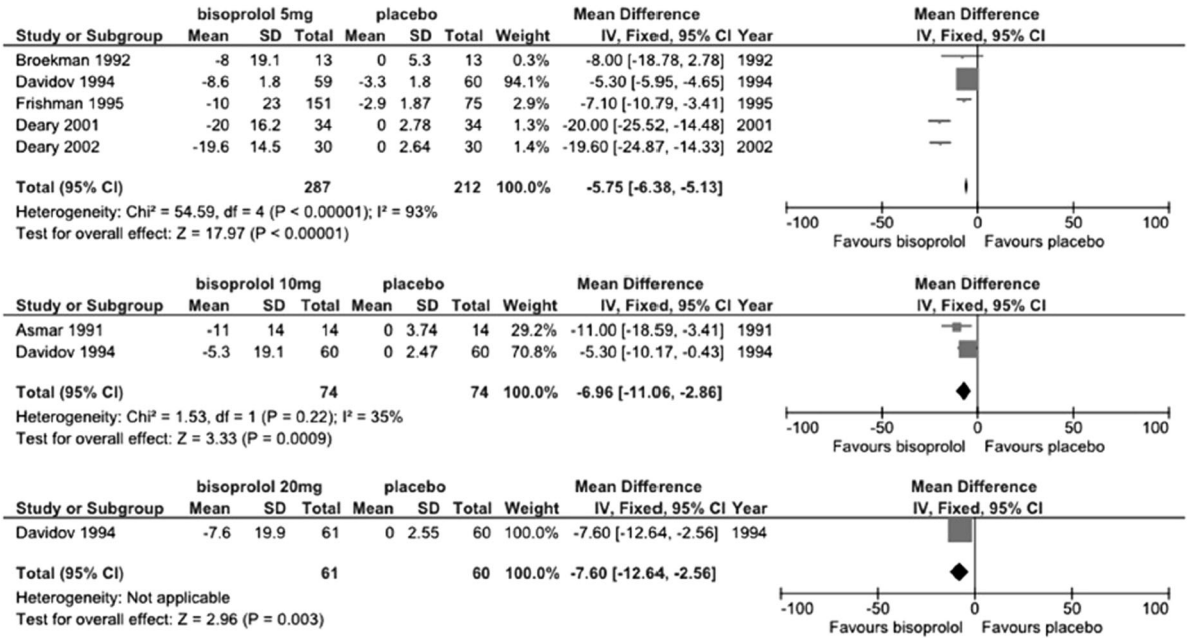


Fig. CQ6-2 SBP-reducing effects of bisoprolol (vs. placebo). Fixed: Fixed effect model, IV: Inverse variance. (Source: Ref. [824])

pressure at 5 mg/day (mean difference in SBP: −5.75 mmHg, 95%CI: −6.38 to −5.13), 10 mg/day (−6.96 mmHg, 95%CI: −11.06 to −2.86), and 20 mg/day (−7.60 mmHg, 95%CI: −12.64 to −2.56) in comparison with a placebo (Figure CQ6-2). Concerning the blood pressure-lowering effects of bisoprolol, a control group consisted of placebo-treated or untreated patients, or the effects were examined with respect to the dose of an interventional drug in the absence of a control group; non-directivity was evaluated as serious. In many references, neither randomization nor blinding was sufficient, and we considered that there was a serious bias risk. Furthermore, serious non-uniformity was noted. Thus, finally, the evidence level was evaluated as very weak by 2-level grading-down.

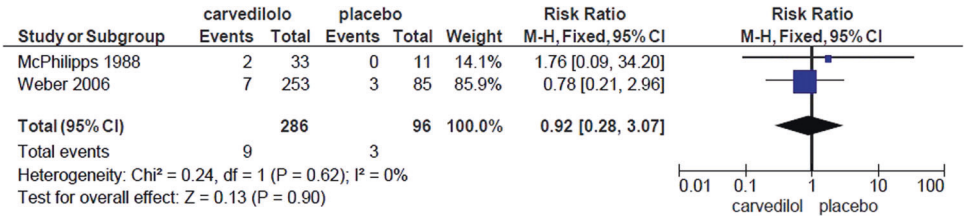


Fig. CQ6-3 Incidence of adverse events related to carvedilol (vs. placebo). Fixed: Fixed effect model, M-H: Mantel-Haenszel method

None of these 8 RCTs evaluated the cardiovascular mortality rate, all-cause mortality, hypotension, or bradycardia as an outcome.

With respect to other adverse events, a meta-analysis of 2 RCTs of carvedilol found there was no increase in their incidence in comparison with a placebo (Figure CQ6-3). However, in these trials, neither randomization nor blinding was sufficient, and the bias risk was evaluated as serious. Although there was no serious problem regarding non-directivity, publication bias, or non-uniformity, there was a serious problem regarding the bias risk. Therefore, finally, the evidence level was evaluated as intermediate by 1-level grading-down. There was no RCT of bisoprolol.

Thus, neither carvedilol nor bisoprolol, which are currently used β-blockers, can be recommended as a first-line drug for hypertensive patients without compelling indications.

LITERATURE SEARCHING

We searched the literature before August 2017 on the PubMed and Cochrane Library. Based on the results of searching, we extracted articles on RCTs regarding this CQ.

Chapter 6 Hypertension associated with organ damage

POINT 6A

1. **In patients undergoing thrombolytic therapy in the hyperacute phase of ischemic stroke, blood pressure should be controlled at <180/105 mmHg within 24 h after treatment**
2. **In the hyperacute (within 24 h after onset) and acute (within 2 weeks after onset) phases of ischemic stroke, for which thrombolytic therapy is not indicated, antihypertensive therapy should be carefully performed if hypertension persists, with a systolic blood pressure (SBP) exceeding 220 mmHg and a diastolic blood pressure (DBP) exceeding 120 mmHg, or if aortic dissection, acute myocardial infarction, heart failure, or renal failure is present. Marked hypotension (shock) must be promptly treated by fluid transfusion or vasopressor administration.**
3. **In the chronic phase of ischemic stroke (1 month or more after onset), the target level of blood pressure control should be <130/80 mmHg. In patients with marked stenosis of the bilateral carotid arteries or occlusion of a main trunk of the cerebral arteries and in unevaluated patients, much attention should be paid so that there may be no excessive decrease in blood pressure, targeting <140/90 mmHg.**
4. **In the acute phase of intracerebral hemorrhage, SBP should be reduced to <140 mmHg as early as possible, and it may be maintained at this level. However, kidney dysfunction related to a decrease in blood pressure must be considered. In the chronic phase, the target of blood pressure control should be <130/80 mmHg.**
5. **In patients with subarachnoid hemorrhage due to ruptured cerebral aneurysms, intensive antihypertensive therapy may be considered to prevent recurrent hemorrhage until the treatment of cerebral aneurysms.**
6. **In the hyperacute phase of cerebrovascular disease, the i.v. administration of a low dose of nicardipine, diltiazem, nitroglycerin or nitroprusside is recommended. In the acute phase, it should be switched to oral antihypertensive drugs if possible. The sublingual administration of nifedipine should be avoided, because it may induce a rapid decrease in blood pressure.**
7. **Oral antihypertensive drugs, such as Ca channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and diuretics, are recommended for patients with cerebrovascular disease.**

1. CEREBROVASCULAR DISEASE

In Japan, cerebrovascular disease accounts for a high percentage of patients with hypertensive organ damage, and the number of patients with cerebrovascular disease,

Table 6-1 Treatment for hypertension complicated by cerebrovascular diseases

		Conditions to treat	Target blood pressure level	Antihypertensive drugs
Hyperacute phase (patients with ischemic stroke in whom thrombolytic therapy[*1] is indicated) (within 24 h after onset)	Ischemic stroke within 4.5 h after onset	Patients awaiting thrombolytic therapy[*1] SBP >185 mmHg or DBP >110 mmHg	During thrombolytic therapy and within 24 h after thrombolytic therapy: <180/105 mmHg, 85–90% of the pretreatment value	Micro-dose drip infusion of CCBs such as nicardipine
Acute phase (within 2 weeks after onset)	Ischemic stroke	SBP >220 mmHg or DBP >120 mmHg	85% of the pretreatment value	Micro-dose drip infusion of CCBs such as nicardipine, or oral drugs (CCBs, ACE inhibitors, ARBs or diuretics)
	Intracerebral hemorrhage	SBP >140 mmHg	SBP <140 mmHg[*2]	
	Subarachnoid hemorrhage (from the onset of ruptured cerebral aneurysm until the treatment of cerebral aneurysm)	SBP >160 mmHg	80% of the pretreatment value[*3]	
Chronic phase (1 month or more after onset)	Ischemic stroke (patietns without marked stenosis of the bilateral carotid arteries or occlusion of a main trunk of the cerebral arteries) Intracerebral hemorrhage Subarachnoid hemorrhage	SBP ≥130 mmHg	<130/80 mmHg	Oral drugs (CCBs, ACE inhibitors, ARBs or diuretics)
	Ischemic stroke (patients with marked stenosis of the bilateral carotid arteries or occlusion of a main trunk of the cerebral arteries, or unevaluated patients)	SBP ≥140 mmHg	<140/90 mmHg	

[*1] In patients in whom endovascular therapy is scheduled, it should be performed in accordance with thrombolytic therapy.

[*2] In patients in whom increased intracranial pressure is expected due to a severe condition, it must be considered that cerebral perfusion pressure may reduce with a decrease in blood pressure, deteriorating symptoms or causing acute renal disorder.

[*3] In patients in whom increased intracranial pressure is expected due to a severe condition or those with acute ischemic stroke or cerebrovascular spasm, cerebral perfusion pressure may reduce with blood pressure, deteriorating symptoms; therefore, antihypertensive treatment should be performed carefully.

particularly those with ischemic stroke, is increasing with the aging of the population. Many patients with cerebrovascular disease develop hypertension in the acute phase, and blood pressure control in the acute phase is an initial problem. In particular, adequate antihypertensive therapy during reperfusion therapy for ischemic stroke (thrombolytic therapy or endovascular treatment) in the hyperacute phase should be reviewed, raising an important issue. Furthermore, hypertension is the most important risk factor involved in the recurrence of cerebrovascular disease, and blood pressure management for the prevention of recurrence is necessary. In hypertensive patients with cerebrovascular disease, subjects to be treated with antihypertensive drugs and the target level of blood pressure control are determined on the basis of the stroke subtype, interval after onset, stroke severity, age, and usage of antithrombotic drugs. In addition, as a high percentage of older hypertensive patients are known to have asymptomatic cerebrovascular disease, blood pressure management in hypertensive patients with asymptomatic cerebrovascular disease is also important.

Treatment for patients with cerebrovascular disease accompanied with hypertension in the Japanese Society of Hypertension (JSH) 2019 Guidelines for the Management of Hypertension is summarized in Table 6-1.

1) Hyperacute/acute phases

In the hyperacute phase, within 24 h, and in the acute phase, within 1–2 weeks after the onset of cerebrovascular disease, a high blood pressure is observed regardless of the stroke subtype: ischemic stroke, intracerebral hemorrhage or subarachnoid hemorrhage. This increase in blood pressure associated with onset is considered to be a biological protective reaction to stress, urinary retention, headache, brain tissue ischemia and an increase in intracranial pressure due to edema and hematoma. In many patients, blood pressure gradually decreases by resting, urination by bladder catheterization, pain control and treatment of brain edema without the administration of antihypertensive drugs. It begins to decrease within 24 h after onset in most patients with ischemic stroke and within a few days in those with intracerebral hemorrhage [833, 834].

The range of autoregulation of cerebral blood flow is shifted to the right (a higher blood pressure level) due to hypertension [835]. Autoregulation is affected in the acute phase of cerebrovascular disease, and cerebral blood flow decreases even with a slight reduction in blood pressure. Thus, a decrease in blood pressure may enlarge ischemic core and ischemic penumbra (area of ischemic territory that is still potentially salvageable for functional recovery with restoration of blood flow) [836]. As vasodilatory capacity of blood vessels in the ischemic area is highly affected, vasodilator drugs only dilate blood vessels of the intact areas, resulting in decrease in blood flow in the ischemic lesion, which is called intracerebral steal phenomenon. For these reasons, intensive antihypertensive treatment in the acute phase of ischemic stroke must be carefully performed [837]. On the other hand, intensive antihypertensive treatment from the acute phase has been conducted in patients with intracerebral hemorrhage.

(1) Target level of blood pressure control

i) Ischemic stroke

In the Guidelines for the Management of Stroke in 2015 [supplement revision in 2017] [838], it is recommended that antihypertensive treatment by i.v. administration should be performed if SBP is >185 mmHg or DBP is >110 mmHg in patients in whom thrombolytic therapy by the i.v. administration of tissue plasminogen activator (t-PA) in the hyperacute phase of ischemic stroke, within 4.5 h after onset, is indicated. SBP and DBP should be controlled at <180 and <105 mmHg, respectively, by 24-h strict blood pressure management involving blood pressure monitoring during and after the treatment. In the American Heart Association (AHA)/American Stroke Association (ASA) 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke [839], similar antihypertensive control is also recommended. A sub-analysis of the ECASS study involving t-PA (1.1 mg/kg) administration within 6 h after onset showed that the rate of patients with no sequelae or mild sequelae was the highest in a group with a blood pressure of 140–170/80–100 mmHg [840]. Furthermore, another study indicated that the outcome after 3 months was good in patients with a low blood pressure/pulse pressure/heart rate ≥8 h after t-PA administration; [841] the level of blood pressure control must be considered. Another study reported that marked variability in blood pressure after t-PA therapy were associated with the onset of symptomatic intracerebral hemorrhage or death; [842] attention should also be paid to blood pressure variability. Concerning endovascular treatment (such as mechanical thrombectomy)-indicated patients, there is no evidence regarding the target of blood pressure control, but management in accordance with thrombolytic therapy should be conducted [838].

Even when thrombolytic therapy is not performed, the target level of blood pressure control should be 85% of the pretreatment value in patients with a SBP of >220 mmHg or a DBP of >120 mmHg (persistent hypertension) and those with aorticdissection, acute myocardial infarction, heart failure, or renal failur [839]. In the AHA/ASA 2018 Guidelines, it is described that the start of antihypertensive therapy within 24 h after onset is not so dangerous [839]. In hypertensive patients with stable neurological signs, the resumption of pre-stroke used antihypertensive drugs 24 h after the onset may be considered if there is no

contraindication [843]. Several observational studies involving Japanese patients indicated that a high blood pressure within 48 h after stroke onset was associated with the neurological deterioration and an poor functional outcome after 3 months, and that the blood pressure during 24 to 48 h after onset was significantly lower in patients with no sequelae or mild sequelae after 3months [844, 845]. However, the optimal blood pressure value is unclear. In addition, it is recommended that marked hypotension should be promptly treated by fluid infusion or vasopressor administration [839].

The ACCESS [846], SCAST [847], PRoFESS subanalysis [848], and CATIS [849] studies examined standard antihypertensive therapy in the acute phase of ischemic stroke. In the ACCESS study [846], patients with ischemic stroke in whom SBP (mean value of at least two sessions of blood pressure measurement) was ≥200 mmHg or diastolic pressure was ≥110 mmHg during 6 to 24 h after admission, or in whom SBP was ≥180 mmHg or diastolic pressure was ≥105 mmHg during 24 to 36 h after admission, were treated with an angiotensin II receptor blocker (ARB), candesartan, for 1 week. Although there was no significant difference in the prognosis of stroke, which was a primary end point, the mortality rate after 1 year and occurrence of cardiovascular events, which were secondary end points, significantly reduced. ARBs were expected to have an organ-protecting effect. Recently, a sub-analysis of the CATIS study showed that the mortality rate after 3 months and incidence of serious functional disturbance (modified Rankin Scale [mRS] 3–6) significantly decreased in a group in which antihypertensive therapy was started during 24 to 48 h after the onset of ischemic stroke [850]. Similarly, some studies indicated that antihypertensive therapy in the acute phase of ischemic stroke improved the outcome [846, 851], but many studies showed that there was no influence on the outcome [847, 849, 852–858]. In the Scandinavian Candesartan Acute Stroke Trial (SCAST) [847], cerebrovascular disease patients (ischemia: 85%; hemorrhage: 15%) with a SBP of >140 mmHg within 30 h after onset were randomly divided into candesartan-treated and non-candesartan-treated groups for 7-day administration, and the occurrence of composite cardiovascular events over 6 months was used as a primary end point. The blood pressures on day 7 in the candesartan-treated and non-candesartan-treated groups were 147/82 and 152/84 mmHg, respectively; in the former, the value was significantly lower. There was no significant difference in the composite end point after 6 months between the two groups. Furthermore, some studies indicated that marked variability in SBP in the acute phase of ischemic stroke or during 4 to 10 days after the onset were associated with an poor functional outcome [859, 860], whereas others reported that there was no influence on the outcome [861]. Thus, the efficacy of standard antihypertensive therapy in the acute phase of ischemic stroke has not been established.

ii) Intracerebral hemorrhage

In the INTERACT2 study involving 2839 intracerebral hemorrhage patients within 6 h of onset, the prognosis were compared between groups in which target SBP as <140 mmHg and <180 mmHg. Death or severe disturbance (mRS 3–6) 90 days after onset, as a primary endpoint, was slightly more frequent in the <180-mmHg group than in the other group. The functional prognosis evaluated based on the results of a shift analysis of the mRS score at 90 days after onset, as a secondary endpoint, was significantly improved in the <140-mmHg group [862]. Post-hoc analysis showed that the outcome was the most favorable in a group in which SBP was maintained at 130–139 mmHg until 7 days after the onset [863].

On the other hand, in the ATACH-2 study [864], 1000 patients with acute intracerebral hemorrhage were randomly assigned to receive intensive antihypertensive therapy (SBP: 110–139 mmHg) or standard antihypertensive therapy (SBP: 140–179 mmHg), and there were no differences in the mortality rate or incidence of serious functional disturbance (mRS 4–6) after 3 months, which were primary endpoints. There were also no differences in hematoma enlargement after 24 h, the neurological deterioration within 24 h, serious adverse events within 72 h, or death within 3 months after the onset, which were secondary endpoints. A sub-analysis of the ATACH-2 study showed that there was a significant increase in the incidence of heart-associated adverse events in patients in whom a SBP of 120–130 mmHg was reached [865]. According to a systematic review (SR) of randomized controlled trials (RCTs) including the INTERACT2 and ATACH-2 studies [866, 867], intensive antihypertensive therapy in the acute phase of intracerebral hemorrhage prevented hematoma enlargement. Furthermore, it was not associated with treatment-related adverse events, suggesting its safety. However, it was reported that there was no significant association between intensive antihypertensive therapy and early neurological deterioration, death within 3 months, or treatment-associated adverse events.

In the ICH ADAPT study [868], 75 patients within 24 h after the onset of intracerebral hemorrhage were randomly assigned to target a SBP of <150 mmHg or <180 mmHg, and there was no difference in cerebral blood flow in the area around the hematoma on perfusion CT, suggesting the safety of intensive antihypertensive therapy in the acute phase of intracerebral hemorrhage.

According to a survey on current blood pressure management for acute intracerebral hemorrhage in Japan [869], SBP control at ≤160 mmHg by i.v. administration of nicardipine was routinely performed. The results of the SAMURAI-ICH, which confirmed the validity of a majority

opinion presented in this survey by a multi-center, cooperative, prospective study design, indicated the safety of SBP control at 120–160 mmHg by the i.v. administration of nicardipine in Japanese patients [870]. Its subanalysis [871] showed that blood pressure control at a lower level in the target range of 120–160 mmHg led to a more favorable outcome. Internationally, several studies also reported that intensive antihypertensive therapy in the acute phase of intracerebral hemorrhage led to an improvement in the functional outcome [872, 873]. On the other hand, many studies indicated that variability in blood pressure in the acute phase of intracerebral hemorrhage were associated with neurological deterioration or a subsequent poor outcome; [859, 874–876] attention must be paid to variability of blood pressure.

Recently, the incidence of anticoagulant-associated intracerebral hemorrhage has increased. However, concerning intracerebral hemorrhage in patients receiving Warfarin, it was reported that the reduction of PT-INR and SBP to <1.3 and <160 mmHg, respectively, within 4 h of onset was associated with the prevention of hematoma enlargement [877].

In the AHA/ASA 2015 Guidelines for the Management of Spontaneous Intracerebral Hemorrhage [878], it is recommended that antihypertensive therapy should be performed if SBP exceeds 220 mmHg in patients with hyperacute-(≤24 h after onset)/acute-phase of intracerebral hemorrhage, and that a SBP of approximately 140 mmHg should be targeted if it ranges from 150 to 220 mmHg. However, based on the above evidence, a strategy to reduce SBP in the acute phase of intracerebral hemorrhage to <140 mmHg as early as possible and maintain this level may be considered. In patients with severe condition in whom an increase in intracranial pressure is expected, it must be considered that cerebral perfusion pressure may decrease with blood pressure, resulting in neurological deterioration. Furthermore, it must be considered that a decrease in SBP to <130 mmHg may cause heart- or kidney-associated adverse events [864, 865].

iii) Subarachnoid hemorrhage

In patients with subarachnoid hemorrhage, it is important to prevent rebleeding. Sufficient control of blood pressure, sedation and pain control are desirable. In the AHA/ASA 2012 Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [879], it is described that antihypertensive treatment should be performed when SBP is >160 mmHg in patients with subarachnoid hemorrhage due to ruptured cerebral aneurysms until the treatment of cerebral aneurysms, and that the target level of blood pressure control should be <160 mmHg. The JSH2019 Guidelines recommend that the target of blood pressure control should be 80% of the pretreatment value when SBP exceeds 160 mmHg in patients with subarachnoid hemorrhage due to ruptured cerebral aneurysms until the treatment of cerebral aneurysms. However, a multicenter study in the Tohoku District of Japan [880] showed that SBP was 120 to 140 mmHg in most patients with rebleeding. Thus, no optimal blood pressure control has been established. Data on the usefulness of the intravenous administration of nicardipine, as an antihypertensive drug in the acute phase of subarachnoid hemorrhage, were published, providing useful information [881, 882]. Furthermore, it must be considered that cerebral perfusion pressure may decrease with blood pressure and resulting in neurological deterioration in patients with severe condition in whom an increase in intracranial pressure is expected and in those complicated with acute ischemic stroke or cerebrovascular spasm.

(2) Antihypertensive drugs to be recommended Drugs that act quickly and allow dose adjustment are desirable regardless of the stroke subtype. CCBs, such as nicardipine and diltiazem, or nitrate drugs, such as nitroglycerine and nitroprusside, which have long been used, are administered by low-dose i.v. infusion [853]. It must be considered that nitrate drugs may increase intracranial pressure, but no study has reported their influence on the clinical outcome [883]. A study indicated that their influence on cerebral blood flow was similar to that of CCBs [884]. Furthermore, the sublingual administration of nifedipine capsules should be avoided, because it may induce a rapid decrease in blood pressure. Antihypertensive treatment by i.v. infusion should be substituted for oral treatment as early as possible. As oral antihypertensive drugs, CCBs, ARBs, ACE inhibitors and diuretics are recommended [853].

Rehabilitation from an acute stage of stroke is necessary for improving activities of daily living (ADL) in stroke patients, but attention must be paid to valiability in blood pressure while conducting rehabilitation at the bedside.

2) Chronic phase

Patients with a history of cerebrovascular disease are known to frequently develop recurrent cerebrovascular disease, and the control of hypertension, which is its greatest risk factor, is extremely important for the treatment of patients in the chronic phase of cerebrovascular disease. According to the results of a retrospective study in Japan, the relationship between blood pressure after cerebrovascular disease and recurrence rate varies markedly among stroke subtypes, and the report of a J-shaped relationship between the recurrence of ischemic stroke and DBP, which is not observed in patients with intracerebral hemorrhage, has attracted attention [885]. In the PRoFESS study, antihypertensive therapy was conducted for 2.5 years (mean) in ischemic stroke patients within 120 days after onset, and the patients were divided into 5 groups based on the mean SBP during the

follow-up period: <120 mmHg, 120–130 mmHg, 130–140 mmHg, 140–150 mmHg, and ≥150 mmHg for analysis [886]. The incidences of recurrent stroke in the <120-mmHg and ≥140-mmHg groups were higher than in the 130–140-mmHg group. In the VISP study [887], patients with non-cardioembolic stroke were divided into 3 groups based on SBP: <120 mmHg, 120–140 mmHg, and ≥140 mmHg, and the recurrence rate was the lowest in the 120–140-mmHg group. On the other hand, another study indicated that the risk of recurrence reduced with a decrease in blood pressure until SBP and DBP reached 130 and 80 mmHg, respectively, in patients with a transient ischemic attack (TIA) or mild stroke, suggesting that there is no J-curve phenomenon [888]. Thus, a consensus regarding the presence of a J-curve phenomenon has not been established [490].

Since 1990, large-scale studies on the relationship between the prevention of recurrent cerebrovascular disease and blood pressure have been carried out [466, 676, 889–893], with SRs [894–898]. Antihypertensive drug therapy significantly reduces the recurrence rate of all types of cerebrovascular disease, the recurrence rate of nonfatal ischemic stroke, and incidences of myocardial infarction and all vascular events.

(1) Target of blood pressure control

i) Ischemic stroke

In the PROGRESS study [676], perindopril (4 mg per day) or a diuretic, indapamide (2 mg per day), was additionally administered to 6105 patients with chronic-phase of cerebrovascular disease (isdhemic stroke: 71%; TIA: 22%; and intracerebral hemorrhage: 11%), with a mean age of 64 years, in addition to conventional treatment. The blood pressure decreased from 147/86 to about 138/82 mmHg, and the recurrence rate of stroke was reduced by 28%. Another study also showed that SBP and DBP decreased by 5 and 2 mmHg, respectively, in the diuretic-treated group, and that the incidence of recurrent stroke reduced by 29% [890]. In addition, a sub-analysis of the PROGRESS study indicated that the incidences of intracerebral hemorrhage and ischemic stroke were lower in patients in whom blood pressure was controlled at a lower level (a SBP of ~120 mmHg) [899].

Rothwell et al. [900] reported that the risk of cerebrovascular disease significantly increased in a group in which the SBP decreased to 140 mmHg among patients with symptomatic, 70% or greater stenosis of the bilateral carotid arteries, whereas there was no increase in this risk even when the SBP decreased to 140 mmHg in patients with 70% or greater unilateral carotid artery stenosis. In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study [901], among patients with symptomatic intracranial artery (internal carotid, middle cerebral, vertebral or basilar artery) stenosis, the blood pressure level was not associated with the risk for ischemic stroke in those with marked (70% or greater) stenosis. In those with moderate (69% or lower) stenosis, the risk for ischemic stroke was high when the SBP was 160 mmHg or above. Yamauchi et al. [902] examined the relationship between blood pressure and recurrent stroke during follow-up with respect to the presence or absence of impaired cerebral perfusion on positron emission tomography in patients with symptomatic atherosclerotic occlusion of a main trunk of the cerebral arteries. In patients with impaired cerebral perfusion, the risk of recurrent stroke was high when the SBP was <130 mmHg. In those without impaired cerebral perfusion, this risk may be high at an elevated blood pressure level. They concluded that it is important to evaluate the presence or absence of impaired cerebral perfusion for blood pressure management. Thus, the hemodynamics may differ between vascular stenosis and obstruction. There is little evidence as a reference for the relationship between blood pressure and the risk for ischemic stroke in patients with obstruction of the unilateral internal carotid or basilar artery. Therefore, in the presence of obstruction of a main trunk of the cerebral arteries or marked stenosis, management matched to individual patients is necessary.

In the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial [466], a randomized comparative study was conducted on 3020 patients with chronic-phase of lacunar infarction by dividing them into two groups: a group with a target SBP of 130–149 mmHg (standard therapy group) and that with a target SBP of <130 mmHg (intensive therapy group), with a mean follow-up of 3.7 years. The type of antihypertensive drug was not limited. The mean SBPs after 1 year in the two groups were 138 and 127 mmHg, respectively. As a primary end point, ischemic stroke/intracranial hemorrhage was observed in 152 (2.8%yr) and 125 (2.2%yr) patients in the standard and intensive therapy groups, respectively; there was no significant difference. Ischemic stroke was present in 131 (2.4%yr) and 112 (2.0%yr) patients, respectively, showing no significant difference. Intracerebral hemorrhage was present in 16 (0.29%yr) and 6 (0.11%yr) patients, respectively; its incidence was significantly lower in the intensive therapy group.

In the PROGRESS study [464], antihypertensive therapy decreased the incidence of intracranial hemorrhage in patients, with a history of stroke or TIA, receiving an antithrombotic drug, and its incidence in the <120-mmHg (SBP) group was significantly lower than in the 120–139-mmHg, 140–159-mmHg, and ≥160-mmHg groups. In the Bleeding with Antithrombotic Therapy (BAT) study [462], 4009 Japanese patients taking antithrombotic drugs for the prevention of recurrent cerebrovascular or heart disease were prospectively enrolled, and hemorrhagic events were investigated over 19 months (median). Intracranial

hemorrhage was observed in 0.3% of patients taking a single antithrombotic drug, 0.6% of those receiving two antiplatelet drugs, 0.6% of those taking Warfarin and 1.0% of those receiving a combination of Warfarin and an antiplatelet drug. The incidence of intracranial hemorrhage was particularly high in patients with a history of cerebrovascular disease. The results suggested that the incidence of intracerebral hemorrhage was lower when the blood pressure at the last clinic visit before the onset was lower in patients taking antithrombotic drugs. The cut-off value was statistically calculated as 130/81 mmHg [465]. A sub-analysis of the CSPS2 study [903] showed that the incidence of hemorrhagic stroke in the aspirin group was higher than in the cilostazol group at all SBP levels. In particular, it was significantly higher in patients with a SBP of >140 mmHg. Therefore, when prescribing aspirin, blood pressure control may be particularly important.

In the JSH2019 Guidelines, the target of blood pressure control for patients with chronic-phase of ischemic stroke is recommended as <130/80 mmHg. However, attention must be paid so that there may be no excessive reduction in blood pressure in patients with marked stenosis of the bilateral carotid arteries or occlusion of a main trunk of the cerebral arteries. In patients with these lesions or unevaluated patients, a blood pressure of <140/90 mmHg should be targeted. Complaints of dizziness, light headedness, tiredness, numbness, weakness, loss of energy or neurological deterioration during treatment may be symptoms of cerebral circulatory insufficiency due to a decrease in blood pressure, and a decrease in the dose or change in the type of antihypertensive drug is necessary. Particular caution is needed in patients with stenosis/occlusion of a main trunk of the cerebral arteries, because dysautoregulation of the cerebral circulation may persist for 3 months or more [904, 905].

ii) Intracerebral hemorrhage

Hypertensive intracerebral hemorrhage may frequently recur in patients in whom blood pressure control is poor [885, 906–909]. With regard to recurrent intracerebral hemorrhage, a study reported that a DBP of 75–90 mmHg was favorable [885], and another study indicated that the recurrence rate was low when DBP was controlled at <90 mmHg [906]. However, the evidence level is low. The PROGRESS study involving patients with chronic-phase of cerebrovascular disease, including those with intracerebral hemorrhage (11%), showed that antihypertensive therapy decreased the incidence of intracerebral hemorrhage by 50% [676], and that there was also a 50% decrease in the incidence of recurrent intracerebral hemorrhage [910]. A sub-analysis of the PROGRESS study [899] indicated that antihypertensive therapy was effective in the prevention of recurrence in intracerebral hemorrhage patients with a SBP of ≥120 mmHg, differing from those with ischemic stroke. Among patients achieving a blood pressure of 112–168 mmHg, the incidence of intracerebral hemorrhage was lower in those with a lower blood pressure. Furthermore, antihypertensive therapy markedly reduced the incidence of intracerebral hemorrhage associated with amyloid angiopathy (by 77%) [911]. The JSH2019 Guidelines recommend that the final target of blood pressure control in patients with intracerebral hemorrhage should be <130/80 mmHg.

iii) Subarachnoid hemorrhage

There is no evidence on the target of blood pressure control in the chronic phase of subarachnoid hemorrhage. The target of blood pressure control was proposed in accordance with that in patients with intracerebral hemorrhage.

(2) Recommended classes of antihypertensive drug In PROGRESS study [676], a combination of an ACE inhibitor and a diuretic was suggested to reduce the recurrence rate of cerebrovascular disease and prevent the occurrence of dementia. In the Morbidity and Mortality After Stroke (MOSES) study [893], primary end points (all deaths and all cardiovascular and cerebrovascular events) and cerebrovascular events (one of the secondary end points) were significantly lower in the ARB (eprosartan) group than in the CCB (nitrendipine) group in spite of no difference in blood pressure reduction between two groups. The ONTARGET study [713] examined death related to vascular events, including stroke, and admission due to heart failure in high-risk vascular disease patients, including those with stroke, and showed the noninferiority of an ARB (telmisartan) to an ACE inhibitor (ramipril). In addition, the demerit (vascular edema) of combination therapy with the two drugs did not exceed its merit.

In the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111], diuretics, ACE inhibitors, ARBs, or a combination of a diuretic and an ACE inhibitor is recommended. Proposing that drugs should be selected for each patient depending on background factors (extracranial obstructive vascular diseases, renal disorders, heart disease and diabetes), they also recommend ARBs and ACE inhibitors for patients with diabetes mellitus or atrial fibrillation. In the ESH-ESC Guidelines 2018 [534], it is recommended that an ACE inhibitor or ARB should be combined with a CCB or diuretic. On the other hand, it is described that β-blockers should be avoided if there is no necessity, because their preventive effects on recurrent cerebrovascular disease are weaker than those of other antihypertensive drugs. As demonstrated by the MOSES study [893], there are also results indicating differences among drugs despite a similar decrease in blood pressure.

Furthermore, some studies ruled out the preventive effects of diuretics and β-blockers on recurrence [912, 913].

Considering the above evidence, the JSH2019 Guidelines recommend CCBs, ARBs, ACE inhibitors and diuretics, which are first-line drugs, regardless of the subtypes of cerebrovascular disease for the treatment of hypertension in the chronic phase. These drugs do not reduce cerebral blood flow on a decrease in blood pressure (unless there is an excessive decrease in blood pressure). Furthermore, antihypertensive drugs should be selected, considering the presence or absence of associated disorders such as diabetes mellitus, metabolic syndrome and chronic kidney disease (CKD).

3) Asymptomatic cerebrovascular disease

Most of the asymptomatic ischemic stroke closely related to hypertension is a small lesion similar to lacunar infarction, a small vessel disease for which hypertension and age are considered to be the greatest risk factors. Furthermore, hypertension is also the most important risk factor for cerebral white matter lesions [914–916]. In addition, asymptomatic intracerebral hemorrhage or microbleeds, which is detected mostly by T2*-weighted MRI, is attracting attention [917, 918]. Their presence and progression are independent risk factors for development of cerebrovascular disease and cognitive impairment [914, 919–926].

In principle, target of blood pressure and useful antihypertensive drugs for hypertensive patients with asymptomatic ischemic stroke or intracerebral hemorrhage are the same as those for chronic phase of cerebrovascular disease, but the results of a CT subanalysis of PROGRESS study [927] suggested that more intensive antihypertensive treatment is desirable. Asymptomatic ischemic stroke is an index of target organ damage along with white matter lesions, and non-dipper, riser and morning surges observed by 24-h blood pressure monitoring are its risk factors [166, 180, 181, 928]. Blood pressure control over 24 h and early in the morning is important.

In addition, asymptomatic carotid artery stenosis and unruptured cerebral aneurysms are also frequently detected, and they have been shown to be risk factors for the occurrence of cerebrovascular disease. With regard to asymptomatic carotid artery stenosis, the evaluation of indications for surgical treatment before the initiation of antihypertensive treatment is important. If the patient has a familial history of subarachnoid hemorrhage or unruptured cerebral aneurysm, intensive antihypertensive treatment is recommended.

Patients with asymptomatic cerebrovascular disease feel high-level anxiety over the condition of cerebrovascular disease and treatment, and hence sufficient informed consent is extremely important.

POINT 6B

[Cardiac hypertrophy]

1. **The regression of cardiac hypertrophy leads to an improvement in prognosis.**
2. **Sustained and sufficient decrease in blood pressure by any major antihypertensive drugs can induce the regression of cardiac hypertrophy. In particular, renin–angiotensin (RA) system inhibitors and CCBs are effective for cardiac hypertrophy.**

[Coronary artery disease]

1. **The target of blood pressure control in patients with coronary artery disease should be <130/80 mmHg.**
2. **First-line drugs for angina pectoris related to organic stenosis of the coronary artery are CCBs and β-blockers with no endogenous sympathomimetic action.**
3. **First-choice drugs for vasospastic angina pectoris are CCBs.**
4. **In patients with old myocardial infarction, β-blockers, renin–angiotensin (RA) system inhibitors and mineralocorticoid receptor (MR) antagonists reduce the mortality and improve the prognosis.**

[Heart failure]

1. **In patients with heart failure, antihypertensive drug therapy not only reduces blood pressure but also improves their quality of life and/or prognosis.**
2. **Standard medical therapy for heart failure with reduced ejection fraction (HFrEF) is combination therapy with an RA system inhibitor, a β-blocker and a diuretic, and it reduces mortality and improves the prognosis.**
3. **In HFrEF patients receiving standard medical therapy, MR antagonists further improve the prognosis.**
4. **When introducing an RA system inhibitor or β-blocker, its dose should be gradually increased from a low dose to a maximum tolerated dose while paying attention to the deterioration of heart failure, hypotension, bradycardia (β-blockers), and renal dysfunction. As individualized treatment in accordance with the etiology, condition, or comorbidities is important in HFrEF patients, the target of blood pressure control cannot be set.**
5. **If a decrease in blood pressure is insufficient despite dose-elevation of an RA system inhibitor, β-blocker, and MR antagonist to their maximum tolerated doses under the adequate use of diuretics in hypertensive**

patients with HFrEF, a long-acting CCB should be added.

6. **In patients with heart failure with preserved ejection fraction (HFpEF), SBP should be targeted to <130 mmHg.**
7. **There is no evidence regarding antihypertensive drugs particularly recommended for hypertensive patients with HFpEF, but antihypertensive drug therapy with a diuretic should be performed.**

[Atrial fibrillation]

1. **Hypertension is a major risk factor for atrial fibrillation, and strict blood pressure control (SBP: <130 mmHg) is effective in preventing the new onset of atrial fibrillation.**
2. **The primary/secondary preventive effects of RA system inhibitors on atrial fibrillation in all**

Table 6-2 Treatment for hypertension complicated by heart diseases

Cardiac hypertrophy		● To achieve regression of cardiac hypertrophy, a sustained and sufficient decrease in blood pressure is necessary. ● RA system inhibitors or long-acting CCBs are the first choice.
Coronary artery disease		● The target of blood pressure control should be <130/80 mmHg. ● First-choice drugs for angina pectoris related to organic stenosis of the coronary artery[*1]: β-blockers and long-acting CCBs ● First-choice drugs for coronary vasospastic angina: CCBs[*2] ※See "CQ7".
Old myocardial infarction		● Standard medical therapy: Combination therapy with an ACE inhibitor (or an ARB if intolerable to ACE inhibitors) and a β-blocker ● Patients with severe systolic dysfunction: An MR antagonist[*3] should be added. ● Relief of congestion: A diuretic should be added. ● Cases in which a decrease in blood pressure is insufficient despite standard medical therapy at gradually increased maximum tolerated doses: A long-acting CCB is added. ※See "CQ8".
Heart failure	Heart failure with reduced ejection fraction (HFrEF)	● Although there are many normo- or hypotensive patients, antihypertensive drugs should be used to improve the QOL or prognosis and prevent heart failure hospitalization in addition to blood pressure control. ● Individualized treatment in accordance with the condition or comorbidities is important; therefore, the target of blood pressure control cannot be set. ● Standard medical therapy: Combination therapy with an ACE inhibitor (or an ARB if intolerable to ACE inhibitors)[*4], a β-blocker[*4], a diuretic and an MR antagonist[*5] ● Cases in which a decrease in blood pressure is insufficient despite standard medical therapy at gradually increased maximum tolerated doses under the adequate use of a diuretic: A long-acting CCB is added. ※See "CQ8".
	Heart failure with preserved ejection fraction (HFpEF)	● A SBP of <130 mmHg should be targeted. ● Antihypertensive drug therapy with a diuretic in accordance with individual conditions ※See "CQ9".
Atrial fibrillation		● New-onset prevention: Blood pressure control to a SBP of <130 mmHg is effective. ● Prevention of the new onset of atrial fibrillation in patients with cardiac hypertrophy or heart failure: Antihypertensive drug therapy with an RA system inhibitor ● Patients with atrial fibrillation: In addition to adequate anticoagulant therapy and heart rate control, a SBP of <130 mmHg should be targeted.

[*1] Coronary artery stenosis or myocardial ischemia is evaluated in cooperation with cardiologists, and coronary revascularization should be performed if necessary.

[*2] They are used to prevent coronary spasm regardless of the presence or absence of hypertension.

[*3] Hyperkalemia must be avoided.

[*4] Administration should be started at a low dose, and the dose should be increased carefully and slowly.

[*5] It is primarily used in patients with a marked reduction in the left ventricular ejection fraction. Hyperkalemia must be avoided.

hypertensive patients are not clear, but these drugs may be effective in preventing the new onset of atrial fibrillation in those with left ventricular hypertrophy or heart failure.

3. **In patients with atrial fibrillation, blood pressure control targeting a SBP of <130 mmHg should be performed in addition to adequate anticoagulant therapy and heart rate control.**

2. HEART DISEASE (TABLE 6-2)

The heart is one of the important target organs of hypertension. Increases in systolic and diastolic pressure loads induce myocardial remodeling such as cardiac hypertrophy and myocardial fibrosis, and coronary endothelial damage. Risk factors, such as dyslipidemia, diabetes mellitus and smoking, increase the risk of coronary atherosclerosis. The progression of myocardial remodeling and coronary atherosclerosis leads to coronary artery disease, heart failure, arrhythmia and sudden death. To decrease the incidence of heart disease and the mortality, it is important to sufficiently and continuously reduce blood pressure [111, 534, 929–931].

1) Cardiac hypertrophy

Hypertension complicated by cardiac hypertrophy increases the mortality and risks of heart failure and cardiovascular events related to coronary artery disease [932]. An additional analysis of the SPRINT study showed that a decrease in SBP to <120 mmHg (blood pressure measured using an automatic office blood pressure meter in a physician-free place: automated office blood pressure [AOBP]) prevented the onset of cardiac hypertrophy, and that it promoted regression [933]. Hypertension treatment-induced regression of cardiac hypertrophy decreases the incidences of cardiovascular events and sudden death [934, 935]. A sub-analysis of the CASE-J study indicated that SBP lowering to <130 mmHg reduced the incidence of cardiovascular events in hypertensive patients with cardiac hypertrophy to a level similar to that in patients without cardiac hypertrophy [513]. Although major antihypertensive drugs promote regression of cardiac hypertrophy, a meta-analysis comparing their effects on regression of cardiac hypertrophy showed that the effects of RA system inhibitors and CCBs were most evident [669].

2) Coronary artery disease

A blood pressure of ≥115/75 mmHg exponentially increases coronary artery disease-related mortality [405]. According to a meta-analysis of the BPLTTC study, blood pressure reduction decreases the incidence of coronary artery disease in hypertensive patients regardless of the type of antihypertensive drug used [936]. In particular, long-acting CCBs and RA system inhibitors prevent the onset of coronary artery disease and cardiovascular events [892, 937–943]. For the primary/secondary prevention of coronary artery disease, antiplatelet therapy, LDL cholesterol-lowering therapy with statins, impaired glucose tolerance/diabetes control, and risk factor management, such as smoking cessation, are important in addition to hypertension treatment [398, 944–946]. In addition to drug therapy, myocardial ischemia should be evaluated in cooperation with cardiologists, and if necessarly, coronary revascularization is recommended to be performed to relieve anginal symptoms and prevent cardiovascular events [947].

Several placebo-controlled RCTs involving patients with coronary artery disease showed that strict SBP lowering prevented coronary artery disease, reducing coronary plaque [724, 892, 939, 941]. A meta-analysis involving 66,504 patients with coronary artery disease indicated that blood pressure lowering to a SBP of ≤130 mmHg decreased the incidence of heart failure by 30% and that of stroke by 20% without increasing all-cause death or cardiovascular death in comparison with blood pressure lowering to a SBP of 136–140 mmHg, and that it decreased the incidences of myocardial infarction and angina pectoris by 10%, respectively, although there was no statistical significance [948]. In addition, a meta-analysis involving 64,162 coronary artery disease patients with a blood pressure of <140/90 mmHg (without hypertension) showed that antihypertensive drug administration decreased the incidence of stroke by 23%, that of myocardial infarction by 20%, that of heart failure by 29%, cardiovascular mortality rate by 17%, and total mortality rate by 13% [949].

The possibility that an excessive decrease in DBP may increase the incidence of cardiovascular events (J-curve phenomenon) in patients with coronary artery disease was considered, but the CQ7 results suggested that, when a SBP of <130 mmHg is targeted, there may be no necessity of avoiding a DBP of <80 mmHg [950]. Based on these results, in the JSH2019 Guidelines, it is recommended that a target blood pressure in patients with coronary artery disease should be <130/80 mmHg.

An increase in the incidence of cardiovascular events in coronary artery disease patients with a low DBP is related to myocardial ischemia in most cases. An additional analysis of the INVEST study and a sub-analysis of the CREDO-Kyoto cohort-1 study showed that coronary revascularization improved the safety of blood pressure control in such patients including older patients [524, 951–953]. Furthermore, a decrease in DBP related to left ventricular (LV) systolic dysfunction, CKD, advanced atherosclerosis (an increase in pulse pressure, a history of myocardial infarction, a history of cerebrovascular disease) or systemic diseases increases the incidence of cardiovascular events (reverse causality) in many

cases. Therefore, in patients with a low DBP, it is important to manage comorbidities or risk factors in addition to myocardial ischemia screening. Blood pressure lowering should be conducted, while checking tolerability such as the appearance of symptoms of cerebral ischemia, renal dysfunction, general fatigue, symptoms of angina pectoris/electrocardiographic changes, especially in very older patients.

(1) Angina pectoris Angina pectoris is caused by the coronary flow-limiting organic stenosis or coronary vasospasm. In Japan, angina pectoris attributed to coronary vasospasm is frequently observed, but the concomitant presence of the two factors is also noted in many patients. First-choice drugs for effort angina related to organic stenosis of the coronary artery are β-blockers without endogenous sympathomimetic action and CCBs (long-acting dihydropyridine CCBs, sustained-release diltiazem preparations) [954, 955]. For patients with resting or resting/effort angina, in which coronary vasospasm may be involved, CCBs are selected as first-choice drugs regardless of the blood pressure level to prevent coronary vasospasm [956–958]. As β-blockers may exacerbate coronary vasospasm, a CCB or a combination of a CCB and a β_1-selective blocker is recommended when the mechanism of angina pectoris is unclear. If a decrease in blood pressure is insufficient, a CCB or RA system inhibitor should be added. Short-acting dihydropyridine CCBs may induce myocardial ischemia by a rapid drop in blood pressure or reflex tachycardia; therefore, they are contraindicated.

(2) Old myocardial infarction For patients with old myocardial infarction, antihypertensive drugs should be used to prevent cardiovascular events and improve the prognosis in addition to blood pressure control. β-blockers with no endogenous sympathomimetic action were found to significantly reduce the recurrences of myocardial infarction and sudden death in patients with old myocardial infarction [959, 960]. In myocardial infarction patients with redeuced LV ejection fraction (LVEF) (<40%) or myocardial infarction/acute coronary syndrome patients within 3 years after the onset, β-blockers (carvedilol, bisoprolol) should be used for the secondary prevention of coronary artery disease [944–946]. In myocardial infarction patients with reduced LVEF, RA system inhibitors prevent LV remodeling and LVEF reduction, and decrease the incidence of cardiac events, such as heart failure and sudden death, improving the prognosis [961–964]. In the Guidelines for the secondary prevention of myocardial infarction in Japan, Europe and the United States, ACE inhibitors are recommended as the first choice of RA system inhibitors, and it is described that ARBs should be selected if intolerable to ACE inhibitors [944–946] (See "CQ8" [965]). In patients with severe LV systolic dysfunction, the addition of an MR antagonist to standard drug therapy with an RA system inhibitor + a β-blocker + a diuretic further improves the prognosis [779, 966].

If blood pressure control is insufficient despite standard treatment at maximum tolerated doses, a long-acting CCB should be added [967, 968].

3) Heart failure

Heart failure is progressive, resulting in a poor outcome. Once symptoms appear, remission and exacerbation may be repeated with the risk of sudden death, leading to death. In the Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (Japan), the following stage classification is presented, and the importance of preventing the onset of heart failure by early therapeutic intervention from stages A/B, in which there is no sign of heart failure, is emphasized: stage A in which there is no organic cardiac abnormality or sign of heart failure despite the presence of risk factors such as hypertension and diabetes mellitus; stage B in which there is no sign of heart failure despite organic cardiac abnormalities; stage C in which signs of heart failure (including its history) are observed; and stage D (resistant heart failure) [716]. Hypertension is the most frequent underlying cause of heart failure [969]. Furthermore, it is an exacerbating factor in all stages, and is an independent prognostic factor for heart failure rehospitalization. Therefore, strict blood pressure control is necessary. Concerning the primary prevention of heart failure in hypertensive patients, the secondary heart failure analyses of the SPRINT and ALLHAT studies indicated the usefulness of antihypertensive therapy with thiazide-type diuretics [92, 970].

(1) Heart failure with reduced ejection fraction (HFrEF)

Many patients with HFrEF (LVEF: <40%) have normal or low blood pressure. In patients with HFrEF, antihypertensive drugs are used to improve the quality of life (QOL), prevent heart failure rehospitalization and improve the prognosis, but not solely to reduce blood pressure. Standard medical therapy for HFrEF is combination therapy with an RA system inhibitor, a β-blocker and a diuretic [716, 929, 930]. RA system inhibitors prevent heart failure rehospitalization in HFrEF patients, improving the long-term outcome regardless of the presence or absence of symptoms of heart failure or the degree of left ventricular dysfunction [961–964, 971–976]. In the guidelines for the diagnosis and treatment of acute and chronic heart failure in Japan, Europe, and the United States, ACE inhibitors are recommended as the first choice of RA system inhibitors for HFrEF, and it is described that ARBs should be used if intolerable to ACE inhibitors [716, 929, 930] (See "CQ8" [965]). β-Blockers (carvedilol, bisoprolol) decrease hospitalization rate in HFrEF patients regardless of the presence or absence of symptoms, improving the long-term outcome

[960, 977–980]. Diuretics are used for the treatment and prevention of pulmonary and/or systemic congestion. MR antagonists further improve the prognosis of HFrEF patients receiving standard medical therapy [779, 966, 981].

When introducing RA system inhibitors or β-blockers, administration should be started at a low dose (1/4-1/2 of the dose for hypertension treatment), and the dose should be gradually increased to a maximum tolerated doses while paying attention to the deterioration of heart failure, hypotension, bradycardia (β-blockers), or renal dysfunction [716].

As individualized treatment in accordance with the etiology, condition, or comorbidities is important in patients with HFrEF, the target of blood pressure lowering cannot be set. Although evidence is insufficient, SBP control at 110–130 mmHg is recommended in the guidelines for the diagnosis and treatment of acute and chronic heart failure in Japan and the United States [716, 930]. However, to protect the heart and improve the QOL/prognosis, standard medical therapy at a lower blood pressure level may be required in many cases if tolerability is present [716, 929]. On the other hand, HFrEF complicated by hypertension promotes LVEF reduction and LV remodeling; therefore, if no sufficient blood pressure lowering effect is obtained despite standard treatment at maximum tolerated doses under the adequate use of diuretics, a long-acting dihydropyridine CCB (amlodipine), which does not deteriorate the outcome of heart failure, should be added [929, 982].

(2) Heart failure with preserved ejection fraction (HFpEF)

Approximately 50% of patients with congestive heart failure have HFpEF (LVEF: ≥50%) [716]. LV diastolic dysfunction and increased vascular stiffness are involved in the pathogenesis of HFpEF [983, 984]. HFpEF is frequent in older persons, especially in women. Hypertension is present in 60 to 90% of patients with HFpEF, being the most frequent underlying disease [985, 986]. In hypertensive patients, diastolic dysfunction is observed from the early stage. A decrease in blood pressure may prevent/reduce the deterioration of diastolic dysfunction by the relief of cardiac hypertrophy/myocardial fibrosis, and reduce peripheral vascular resistance/cardiac after-load by preventing vascular stiffening [987]. In the JSH2019 guidelines, it is recommended that a target SBP for HFpEF patients should be <130 mmHg to prevent heart failure rehospitalization based on the results of "CQ9" [988], although evidence regarding the improvement of prognosis is insufficient. As tachycardia, particularly atrial fibrillation, often induces acute exacerbation, its prevention and appropriate control of the heart rate are important. Furthermore, it is also important to control diabetes mellitus, CKD, dyslipidemia, and obesity, which are frequently observed in the presence of HFpEF. The possibility of diastolic dysfunction due to latent coronary artery diseases should also be considered.

No standard medical therapy for HFpEF, to improve the prognosis, based on evidence from large-scale RCTs has been established [989–993]. However, a large-scale, prospective study of HFpEF (Swedish Heart Failure Registry) showed that the total mortality rate was low in the RA-system-inhibitor-treated group [994]. According to several studies, candesartan (CHARM-Preserved) and spironolactone (TOPCAT) decreased the heart failure hospitalization [989, 993], and another study with carvedilol (J-DHF) suggested decreases in cardiovascular death /hospitalization [992]. On the other hand, a secondary analysis regarding heart failure by the ALLHAT Collaborative Research Group indicated that diuretics were more useful than RA system inhibitors and CCBs for preventing the onset of HFpEF [970]. Therefore, the usefulness of antihypertensive drug therapy with a diuretic in accordance with individual conditions in patients with HFpEF is suggested.

(3) Acute heart failure or acute exacerbation of chronic heart failure with elevated blood pressure Concerning the mechanism of acute heart failure/acute exacerbation with elevated blood pressure, blood pressure is increased due to cardiac after-load mismatch related to an excessive increase in peripheral vascular resistance in some cases, or HFpEF initially occurs due to insufficient hypertension treatment in others. In other cases, acute coronary syndrome with elevated blood pressure is observed [716]. As initial management, oxygen administration should be performed. To patients with pulmonary congestion, nitrates (nitroglycerin, isosorbide dinitrate) should be administered sublingually or using a spray, but treatment in accordance with the condition must be promptly performed; therefore, patients should be referred to cardiology-specialized institutions without hesitation (See Section 1 "5) Acute heart failure" of Chapter 12).

(4) Prevention of recurrent heart failure Both HFrEF and HFpEF may acutely exacerbate, resulting in repeated decompensated heart failure even if the remission of symptoms/signs and a stable state are achieved by acute-phase treatment [716]. Important risk factors for acute exacerbation include hypertension, infection, tachycardia such as atrial fibrillation, myocardial ischemia, anemia, excessive salt/water intake, fatigue, heavy physical efforts, and drug discontinuation. Kidney dysfunction related to factors, such as dehydration, must also be considered. Measurement of body weight, blood pressure, and pulse rate at home is useful for the early prediction of acute exacerbation. β-Blockers, RA system inhibitors, and diuretics should be regulated (dose-elevation/-reduction, discontinuation) in consultation with cardiologists.

Comprehensive cardiac rehabilitation involving exercise therapy by multidisciplinary team is useful for the treatment and prevention of chronic heart failure [716].

4) Atrial fibrillation

Atrial fibrillation and hypertension are concomitantly present in many cases. The incidences of the two diseases increase with age. Atrial fibrillation increases the risk of systemic thromboembolism, especially cardiogenic cerebral embolism. Furthermore, it induces cardiac dysfunction, contributing to deterioration to heart failure, cardiovascular events, and an increase in the mortality rate.

Hypertension is a primary risk factor for the onset of atrial fibrillation. The activation of the sympathetic nervous system/RA system, atrial enlargement, atrial fibrosis, and left ventricular remodeling such as left ventricular hypertrophy and diastolic dysfunction may be involved in the pathogenesis of atrial fibrillation [995]. Hypertension is also involved in the onset of coronary artery disease, leading to an increase in the risk of atrial fibrillation. Even in patients with a high normal blood pressure or an elevated blood pressure, the risk of atrial fibrillation increases [19, 996–998], and strict blood pressure control (SBP: <130 mmHg) may be effective in preventing the new onset of atrial fibrillation [410, 999]. The Suita study involving a general population consisting of residents showed that risk factors for the onset of atrial fibrillation included obesity, excessive alcohol consumption and smoking in addition to age and blood pressure [19]. The improvement of these lifestyle-related factors in addition to blood pressure control may prevent the new onset of atrial fibrillation.

The concomitant presence of atrial fibrillation is an important risk factor for the onset of cardiovascular events regardless of the blood pressure level, but the risks of stroke, arterial embolism and all-cause death increase in a blood pressure-dependent manner in patients with atrial fibrillation [1000, 1001]. Therefore, blood pressure control is also important in patients with chronic atrial fibrillation, and a SBP of <130 mmHg should be targeted to prevent events, such as stroke, based on the results of large-scale clinical studies involving patients with atrial fibrillation [1000]. In patients with atrial fibrillation, adequate anticoagulant therapy is necessary to prevent arterial embolism, such as cardiogenic cerebral embolism. Thus, strict blood pressure control is also essential so that hemorrhagic complications related to anticoagulant administration may be prevented [1002] (See Chapter 3 8. “4) Blood pressure control in hypertensive patients receiving antithrombotic drugs”) .

As antihypertensive drugs that contribute to the prevention of atrial fibrillation, RA system inhibitors may be effective, but primary prevention (to prevent its new onset) must be distinguished from secondary prevention (to decrease the frequency of attacks and prevent recurrence/a chronic state). Concerning primary prevention, longitudinal, observational studies in Japan and other countries demonstrated the preventive effects of RA system inhibitors on atrial fibrillation in hypertensive patients [1003, 1004]. However, the results differed among post-hoc/meta-analyses of RCTs; [1005–1009] the preventive effects of RA system inhibitors on the new onset of atrial fibrillation in hypertensive patients are not clear. However, RA system inhibitors may be useful in patients with left ventricular hypertrophy or heart failure based on a post-hoc analysis of the LIFE study and a meta-analysis involving 87,048 patients in 23 trials [1005, 1007, 1008]. Furthermore, β-blockers are effective in preventing the new onset of atrial fibrillation in heart failure patients with reduced left ventricular ejection fraction (HFrEF) [1010].

Concerning the secondary prevention of atrial fibrillation, the results differed among reports from RCTs involving hypertensive patients [1009, 1011], but the efficacy of RA system inhibitors for recurrent atrial fibrillation was negated based on the results of major RCTs involving hypertensive patients in Japan and other countries [1012–1014]. Briefly, the usefulness of RA system inhibitors for the secondary prevention of atrial fibrillation, that is, the reduction in the frequency of attacks and the prevention of recurrence/a chronic state in patients with paroxysmal atrial fibrillation or after defibrillation, is not clear, as described for primary prevention.

In patients with chronic atrial fibrillation, adequate blood pressure and heart rate control is important to prevent the onset of heart failure. In particular, for heart rate control in patients with tachycardia-related atrial fibrillation, the use of β-blockers or non-dihydropyridine CCBs should be considered.

POINT 6C

1. **In patients with CKD, risk factors for cardiovascular diseases, such as hypertension and abnormal diurnal rhythm in blood pressure, are frequently observed, and the risk of cardiovascular events is high.**
2. **For the early detection of CKD, urinalysis and calculation of the estimated glomerular filtration rate (eGFR) should be performed in all hypertensive patients. In CKD patients with diabetes mellitus (diabetic nephropathy, diabetic kidney disease), the urinary albumin level should be evaluated using the urinary albumin-to-creatinine (Cr) ratio (mg per g Cr). In those without diabetes mellitus, the urinary protein-to-creatinine ratio (gram per g Cr) should be measured when a qualitative test for urinary**

protein shows (±) or higher, and patients with a value of 0.15 gram per gram Cr or above should be regarded as positive for proteinuria.

3. **Regarding lifestyle, salt restriction, maintenance of appropriate body weight, smoking cessation and restriction of protein intake in accordance with renal function should be practiced. Salt intake should be <6 g per day. In older patients, strict salt or protein restriction may reduce the GFR, or induce sarcopenia and frailty. Guidance should be conducted under comprehensive evaluation in accordance with their individual conditions. Exercise therapy should be performed under a safe environment in accordance with renal function, age, and patient background.**
4. **When blood pressure exceeds the target level of blood pressure control, antihypertensive drug therapy should be promptly started, in addition to lifestyle modifications.**
5. **Target of blood pressure control: If proteinuria is present, a blood pressure of <130/80 mmHg should be targeted. If proteinuria is absent in the absence of diabetes mellitus, individualized management should be performed, considering the balance between advantages and disadvantages, renal function and age. In particular, attention must be paid to the rate of reduction in blood pressure in older patients, and an excessive decrease in blood pressure should be avoided.**
6. **First-choice drugs: If proteinuria is present, RA system inhibitors should be selected. If proteinuria is absent in the absence of diabetes mellitus, RA system inhibitors, CCBs, or thiazide-type diuretics should be selected.**
7. **A decrease in the urinary protein level is strongly associated with the prevention of end-stage kidney disease (ESKD). It is important to decrease the urinary protein level as much as possible.**
8. **In patients undergoing hemodialysis, there is a U-shaped relationship between SBP at the start of dialysis and hard outcomes such as all-cause mortality, and the minimum risk is present at approximately 160 mmHg. Furthermore, the blood pressure decrease during a dialysis session is also associated with hard outcomes; therefore, it is rather practical to individually determine the target of blood pressure control, referring to their own home blood pressure.**
9. **In patients with kidney transplantation, blood pressure control should be performed in accordance with the CKD stage corresponding to their renal function.**

3. KIDNEY DISEASE

1) Renal function and blood pressure

There is a close association between hypertension and the kidney. The kidney has an important role in the pathogenesis of hypertension. On the other hand, hypertension causes renal dysfunction, leading to CKD. Once CKD develops, hypertension becomes severe, and a vicious circle is established. In CKD patients, abnormalities in the diurnal rhythm of blood pressure, such as the disappearance of a nocturnal decrease, are frequently observed, becoming a risk factor for the onset of cardiovascular diseases [1015–1017]. In addition, CKD is often complicated by sleep apnea syndrome, thereby exacerbating hypertension [1018, 1019]. Therefore, in hypertensive patients with CKD, in addition to treatment for the primary disease of CKD, strict management of blood pressure over 24 h is important.

Renal function declines with age after the 30s, but the rate of age-associated decrease in the GFR estimated from the Japanese health screening data is very low (about 0.3 mL min^{-1} per year) [1020]. On the other hand, the GFR may decrease at a rate of 4–8 mL min^{-1} per year in hypertensive patients [1021]. The Japanese health screening data showed that aging, diabetes mellitus and hypertension were important risk factors for the appearance of proteinuria or for the occurrence of CKD with a GFR of <60 mL min^{-1} per 1.73 m^2 [22, 24].

In Japan, major primary diseases in patients undergoing maintenance dialysis include diabetic nephropathy, chronic glomerulonephritis and nephrosclerosis. The rate of patients with diabetic nephropathy has increased, reaching a plateau for the past few years [1022, 1023]. Furthermore, the number of patients for whom dialysis was newly introduced due to chronic glomerulonephritis has been decreasing, whereas the incidence of nephrosclerosis-related renal failure has been increasing, by reflecting the rapid aging of society; the number of newly-introduced dialysis patients with nephrosclerosis is almost comparable to that with chronic glomerulonephritis [1023]. Blood pressure and urinary protein levels are known to be strong risk factors contributing to the onset of ESKD. In a prospective cohort study involving the general population, the incidence of ESKD was the lowest in the normal blood pressure group. It increased with the blood pressure level, and there was no J-curve phenomenon [21, 1024].

2) Diagnosis of CKD and its significance

The etiology of kidney damage and its clinical significance have changed. Recently, it was shown that patients with urinalysis abnormalities, such as slight kidney hypofunction and albuminuria, frequently developed cardiovascular diseases, such as myocardial infarction and stroke, before

Primary disease		Proteinuria category		A1	A2	A3
Diabetes		Quantification of urinary albumin (mg/day) Urinary albumin/Cr ratio (mg/gCr)		Normal	Microalbuminuria	Manifest albuminuria
				<30	30-299	≥300
Hypertension Nephritis Multiple cystic kidney Transplanted kidney Unclear Others		Quantification of urinary protein (g/day) Urinary protein/Cr ratio (g/gCr)		Normal	Slight proteinuria	Marked proteinuria
				<0.15	0.15-0.49	≥0.50
GFR category (mL/min/1.73 m²)	G1	Normal or high	≧90			
	G2	Normal or slightly low	60-89			
	G3a	Slightly/moderately low	45-59			
	G3b	Moderately/markedly low	30-44			
	G4	Markedly low	15-29			
	G5	ESKD	<15			

The stage of severity is evaluated based on the GFR and proteinuria categories.
The severity is evaluated using the primary disease-/GFR category-/proteinuria category-based stage. The severity of CKD is evaluated in accordance with staging involving the risks of death, ESKD, and cardiovascular death. The risks increase with an elevation of the stage

Fig. 6-1 Definition of CKD and severity classification. (Source: Ref. [241] [KDIGO 2012 CKD Guidelines [245] was modified for Japanese patients.])

switching to renal replacement therapy due to progression to renal failure [1025, 1026]. To detect and manage kidney damage in the early stage, the entity of CKD was proposed [1027]. In addition to kidney-inherent diseases, such as glomerulonephritis, lifestyle-related diseases, such as hypertension, diabetes mellitus, and metabolic syndrome, as well as aging, are involved in the etiology of CKD. If hypertensive patients have CKD with proteinuria, antihypertensive therapy must be started in addition to lifestyle modifications, regarding the risk level as the severest (grade III). Therefore, for risk stratification and organ damage assessment, CKD screening (proteinuria measurement, calculation of the eGFR) is necessary in all hypertensive patients, and albuminuria should be measured in patients with diabetes mellitus or early diabetic nephropathy.

(1) Definition of CKD and severity classification The definition of CKD and severity classification are shown in Figure 6-1 [245]. The severity of CKD is classified based on the GFR and albumin-/proteinuria [241].

In children, this severity classification is not used, and GFR-based staging should be used. In children with CKD, the relationship between the severity and urinary protein level has not been sufficiently examined.

The severity classification of CKD was prepared on the assumption that its etiology may not matter, but diabetes mellitus differs from other diseases in severity; therefore, the former was distinguished from the latter. As this classification is based on the cause (C), GFR (G), and albuminuria (A), it is termed "CGA classification".

The category of renal function was established based on the GFR, but it was shown that the risks of cardiovascular diseases and renal failure differed in patients with a GFR of <45 mL/min/1.73m^2, and the G3 category was divided into G3a, in which the GFR ranges from 45 to 59 mL/min/1.73m^2, and G3b, in which it ranges from 30 to 44 mL/min/1.73m^2.

(2) Evaluation of renal function For GFR measurement, inulin clearance is measured as a gold standard method. However, this method is complex, and is not appropriate for simple screening in clinical practice. Various estimation formulae are established (Table 6-3).

(3) Measurement of urinary albumin/protein levels Albuminuria is evaluated based on the urinary albumin creatinine ratio (ACR). ACR measurement can be performed using casual urine samples, but the first urine collected early in the morning should be used. If the value is ≥30 mg/gCr (microalbuminuria or severer), two more sessions of measurement should be repeated, or the condition must be confirmed using 24-h urine. In Japan, precise quantitative albumin measurement at 3-month intervals is covered by health insurance for "patients with diabetes mellitus or early diabetic nephropathy".

In the test paper method, a urinary protein level of (1+) corresponds to 30 mg/dL, that of (2+) corresponds to 100 mg/dL, and that of (±) corresponds to 10–15 mg/dL. If the urinary protein level on a qualitative reaction test is (±) or higher, quantitative evaluation should be conducted. When evaluating proteinuria using casual urine samples, the

Table 6-3 eGFR

- eGFR based on the serum creatinine level (eGFRcreat)
  eGFRcreat (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times$ age (years)$^{-0.287}$ (woman: ×0.739)
  Cr: Serum creatinine concentration (mg/dL). The Cr value measured using the enzymatic method should be used.
  Seventy-five percent of patients show values in the range of the actual GFR±30%.
  As the serum Cr level is influenced by the muscle mass, caution is needed in older patients with a reduced muscle mass.
- GFR-estimating formulae based on the serum cystatin C level, which is not influenced by the muscle mass
  Man: eGFRcys (mL/min/1.73 m^2) = $(104 \times \text{Cys-C}^{-1.019} \times 0.996^{\text{age}}) - 8$
  Woman: eGFRcys (mL/min/1.73 m^2) = $(104 \times \text{Cys-C}^{-1.019} \times 0.996^{\text{age}} \times 0.929) - 8$
  Cys-C: Serum cystatin C concentration (mg/L)
  The serum Cys-C level is influenced by pregnancy, HIV infection, and thyroid dysfunction; therefore, caution is needed.

These estimation formulae were corrected, assuming that the standard body surface area may be 1.73 m^2 (corresponding to 170 cm, 63 kg). Therefore, if accurate renal function assessment is necessary on occasions including the preparation of drug administration plans, the value should be corrected for the patient's body surface area (BSA).

These estimation formulae are applicable for patients aged ≥18 years. For renal function assessment in children, evaluation methods for children should be used.

value corrected for the urinary creatinine concentration [urinary protein/creatinine ratio (g/gCr)] should be adopted, and the condition should be classified into normal (<0.15 g/gCr), mild (0.15–0.49 g/gCr), and severe (≥0.50 g/gCr). Briefly, in the present guidelines, we recommended that urinary protein should be quantified if the test paper method shows a urinary protein level of (±) or higher. Patients with a urinary protein/creatinine ratio of ≥0.15 g/gCr are regarded as having proteinuria. On the basis of this, the target of blood pressure control should be established, and antihypertensive drugs should be selected.

3) Diabetic nephropathy, diabetic kidney disease

Diabetics with kidney damage tend to be regarded as having diabetic nephropathy. Recently, it was shown that the etiology and condition of kidney damage in the presence of diabetes mellitus varied [1028]. Diabetic nephropathy, which had been recognized, gradually reduces renal function by excessive glomerular filtration, microalbuminuria, manifest proteinuria, and nephrosis under insufficient long-term blood glucose control as a background factor. A recent study indicated that there were many patients with rapid renal hypofunction in the normal to microalbuminuria stages (rapid/fast decliners) [1029]. Furthermore, it was reported that there were patients with a linear decline of the GFR, as well as those with a rapid reduction in the kidney function from a specific stage (nonlinear decline).

Thus, conditions other than "classical" diabetic nephropathy showing a typical course have been clarified, and these are comprehensively termed "diabetic kidney disease". The definition of diabetic kidney disease has not been established. Diabetes mellitus-related vascular disorder and aging may be involved in its pathogenesis.

4) Lifestyle modifications

Lifestyle modifications and the rapid aging of society are involved in an increase in the number of patients with CKD. Obesity and an excessive salt intake accelerate kidney damage by mechanisms dependent on and independent of blood pressure. Lifestyle modifications are the most basic and important factors in the treatment of CKD, in which restricting salt intake, maintaining an appropriate body weight, cessation of smoking and optimization of protein intake are essential.

Restriction of salt intake is important for controlling blood pressure and for preventing the progression of renal dysfunction. As salt sensitivity is often increased in hypertensive patients with CKD, restriction of salt intake would be effective for reducing blood pressure [1030]. Salt restriction improves the hypotensive and antiproteinuric effects of ACE inhibitors and ARBs [1031, 1032]. Salt intake should be restricted to <6 g per day. It is important to promote salt restriction step by step while monitoring blood pressure and urinary protein excretion. In older patients, malnutrition (frail) or a reduction in the GFR must also be considered.

Several studies indicated the involvement of obesity in the onset of CKD or ESKD [565, 1033, 1034]. Weight loss achieved by interventions reduces albuminuria [1035, 1036], but no interventional study has yet investigated its long-term effects on renal function. Several studies have reported that abdominal obesity is significantly associated with the total mortality rate and incidence of cardiovascular diseases in CKD patients with an eGFR of 15 mL min^{-1} per 1.73 m^2 or higher (CKD stage 1–4) [1037, 1038]. On the other hand, a meta-analysis involving CKD stage 3–5 patients, including those undergoing dialysis, showed that the total mortality rate was lower in the high BMI group [1039]. The relationship between obesity and severe CKD patients' prognosis remains to be clarified.

Several studies indicated that metabolic syndrome was a risk factor for the onset of CKD [1040, 1041]. Furthermore, another study showed that metabolic syndrome was correlated with the prognosis of CKD patients [1042].

Smoking has been reported to exert adverse effects on proteinuria and renal dysfunction in both diabetic and nondiabetic nephropathy patients [1043, 1044]. It has been established that smoking is a risk factor for cardiovascular diseases. Considering that the risk of cardiovascular death is high in CKD patients, smoking cessation is crucial.

The excessive ingestion of protein increases excessive glomerular filtration, influencing the functional prognosis of the kidney. Protein metabolites cause the accumulation of uremic substances on renal hypofunction. To investigate renal functional prognosis-improving effects, many RCTs and meta-analyses of them were conducted [1045–1048], and it has been indicated that protein restriction decreases the relative risks of ESKD and death.

However, strict restriction of protein intake induces various risks. In older patients, sarcopenia or frail may exacerbate. If proteinuria is absent, the rate of reduction in renal function is slow, and restriction of protein intake is not clinically relevant. Standardized guidance for restriction of protein intake is inappropriate, and guidance should be performed under an environment of team practice involving specialists and administrative dietitians by comprehensively evaluating individual patients' conditions, risks and adherence. In the "Standards for dietary therapy for chronic kidney disease in 2014" prepared by the Japanese Society of Nephrology, reference values of protein intake with respect to the stage of CKD are presented (stage G3a: 0.8–1.0g per kg standard body weight per day, stage G3b or higher: 0.6–0.8g per kg standard body weight per day) [1049].

Concerning exercise therapy, guidance should be given in accordance with the renal function, age, and patient background. Even in CKD patients with a GFR of <60 mL min^{-1} per 1.73 m^2 (including those undergoing dialysis), exercise therapy reduces blood pressure and central blood pressure and improves cardiopulmonary functions, improving the quality of life [1050]. In CKD patients with obesity or metabolic syndrome, exercise therapy is effective in reducing obesity or improving maximum oxygen intake. In CKD patients, exercise therapy should be performed under a safe environment after sufficiently understanding the individual's clinical background.

5) Treatment with antihypertensive drugs

The following points are important for treating hypertensive patients with CKD: 1) the goal of blood pressure control is to prevent the onset of cardiovascular diseases and deterioration of CKD/progression to ESKD, 2) to achieve this goal, the target of blood pressure control should be established, and the most appropriate antihypertensive drug should be selected, and 3) indices that are necessary to establish the target of blood pressure control and select antihypertensive drugs are fixed. Standardization in accordance with guidelines is important, but it is necessary to provide individualized care based on individual patients' age or the presence or absence of complications and promote home blood pressure measurement in clinical practice. In particular, attention must be paid to the rate of decrease in blood pressure in older patients, and an excessive decrease in blood pressure should be avoided. Antihypertensive drug therapy for diabetic nephropathy or diabetic kidney disease is described in Chapter 7.

(1) Target of blood pressure control In non-diabetic CKD patients with proteinuria, the presence or absence of proteinuria plays an important role in the establishment of the target of blood pressure control.

If proteinuria is present, or if the severity of CKD is evaluated as proteinuria category A2 or A3, a target blood pressure should be established as <130/80 mmHg.

There is little evidence regarding the usefulness of strict blood pressure control to <130/80 mmHg for the prevention of cardiovascular diseases and progression to ESKD in the absence of proteinuria in non-diabetic CKD patients with proteinuria. Considering the balance between advantages and disadvantages, baseline renal function- and age-matched individualized management is necessary.

(2) Selection of antihypertensive drugs If proteinuria is present, or if the severity of CKD is evaluated as proteinuria category A2 or A3, an RA system inhibitor should be selected as a first-choice drug.

If proteinuria is absent (A1 category), an RA system inhibitor, CCB or thiazide-type diuretic should be selected, because there is little evidence to recommend an RA system inhibitor as a first-choice drug.

6) Patients undergoing dialysis and post-transplantation

As the body fluid volume-regulating capacity is markedly reduced due to renal dysfunction in patients undergoing hemodialysis, factors that influence blood pressure, such as the retention of body fluid and severity of atherosclerosis, markedly differ among individual patients. Therefore, it is difficult to establish a standardized administrative parameter for patients undergoing hemodialysis despite the publication of many clinical studies using the prognosis or cardiovascular events as an index, and there is no description in the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111] or 2014 JNC 8 evidence-based guidelines for the management of high blood pressure in adults [686]. There are sometimes marked changes in blood pressure before and after dialysis, and a basic aspect, that is, which blood pressure, including the weekly mean [1051], should be adopted as an index for management, remains controversial. The standards for these changes proposed by the Japanese Society for Dialysis Therapy do not apply to all patients. Many studies suggested a U-shaped relationship between SBP at the start of dialysis and various hard outcomes, as reported for other patient groups, but the minimum risk is at a higher level than non-dialysis patients, approximately 160 mmHg [1052, 1053]. According to the data on 9132 patients undergoing dialysis in Japan, there

was a U-shaped association between SBP and DBP at the start of dialysis and the total mortality rate (minimum risk: SBP, 140–159 mmHg; and DBP, 65–74 mmHg). The hazard ratios (95% confidence interval) were 1.24 (1.01–1.53) per 20-mmHg increase in SBP and 1.23 (1.05–1.44) per 10-mmHg increase in DBP [1054]. On the other hand, many studies indicated that a decrease in blood pressure during dialysis was involved in a hard outcome [1055–1058]. Therefore, currently, it is difficult to establish the numerical target of blood pressure control in patients undergoing hemodialysis. It may be realistic to establish a safety range in each patient with reference to home blood pressure in a broad range in which arteriovenous fistula blood flow is maintained in the absence of hemorrhagic complications, with no decrease in blood pressure during dialysis. The basis of treatment consists of salt intake improvement [1059] and adequate dry weight (optimal body weight) control. The cardioprotective and prognosis-improving effects of ACE inhibitors, ARBs, CCBs and β-blockers have been reported, but no large-scale study has examined these effects; this issue should be further investigated.

In patients who underwent kidney transplantation, hypertension is frequently observed due to the influence of immunosuppressive drugs including calcineurin inhibitors [1060, 1061]. As the transplanted kidney function is not normal, blood pressure control should be performed in accordance with the stage of CKD corresponding to renal dysfunction. Guidelines involving this content were proposed by the Japanese Society for Clinical Renal Transplantation in 2011 [1062], and blood pressure should be controlled in accordance with the Evidence-based Clinical Practice Guideline for CKD 2018 published by the Japanese Society of Nephrology [241] and JSH2019 Guidelines.

POINT 6D

[VASCULAR DISEASES]

1. **Acute aortic dissection is a hypertensive emergency that requires immediate blood pressure reduction and control of the heart rate.**
2. **In the acute phase of aortic dissection, SBP should be maintained at 100–120 mmHg. In the chronic phase, it should be maintained at <130 mmHg.**
3. **Strict antihypertensive treatment for thoracic aortic aneurysm is important, and SBP should be maintained at 105–120 mmHg.**
4. **Abdominal aortic aneurysms are primarily associated with arteriosclerosis, and it is important to control risk factors including hypertension.**
5. **The purpose of treatment for obstructive atherosclerosis is to alleviate ischemic symptoms and prevent cardiovascular events, which frequently develop. Strict blood pressure control is important.**
6. **To patients with heart failure or coronary artery disease, for whom β-blockers are positively indicated, β-blockers should be carefully administered so that there may be no exacerbation of the ischemic limb's condition.**

4. VASCULAR DISEASES

1) Aortic aneurysm

(1) Aortic dissection Acute aortic dissection is a hypertensive emergency that requires immediate blood pressure reduction, control of the heart rate, pain control and complete rest. The site and morphology of dissection and the presence or absence of peripheral circulatory disorders due to stenosis/obstruction of arteries branching from the aorta should be evaluated continuously and carefully. As a rule, surgery should be promptly performed to treat Stanford type A dissection, and drug therapy should be administered to treat Stanford type B dissection [1063].

Although there is no evidence regarding a decrease in blood pressure, SBP should be maintained at 100–120 mmHg by the continuous infusion of a CCB (nicardipine, diltiazem), nitroglycerin or nitroprusside in combination with a β-blocker [1063]. When combining diltiazem with a β-blocker, bradycardia must be considered.

Several studies have indicated that, in the chronic phase, β-blockers decrease the number of dissection-associated events [1064, 1065]. To prevent re-dissection or rupture, the target SBP should be <130 mmHg [1066].

(2) Aortic aneurysm As aortic aneurysm is asymptomatic in most patients, it is often detected incidentally on health screening or on examination for other diseases. Once it ruptures, the mortality rate is very high, and even if patients come to the hospital in a stage of threatened rupture the survival rate is low because of unstable hemodynamics [1067].

Strict antihypertensive treatment for thoracic aortic aneurysm is important, and SBP should be maintained at 105–120 mmHg, although no evidence has been established. The superiority of β-blockers, ACE inhibitors and ARBs for inhibiting an increase in the aneurysmal diameter or preventing rupture in patients with Marfan's syndrome remains to be clarified [1068–1074], but β-blockers are used for standard treatment [1063].

There is no established evidence regarding the effects of strict antihypertensive therapy or β-blockers on abdominal aortic aneurysm [1075, 1076]. Concerning ACE inhibitors and ARBs, many studies also indicated that there was no influence on the rate of aneurysmal enlargement [1077–1080]. However, undoubtedly, atherosclerosis is closely

associated with the etiology of abdominal aortic aneurysm, smoking cessation is important [1081]. Ultrasonography is useful for the diagnosis of abdominal aortic aneurysm or evaluation of the aneurysmal diameter. If there is a slight increase in the aneurysmal diameter, surgery should be considered at an appropriate time [1063, 1082].

2) Obstructive atherosclerosis

Recently, the number of patients with obstructive atherosclerosis has increased. Peripheral circulatory disorders due to atherosclerotic vascular lesions are classified according to their severity into Fontaine grade I (no symptom, numbness, coldness), grade II (intermittent claudication), grade III (pain at rest) and grade IV (gangrene/ischemic ulcer). Although advances in revascularization have increased the number of patients with the alleviation of ischemic symptoms, the objectives of treatment are not only the alleviation of symptoms of ischemia, but also the prevention of cardiovascular events, which often complicate peripheral circulatory disorders.

Systematic execution of an exercise program under supervision has been reported to be effective for alleviating ischemic symptoms in the lower limbs [1083]. Strict blood pressure control often fails to improve ischemic symptoms in the lower limbs, but is quite important for preventing cardiovascular events along with the control of risk factors including smoking cessation [1084]. Among patients with diabetes mellitus, the incidence of cardiovascular diseases in the strict blood pressure control group (mean blood pressure: 128/75 mmHg) was lower than in the placebo group (137/81 mmHg) [1085], and the amputation of a lower limb or mortality rate in diabetics was strongly correlated with the SBP reached [1086, 1087]. Therefore, appropriate target of blood pressure control or antihypertensive drugs should be selected according to the complications or patient's conditions that require careful use of drugs (See this Chapter and Chapter 7 "Hypertension complicated by other diseases").

The administration of ACE inhibitors to patients with symptomatic obstructive atherosclerosis has been reported to prevent cardiovascular events [892] and improve the walking distance [1088]. β-blockers have been considered to exacerbate ischemic symptoms in the lower limbs; however, there was no marked exacerbation of symptoms/prognosis in RCTs involving patients with intermittent claudication [1089–1091]. To patients with heart failure or coronary artery disease, for whom β-blockers are positively indicated, β-blockers should be carefully administered so that there may be no exacerbation of the ischemic limb's condition. Physicians should refer patients with severe atherosclerotic peripheral arterial disease to a specialist, because percutaneous transluminal angioplasty or surgical circulatory reconstruction is required in some cases.

CQ7 FOR BLOOD PRESSURE CONTROL IN HYPERTENSIVE PATIENTS WITH CORONARY ARTERY DISEASE, IS IT NECESSARY TO AVOID A DBP OF <80 MMHG?

►In patients with coronary artery disease, a SBP of <130 mmHg should be targeted as priority, and it is not necessary to avoid a DBP of <80 mmHg.

Recommendation grade: 2 Evidence level: B

SUMMARY OF EVIDENCE

There was no evidence involving direct comparison of the outcome between strict and standard blood pressure control groups or specific value-targeted groups in an RCT involving hypertensive patients with coronary artery disease. Seven placebo-controlled RCTs involving patients with coronary artery disease, in which a DBP of <80 mmHg was achieved in the antihypertensive-drug intervention group, were extracted from a SR, and a meta-analysis was conducted to examine the influence on the outcome. In these RCTs, a SBP of <130 mmHg was achieved in the intervention group. The rate of patients in whom a DBP of <70 mmHg was achieved could not be analyzed because there were no RCT-based data. This meta-analysis showed the non-directivity of subjects (incidence of hypertension) and non-consistency of a portion (myocardial infarction, angina pectoris, coronary artery revascularization) of the outcome.

INTERPRETATION

With respect to the primary prevention of coronary artery disease, the risk of coronary artery disease-related death exponentially increased with an increase in blood pressure (SBP: ≥115 mmHg, DBP: ≥70 mmHg) according to a meta-analysis of large-scale prospective epidemiological studies [405]. In Japanese patients, the incidence of acute myocardial infarction was the lowest in patients with a SBP of <120 mmHg, and it increased with an increase in the blood pressure level [1092]. The BPLTTC meta-analysis regarding antihypertensive drug therapy and cardiovascular events involving hypertensive patients showed that the incidences of coronary artery disease and cardiovascular death decreased with the rate of decrease in SBP regardless of the type of antihypertensive drug used [936].

Concerning the target of blood pressure control for the prevention of all-cause/cardiovascular death in patients with coronary artery disease or the secondary prevention of coronary artery disease, RCT-based evidence is not sufficient. Bangalore et al. conducted a SR/meta-analysis of 16 RCTs involving 66,504 patients to examine the association between the SBP level reached by the administration of antihypertensive drugs to patients with coronary artery disease and outcome, and reported that positive blood

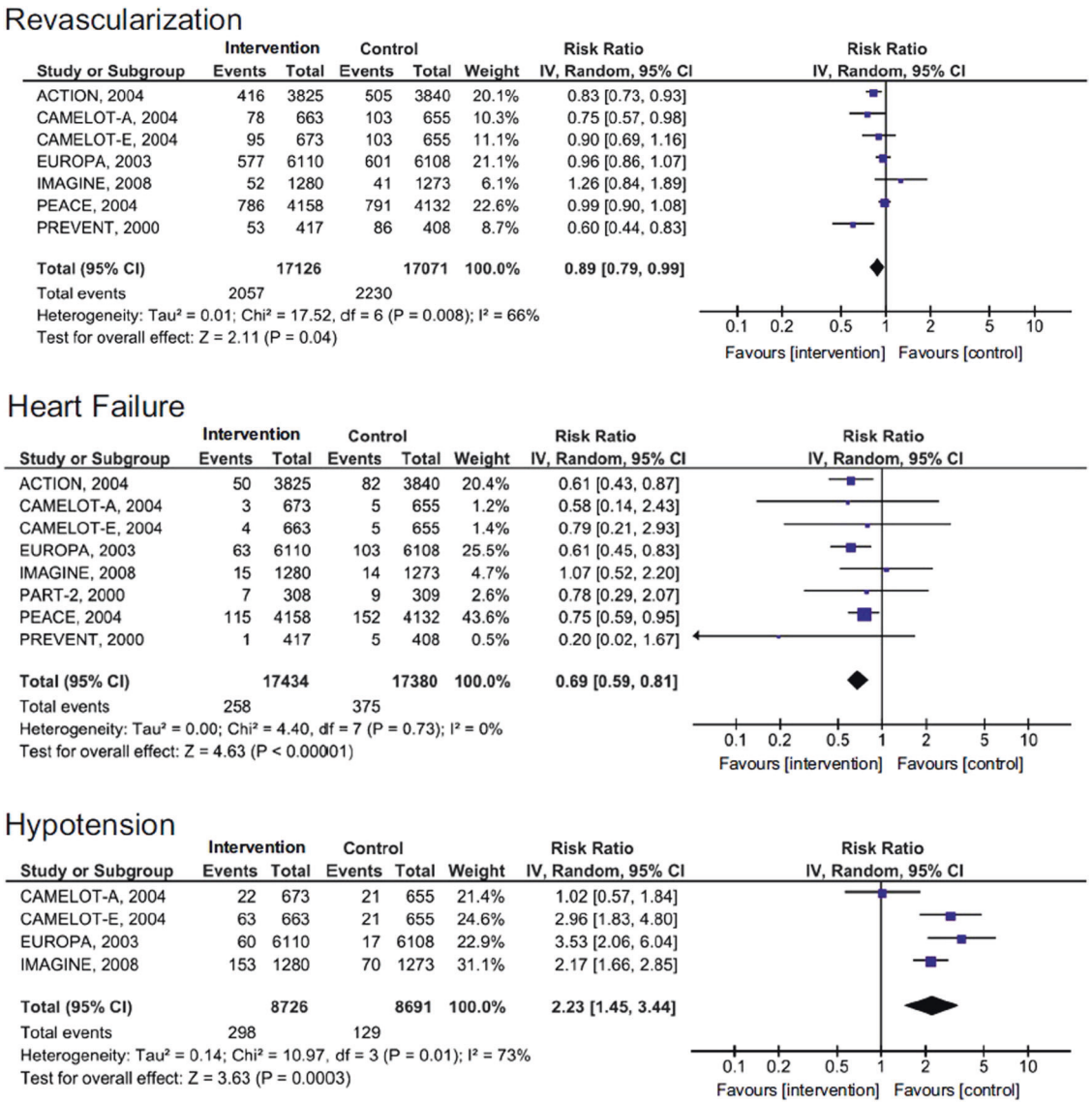


Fig. CQ7-1 Influence of a decrease in DBP to <80 mmHg in patients with coronary artery disease. IV: Inverse variance, Random: Random effect model. (Source: Ref. [950])

pressure control targeting a SBP of 131–135 mmHg decreased the incidences of heart failure and stroke by 15 and 10%, respectively, without increasing the total and cardiovascular mortality rates in comparison with standard blood pressure control targeting a SBP of 136–140 mmHg, and that further strict blood pressure control to ≤130 mmHg decreased the incidences of heart failure and stroke by 30 and 20%, respectively, as well as, those of myocardial infarction and angina pectoris by 10% each, although there were no significant decreases in the latter [948]. Therefore, blood pressure control targeting a SBP of <130 mmHg is recommended for patients with coronary artery disease from the viewpoint of heart failure/stroke prevention, of which the clinical significance has increased in Japan.

On the other hand, the coronary blood flow is maintained in the diastolic phase of the coronary artery, and a reduction in diastolic coronary perfusion pressure below a specific level related to a decrease in blood pressure in patients with coronary artery disease may cause myocardial ischemia, increasing the incidence of cardiac events (J-curve phenomenon); the target of DBP control remains controversial. The Syst-Eur [1093] and CLARIFY [528, 1094] studies indicated that there was an increase in the incidence of cardiac or cardiovascular events in patients in whom a DBP of <70 mmHg was achieved, and the INVEST [524] and ARIC [1095] studies reported such an increase in those with a DBP of <60 mmHg. In addition, the SPRINT [1096] study showed such an increase in those with a DBP of

<55 mmHg. However, these were post-hoc analyses/sub-analyses of RCTs [524, 1093, 1096] or observational studies [528, 1094, 1095], and they have the following limitations: no study prospectively compared the incidence of cardiovascular events among the blood pressure levels achieved, establishing the target of blood pressure control; patient groups based on blood pressure category were not randomized, and there were marked deviations in background factors; the number of patients in the low blood pressure group, in which cardiovascular events may increase, was markedly smaller than in the other groups, statistically contributing to a marked deviation and power insufficiency; and the rate of older patients or high-risk patients tended to be higher in the low blood pressure group. In the HOT study, a prospective RCT in which blood pressure lowering effects related to several targets of blood pressure control were compared, neither SBP nor DBP showed any J-curve phenomenon [490].

We examined whether a DBP of <80 or <70 mmHg should be avoided for blood pressure control in hypertensive patients with coronary artery disease. Initially, we conducted a SR of RCTs involving hypertensive patients with coronary artery disease, in which the outcome was directly compared between the strict and standard blood pressure control groups or between ≥2 groups in which a target SBP or DBP was established. However, no corresponding evidence was found. Newly, we performed a SR of large-scale placebo-controlled RCTs involving patients with coronary artery disease in which a DBP of <80 mmHg was achieved in the antihypertensive drug intervention group [950], and 7 trials were extracted [938, 940, 941, 1097–1100]. These 7 trials were included in 15 RCTs adopted in a meta-analysis (Bangalore et al.) [948] in which the association between the SBP level achieved by antihypertensive drug administration to patients with coronary artery disease and outcome was examined. The SBP achieved in the antihypertensive drug intervention group was ≤130 mmHg.

Using the 7 RCTs, the influence on all-cause death, cardiovascular death, myocardial infarction, angina pectoris, coronary revascularization, and stroke in the antihypertensive drug intervention group was compared with that in the control group (DBP: ≥80 mmHg) by a meta-analysis. In the intervention group achieving a DBP of <80 mmHg, the incidence of heart failure decreased by 31% (P<0.00001), and the rate of patients undergoing coronary revascularization decreased by 11% ($P = 0.04$); there were significant decreases (Figure CQ7-1). In this group, the total mortality rate, cardiovascular mortality rate, incidence of myocardial infarction, that of angina pectoris, and that of stroke were 6, 6, 13, 12, and 13% lower than in the control group, respectively ($P = 0.12$, $P = 0.40$, $P = 0.10$, $P = 0.08$, and $P = 0.16$, respectively), although there were no significant differences [950]. The incidence of hypotension was 2.2 times higher in the intervention group (P=0.0003) (Figure CQ7-1). Concerning renal dysfunction, only 1 RCT in which there was no significant difference between the two groups was reported, and it was impossible to conduct a meta-analysis. In addition, a meta-analysis of 4RCTs in which a DBP of <75 mmHg was achieved was carried out, and the incidence of heart failure significantly decreased (by 22%, $P = 0.02$) in the antihypertensive drug intervention group in comparison with the control group (DBP: ≥75 mmHg) (Figure CQ7-2), although the analytical power was insufficient due to a small number of patients. The risks of all-cause death, cardiovascular death, myocardial infarction, angina pectoris, stroke and coronary revascularization were similar between the two groups [950]. There was no RCT-based report on a DBP of <70 mmHg, and analysis was impossible.

Of 7 RCTs in which a DBP of <80 mmHg was achieved, ACE inhibitors had been used in all patients in 3 in which a DBP of <75 mmHg was achieved by CCBs or ACE inhibitors. The results suggest the direct coronary vasodilative actions of CCBs, as well as improving effects of ACE inhibitors on the coronary blood flow autoregulation [1101].

A post-hoc analysis of the INVEST study, which demonstrated the J-curve phenomenon, showed that coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery) decreased the

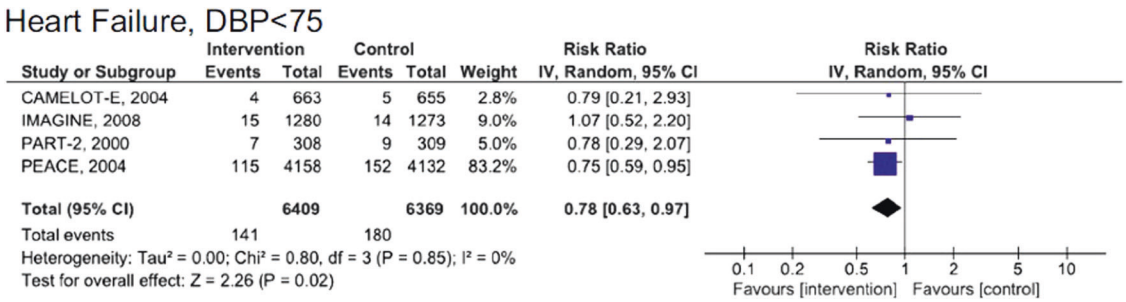


Fig. CQ7-2 Influence of a decrease in DBP to <75 mmHg in patients with coronary artery disease. IV: Inverse variance, Random: Random effect model. (Source: Ref. [950])

incidence of cardiac events at a low DBP by 50% [524]. Another post-hoc analysis of the INVEST study indicated that the incidence of cardiac events was the lowest at a blood pressure of 125/55 mmHg in the coronary bypass group, with no J-curve phenomenon [951]. Therefore, the results suggest that myocardial ischemia related to the coronary flow-limiting stenotic lesions requiring coronary revascularization is etiologically involved in >50% of cardiac events at a low DBP. In addition, a sub-analysis of the CREDO-Kyoto registry cohort-1 study involving patients with coronary artery disease after coronary revascularization showed that the crude cardiovascular mortality rate increased at a DBP of <70 mmHg, whereas independent risk factors for cardiovascular mortality included CKD, a history of myocardial infarction, heart failure/reduced LVEF, a history of stroke, and an increase in pulse pressure; a low DBP was not a significant factor [952]. According to an age-stratified analysis of the CREDO-Kyoto registry cohort-1 study, there was no J-curve phenomenon of cardiovascular death after improvement even at a DBP of <60 mmHg in very older patients aged ≥75 years [953].

Therefore, the J-curve phenomenon may be essentially associated with "reverse causality" that the risk of cardiovascular events is high in patients with a low DBP due to concomitant diseases in addition to myocardial ischemia related to stenotic coronary lesions or those in whom blood pressure may excessively drop upon antihypertensive therapy. An extremely low DBP is a marker of the high risk of cardiac events, but it may not be an etiological factor for cardiac events with a direct causal relationship.

Conclusion

When a DBP of <80 mmHg was achieved with a decrease in SBP to <130 mmHg in patients with coronary artery disease, the incidence of heart failure and coronary revascularization decreased in comparison with patients in whom a DBP of ≥80 mmHg was achieved, and the risks of all-cause death, cardiovascular death, myocardial infarction, angina pectoris and stroke were similar. Therefore, a SBP of <130 mmHg should be targeted as priority, and it is not necessary to avoid a DBP of <80 mmHg. As there is no evidence regarding a DBP of <70 mmHg, blood pressure control should be carefully performed while confirming the absence of ischemic symptoms/findings of vital organs, such as cerebral ischemia and renal dysfunction, in addition to the screening and management of myocardial ischemia related to stenotic coronary lesions, advanced atherosclerosis, systemic atherosclerotic disease (polyvascular disease), heart failure, CKD and wasting systemic disease.

LITERATURE SEARCHING

We searched the literature from January 1965 until July 2017 on the PubMed and in July 2017 on the Cochrane Library. Based on the results of searching, we extracted articles regarding this CQ.

CQ8 ARE ACE INHIBITORS MORE APPROPRIATE THAN ARBS IN HYPERTENSIVE PATIENTS WITH MYOCARDIAL INFARCTION OR HEART FAILURE?

►Evidence regarding hypertensive patients with myocardial infarction or heart failure with a reduction in left ventricular ejection fraction (LVEF) (heart failure with reduced ejection fraction [HFrEF]) is insufficient, and we could not conclude the superiority/inferiority or equivalence of ACE inhibitors and ARBs. At present, we propose that ACE inhibitors should be selected in preference to ARBs in accordance with recommendations of current guidelines without focusing hypertension for patients with myocardial infarction or HFrEF.

Recommendation grade: 2 Evidence level: D

SUMMARY OF EVIDENCE

There was no evidence based on an RCT directly comparing the influence of ACE inhibitors and ARBs on the outcome in hypertensive patients with myocardial infarction or heart failure. We conducted a SR of RCTs in which the effects of ACE inhibitors and ARBs on the outcome were compared in patients with myocardial infarction or heart failure, without focusing on hypertensive patients. Among such RCTs, a meta-analysis was performed using RCTs in which the number of hypertensive patients was clear. In 6 RCTs, the rate of hypertensive patients ranged from 36 to 69%, but only 1 RCT involved a mean SBP of ≥140 mmHg at the time of registration. Therefore, there is a great problem regarding the non-directivity of subjects; there may be a bias risk. There was a non-consistency of a portion of the outcome (cardiovascular death/all-cause death, cardiovascular diseases, adverse events). In most subjects of the RCTs adopted in this review, HFrEF was present; patients with heart failure with preserved ejection fraction (HFpEF) could not be evaluated.

INTERPRETATION

The usefulness of ACE inhibitors for the secondary prevention of cardiovascular events in patients with myocardial infarction has been established [946]. The ISIS-4 [1102]

and GISSI-3 [1103] studies indicated the efficacy of administration early after the onset of myocardial infarction, and the SAVE [961], AIRE [963], and TRACE [964] studies demonstrated that ACE inhibitors prevented all-cause death, sudden death, recurrent myocardial infarction and heart failure in LVEF-reduced patients with old myocardial infarction in comparison with a placebo. Concerning the secondary prevention of myocardial infarction with ARBs, the OPTIMAAL study involving acute myocardial infarction patients with a high risk of heart failure showed that the mortality rate in the losartan group was slightly higher than in the captopril group, although there was no significant difference [976]. The VALIANT study involving patients with heart failure or myocardial infarction patients with reduced LVEF indicated that the total mortality rate, cardiovascular mortality rate, incidence of recurrent myocardial infarction and heart failure hospitalization were similar between the valsartan and captopril groups [962]. Furthermore, a meta-analysis of the BPLTTC study comparing ACE inhibitors with ARBs showed that the ACE inhibitors exhibited preventive effects on coronary artery disease in addition to blood pressure lowering effects, differing from the ARB [666].

Several placebo-controlled RCTs, such as CONSENSUS-1 [1104] and SOLVD [971], demonstrated that ACE inhibitors prevented all-cause death and various cardiovascular events in patients with HFrEF. These drugs also improved the prognosis of patients with an asymptomatic reduction in LVEF, preventing heart failure hospitalization [972, 1105].

With respect to the effects of ARBs in patients with HFrEF or an asymptomatic reduction in LVEF, the CHARM-Alternative trial involving patients intolerant to ACE inhibitors indicated that an ARB prevented cardiovascular death and heart failure hospitalization in comparison with a placebo [975]. However, according to the ELITE II [1106] study involving older patients with heart failure, as well as the VALIANT [962] trial involving patients with heart failure or myocardial infarction patients with reduced LVEF, ARBs were not superior to ACE inhibitors in the preventive effects on death or cardiovascular events, although their tolerability was improved.

Based on these results, it is recommended that an ACE inhibitor should be initially administered, as the first choice of renin–angiotensin (RA) system inhibitors, to patients with reduced LVEF and patients with old myocardial infarction, regardless of the presence or absence of heart failure symptoms and hypertension, and that an ARB should be used if intolerable to ACE inhibitors in the "Guidelines for the Secondary Prevention of Myocardial Infarction" prepared by the Japanese Circulation Society (a version revised in 2011) [946] and the "Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure" published by the Japanese Circulation Society/Japanese Heart Failure Society (a version revised in 2017) [716].

However, it is controversial whether an ACE inhibitor should be administered in preference to an ARB to hypertensive patients with myocardial infarction or heart failure. We searched RCTs in which the effects of ACE inhibitor or ARB administration on the outcome (recurrent or new-onset myocardial infarction, outcome of heart failure, cardiovascular/total mortality rates, onset of cardiovascular diseases, adverse events, alleviation of kidney damage/proteinuria, onset of atrial fibrillation) were examined in hypertensive patients with myocardial infarction or heart failure, by a SR. However, there was no such RCT-based evidence. Therefore, we newly investigated RCTs in which the effects of ACE inhibitors and ARBs on the outcome were compared in patients with myocardial infarction or heart failure, without focusing on hypertensive patients [965], and conducted a meta-analysis by selecting 6 RCTs in which the number of hypertensive patients was clear from the corresponding articles [713, 962, 976, 1106–1108].

This meta-analysis involving hypertensive patients with myocardial infarction or heart failure (Figure CQ8-1) showed that there were no significant differences in recurrent or new-onset myocardial infarction (relative risk (RR): 0.97 [95% confidence interval: 0.88–1.06], $P = 0.45$), cardiovascular/all-cause death (RR: 0.98 [0.91–1.05], $P = 0.49$), heart failure hospitalization (RR: 0.98 [0.84–1.14], $P = 0.79$), or cardiovascular diseases (RR: 1.02 [0.94–1.11], $P = 0.61$) between ACE inhibitors and ARBs [965]. On the other hand, concerning adverse events, the rate of patients who dropped out due to adverse events was significantly higher in those treated with ACE inhibitors (RR: 1.40 [1.11–1.77], $P = 0.004$). Frequent adverse events related to ACE inhibitors included cough, taste disorder, eruption and angioedema. Those related to ARBs included a decrease in blood pressure and kidney damage. However, no adverse event could be analyzed by meta-analysis. According to an RCT, there were no differences in the alleviation of kidney damage/proteinuria (RR: 0.96 [0.88–1.05]) or onset of atrial fibrillation (RR: 1.03 [0.92–1.16]) between the ACE inhibitor and ARB groups [713].

Of the 6 RCTs, the mean SBP at the time of registration was ≥140 mmHg in 1 (ONTARGET (rate of hypertensive patients: 67%)) [713]. However, blood pressure data from only patients with a history of myocardial infarction accounting for approximately 50% of the registered patients were unclear, and individual data could not be analyzed. The OPTIMAAL [976], VALIANT [962] and T-VENTURE [1107] studies involving patients with acute myocardial infarction showed that a history of hypertension was present in 36, 55, and 57% of the patients, respectively,

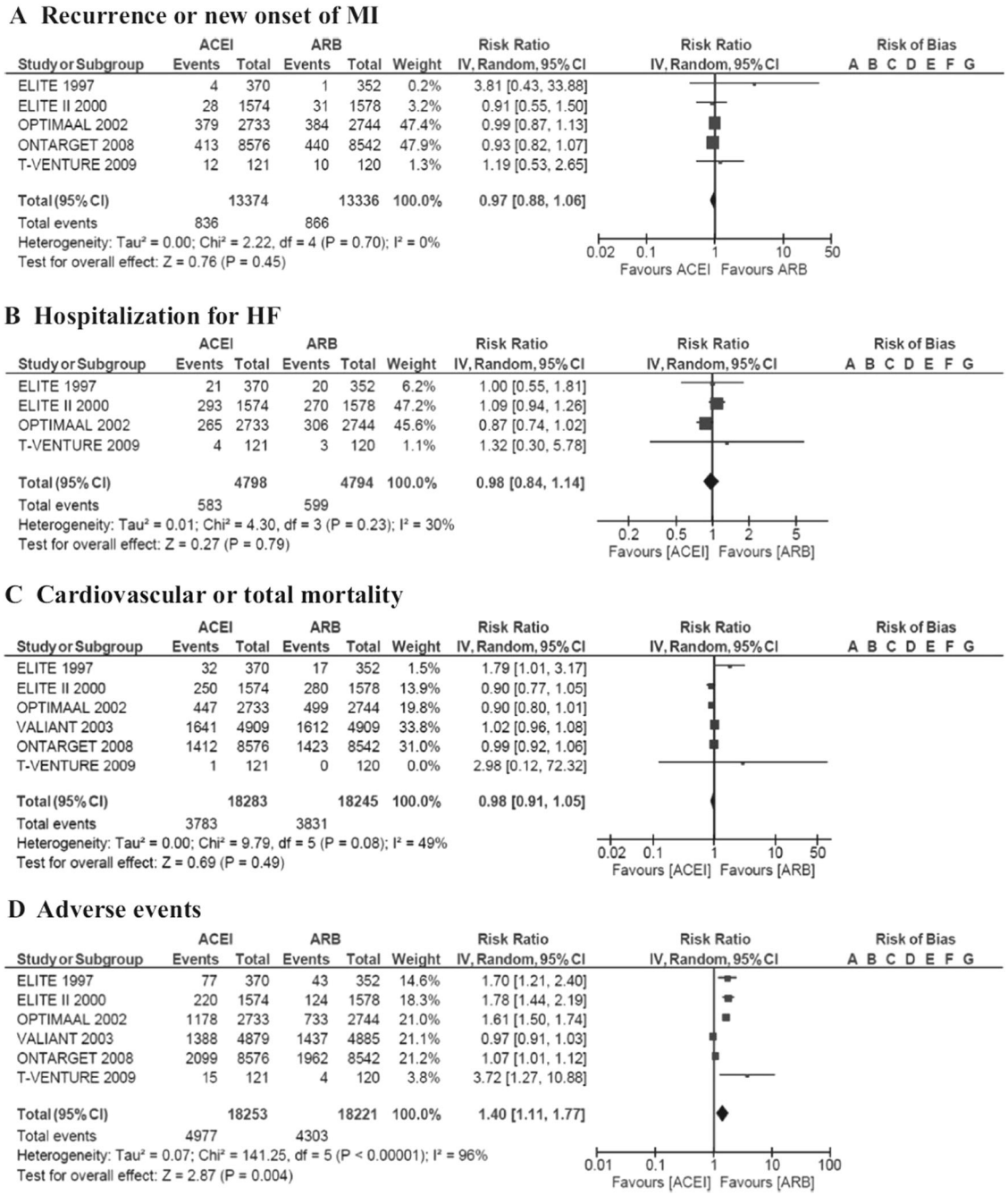


Fig. CQ8-1 Comparison of the effects of ACE inhibitors and ARBs in hypertensive patients with myocardial infarction or heart failure IV: Inverse variance, Random: Random effect model. (Source: Ref. [965])

whereas the mean SBP at the time of registration was 120 to 129 mmHg. The ELITE I [1108] and ELITE II [1106] studies involving patients with chronic heart failure indicated that the rates of hypertensive patients were 50 and 57%, respectively, and that the mean SBPs at the time of registration were 137 and 134 mmHg, respectively. Therefore, currently, there may be no sufficient evidence to examine the superiority of ACE inhibitors to ARBs in hypertensive patients with myocardial infarction or chronic heart failure at the time of intervention.

According to the Cochrane Database Systematic Review, in which the effects of ARBs in patients with heart failure were investigated, ARBs increased the incidence of new-onset myocardial infarction in comparison with a placebo (RR: 1.44 [1.03–2.01], P=0.0033), although there were no significant differences in the cardiovascular/total mortality rates [1109]. Compared with placebo, ARB significantly

reduced heart failure hospitalization in HFrEF patients (RR: 0.71 [0.61–0.82], $P < 0.00001$) and HFpEF patients (RR: 0.90 [0.81–1.00], $P = 0.048$) [1109]. When comparing ARBs with ACE inhibitors, there were no differences in the incidence of myocardial infarction (RR: 1.00 [0.62–1.63], $P = 0.99$), that of heart failure (RR: 0.96 [0.83–1.11], $P = 0.58$), total mortality rate (RR: 1.05 [0.91–1.22], $P = 0.48$), or cardiovascular mortality rate (RR: 1.08 [0.91–1.28], $P = 0.36$) [1109]. The Cochrane Database Systematic Review, in which the effects of ACE inhibitors and ARBs were compared in hypertensive patients, also showed that there were no differences in the total mortality rate (RR: 0.98 [0.84–1.10], $P = 0.77$) or cardiovascular mortality rate (RR: 0.98 [0.85–1.13], $P = 0.76$) between the two groups [737]. According to the above two SRs, the incidence of adverse events in patients treated with ARBs was significantly lower than in those treated with ACE inhibitors (RR: 0.63 [0.52–0.76], $P < 0.00001$ [1109], RR: 0.83 [0.74–0.93], $P = 0.001$ [737], respectively).

Conclusion

In this SR/meta-analysis, there was a great problem regarding the non-directivity of the subjects (incidence of hypertension or blood pressure at the time of registration), and there may be a bias risk; no sufficient evidence regarding the superiority/inferiority or equivalence of ACE inhibitors and ARBs in hypertensive patients with myocardial infarction or chronic heart failure at the time of intervention could be obtained. Therefore, at least at present, physicians must follow the recommendations of current guidelines without focusing hypertension that ACE inhibitors should be selected as priority for patients with myocardial infarction or HFrEF. In the future, a large-scale RCT involving Japanese patients may provide a clear answer to this CQ.

LITERATURE SEARCHING

We searched the literature from January 1966 until July 2017 on the PubMed and in July 2017 on the Cochrane Library. Based on the results of searching, we extracted articles regarding this CQ.

CQ9 IS A TARGET SBP OF <130 MMHG RECOMMENDED FOR PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)?

►We recommend a target SBP of <130 mmHg as heart failure hospitalization is prevented in patients with HFpEF.

Recommendation grade: 2 Evidence level: C

SUMMARY OF EVIDENCE

There was no evidence based on an RCT in which the outcome was directly compared between strict and standard blood pressure control groups or specific value-targeted groups among heart failure patients with preserved ejection fraction (HFpEF). We extracted 11 RCTs in which blood pressures before and after intervention were clear from RCTs involving HFpEF patients in which the results were compared between the antihypertensive drug intervention and control groups, and conducted a meta-analysis to examine changes in SBP before and after intervention, as well as the outcome. In most subjects, the double-blind method was adopted. This meta-analysis had a limitation: the non-directivity of subjects (definition of HFpEF, rate of hypertensive patients) or intervention methods; there may have been a bias risk in some RCTs. In several RCTs in which an outcome of heart failure had not been defined prior to the start of the trial, points were deducted as other biases.

INTERPRETATION

HFpEF accounts for >50% of patients admitted due to heart failure, who raise an important clinical issue, with a recent, rapid increase in their number. As the pathophysiology of HFpEF, increased vascular stiffness is important in addition to left ventricular diastolic dysfunction; therefore, strict blood pressure control may be useful for its primary/secondary prevention [983, 984, 1110]. In the 2017 American College of Cardiology (ACC)/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111], a target SBP of <130 mmHg is recommended for patients with HFpEF based on the results of the SPRINT [92] trial. It was also adopted in the "Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure" prepared by the Japanese Circulation Society/Japanese Heart Failure Society (a version revised in 2017) [716]. However, the target level was not established based on direct RCT-based evidence.

We conducted a SR to examine whether blood pressure control targeting a SBP of <130 mmHg is recommendable for patients with HFpEF. There was no RCT involving patients with HFpEF in which the outcome was directly compared among several groups targeting different blood pressure values or between strict and standard blood pressure control groups. Next, we performed a SR involving outcome comparison between drug intervention and control groups consisting of HFpEF patients [988], and detected 18 RCTs and 1 meta-analysis [970, 989–993, 1111–1123]. A meta-analysis of these RCTs showed that there was a decrease in heart failure hospitalization in the intervention group in comparison with the control group (relative risk

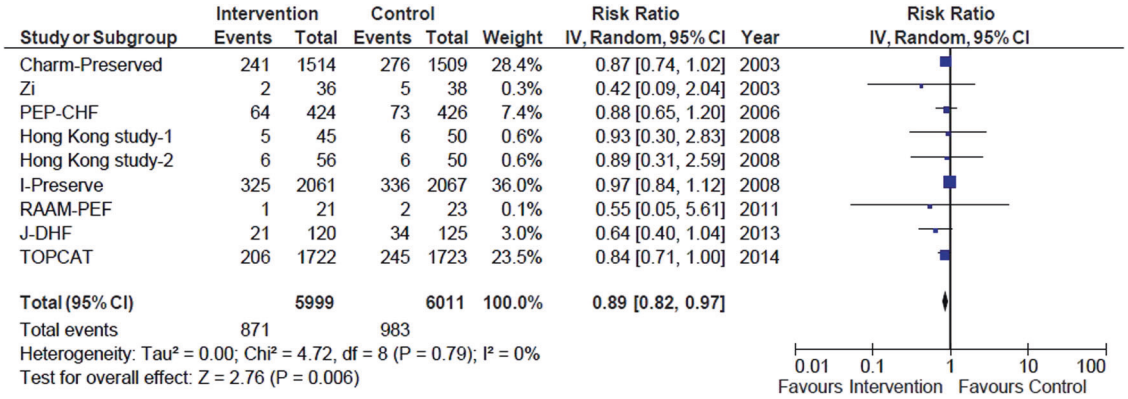


Fig. CQ9-1 Comparison of the outcome for heart failure hospitalization between the drug intervention and control groups among patients with HFpEF (9 RCTs in which blood pressure changes before and after intervention were clear) IV: Inverse variance, Random: Random effect model. (Source: Ref. [988])

[RR]: 0.88 [95% confidence interval: 0.81–0.95], $P = 0.001$), whereas intervention increased the incidence of renal dysfunction (RR: 1.52 [1.31–1.76], $P < 0.0001$).

Of these RCTs, we extracted 11 [989–993, 1111–1116] in which the blood pressure values before and after intervention were clear, analyzed changes in SBP before and after intervention, and conducted a meta-analysis regarding all-cause/cardiovascular death, heart failure hospitalization, renal dysfunction and hypotension [988]. The rate of heart failure hospitalization decreased in the intervention group (134.7→130.2 mmHg) in comparison with the control group (134.4→133.3 mmHg) (RR: 0.89 [0.82–0.97], P=0.006, Figure CQ9-1). On the other hand, the incidence of renal dysfunction in the former (134.3→129.6 mmHg) was higher than in the latter (134.0→132.8 mmHg) (RR: 1.52 [1.31–1.76], P<0.00001). There was no significant difference in the total mortality rate between the intervention (134.5→129.8 mmHg) and control (134.2→132.9 mmHg) groups (RR: 0.98 [0.91–1.06], $P = 0.69$). The cardiovascular mortality rate was similar between the two groups (134.6→130.3 and 134.4→133.3 mmHg, respectively) (RR: 0.99 [0.89–1.09], $P = 0.80$). There was no significant difference in the incidence of hypotension between the two groups (136.8→131.8 and 136.4→136.0 mmHg, respectively) (RR: 1.36 [0.75–2.46], $P = 0.31$). We could not examine nonfatal myocardial infarction, cardiovascular events, vertigo, fall/syncope or symptomatic hypotension because there was no corresponding RCT.

This analysis has several limitations: The RCTs analyzed did not adopt a study design to examine the outcome by the direct intervention of blood pressure. As the results were compared between the drug intervention and control groups, the influence of differences in blood pressure control and antihypertensive drugs must be considered. The subjects varied widely among the RCTs. A consensus regarding the definition of heart failure has not been reached: the presence or absence of heart failure symptoms/signs, Framingham risk score, and previous admission due to heart failure. The definition of HFpEF also varies: left ventricular ejection fraction, ≥35 to ≥50%. Furthermore, the rate of hypertensive patients varied (28 to 100%) among the RCTs, and the mean SBPs at the time of registration in both the drug intervention and control groups were approximately 135 mmHg; patients in whom blood pressure control had been essentially good may have accounted for >50%. The difference in achieved blood pressure levels between the two groups was approximately 3–4 mmHg, but we emphasize that heart failure hospitalization decreased in the intervention group in which a SBP of approximately 130 mmHg was achieved.

The EXCEED study indicated that strict blood pressure control to a SBP of <130 mmHg more markedly improved the left ventricular relaxing capacity in untreated hypertensive patients with left ventricular diastolic dysfunction in comparison with standard blood pressure control to a SBP of 130–139 mmHg [987], suggesting a mechanism involved in a strict-blood-pressure-control-related decrease in the heart failure-related admission rate, as shown by this meta-analysis.

Conclusion

To prevent heart failure hospitalization in patients with HFpEF, blood pressure control targeting a SBP of <130 mmHg should be performed while paying attention to tolerability such as renal dysfunction. In the future, an RCT should be carried out to directly compare specific-value-targeted groups consisting of patients with HFpEF.

LITERATURE SEARCHING

We searched the literature from January 1966 until July 2017 on the PubMed and EMBASE, and on July 24, 2017 on the Cochrane Library. Based on the results of searching, we extracted articles regarding this CQ.

CQ10

[CQ10-1] Should RA system inhibitors be used as a first-choice drug for antihypertensive therapy in CKD patients without diabetes mellitus (urinary protein: +)?

[CQ10-2] Should RA system inhibitors be used as a first-choice drug for antihypertensive therapy in non-diabetic CKD patients with proteinuria (urinary protein: -)?

►[CQ10-1] We recommend RA system inhibitors as a first-choice drug for antihypertensive therapy in non-diabetic CKD patients with proteinuria (urinary protein: +).

Recommendation grade: 1 Evidence level: A

►[CQ10-2] We recommend one of standard first-choice drugs (RA system inhibitors, CCBs, and thiazide-type diuretics) for antihypertensive therapy in non-diabetic CKD patients with proteinuria (urinary protein: -).

Recommendation grade: 2 Evidence level: C

SUMMARY OF EVIDENCE

CQ10-1: A meta-analysis of 29 RCTs [1124–1152] showed that renin–angiotensin (RA) system inhibitors significantly reduced the urinary protein level in CKD patients without diabetes mellitus (urinary protein: +), preventing the progression of renal failure. On the other hand, RA system inhibitors significantly increased the incidence of hyperkalemia, although its incidence was low. There were no significant differences in the total mortality rate, incidence of cardiovascular diseases, that of hypotension, or that of acute kidney damage between RA system inhibitors and other antihypertensive drugs.

CQ10-2: A meta-analysis of 8 RCTs [1151, 1153–1160] showed that RA system inhibitors significantly decreased the incidence of microalbuminuria in non-diabetic CKD patients with proteinuria (urinary protein: -). However, there was no significant influence on the progression of renal failure, onset of cardiovascular diseases, or total mortality. Concerning hyperkalemia, hypotension and acute kidney damage, no interventional or observational study to be evaluated was extracted.

INTERPRETATION

1) Establishment of CQ

To avoid subjects' overlapping with CQ12, which was established to examine the selection of antihypertensive drugs for hypertension complicated by diabetes mellitus, this CQ involved only non-diabetic CKD patients with proteinuria. Considering that different antihypertensive drugs are recommended with respect to the presence or absence of proteinuria in the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease [245], JSH2014 Guidelines for the Management of Hypertension [108], and 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111], we also conducted a SR on this CQ by dividing the subjects into two groups (urinary protein (+) and (-) groups). In this CQ, patients with a urinary protein level of ≥0.15 g/day (or ≥0.15 g/gCr) were regarded as having proteinuria. In accordance with CQ10-1 and 10-2, outcomes were established as follows: as advantages, 1) inhibition of renal failure progression, 2) a decrease in the total mortality rate, 3) a decrease in the incidence of cardiovascular diseases, 4) a decrease in the incidence of proteinuria or microalbuminuria; as disadvantages, 5) an increase in the incidence of hyperkalemia, 6) an increase in the incidence of hypotension, and 7) an increase in the incidence of acute kidney impairment (AKI) [1161].

2) SR subject research

Of RCTs of RA system inhibitors involving non-dialysis CKD patients, we extracted ones in which diabetics accounted for ≤30% of participants, and hypertensive patients accounted for ≥50%. In RCTs involving subgroup analysis, data from a population meeting this condition were extracted/used. We excluded RCTs in which two or more RA system inhibitors were compared or the effects of combination therapy with several RA system inhibitors were examined. Of the RCTs extracted, ones in which most participants showed urinary protein (+) were used for a meta-analysis regarding CQ10-1 based on information on the urinary protein level at the start of the trial, and ones in which most participants showed urinary protein (-) were used for a meta-analysis regarding CQ10-2. However, in previously published guidelines, the ALLHAT [1157, 1158] trial had been adopted as evidence regarding CKD patients without proteinuria based on the patient background, although there was no participant information on urinary protein in this trial. Considering this, such patients were also included for a meta-analysis regarding CQ10-2. In the AASK [1151] trial, the subjects were divided into two subgroups based on the presence or absence of proteinuria, and assigned to respective SRs.

3) Analysis involving non-diabetic CKD patients with proteinuria (urinary protein: +)

For an SR on CQ10-1, 29 RCTs were used [1124–1152]. Concerning the progression of renal failure, a meta-analysis

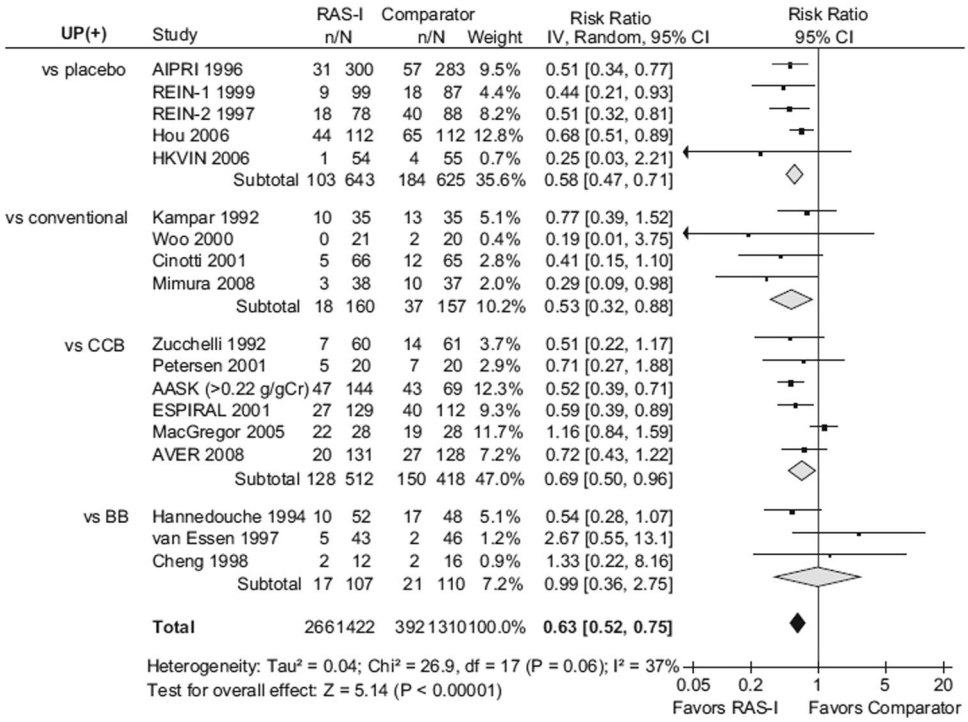


Fig. CQ10-1 Meta-analysis of 18 RCTs regarding the effects of RA system inhibitors on inhibition of renal failure progression as an outcome in non-diabetic CKD patients with proteinuria (urinary protein: +). IV: Inverse variance, Random: Random effect model. (modified from Ref. [1161])

of 18 RCTs establishing progression to ESKD or a 2-fold increase in the serum creatinine level (or an index in accordance with it) as an outcome showed that RA system inhibitors significantly inhibited the progression of renal failure (Figure CQ10-1, risk ratio [RR]: 0.63, 95% confidence interval [CI]: 0.52–0.75). With respect to urinary protein, a meta-analysis of 23 RCTs indicated that RA system inhibitors significantly reduced the urinary protein level, with a consistency (difference in the mean value in comparison with the control group: −0.42 g/day, 95%CI: −0.58 – −0.26). In this SR, there were no significant differences in the total mortality rate or incidence of cardiovascular diseases, which was possibly related to a small number of events in the RCTs extracted (cardiovascular diseases, RR: 0.77, 95%CI: 0.51–1.16). Concerning disadvantageous outcomes, there was a significant increase in the incidence of hyperkalemia, although its incidence was low (RR: 2.01, 95%CI: 1.07–3.77). There was no significant influence on the incidences of hypotension or AKI. In conclusion, the development of hyperkalemia must be considered, but advantages exceeded disadvantages; therefore, we recommend RA system inhibitors as a first-choice drug for antihypertensive therapy in non-diabetic CKD patients with proteinuria (urinary protein: +).

4) Analysis involving non-diabetic CKD patients with proteinuria (urinary protein: −)

For an SR on CQ10-2, 8 RCTs were used [1151, 1153–1160]. A meta-analysis of 5 RCTs showed that RA system inhibitors significantly decreased the urinary excretion of albumin, with a consistency (difference in the mean value in comparison with the control group: −16.3 mg/day, 95%CI: −30 – −0.26). However, there was no significant difference in the progression of renal failure (progression to ESKD or a 2-fold increase in the serum creatinine level) (Figure CQ10-2, RR: 1.02, 95%CI: 0.63–1.67). However, 3 of the 5 RCTs were small-scale trials involving patients with multiple cystic kidneys [1154, 1156, 1160], and the results of the other trials, especially the ALLHAT [1157] trial, were significant. Similarly, there was no significant influence of RA system inhibitors on total mortality or cardiovascular diseases in comparison with the control group (cardiovascular diseases, RR: 1.09, 95%CI: 0.99–1.20). Concerning hyperkalemia, hypotension, and AKI as disadvantageous outcomes, no RCT to be evaluated was extracted. In conclusion, RA system inhibitors for antihypertensive therapy in non-diabetic CKD patients with proteinuria (urinary protein: -) decreased the incidence of albuminuria, but there was no significant influence on progression to ESKD or cardiovascular diseases. Therefore, we recommend RA system inhibitors, CCBs, and

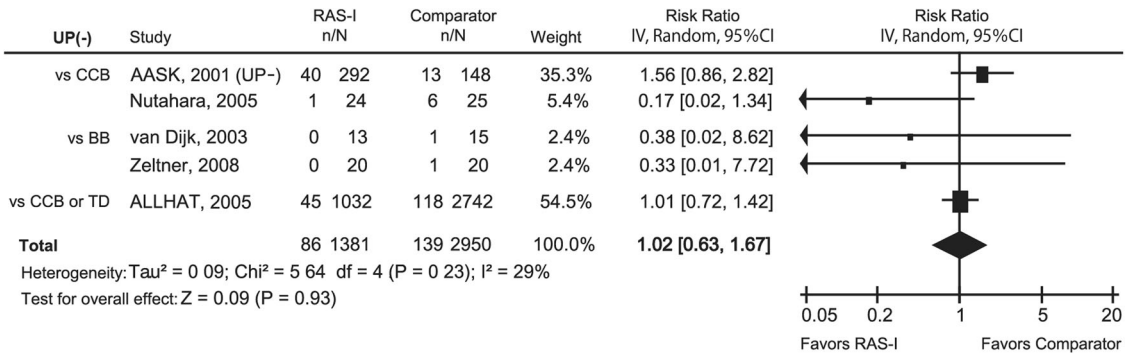


Fig. CQ10-2 Meta-analysis of 5 RCTs regarding the effects of RA system inhibitors on the inhibition of renal failure progression as an outcome in non-diabetic CKD patients with proteinuria (urinary protein: -). IV: Inverse variance, Random: Random effect model. (modified from Ref. [1161])

thiazide-type diuretics for non-diabetic CKD patients with proteinuria (urinary protein: -).

5) Definition of proteinuria

In the JSH2019 Guidelines, patients with a urinary protein level of ≥0.15 g/day (or ≥0.15 g/gCr) are regarded as having proteinuria. Based on this, we also regarded patients with a urinary protein level of ≥0.15 g/day (or ≥0.15 g/gCr) as showing urinary protein (+) in this CQ. With respect to the urinary protein level at which RA system inhibitors are recommended, RA system inhibitors are recommended as a first-choice drug for CKD patients with a urinary albumin level of ≥300 mg/day (or ≥300 mg/gCr) in the KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease [245] and 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111]. However, we adopted the urinary protein level as a parameter, considering that urinary microalbumin measurement in patients without diabetes mellitus is not covered by health insurance in Japan. Cinotti et al. reported that ACE inhibitors prevented progression to renal failure even in CKD patients with a mean urinary protein level of approximately 0.5 g/day at the start of their study [1136]. However, there is little evidence regarding inhibition of renal failure progression by RA system inhibitors in diabetes-free CKD patients with a urinary protein level of 0.15–0.49 g/day, which corresponds to A2 according to the CKD severity classification; therefore, antihypertensive drugs to be recommended remain controversial.

LITERATURE SEARCHING

We searched the literature before August 2017 on the PubMed, Cochrane Library, and Ichushi-Web. Based on the results of searching, we extracted articles regarding this CQ.

Q6 SHOULD A BLOOD PRESSURE OF 130/80 MMHG BE TARGETED IN NON-DIABETIC CKD PATIENTS WITH PROTEINURIA (URINARY PROTEIN: +)?

- In all hypertensive patients, urinalysis should be conducted, and the eGFR (estimated GFR) should be calculated.
- In urinary protein (±) or higher patients without diabetes mellitus, the urinary protein/creatinine ratio (g/gCr) should be measured using the test paper method. Those with a urinary protein level of ≥0.15 g/gCr are regarded as having proteinuria.
- We recommend a target blood pressure of <130/80 mmHg for diabetes-free CKD patients with proteinuria.

INTERPRETATION

In non-diabetic CKD patients with proteinuria, the presence or absence of proteinuria is important for establishing the target of blood pressure control.

A cohort study involving patients with an eGFR of <60 mL/min/1.73 m^2 among participants in the Kidney Early Evaluation Program (KEEP) indicated that the risk of ESKD was the lowest in a group with a SBP of 130–139 mmHg, and that the hazard ratio increased 1.27-fold in the 140–149-mmHg group and 1.36-fold in the ≥150-mmHg group [1162]. From the AASK study involving African Americans with nephrosclerosis, the results of cohort analysis were reported [499]. During the interventional study period, blood pressure was maintained at 141/86 mmHg in the standard blood pressure control group and at 130/78 mmHg in the strict blood pressure control group. Subsequently, a blood pressure of <130/80 mmHg was targeted in the two groups. As a result, strict blood pressure control improved the renal prognosis (2-fold increase in the creatinine level, ESKD, death) only in a group with a

baseline urinary protein level of ≥0.22 g/gCr. In addition, a meta-analysis of 11 RCTs, which was conducted to investigate the efficacy of strict blood pressure control, showed that strict blood pressure control improved the renal prognosis (2-fold increase in the creatinine level, ≥50% decrease in the GFR, ESKD) by approximately 27% in comparison with standard blood pressure control (mean SBP: 131.7 mmHg vs. 141.5 mmHg, respectively) only in a group with proteinuria at baseline [379]. The long-term cohort MDRD study [495] indicated that strict blood pressure control (mean blood pressure: <92 mmHg) significantly inhibited progression to ESKD in patients with a GFR of 13–55 mL/min and a urinary protein level of ≥1 g/day.

An additional analysis of the SPRINT study involving CKD patients showed that the incidence of complex cardiovascular events in the strict blood pressure control group, in which a blood pressure of <120 mmHg was targeted (blood pressure reached 123.3/66.9 mmHg), was slightly lower than in the standard blood pressure control group (blood pressure reached 136.9/73.8 mmHg), as demonstrated in the study, and the total mortality rate was significantly lower [1163]. On the other hand, the rate of decrease in the eGFR in the strict blood pressure control group was accelerated in comparison with the standard blood pressure control group from 6 months after the start of intervention (−0.47 mL/min/1.73 m^2/year vs. −0.32 mL/min /1.73 m^2/year, respectively). Furthermore, the incidence of adverse events, such as electrolyte abnormalities and acute renal failure, also significantly increased in the strict blood pressure control group. In the two groups, older patients (mean age: 72 and ≥75 years, respectively) accounted for ≥43% of the subjects. In the two groups, the baseline eGFR was 47.9 mL/min/1.73 m^2, and the urinary ACR was approximately 80 mg/gCr. Based on the study, the target of blood pressure control in hypertensive patients with CKD was changed to <130/80 mmHg regardless of the presence or absence of proteinuria in the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111].

On the other hand, a post-analysis of the SPRINT study indicated that the preventive effects of strict blood pressure control on cardiovascular events disappeared in a group with an eGFR of <45 mL/min/1.73 m^2, increasing the risk of acute renal impairment [1164]. In addition, the influence of strict blood pressure control on the onset of CKD was analyzed involving the ACCORD and SPRINT studies [1165]. Strict blood pressure control increased the incidence of new-onset CKD (>30% decrease in the eGFR and <60 mL/min/1.73 m^2) in both the diabetes and non-diabetes groups 3 years after the start of intervention.

With respect to the efficacy of strict blood pressure control (<130/80 mmHg) in CKD patients without proteinuria, there is little evidence involving Japanese patients. Considering the balance between advantages and disadvantages, baseline renal function- and age-based individualized management is necessary.

Thus, the target of blood pressure control should be established as <130/80 mmHg in non-diabetic CKD patients with proteinuria if proteinuria is present.

Chapter 7. Hypertension complicated by other diseases

POINT 7A

[Diabetes mellitus]

1. **The target of blood pressure control in hypertensive patients with diabetes mellitus should be <130/80 mmHg. The target home blood pressure should be <125/75 mmHg. However, a reduction in organ perfusion related to a decrease in blood pressure must be considered in patients with coronary artery disease or peripheral arterial disease.**
2. **In patients with a blood pressure of ≥140/90 mmHg, treatment with antihypertensive drugs should be promptly started. In those with a blood pressure of 130–139/80–89 mmHg, lifestyle modifications should be promptly attempted to reduce blood pressure. If a decrease in blood pressure is not achieved by lifestyle modifications, drug therapy should be promptly considered.**
3. **When selecting antihypertensive drugs for hypertensive patients with diabetes mellitus, a Ca channel blocker (CCB) and low-dose thiazide diuretic are recommended in addition to an angiotensin II receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor.**
4. **In patients with microalbuminuria or proteinuria, an ARB or ACE inhibitor should be predominantly selected, and a CCB and low-dose thiazide diuretic should be used concomitantly for blood pressure control.**

1. DIABETES MELLITUS

In diabetics, blood pressure should be measured on every consultation, and physicians should instruct them to measure blood pressure at home. In diabetics, blood pressure should be measured in a recumbent and standing as well as a sitting position, because orthostatic hypotension is observed in some patients. The frequency of hypertension is about two times higher in diabetics than in non-diabetics. In addition, the frequency of diabetes mellitus is 2–3 times

higher in hypertensive patients [1166]. An etiological relationship between the two diseases has been suggested. Type 2 diabetes and hypertension are major factors of metabolic syndrome, having obesity and insulin resistance as common background factors in some cases.

Microvascular complications characterizing diabetes mellitus include nephropathy, neuropathy and retinopathy. The progression of these conditions may reduce activities of daily living (ADL), affecting the quality of life (QOL). Hypertension is a risk factor for the deterioration of microvascular disease. Furthermore, both diabetes mellitus and hypertension are important risk factors for macrovascular disease. When the two diseases are concomitantly present, the incidences of cerebrovascular disease and coronary artery disease markedly increase [1167]. Therefore, in addition to lifestyle modifications, strict blood pressure/glucose control is important for the prevention and treatment of microvascular and macrovascular diseases in hypertensive patients with diabetes mellitus.

1) Target of blood pressure control

For diabetes treatment, multidisciplinary blood glucose/blood pressure/lipid control is necessary. In diabetics with elevated BP, treatment should be started when blood pressure is ≥130/80 mmHg. Non-drug therapies, weight control and exercise therapy are expected to promote a decrease in blood pressure associated with an improvement in glucose tolerance by improving insulin sensitivity. Therefore, for hypertensive patients with diabetes mellitus, strict lifestyle modifications, including weight control, exercise and restriction of salt intake, in addition to blood glucose control and the simultaneous initiation of antihypertensive medication are the principal treatments. If the target of blood pressure control is expected to be achieved on reassessment after 1 month solely by lifestyle modifications in patients with a blood pressure of 130–139/80–89 mmHg, control by such modifications alone may be attempted over a period not exceeding 3 months.

The level of blood pressure control in hypertensive patients with diabetes mellitus was examined in Section "CQ11". The target office and home blood pressures in these patients are <130/80 and <125/75 mmHg, respectively. A meta-analysis of 13 studies involving patients with diabetes/impaired glucose tolerance, including more than 100 patients in whom the systolic blood pressure (SBP) at the completion of the study could be reduced to ≤135 mmHg, was performed. The results showed that the onset of stroke could be prevented by reducing SBP to <120 mmHg, although there were no significant differences in the total mortality rate, cardiovascular mortality rate, incidence of myocardial infarction or incidence of heart failure between patients in whom SBP was reduced to ≤135 mmHg and those in whom it was reduced to ≤130 mmHg [1168]. Another meta-analysis, in which the final SBP and diastolic blood pressure (DBP) in an interventional study and the risks of myocardial infarction and stroke during the follow-up period were investigated in diabetics, also showed the preventive effects of reducing SBP and DBP to <130 and <80 mmHg, respectively, on stroke, although there was no further decrease in the risk of myocardial infarction [1169]. In the J-DOIT3 study, the preventive effects of multidisciplinary diabetes control on complications in Japanese patients were examined; intervention was started at a baseline blood pressure of 134/80 mmHg, establishing the target of blood pressure control as <120/75 mmHg in the intensive therapy group and <130/80 mmHg in the conventional therapy group, and the results of 9-year follow-up were reported [1170]. Although antihypertensive drugs had not been used in all subjects, a blood pressure of 123/71 mmHg was achieved in the intensive therapy group, and that of 129/74 mmHg was achieved in the conventional therapy group. The former showed a 58% decrease in the incidence of stroke in comparison with the latter, as well as a 14% decrease in the incidence of coronary artery disease. The incidence of stroke significantly decreased in proportion to the rate of decrease in blood pressure. Considering the above evidence, a target office blood pressure is also established as <130/80 mmHg in the present guidelines.

In patients with complications, caution is needed. In the INVEST Diabetes Cohort Study, in which hypertensive patients with coronary artery disease, aged over 50 years, were assigned to take a combination of sustained-release verapamil tablets and trandolapril or that of atenolol and a thiazide diuretic, the incidence of cardiovascular events was compared among three groups: poor (a blood pressure of ≥140 mmHg was reached), standard (a blood pressure of 130–140 mmHg was reached) and strict (a blood pressure of <130 mmHg was reached) control groups. In the standard control group, the incidence of cardiovascular events was lower than in the poor control group. There was no significant difference between the standard and strict control groups. In the latter, the total mortality rate was higher than in the former [526]. Furthermore, a stratified analysis of the INVEST showed that a reduction in blood pressure to <130 mmHg markedly increased the incidence of cardiovascular events in patients with peripheral arterial disease [1171]. Therefore, a reduction in organ perfusion related to a decrease in blood pressure should be considered in patients with atherosclerotic coronary artery disease or peripheral arterial disease. Non-clinic (home or ambulatory) blood pressure assessment should be positively performed.

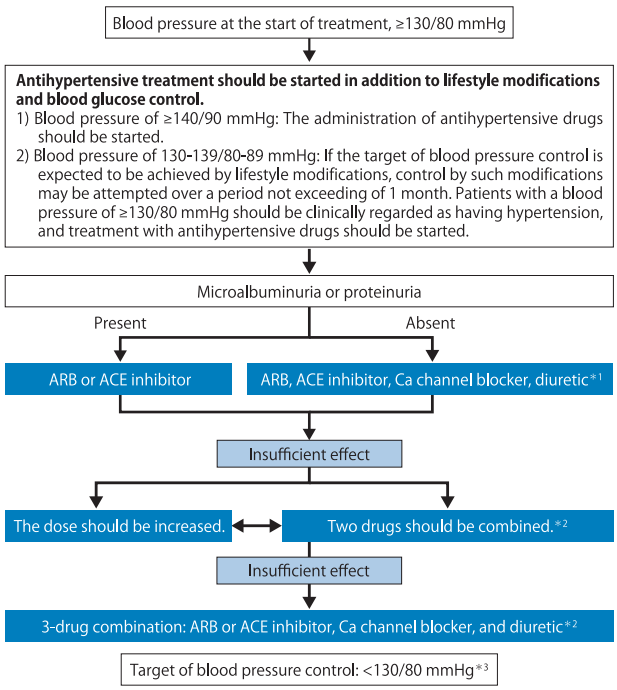
2) Selection of antihypertensive drugs

Concerning the selection of antihypertensive drugs for hypertension complicated by diabetes mellitus, first-choice

drugs include CCBs and low-dose thiazide diuretics in addition to ARBs and ACE inhibitors based on Section "CQ12". However, an ARB or ACE inhibitor should be selected if microalbuminuria (≥30 mg/gCr) or proteinuria is present.

In drug therapy for hypertension with diabetes mellitus, sufficient consideration of the effects of each antihypertensive drug on insulin sensitivity and glucose/lipid metabolism is necessary. Diuretics and β-blockers have been reported to reduce insulin sensitivity and increase the triglyceride level. Furthermore, β-blockers make symptoms of hypoglycemia less perceivable, and disadvantages of both drugs for blood glucose control have been indicated. ACE inhibitors, ARBs [691, 1172] and long-acting dihydropyridine CCBs improve insulin sensitivity and exert no adverse effect on lipid metabolism. A comparison of the three classes of drug showed that ARBs and ACE inhibitors were more effective than CCBs in suppressing the new occurrence of diabetes mellitus [691, 726, 937]. Although α-blockers improve glucose/lipid metabolism, whether they prevent target organ damage is unclear. In Section "CQ12", there were no marked differences in the incidence of cerebrovascular events between ARBs/ACE inhibitors and other drugs. Therefore, when treating diabetics without microalbuminuria or proteinuria, CCBs or low-dose thiazide diuretics should be administered in addition to ARBs or ACE inhibitors as antihypertensive drugs.

With respect to the effects of various antihypertensive drugs on diabetic nephropathy complicated by microalbuminuria or proteinuria, ACE inhibitors have been shown to prevent decreases in renal function and reduce the frequency of transition to dialysis therapy, even in nonhypertensive patients with type 1 diabetes associated with proteinuria [1173]. The J-MIND study performed in Japan [1174] showed that CCBs and ACE inhibitors had comparable effects on proteinuria and renal function in patients with diabetic nephropathy. RENAAL [698], IDNT [1175, 1176], IRMA-2 [1177] and MARVAL [1178] also suggested the effectiveness of ARBs for the treatment of type 2 diabetic nephropathy. In Japan, the INNOVATION Study [1179] also showed the usefulness of ARBs. Furthermore, the ROADMAP Study [1180] indicated the preventive effect of ARBs on microalbuminuria in type 2 diabetics. Based on the above evidence regarding the effects on diabetic nephropathy, renin–angiotensin (RA) system inhibitors (ARBs or ACE inhibitors) are recommended for the treatment of diabetic nephropathy. If the hypotensive effects of a first-choice drug are insufficient, an ARB/ACE inhibitor, CCB or low-dose thiazide diuretic should be combined as a second-choice drug; if a further decrease in blood pressure is necessary, three drugs should be used simultaneously. A combination of an ARB and an ACE inhibitor should be avoided. In GUARD [705], in which CCBs and diuretics were compared as a drug to be combined with an RA system inhibitor for the treatment of diabetic nephropathy, combination therapy with a diuretic was more effective for controlling proteinuria, but combination therapy with a CCB was more effective for maintaining the estimated glomerular filtration rate (eGFR). The diabetes subanalysis of the ACCOMPLISH Study [755], in which the usefulness of combination therapy with an ACE inhibitor and a long-acting CCB or a thiazide diuretic was compared in hypertensive patients with coronary artery disease, left ventricular hypertrophy, peripheral arterial disease or renal dysfunction, showed that a CCB was more useful than a diuretic for preventing cardiovascular events. In the OSCAR Study [702], ARB therapy at an increased dose was compared with combination therapy with a CCB in hypertensive patients with a history of cardiovascular diseases or those with type 2 diabetes mellitus who had undergone antihypertensive treatment with an ARB. With regard to fatal or nonfatal cardiovascular diseases (including diabetic complications, deterioration of the renal function and non-cardiovascular death) as a primary end point, there was no significant difference in the incidence, overall, but it was significantly lower in the CCB-combined group among patients with a history of cardiovascular diseases. However, among diabetics without a history of cardiovascular diseases, the incidence was slightly lower in the ARB dose-increased group, although there was no significant



*1 Low-dose thiazide diuretic
*2 Combination therapy with an ARB and ACE inhibitor should be avoided.
*3 In patients with atherosclerotic coronary artery disease or peripheral arterial disease and older patients, a reduction in organ perfusion related to a decrease in blood pressure must be considered.

Fig. 7-1 Treatment plan for hypertension complicated by diabetes mellitus

difference between the two groups. In the ONTARGET Study [713] involving diabetics and non-diabetics, the results were compared between monotherapy with an ACE inhibitor or ARB and combination therapy. In the combination therapy group, hyperkalemia, renal dysfunction and an excessive decrease in blood pressure were more frequent. In the ALTITUDE Study, in which combination therapy with a renin inhibitor (aliskiren) or placebo was introduced in high-risk diabetics taking an ACE inhibitor or ARB, adverse events, such as hyperkalemia, renal dysfunction and an excessive decrease in blood pressure more frequently occurred in the aliskiren-combined group, and this combination therapy was discontinued in the early phase [748]. Based on these results, aliskiren is contraindicated for diabetics taking an ACE inhibitor or ARB as a rule. A combination of two or more classes of RA system inhibitors, including direct renin inhibitors (DRIs), is not recommended. When combining them, careful follow-up is needed. In patients with HFrEF, angina on effort or old myocardial infarction, the use of β-blockers should be considered because of their cardioprotective effects. Figure 7-1 shows a therapeutic flowchart for hypertension treatment in patients with diabetes mellitus.

2. DYSLIPIDEMIA

The serum low-density lipoprotein (LDL)-cholesterol level is a predictor of atherosclerotic disease in Japanese [1181]. An epidemiological survey in Japan indicated that, in addition to hyper-LDL cholesterolemia, increases in the total cholesterol, non-HDL cholesterol, and neutral fat (triglyceride (TG)) levels and a decrease in the high-density lipoprotein (HDL)-cholesterol level were risk factors for the onset of coronary artery disease/death. Of course, dyslipidemia complicated by hypertension further increases the risk of atherosclerotic disease. In the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017, stratification was conducted based on the Suita score, in which the incidence of coronary artery disease over 10 years was established as an outcome, to establish the target of LDL-cholesterol control from the viewpoint of coronary artery disease prevention [1182]. The total Suita score increased, depending on the severity of hyper-LDL cholesterolemia and hypo-HDL cholesterolemia or current blood pressure values; strict LDL-cholesterol control was proposed. A meta-analysis of 10 cohort studies in Japan (EPOCH-JAPAN) [10] showed that the risks of cardiovascular diseases, stroke, myocardial infarction, CKD and death increased with an increase in blood pressure, exceeding a normal range (SBP: <120 mmHg and DBP: <80 mmHg). In the ASCOT-LLA study [1183], serum LDL-cholesterol-reducing therapy prevented the occurrence and recurrence of coronary artery disease and stroke in hyper-LDL cholesterolemia patients with hypertension. In hypertensive patients with dyslipidemia, lifestyle modifications, smoking cessation, energy intake/weight control, saturated fatty acid/alcohol/cholesterol/trans-fatty acid intake control, and activity/physical strength enhancement must be attempted after evaluating the global risk of dyslipidemia. For patients with hyper-LDL cholesterolemia, statins should be selected as a first-choice drug. The target of LDL-cholesterol control should be <120 mg/dL in a primary prevention high-risk group and <100 mg/dL for secondary prevention. In patients with familial hypercholesterolemia, acute coronary syndrome, or diabetes mellitus, a target LDL-cholesterol level of <70 mg/dL should be considered in accordance with other high-risk conditions (non-cardiogenic cerebral infarction, peripheral arterial disease, CKD, metabolic syndrome, duplicated major risk factors, smoking) [1182]. In the American College of Cardiology (ACC)/American Heart Association (AHA) lipid control guidelines for cardiovascular risk reduction in adults in 2013 [396], it is recommended that moderately to highly strong statins should be used in 40- to 75-year-old patients in whom the risk of atherosclerotic cardiovascular events within 10 years is evaluated as ≥7.5% using the Pool Cohort Equation, but no target LDL-cholesterol level for each patient is established, differing from the establishment of the target of control in Japan. In the PATROL study [1184], high-risk patients with hyper-LDL cholesterolemia were randomly assigned to receive pitavastatin, rosuvastatin, or atorvastatin, which are strong statins, and the safety and efficacy of treatment for achieving a target LDL-cholesterol level were examined. The efficacy of pitavastatin and incidence of drug-associated adverse effects were similar to those of rosuvastatin and atorvastatin. Furthermore, these parameters were similar between rosuvastatin and atorvastatin. These results suggest that any of the 3 strong statins may be used for treatment in Japanese patients. Recently, the subcutaneous injection of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor has been performed in high-risk patients, showing LDL-cholesterol-reducing effects [1185, 1186], but there has been no influence on blood pressure.

For hypertensive patients with dyslipidemia, antihypertensive drugs that do not influence lipid metabolism (lipid neutral), such as ARBs, ACE inhibitors and CCBs, or drugs that slightly improve it (α-blockers) [1187] should be selected. Some ARBs improve lipid metabolism via the agonistic actions of PPARγ [1188], but it is unclear whether marked effects are obtained. Dyslipidemia is associated with the RA system with respect to insulin resistance and vascular endothelial function. However, in clinical practice, combination therapy with an antihypertensive drug and a statin is appropriate. In patients with hypertriglyceridemia, the administration of a fibrate drug should be considered. In

those with hypo-HDL cholesterolemia, lifestyle modifications may increase the HDL-cholesterol level by approximately 10%, but, currently, there is no drug that corrects it.

POINT 7B

[Obesity]

1. **In hypertensive patients with obesity, ≥3% weight control by dietary and exercise therapies may have significant hypotensive effects.**

[Metabolic syndrome]

1. **Metabolic syndrome is an important risk factor for cardiovascular diseases. In addition to the management of other risk factors, strict blood pressure control should be performed.**
2. **When selecting antihypertensive drugs, the reduction of visceral fat-type obesity, improvement of insulin resistance and onset of diabetes mellitus must be considered. ARBs and ACE inhibitors are recommended.**
3. **It is recommended that grade I or severer hypertension patients on specific health checkups/health guidance should consult a hospital, as a rule, and that those with risk factors for cardiovascular diseases should promptly consult a hospital. Information must be given to those without other risk factors. In this case, after informing patients of a diagnosis of hypertension, health care professionals should instruct them to modify their lifestyle and undergo additional examination in the hospital after 1 month.**

3. OBESITY

In obese patients, the incidence of hypertension is 2–3 times higher than in non-obese persons [1189]. In particular, excessive weight gain from a young age is an important risk factor for hypertension. The sympathetic nervous system, sodium retention/salt sensitivity and insulin resistance have been suggested to be involved in the etiology of hypertension associated with obesity [1190]. On the other hand, sleep apnea syndrome is occasionally observed in obese patients, and it may be a factor involved in the occurrence and progression of hypertension. A study reported that a 4- to 5-kg decrease in body weight significantly reduced blood pressure [563]. Significant hypotensive effects may be obtained by achieving ≥3% weight loss [548]. For antihypertensive therapy in obese patients, weight control by dietary and exercise therapies should be attempted first; however, if the decrease in blood pressure is insufficient even after guidance in weight control, drug therapy should be introduced. The primary objective of antihypertensive drug therapy is to achieve the target of blood pressure control. However, ARBs and ACE inhibitors are recommended because of their effects on abnormal glucose metabolism and insulin resistance. In CASE-J [937], a large-scale clinical study conducted in Japan, the new occurrence of diabetes mellitus, as a secondary end point, in the candesartan (ARB) group was significantly lower than in the amlodipine group. The preventive effect was more marked in obese patients with a body mass index (BMI) of ≥25 kg/m^2 based on the results of subanalysis. In the ACCOMPLISH Study, in which the usefulness of combination therapy with an ACE inhibitor and a long-acting CCB or thiazide diuretic was examined in hypertensive patients with a high risk of cardiovascular diseases, the

Table 7-1 Diagnostic criteria for metabolic syndrome

New criteria prepared by 8 societies (April 2005)		
- Intraperitoneal fat accumulation		
Waist circumference	Men: ≥85 cm	Women: ≥90 cm
(Visceral fat area: corresponding to ≥100 cm^2 in both men and women)		
In addition to the above criterion, 2 or more of the following items must be met:		
- Lipid levels		
Hypertriglyceridemia	≥150 mg/dL	
and/or		
Hypo-HDL cholesterolemia	<40 mg/dL	(men and women)
- Blood pressure		
SBP	≥130 mmHg	
and/or		
DBP	≥85 mmHg	
- Blood glucose level		
Fasting hyperglycemia	≥110 mg/dL	

CCB significantly prevented cardiovascular events in comparison with the diuretic, but the effects of the two drugs were similar in obese patients with a BMI of ≥30 kg/m^2 [755]. Therefore, in the presence of obesity, resistant hypertension is not rare. If a sufficient decrease in blood pressure is not achieved with ARBs or ACE inhibitors, combination therapy with long-acting CCBs or thiazide diuretics should be considered. Thiazide diuretics do not influence metabolism at a half of the standard dose.

4. METABOLIC SYNDROME

The concurrence of hypertension, dyslipidemia (hypertriglyceridemia and hypo-HDL cholesterolemia), obesity and abnormal glucose metabolism has been shown by many epidemiological studies to synergistically increase the risk of atherosclerotic diseases, including coronary artery disease. Insulin resistance is involved as a common background factor in these diseases, which are risk factors, and the accumulation of metabolic diseases is termed "metabolic syndrome" [1191]. Diagnostic criteria in Japan were proposed in April 2005 by a joint committee of eight relevant scientific societies, including the Japanese Society of Hypertension (JSH) [1192]. According to the criteria shown in Table 7-1, hypertension with metabolic syndrome is associated with visceral fat-type obesity concurrent with either abnormal glucose or lipid metabolism. The main target diseases related to metabolic syndrome are cardiovascular diseases and diabetes mellitus. In the Tanno-Sobetsu Study, the incidences of the former and latter were 1.87 [35] and 2.17 [1193] times higher, respectively, in patients with metabolic syndrome, suggesting that visceral fat-type obesity control contributes to the prevention of hypertension [1194]. The aim of hypertension treatment in patients with metabolic syndrome is the reduction of visceral fat-type obesity by dietary and exercise therapies. If antihypertensive drugs are used, ARBs, ACE inhibitors, CCBs and α-blockers that reduce insulin resistance may be desirable. Prevention of the new occurrence of diabetes mellitus is related to the alleviation of insulin resistance, and ARBs or ACE inhibitors are more useful than other drugs, as suggested by CASE-J [937], VALUE [691] and ALLHAT [726]. However, there is no sound evidence that RA system inhibitors are effective in the prevention of cardiovascular diseases in hypertensive patients with metabolic syndrome [726].

1) Blood pressure control in specific health checkups/health guidance

Since April 2008, specific health checkups/health guidance has been carried out. In this program, the entity of metabolic syndrome is introduced, and specific health guidance is indicated for individuals meeting an abdominal circumference of ≥85cm for men and ≥90cm for women or a BMI of ≥25 kg/m^2 and having other risk factors, to prevent lifestyle-related diseases by lifestyle modifications by health guidance [1195]. For the primary prevention of cardiovascular diseases in Japan, it is very important to correct abnormal glucose metabolism, a high blood pressure and abnormal lipid metabolism, primarily in patients with visceral fat-type obesity. The details of specific health checkups/health guidance as a strategy for the prevention/management of hypertension are shown in Table 7-2. According to reports on the outcome of specific health checkups/health guidance in 2014 and 2015 [1196, 1197], SBP and DBP significantly decreased by 4.5 and 3 mmHg, respectively, in those achieving ≥3% weight loss within 1 year among positively supported subjects whose mean age and BMI were 48.3 years and 27.7 kg/m^2, respectively. Blood pressure measurement on specific health checkups and subsequent strategies are also presented in Table 7-2.

Table 7-2 Approaches to hypertension on specific health checkups/health guidance

(1) Measurement of blood pressure: After two sessions of blood pressure measurement, the mean value should be adopted.

(2) Strategies after blood pressure measurement

① When conducting health checkups or health guidance, home blood pressure must be considered in addition to the blood pressure value measured.

② Health care professionals must instruct patients with a blood pressure of ≥130/85 mmHg (criterion for health guidance) to promote lifestyle modifications. However, patients with a home blood pressure of <125/80 mmHg are regarded as showing a white coat phenomenon even if blood pressure on a health checkup is ≥130/85 mmHg; the blood pressure is not evaluated as high.

③ Even if blood pressure on a health checkup is <130/85 mmHg, patients with a home blood pressure of ≥125/80 mmHg are regarded as having high blood pressure/hypertension. Those with a home blood pressure of ≥135/85 mmHg are regarded as having mask hypertension, and they are advised to consult a hospital.

④ Patients with a blood pressure of ≥140/90 mmHg are advised to consult a hospital, as a rule. At this point, home blood pressure should be checked.

If grade I hypertension (140–159/90–99 mmHg) is complicated by diabetes mellitus or CKD, health care professionals must advise patients to promptly consult a hospital.

In addition, health care professionals should also advise patients with a blood pressure of ≥160/100 mmHg (grade II hypertension or severer) to promptly consult a hospital.

⑤ Risk-factor-free patients with grade I hypertension:

As a rule, such patients are advised to consult a hospital. However, information should be provided on the assumption that they may consult a hospital. When providing information, health care professionals should inform persons undergoing a specific health checkup of hypertension, present the lifestyle-improving effects of salt restriction and dietary/exercise therapies, and advise them to consult a hospital after 1 month by home blood pressure measurement.

Table 7-3 Findings suggesting OSAS

Symptoms	Sleepiness, reduced concentration, depression, indefinite complaints (headache and malaise) early in the morning, marked snoring, apnea (frequently indicated by patients' families), frequent awakening during the night, nocturia and nocturnal dyspnea (feelings of suffocation)
Physical findings	Obesity, micrognathis, tonsillar hypertrophy and low palatal arch with long low-hanging soft palate
Blood pressure features	Resistant hypertension, morning hypertension and nighttime hypertension
Findings	Left ventricular hypertrophy (especially in patients with normal office and home blood pressures), heart failure, cerebrovascular disorder, nocturnal cardiovascular events (including atrial fibrillation and supraventricular or ventricular arrhythmia), metabolic syndrome, CKD and dialysis

POINT 7C

[Sleep apnea syndrome]

1. **In patients with snoring/apnea, nocturia, nocturnal dyspnea, nighttime cardiovascular events or resistant hypertension in addition to sleepiness during the daytime, obstructive sleep apnea syndrome (OSAS) should be suspected.**
2. **In OSAS patients, non-dipper-/riser-type nocturnal hypertension with marked blood pressure variability is frequently observed. OSAS should be suspected if home blood pressure measurement suggests morning hypertension.**
3. **In hypertensive patients with OSAS, continuous positive airway pressure (CPAP) therapy should be performed in addition to salt restriction/weight control. Strict antihypertensive treatment involving nighttime blood pressure should be performed.**

5. SLEEP APNEA SYNDROME

OSAS is a disease in which hypoxia occurs periodically during sleep due to respiratory arrest caused by collapse of the upper airway. It is a risk factor for cardiovascular diseases, such as coronary artery disease and heart failure [1198, 1199], and cerebrovascular diseases, including silent cerebral infarction [1200], in addition to nighttime sudden cardiac death. Moreover, OSAS is the etiology of hypertension, and is the most frequent underlying cause of secondary hypertension [801]. OSAS is frequently observed in Japanese patients with hypertension [1201–1204]. The diagnosis and treatment of OSAS in hypertensive patients are very important. OSAS increases with obesity or age, but, in Japan, it is also frequently observed in nonobese individuals with particular skeletal characteristics of the face such as micrognathia, tonsillar hypertrophy or low palatal arch with long low-hanging soft palate (even when the tongue is pushed with a tongue depressor, the uvula or posterior wall of the pharynx cannot be examined) [1205]. Although many patients consult a hospital with symptoms, such as daytime sleepiness, reduced concentration and a depressive state, symptoms are often absent in hypertensive patients; most patients consult a hospital because of snoring or apnea indicated by the patient's family. In patients with nocturia, nocturnal dyspnea (feelings of suffocation), heart failure, a history of nocturnal cardiovascular events (myocardial infarction, stroke, acute aortic dissection, supraventricular or ventricular arrhythmia), resistant hypertension (particularly resistant morning hypertension) or left ventricular hypertrophy under non-hypertensive range, as well as those undergoing dialysis, it is important to suspect OSAS (Table 7-3) [1202, 1206]. OSAS is diagnosed and staged by polysomnography (PSG), and it is considered to be mild when the apnea-hypopnea index (AHI: number of apneic or hypopneic periods per hour) is 5–14, moderate when it is 15–29 and severe when it is ≥30 [1207]. In hypertensive patients with symptoms or organ damage showing an AHI of ≥15, treatment must be considered (borderline for the secondary prevention of cardiovascular diseases). In those with an AHI of ≥30, aggressive treatment including CPAP should be performed (borderline for the primary prevention of cardiovascular diseases) [1206]. In the health insurance system, an AHI of ≥20 on nighttime PSG or that of ≥40 (severe status) on limited PSG is a borderline at which CPAP is possible [1206]. In patients with OSAS, non-dipper-type nocturnal hypertension is frequently observed in addition to an increase in blood pressure during the daytime, and often detected as morning hypertension by home blood pressure measurement [1199].

OSAS precedes non-dipper-type nocturnal hypertension [1208]. In OSAS patients, non-dipper-type hypertension is also associated with the progression of CKD [1209]. In addition, a marked surge of nighttime blood pressure is observed in the recovery phase after apnea events with a marked reduction in the oxygen saturation, and such a change in nighttime blood pressure [1200] may induce nocturnal cardiovascular events. Recently, it has become possible to measure nighttime blood pressure [173–175, 1210] and its surge after apnea events using a home sphygmomanometer [1211–1214]. The enhancement of sympathetic activity, decreased pressure receptor/chemoreceptor sensitivity, activation of the renin–angiotensin–

aldosterone system and increases in oxidative stress and inflammatory reactions are complexly involved in OSAS-related hypertension or an increase in fluctuation of the blood pressure [1202]. A study indicated that OSAS-related intermittent hypoxia evaluated using the oxygen desaturation index (ODI) rather than the AHI was associated with hypertension [1215]. As OSAS is closely associated with lifestyle, lifestyle should be initially modified. In addition to salt restriction, weight control must be promoted in obese patients, and smoking and alcohol consumption before retiring should be avoided. Indeed, when comparing the hypotensive effects of CPAP therapy, weight control by dietary therapy, and CPAP + dietary therapy in obese patients with OSAS, including normotensive patients, CPAP + dietary therapy had the most potent hypotensive effects [1216]. CPAP therapy should be predominantly performed in patients with grade I/II hypertension complicated by severe OSAS [1199] (however, in the health insurance system, an AHI of ≥20 on overnight full PSG or that of ≥40 (severe status) on limited PSG is a borderline at which CPAP is possible). Some patients with grade III or severer hypertension require drug therapy from the initial consultation. In most severe-status patients, CPAP therapy lowered blood pressure [1209, 1217, 1218], allowed a dipper pattern to replace the non-dipper pattern [1219], reduced a nocturnal surge of blood pressure [1199] and improved the cardiovascular prognosis [1220]. A long-term follow-up study also showed that CPAP therapy prevented the new onset of hypertension in patients with OSAS [1221]. In clinical practice, we have encountered OSAS patients with good adherence in whom hypotensive effects were obtained, but previous randomized controlled trials (RCTs) of CPAP therapy showed that adherence was poor in OSAS patients without sleepiness, and that the hypotensive effects of CPAP therapy were weak. In addition, no RCT demonstrated its preventive effects on cardiovascular events [1222–1225]. Therefore, in the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, the efficacy of CPAP therapy for hypertension is evaluated as class IIb [111]. Thereafter, a meta-analysis of 7 RCTs in which the results were reviewed with respect to the presence or absence of CPAP therapy indicated that CPAP therapy for ≥4 h significantly decreased the incidence of cardiovascular events, suggesting the importance of adherence [1226]. In OSAS patients in whom CPAP therapy is impossible or adherence is poor, oral appliances are also useful [1227, 1228]. Therefore, patients should be referred to specialists including otorhinolaryngologists and oral surgeons if necessary. As the risk of cardiovascular diseases is high in hypertensive patients with OSAS, the target level of blood pressure control should be established, considering an increase in negative intrathoracic pressure load on the thoracic aorta and heart on apneic events (which may reach 80 mmHg); strict antihypertensive therapy, particularly with the control of nighttime blood pressure, should be performed. However, there is no evidence regarding the usefulness of specific antihypertensive drugs [1200]. According to a study, β-blockers more markedly reduced nighttime SBP/DBP compared with CCBs, ACE inhibitors and ARBs (no significant difference between β-blockers and diuretics), although there were no differences in the rate of decrease in daytime/waking blood pressure among these antihypertensive drugs [1229]. However, another study indicated that monotherapy with antihypertensive drugs, including β-blockers, reduced daytime blood pressure, whereas it was difficult to control nighttime blood pressure during sleep [1230]. A consensus regarding the efficacy of β-blockers has not been reached. In OSAS patients with obesity, the RAA system is enhanced, and the concomitant development of left ventricular hypertrophy is frequent; therefore, RA system inhibitors may be useful. In hypertensive OSAS patients with heart failure, the administration of diuretics may reduce laryngeal edema, thereby relieving OSAS [1231]. According to several studies, in patients with resistant hypertension, spironolactone administration [1232], negative-pressure aspiration of the lower limbs [1233] and renal denervation [1234] decreased blood pressure and the frequency of sleep apnea events, although the number of patients was small. Central sleep apnea syndrome is observed in some patients, showing a poor prognosis. However, it is rare in hypertensive outpatients without severe heart failure.

POINT 7D

[Gout/hyperuricemia]

1. **Patients with a serum urate level of >7.0 mg/dL are regarded as having hyperuricemia. Lifestyle guidance, such as reduction of body weight by the optimization of energy intake, restriction of purine/fructose/alcohol intake, and routine practice of aerobic exercise, should be started.**
2. **If the serum urate level is ≥8.0 mg/dL in hypertensive patients, the initiation of urate-lowering drugs should be considered. The target of control of the serum urate level should be ≤6 mg/dL.**
3. **As antihypertensive drugs, those that have favorable effects on urate metabolism should be selected. As diuretics (thiazide and loop diuretics) may increase the urate level, changes in the serum urate level must be monitored if these diuretics are required. β-Blockers also slightly increase the urate level. CCBs, ARBs and ACE inhibitors have no adverse effect on urate metabolism. Losartan promotes urate**

excretion, reducing the urate level. CCBs and losartan reduce the risk of gout in hypertensive patients.

4. **Urate-lowering drugs should be selected on the basis of the classification of disease type. For patients with renal dysfunction, a drug and its dose should be carefully selected. New xanthine oxidase inhibitors may be effective regardless of the disease type or the presence or absence of renal dysfunction.**

6. GOUT/HYPERURICEMIA

Hyperuricemia frequently occurs in hypertensive patients. Its incidence in untreated men with hypertension on health checkups is reportedly 16.8% [1235]. On the other hand, the incidences of hyperuricemia (urate level: >7 mg/dL or patients receiving urate-lowering drugs) in hypertensive men and women who had consulted special outpatient clinics for hypertension were 40.6 and 8.6%, respectively [1236]. As a condition in which hypertension is frequently complicated by hyperuricemia, metabolic disturbance, represented by metabolic syndrome, has been reported. The presence of obesity or insulin resistance increases urate production, causing hyperuricemia by a reduction in urate excretion associated with enhanced sodium resorption in the renal tubules. Furthermore, enhanced sodium resorption increases the body fluid volume, and enhances the sympathetic nervous system, contributing to an increase in blood pressure. Kidney dysfunction related to hypertension or the use of diuretics induces hyperuricemia with a reduction in urate excretion.

Meta-analyses showed that hyperuricemia was a risk factor for the new onset of hypertension, and that urate-lowering therapy significantly reduced blood presusre [1237, 1238]. Furthermore, several studies indicated that hyperuricemia was an independent risk factor for cardiovascular diseases [1239, 1240], but no large-scale clinical study has examined the preventive effects of urate-lowering therapy on cardiovascular events. Whether urate is an independent risk factor or disease marker remains controversial.

In the Guidelines for the Management of Hyperuricemia and Gout (version III) [1241], which were prepared by the Japanese Society of Gout and Nucleic Acid Metabolism, it is proposed that patients with a serum urate level of >7.0 mg/dL should be regarded as having hyperuricemia, and that life guidance should be started. Its items include reduction of body weight by the optimization of energy intake, restriction of purine/fructose/alcohol intake, and routine practice of aerobic exercise. In particular, patients must be primarily instructed to reduce body weight and restrict alcohol intake. If the urinary pH is low, the ingestion of alkaline foods should be recommended to improve the solubility of urate in urine. In addition, the urine volume should be maintained at ≥2000 mL/day by sufficient water ingestion to decrease the urinary saturation of urate.

If the serum urate level is ≥8.0 mg/dL in hypertensive patients with hyperuricemia, the initiation of urate-lowering drug administration should be considered, establishing the target of urate control as ≤6.0 mg/dL. There is evidence that the use of urate-lowering drugs prevents renal dysfunction in patients with kidney damage [1241]. Urate-lowering drugs include urate synthase inhibitors (xanthine oxidase inhibitors) and urate transporter 1 (URAT1) inhibitors, which promote urate excretion. The most frequent disease type of hyperuricemia with hypertension is underexcretion type; therefore, urate excretion-promoting drugs, benzbromarone and probenecid, are effective, but it is necessary to alkalinize urine by combination therapy with fixed combination drugs of sodium bicarbonate or those of Na citrate/K citrate. The dose of a urate synthase inhibitor, allopurinol, must be regulated in patients with renal dysfunction. However, febuxostat and topiroxostat may be effective regardless of the disease type; they can be used relatively safely even in patients with renal dysfunction [1242–1244].

In hypertensive patients with hyperuricemia, it is necessary to select antihypertensive drugs, considering urate metabolism. Both thiazide and loop diuretics increase the urate level, and β-blockers may also increase it. On the other hand, CCBs do not influence urate metabolism. Some CCBs were reported to have urate-lowering effects. Similarly, neither ARBs nor ACE inhibitors influence urate metabolism. An ARB, losartan, inhibits URAT1, and, clinically, this drug was reported to reduce the urate level. Therefore, it is appropriate for the treatment of hypertension complicated by hyperuricemia [1245, 1246]. According to a study, combination therapy with losartan and a CCB decreased the risk of gout [735]. Hypertension complicated by obesity, metabolic disturbance, or renal disorder tends to be resistant. To achieve the target of blood pressure control, combination therapy with a diuretic is required in many cases. In older patients or hypertensive patients with metabolic syndrome or CKD, salt sensitivity is high, and diuretics are effective. However, they should be used, considering urate control.

POINT 7E

[Bronchial asthma and chronic obstructive pulmonary disease (COPD)]

1. **In hypertensive patients with bronchial asthma, β- and αβ- blockers should be avoided.**
2. **ACE inhibitors cause dry cough as an adverse effect. As this symptom is sometimes difficult to differentiate from cough related to bronchial asthma, these**

drugs are not recommended for hypertensive patients with bronchial asthma.

3. **In hypertensive patients with bronchial asthma, CCBs, ARBs and low-dose diuretics may be used.**
4. **In hypertensive patients with COPD, CCBs, ACE inhibitors, ARBs and low-dose diuretics may be used.**
5. **In hypertensive patients with COPD, the administration of β-blockers is possible, but selective β1-blockers should be used.**

7. BRONCHIAL ASTHMA AND COPD

Bronchial asthma and COPD are classified as obstructive pulmonary diseases. Bronchial asthma refers to eosinophilic inflammation of the airway, whereas COPD is a systemic inflammatory disease in which neutrophils are involved, and is often complicated by cardiovascular diseases. In particular, hypertension is the most frequent complication in patients with COPD [1247].

It is unclear whether salt is involved in the enhancement of airway hypersensitivity [1248]. However, salt restriction has no adverse effect on bronchial asthma or COPD. Exercise therapy is also recommended for COPD patients, but there are some patients with exercise-induced bronchial asthma. When selecting antihypertensive drugs, different approaches for bronchial asthma and COPD are necessary.

1) Bronchial asthma

Both CCBs and α-blockers relieve tension of the bronchial smooth muscle, and they do not affect the respiratory function of patients with bronchial asthma. ACE inhibitors do not influence the asthma symptoms or respiratory function of hypertensive patients with bronchial asthma [1249]. However, cough, as an adverse effect, is sometimes difficult to differentiate from the exacerbation of bronchial asthma, and ACE inhibitors should be avoided. ARBs do not exacerbate cough or suppress the respiratory function in patients with bronchial asthma. Antihypertensive diuretics (thiazide diuretics and thiazide analogues) do not influence the respiratory function, and they may be used. However, hypokalemia must be considered in patients orally treated with steroids. As β-blockers increase airway resistance by blocking β_2-receptors in the bronchial smooth muscle, they must not be administered to patients with bronchial asthma (contraindicated as a rule). In addition, the use of αβ-blockers should also be avoided. To bronchial asthma patients with heart failure requiring the use of β-blockers, selective β_1-blockers should be administered at a low dose while strictly monitoring the morbid state.

2) COPD

In patients with COPD, ACE inhibitors, ARBs, CCBs and antihypertensive diuretics can be routinely used, because there are no data on the exacerbation of COPD and increase in the mortality rate. According to a study, combination therapy with two antihypertensive drugs, including a diuretic, was more effective than diuretic-free combination therapy in the prevention of heart failure in COPD patients [1250]. However, antihypertensive diuretics increase the viscosity of bronchial secretions (sputum), and should be used at a low dose while guiding an appropriate water intake. According to several studies, β-blockers were safe and effective in COPD patients with coronary heart disease or heart failure, receiving bronchodilators [1251–1253]. Currently, the use of β-blockers is not contraindicated for hypertensive patients with COPD, but selective β_1-blockers should be used rather than non-selective β-blockers [1252, 1254].

POINT 7F

[Liver diseases]

1. **As the plasma concentrations of antihypertensive drugs to be metabolized in the liver increase in hypertensive patients with severe liver dysfunction, adjustment including a reduction in the dose is necessary.**
2. **Non-selective β-blockers may reduce the risks of gastrointestinal bleeding and death in patients with liver cirrhosis.**
3. **RA system inhibitors may prevent fibrosis of the liver.**

8. LIVER DISEASES

In patients with advanced liver cirrhosis, blood pressure tends to decrease by changes in the hemodynamics and concentrations of physiologically active agents in blood, but standard antihypertensive treatment should be performed if hypertension is present. If edema is noted, there is a possibility of secondary aldosteronism, and attention to changes in the plasma electrolyte concentrations is necessary when administering diuretics. Liver cirrhosis may induce a delay in the activation of prodrugs and a rise in the plasma concentrations of drugs to be metabolized in the liver. As the blood concentrations of antihypertensive drugs to be metabolized in the liver may increase excessively in patients with advanced liver cirrhosis, caution, such as a reduction of the dose and prolongation of administration intervals, is necessary at initial use. Drug-induced hepatopathy due to

labetalol and methyldopa is well-known, and these drugs must not be administered to patients with liver dysfunction.

A meta-analysis showed that non-selective β-blockers, such as propranolol, reduced portal pressure, lowering the risks of gastrointestinal bleeding and death in liver cirrhosis patients [1255]. On the other hand, antihypertensive diuretics, such as hydrochlorothiazide, chlorthalidone and furosemide, should be used carefully in liver cirrhosis patients, because they may induce hepatic coma by their rapid diuretic action. A study suggested that RA system inhibitors, such as ARBs and ACE inhibitors, prevent fibrosis in the transitional period from chronic hepatitis to liver cirrhosis [1256]. Furthermore, several studies indicated that RA system inhibitors were also useful for reversing pathological changes such as fibrosis in patients with non-alcoholic steato-hepatitis (NASH) [1257, 1258]. Cilazapril may increase the blood concentrations of active metabolic substances in liver cirrhosis patients with ascites, causing serious hypotension. Therefore, this drug is contraindicated.

CQ11. SHOULD A TARGET SBP FOR DRUG THERAPY FOR HYPERTENSION WITH DIABETES MELLITUS BE ESTABLISHED AS <130 MMHG RATHER THAN <140 MMHG TO REDUCE THE RISK OF CARDIOVASCULAR DISEASES?

►To reduce the risk of cardiovascular diseases, we recommend that a SBP of <130 mmHg (systolic home blood pressure: <125 mmHg) should be targeted.

Recommendation grade: 2, Evidence level: B

SUMMARY OF EVIDENCE

According to a systematic review (SR) of 4 previous studies [481, 1259–1261], there were significant differences in the preventive effects on cardiovascular diseases between patients in whom a SBP of ≥130 mmHg was reached and those in whom an SBP of <130 mmHg was reached, but there were no significant differences between patients in whom an SBP of <140 mmHg was reached and those in whom an SBP of <130 mmHg was reached. The results of the J-DOIT3 study [1170] showed the preventive effects on cardiovascular diseases in Japanese patients with diabetes mellitus achieving an SBP of <130 mmHg. This is the basis of "CQ11".

INTERPRETATION

We attempted a meta-analysis and SR to "CQ11", as described in the Standard Operating Procedures, but the results were consistent with those of previous studies; therefore, we examined this issue using these studies. According to an SR described by Emdin et al. [1261], the risks of total mortality, cardiovascular events, coronary artery disease, stroke, retinopathy and albuminuria significantly reduced with a 10-mmHg decrease in SBP in a group with a baseline blood pressure of ≥140 mmHg, whereas there were no significant effects on heart failure or renal failure. In the same SR, the influence on the clinical outcome was compared between patients in whom an SBP of ≥130 mmHg was reached and those in whom an SBP of <130 mmHg was reached. The results are helpful as a reference when reviewing "CQ11". There was no decrease in the risk of total mortality, cardiovascular events, or coronary artery disease in the <130-mmHg group, but there were significant decreases in the risks of stroke and albuminuria progression in this group. Other meta-analyses and SRs also indicated similar results [481, 1259, 1260], but these SRs did not involve a meta-analysis of RCTs comparing patients achieving an SBP of <130 mmHg with those achieving an SBP of <140 mmHg; they do not provide evidence regarding "CQ11". In addition, the primary endpoint of each RCT was not limited to cardiovascular diseases. Furthermore, the number of patients in whom an SBP of <130 mmHg was reached was markedly smaller than that of those in whom an SBP of <140 mmHg was reached; these SR were considered to be insufficient as evidence for recommendations from "CQ11".

In the J-DOIT3 study [1170], which was published in 2017, the preventive effects of multidisciplinary diabetes control on complications were examined in Japanese patients. Establishing the target of blood pressure control as <120/75 mmHg in the intensive therapy group and <130/80 mmHg in the conventional therapy group, intervention was started from a baseline blood pressure of 134/80 mmHg, and follow-up was carried out for about 8.5 years. Although antihypertensive drug therapy had not been performed in all subjects, blood pressures of 123/71 and 129/74 mmHg were achieved in the intensive and conventional therapy groups, respectively. The results of post-treatment analysis suggested that the incidence of cerebrovascular events decreases by 58% in the intensive therapy group in comparison with the conventional therapy group. In the JSH2014 Guidelines, it is described that blood pressure control at a lower level is more advantageous with respect to the primary prevention of stroke, which is more frequent in Japanese diabetics than in Europe and the United States. Evidence to "CQ11" could be obtained from the efficacy of multidisciplinary diabetes control involving a blood pressure of <130 mmHg in cerebrovascular disease prevention, which was demonstrated in the J-DOIT3 study. The recommendation grade was established as 2, and the evidence level was established as B, considering the following points: evidence was based on a single RCT; the purpose of the study was multidisciplinary diabetes control, and the study did not involve hypertensive patients with

diabetes mellitus; and antihypertensive therapy had not been performed in all patients.

Recently, a meta-analysis based on individual participants data (IPD) from the ACCORD and SPRINT studies, in which an SBP of <120 mmHg was targeted, was conducted [1262]. In the SPRINT study, automatic office blood pressure (AOBP) measurement was performed, and it must be considered that AOBP is lower than a routine office blood pressure value. However, the results showed that the incidence of cerebrovascular events in a group targeting an SBP of <120 mmHg was significantly lower than in a group targeting an SBP of <140 mmHg (hazard ratio [HR]: 0.83, 95% confidence interval [CI]: 0.74–0.92, P<0.001). There was no significant interaction between the treatment response and presence or absence of diabetes mellitus. In particular, in the group targeting an SBP of <120 mmHg, stroke and heart failure were prevented by 25%, and there was no significant interaction between the treatment response and baseline age, sex, race, or cardiovascular diseases, suggesting that blood pressure control at a lower level is effective in a population involving diabetics.

Similarly, in the ACCORD study, subjects with cardiovascular risk factors in accordance with the SPRINT registration criteria in the conventional blood glucose control group were divided into two subgroups: intensive blood pressure control group (n=652) and conventional blood pressure control group (n=632), and re-analysis was conducted [1263]. As a background factor, the Framingham 10-year cardiovascular disease risk scores in the two groups were 14.5 and 14.8%, respectively. The mean SBP at the completion of the study were 120 and 134 mmHg, respectively ($P < 0.001$). In the intensive blood pressure control group, the incidence of cardiovascular death + nonfatal myocardial infarction + nonfatal stroke + revascularization (all procedures) + heart failure (HR: 0.79, 95%CI: 0.65–0.96, $P = 0.02$), as well as that of cardiovascular death + nonfatal myocardial infarction + nonfatal stroke (HR: 0.69, 95%CI: 0.51–0.93, $P = 0.01$), decreased, but the incidence of treatment-associated adverse events was high (4.1 vs. 2.1%, respectively, $P = 0.003$).

Furthermore, Eguchi et al. [1264] investigated two cut-off values of SBP: 135 and 125 mmHg based on home blood pressure measurement in 1057 diabetics and 3251 non-diabetics. After multivariate adjustment, the development of cardiovascular events, such as stroke, myocardial infarction, sudden death and acute aortic dissociation, was regarded as an outcome. A cut-off value of ≥135 mmHg was predictive of the onset of cardiovascular events in both the diabetes and non-diabetes groups. A cut-off value of ≥125 mmHg was an independent prognostic factor (HR: 4.35, 95%CI: 1.04–18.25, $P = 0.045$) in the diabetes group, but there was no such association in the non-diabetes group, supporting a target home blood pressure of <125 mmHg in diabetics.

Thus, there is evidence regarding the opinion that blood pressure should be initially decreased by ≥10 mmHg in diabetics with an SBP of ≥140 mmHg. Considering multidisciplinary diabetes treatment in Japan based on the results of the J-DOIT3 study, we recommend that the administration of antihypertensive drugs should be started in diabetics with an SBP of ≥140 mmHg, and that blood pressure control by lifestyle modifications should be attempted in a period of ≤1 month if the target of blood pressure control (SBP: <130 mmHg) is expected to be achieved in the

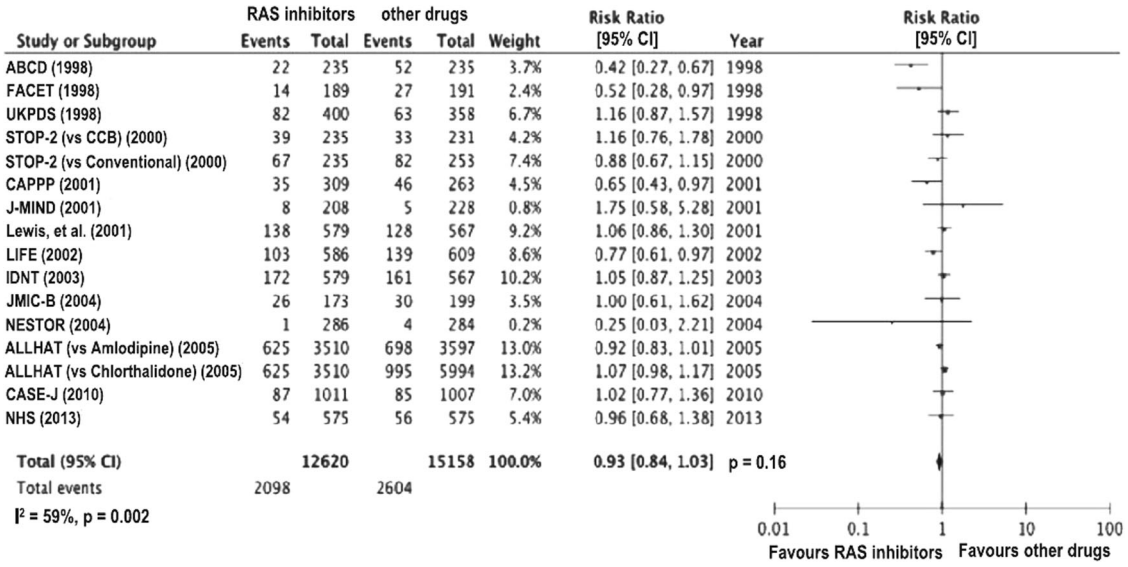


Fig. CQ12-1 Meta-analysis of RA system inhibitors and other drugs using the onset of cardiovascular diseases as an outcome. M-H: Mantel-Haenszel method, Random: Random effect model. (Source: Ref. [1279])

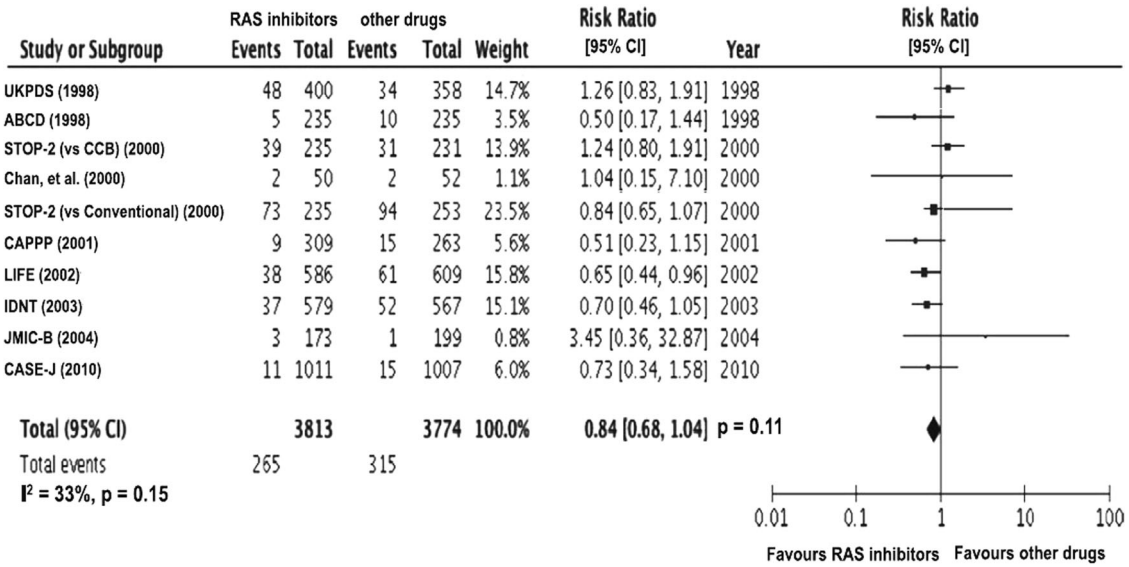


Fig. CQ12-2 Meta-analysis of RA system inhibitors and other drugs using cardiovascular disease-related death as an outcome M-H: Mantel-Haenszel method, Random: Random effect model. (Source: Ref. [1279])

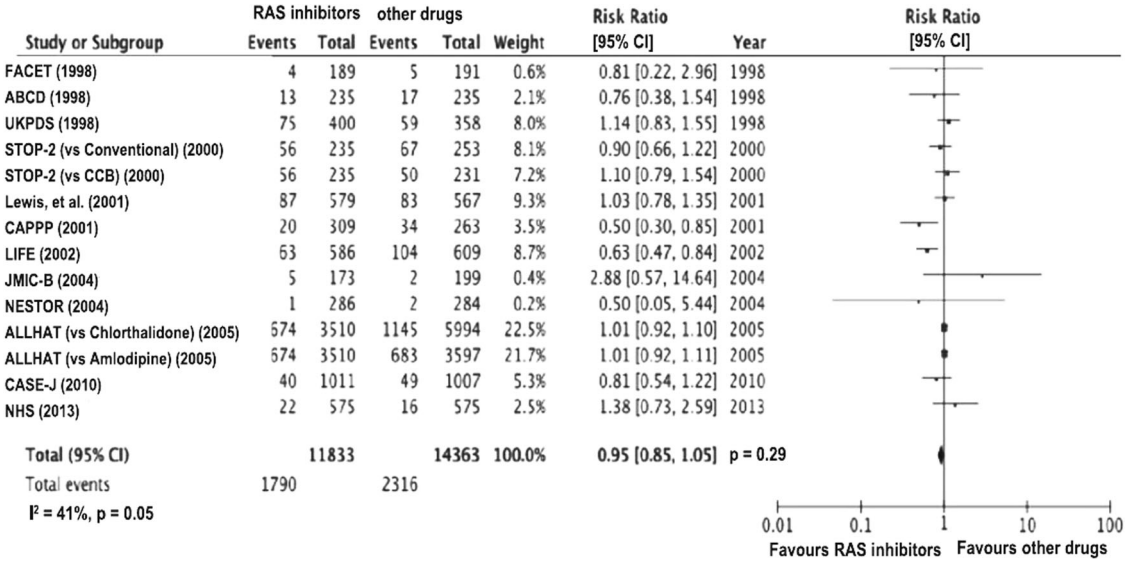


Fig. CQ12-3 Meta-analysis of RA system inhibitors and other drugs using all-cause death as an outcome M-H: Mantel-Haenszel method, Random: Random effect model. (Source: Ref. [1279])

JSH2019 Guidelines, as recommended in the JSH2014 Guidelines for the Management of Hypertension [108], 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111], and 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension [236]. However, if it is considered difficult to achieve the target of blood pressure control by lifestyle modifications, the administration of antihypertensive drugs should be promptly started, targeting an SBP of <130 mmHg.

However, concerning the target of blood pressure control in hypertensive patients with diabetes mellitus, a target SBP is established as <140 mmHg in some guidelines including those prepared by the American Diabetes Association (ADA). In other guidelines, it is established as <130 mmHg. Respective values were introduced by utilizing evidence-based medicine (EBM), but they depend on consensus-related factors. In the former, the necessity of improving the guideline achievement rate by presenting a realistic blood pressure value that can be achieved is considered. In the latter, it is emphasized that strict blood pressure control is useful for the prevention of stroke, heart disease, and kidney disease. However, both may play a role as treatment guidelines. In any case, it is necessary to examine complications, as well as the duration of diabetes mellitus, in

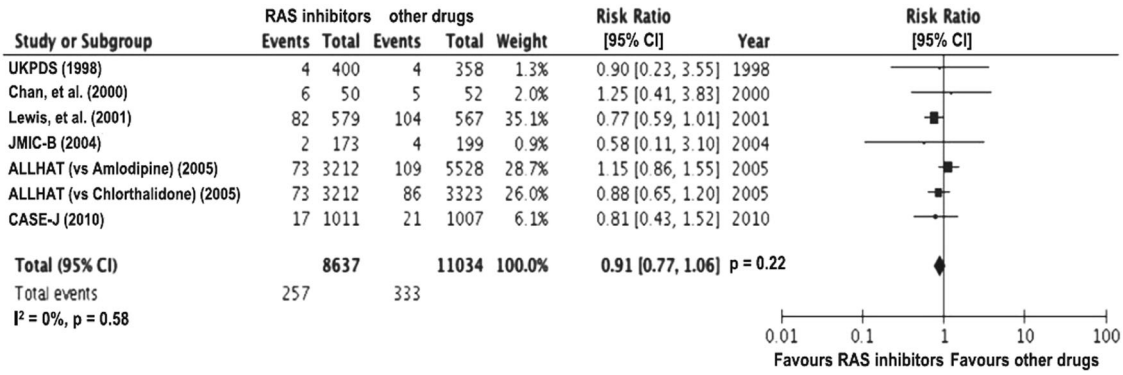


Fig. CQ12-4 Meta-analysis of RA system inhibitors and other drugs using renal dysfunction as an outcome in patients with renal dysfunction M-H: Mantel-Haenszel method, Random: Random effect model. (Source: Ref. [1279])

patients. Individualized blood pressure control is important [1265, 1266].

CQ12. SHOULD ARBS AND ACE INHIBITORS BE PREDOMINANTLY USED RATHER THAN CCBS AND THIAZIDE DIURETICS FOR ANTIHYPERTENSIVE TREATMENT FOR HYPERTENSION WITH DIABETES MELLITUS?

►As first-choice antihypertensive drugs for hypertensive patients with diabetes mellitus, ARBs, ACE inhibitors, CCBs and thiazide diuretics are recommended. However, ARBs or ACE inhibitors should be selected if microalbuminuria or proteinuria is present.

Recommendation grade: 2, Evidence level: B

SUMMARY OF EVIDENCE

A meta-analysis of 16 studies [1157, 1174–1176, 1267–1278] comparing renin–angiotensin (RA) system inhibitors with other antihypertensive drugs was conducted [1279]. Overall, similar hypotensive effects were obtained in two groups. Although RA system inhibitors tended to be more advantageous with respect to the onset of cardiovascular diseases (Figure CQ12-1), cardiovascular death (Figure CQ12-2) and all-cause death (Figure CQ12-3), no significant effects could be confirmed. There was no marked difference in the incidence of renal dysfunction (a 2-fold increase in the serum creatinine level, the development of end-stage kidney disease [ESKD]) as an adverse outcome between the two groups. Based on these results, there may be no evidence to recommend RA system inhibitors as a first-choice drug for hypertension with diabetes mellitus rather than other antihypertensive drugs if similar hypotensive effects are obtained.

The results were examined with respect to the presence or absence of renal dysfunction. Subjects were selected using exclusion criteria, such as a serum creatinine level of ≥1.7 mg/dL, in previous studies, and eGFR-based sensitivity analysis was not performed; therefore, even most articles used for an overall review were not suitable for examination with respect to the presence or absence of renal dysfunction. When limiting articles to those involving urinary albumin-/protein-positive patients with renal dysfunction, 1 to 3 articles with respect to the outcome were investigated, and there was no difference in any outcome between RA system inhibitors and other antihypertensive drugs
(Figure CQ12-4). As the number of articles involving subjects with normal kidney function alone was extremely small among those adopted in this SR, respective outcomes could not be examined.

However, in this SR, the outcome was limited to cardiovascular events, and no other outcome to be raised in diabetics was reviewed. In particular, concerning the deterioration of diabetic nephropathy, many clinical studies indicated the usefulness of ACE inhibitors and ARBs for the protection of kidney function. These drugs should be predominantly used in hypertensive patients with microalbuminuria or proteinuria. Concerning cardiovascular complications, strong evidence was presented, but no outcome could be obtained with respect to the selection of antihypertensive drugs for kidney protection; the recommendation grade was established as 2, and the evidence level was established as B, depending on individual evidence.

INTERPRETATION

In the SR to “CQ12”, the usefulness of RA system inhibitors for drug therapy for diabetic complications was not demonstrated. Therefore, we recommend ARBs, ACE inhibitors, CCBs and thiazide diuretics as first-choice drugs for hypertension complicated by diabetes mellitus. Previous guidelines describe the usefulness of RA system inhibitors, CCBs and low-dose thiazide diuretics for the prevention of cardiovascular events in hypertensive patients with diabetes

mellitus. When administering thiazide diuretics, their influence on glucose/lipid metabolism by the exacerbation of insulin resistance, as well as adverse effects on the metabolic system, such as hypokalemia and hyperuricemia, must be considered. If necessary, low-dose thiazide diuretics should be used. With respect to the prognosis of type 2 diabetics with macroangiopathy, the LIFE study showed that ARBs significantly prevented the onset of cardiovascular diseases in comparison with β-blockers [1271]. ACE inhibitors, ARBs and CCBs should be selected from the viewpoint of cardiovascular event prevention. If the hypotensive effects of RA system inhibitors are insufficient, combination therapy with a CCB or low-dose thiazide diuretic as a second-choice drug should be performed. If a further decrease in blood pressure is required, 3 drugs should be combined, of which the usefulness has been demonstrated. To achieve the target of blood pressure control accurately, combination therapy with an ARB, ACE inhibitor, CCB and thiazide diuretic is required in some cases, considering fixed-combination drugs.

Furthermore, the usefulness of RA system inhibitors in the presence of renal dysfunction with microalbuminuria or severer is clear, although it cannot be verified as a marked difference by this SR. In diabetics, an insulin-resistance-mediated mechanism may be involved in the onset of albuminuria. With respect to the effects on diabetic nephropathy with microalbuminuria or proteinuria, ACE inhibitors were shown to prevent renal hypofunction in type 1 diabetics with proteinuria, decreasing the number of patients requiring a transition to dialytic therapy [1173]. Concerning the effects of ARBs on type 2 diabetic nephropathy, the RENAAL [699], IDNT [1175, 1176], IRMA-2 [1177] and MARVAL [1178] studies demonstrated their usefulness. In Japan, the INNOVATION study [1179] also indicated the usefulness of ARBs. Furthermore, the ROADMAP study [1180] showed the preventive effects of ARBs on microalbuminuria in type 2 diabetics. Based on the above evidence regarding the effects on diabetic nephropathy, we particularly recommend ACE inhibitors and ARBs as first-choice drugs for hypertensive patients with diabetic nephropathy in the presence of microalbuminuria or proteinuria.

Chapter 8. Hypertension in older persons

POINT 8

1. **Lifestyle modification should be positively performed, but strategies should be individually selected, considering the patient's quality of life (QOL).**
2. **Drug therapy should be indicated for patients with a blood pressure of ≥140/90 mmHg on principle. However, whether the administration of antihypertensive drugs should be started must be individually evaluated in the following patients: those aged over 75 years with a systolic blood pressure (SBP) of 140–149 mmHg or those who are unable to consult an outpatient clinic by themselves (including those with frailty, those with dementia, those requiring nursing, and end-of-life patients).**
3. **Antihypertensive drugs involving combination therapy should be selected, as described for non-older patients.**
4. **The administration of antihypertensive drugs should be started at 1/2 of the standard dose especially in patients aged ≥75 years, and the dose should be gradually increased to achieve the final target of blood pressure control. When confirming tolerability, adverse effects, organ damages and QOL must also be considered.**
5. **As a rule, a blood pressure of <130/80 mmHg should be targeted in older patients, aged 65 to 74 years, who are able to consult an outpatient clinic in a good health status if they are tolerable. In those aged ≥75 years, a blood pressure of <140/90 mmHg should be targeted.**
6. **If a target blood pressure is established as <130/80 mmHg due to concomitant diseases, a blood pressure of <130/80 mmHg should be individually targeted even in patients aged ≥75 years if it is tolerable.**
7. **For antihypertensive drug therapy, the target and speed of blood pressure control should be individually evaluated in patients with vascular stenosis (≥75% stenosis of the bilateral carotid arteries, significant coronary stenosis), those with abnormalities in blood pressure regulation (orthostatic hypotension, orthostatic hypertension, postprandial decrease in blood pressure), and those who are unable to consult an outpatient clinic by themselves (including those with frailty, those with dementia, those requiring nursing, and end-of-life patients).**
8. **In older patients, dose-reduction or discontinuation (including transient discontinuation) is sometimes necessary due to dehydration, reduction in dietary intake or environmental changes. In those with a low organ reserve, pre-administration guidance for drug therapy, such as management at the time of home blood pressure reduction, should be performed.**

1. CHARACTERISTICS OF HYPERTENSION IN OLDER PERSONS

Japan is a super-aged society in which older persons aged over 65 years account for 27.3% of the population (in 2017) and those aged over 75 years account for 13.3% [1280]. Hypertension increases with age, and, according to the National Health and Nutrition Survey of Japan (2015), hypertension is prevalent in 63% of those aged 65–74 years and 74% of those aged over 75 years. Generally, older persons have concomitant diseases and often show atypical presentations. There are marked individual differences in the physiological function even at the same age. In Japan, approximately 5- to 10-year rejuvenation involving the degree of health is promoted [1281]. When dividing older persons based on age, caution is needed. In particular, older persons aged over 75 years often show pathophysiological changes differing from those in non-older persons, and the concomitant development of specific conditions, such as frailty, cognitive impairment and polypharmacy, is frequently observed [1282]. The contents described in this chapter are more important for treating older persons aged over 75 years. Age-related physiological/pathological changes associated with blood pressure control in hypertensive patients and the characteristics of hypertension in older patients associated with these age-related changes or the progression of atherosclerosis are shown in Tables 8-1 and 8-2, respectively.

Table 8-1 Age-related physiological/pathological changes associated with blood pressure control in older persons

- Cardiovascular system
  Atherosclerosis/reduction of vascular elasticity, left ventricular hypertrophy/diastolic dysfunction.
- Nervous system
  Impairment of the baroreceptor reflex, reduction of β-receptor function.
- Water/electrolyte metabolism
  Impairment of body fluid regulation related to deterioration in renal function, vulnerability of electrolyte homeostasis (particularly, hyponatremia and hypokalemia).
- Glucose metabolism
  Increased insulin resistance, impaired glucose tolerance.
- Endocrine system
  Impairment of both pressor and depressor systems such as renin–angiotensin, kallikrein–kinin, prostaglandin and renal dopamine systems.

2. CRITERIA FOR HYPERTENSION IN OLDER PERSONS AND EPIDEMIOLOGICAL FINDINGS

A positive correlation was observed between an increase in blood pressure and the logarithmically transformed cardiovascular mortality rate in the Hisayama Study [135] and in the meta-analysis of approximately one million people with no history of cardiovascular diseases in 61 prospective studies [405]. This correlation was still observed in those in their 80s, and absolute cardiovascular risk increased with age, whereas the slope of correlation became gentler in old age. The NIPPON DATA80 [1283] which is a 19-year follow-up study in Japan, and EPOCH JAPAN10 study also showed that the cardiovascular mortality increased with blood pressure elevation in patients aged ≥75 years. On the other hand, there are epidemiological studies that report the presence of a cut-off value of blood pressure related to increases in the risk of cardiovascular diseases and mortality rate [1284]. However, the cut-off value may be influenced by the analytical method, number of subjects, observation period and outcome (disease onset or disease-related death).

On the basis of these results, basically, cardiovascular risk is lower at a lower blood pressure even in older persons. The same criterion of hypertension as that for non-older persons was set for older persons to prevent the onset and progression of cardiovascular diseases.

Table 8-2 Aging-related changes and characteristics of hypertension in older patients

Age-related physiological/pathological changes associated with blood pressure control	Influence on relevant conditions
Atherosclerosis, a reduction in vascular elasticity, and baroreceptor reflex dysfunction	• Increase in the incidence of isolated systolic hypertension • Increase in orthostatic hypotension, orthostatic hypertension or postprandial hypotension • Increase in fluctuation of blood pressure
Renal dysfunction, increased insulin resistance	• Increase in salt sensitivity
Complex, influence of aging-related factors	• Increase in white coat hypertension • Increase in the non-dipper-type nighttime blood pressure • Increase in the Impairment of autoregulation of blood flow in vital organs • Decreases in perfusion and reserve of blood flow in vital organs • Susceptibility of heart failure

Table 8-3 Conditions to be evaluated for the establishment of a target blood pressure or selection of antihypertensive drugs in older persons and screening methods

Purpose of diagnosis	Condition to be evaluated	Screening method
Evaluation of conditions requiring individualized assessment for the establishment of the target or speed of blood pressure control	≥75% stenosis of the bilateral carotid arteries	Auscultation of carotid murmurs
	Significant coronary stenosis	Inquiry, stress electrocardiography[*1]
	Orthostatic hypotension, orthostatic hypertension	Inquiry, blood pressure on standing up
	Postprandial blood pressure reduction	Inquiry of postprandial dizziness
	Frailty[*2]	Inquiry, physical findings
	Dementia	Confirmation of residual drugs, cognitive function test[*3]
	Reduction in physical ability (inability to consult an outpatient clinic alone), nursing care requirement, end of life	Inquiry
Evaluation of conditions for which specific antihypertensive drugs are positively indicated	History of myocardial infarction	Electrocardiography
	Heart failure	Inquiry, physical findings
	Angina pectoris	Inquiry, stress electrocardiography[*1]
	CKD with proteinuria	Urinalysis, eGFR (serum creatinine)
	Diabetes mellitus	Fasting blood glucose
Evaluation of conditions associated with contraindications for specific antihypertensive drugs	Sodium/potassium deficiency	Serum sodium/potassium
	Acute renal failure	eGFR (serum creatinine)
	Marked bradycardia or severe conduction disturbance	Electrocardiography
	Bronchial asthma	Inquiry, physical findings

[*1] In some older persons, a standard exercise tolerance test cannot be performed due to physical dysfunction, or the high risk of falling; the necessity of screening tests should be individually evaluated. Examination methods that are available for such patients include drug-loaded myocardial scintigraphy and CT of the coronary artery. However, the use of these methods must be carefully considered.

[*2] There are various diagnostic criteria for frailty, but caution is needed when ≥3 of the following factors are present: non-intended weight loss, muscle weakness, fatigue, a reduction in the walking speed, and a reduction in physical activities [1286].

[*3] A cognitive function test as a screening test may be performed when possible. An inquiry from the patient's family is important.

3. DIAGNOSIS

1) Diagnosis considering the characteristics of older persons

Concerning the blood pressure level, comprehensive diagnosis is necessary (Table 8-2). In older patients with hypertension, blood pressure fluctuates widely, and measurement conditions readily affect blood pressure [1285]. For diagnosis, home blood pressure, 24-h ambulatory blood pressure (ABP), and blood pressures measured at day-service centers should be adopted in addition to office blood pressures measured at several opportunities. As the incidences of orthostatic hypotension and a postprandial decrease in blood pressure are high, blood pressure on standing up should also be measured on the initial consultation or on changing the prescription. Orthostatic hypotension is related to the progression of atherosclerosis in many cases, being a predictor of a poor prognosis.

2) Diagnostic consideration of secondary hypertension

In addition to differential diagnosis in a treatment plan on the initial visit, attention to secondary hypertension should be paid in patients who show a marked increase in blood pressure in a short period, poor control, an excessive decrease in blood pressure after angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) administration, and treatment resistance. In particular, renovascular hypertension (RVHT) due to atherosclerosis, primary aldosteronism (PA) as endocrine hypertension, thyroid dysfunction, sleep apnea syndrome, or drug-induced hypertension must be considered in older patients. Concerning drug-induced hypertension, an inquiry regarding prescriptions in other hospitals/clinics or department and health foods/supplements is important. An inquiry regarding Licorice-containing substances (such as traditional Chinese herbal medicines) and non-steroidal anti-inflammatory drugs (NSAIDs) is essential. Attention must be paid to an increase in blood pressure in older patients undergoing molecular target therapy for diseases such as cancer and age-related macular degeneration.

3) Conditions to be evaluated for the establishment of a target blood pressure or selection of antihypertensive drugs

Many older persons have several asymptomatic organ damages. Furthermore, conditions to be individually evaluated when establishing the target or speed of blood pressure control or selecting antihypertensive drugs are present in older persons. These conditions and screening methods are shown in Table 8-3 [1286].

4. TREATMENT

1) Effects of antihypertensive therapy in older persons

In older patients, medical intervention should aim either to maintain their activities of daily living (ADL) or to prevent a decline in ADL. The prevention of cardiovascular diseases, a major complication of hypertension, is consistent with this purpose. In addition, the influence on factors requiring nursing care, such as cognitive function and falling/fracture, is also important. According to a meta-analysis of nine major clinical studies on the treatment of hypertension in older patients (aged over 60 years), antihypertensive drug treatment significantly reduced all-cause mortality by 12%, death from stroke by 36%, death from coronary artery disease by 25%, the incidence of stroke by 35% and that of coronary artery disease by 15% [1287].

In the Hypertension in the Very Elderly Trial (HYVET), involving patients with hypertension (mean blood pressure: 173/91 mmHg) aged over 80 years, treatment was performed using diuretics (ACE inhibitors were added when the antihypertensive effect was insufficient) with a target of <150/80 mmHg, and a significant 30% decrease in the incidence of stroke, 21% decrease in all-cause mortality, 64% decrease in the incidence of heart failure and 34% decrease in the incidence of cardiovascular events were observed [381]. In addition, there was no increase in the incidence of dementia [1288], and the incidence of fracture decreased [1289].

2) Lifestyle modifications

In older people, non-pharmacological therapies (lifestyle modifications), such as restriction of salt intake, exercise, and weight control, are useful [415], and should be positively promoted. However, marked changes in lifestyle may impair QOL, and, hence, individualized management should be performed in reference to a generally recommended target level, considering older persons' specificity and concomitant diseases. The following contents are individually described in reference to the Guidelines for the Management of Hypertension in Older Patients 2017 [1290].

(1) Restriction of salt intake As older people generally have high salt sensitivity, salt intake restriction is effective. The target of salt intake restriction should be 6 g per day, but caution is needed because excessive salt intake restriction may cause dehydration on massive sweating. Furthermore, extreme changes in the taste reduce dietary intake, leading to malnutrition in some cases. Therefore, for guidance, the management of the general condition must also be emphasized. Generally, a potassium-rich diet is recommended, but hyperkalemia must be considered in patients with renal dysfunction. Calcium intake should be 800 mg per day or more for the prevention of osteoporosis.

(2) Exercise Exercise therapy is also appropriate for older hypertensive patients receiving antihypertensive drugs (mean age of 75 years) [1291]. Regarding the type of exercise, aerobic exercise is recommended, but we recommend walking at a standard speed, but not fast walking, considering the risk of falling, an increase in the risk of arthropathy, and cardiac load [1290]. As a strategy to prevent sarcopenia in older persons, resistance exercise is recommended. Its usefulness for lowering blood pressure has been indicated, but there are few studies involving patients aged ≥75 years. If there are complications, such as coronary artery disease, heart failure, renal failure and bone or joint disease, medical check is necessary before exercise, and whether exercise therapy should be performed must be individually evaluated based on specialists' opinions.

(3) Weight control In obese patients, the desirable body weight should be targeted, but rapid weight loss may be harmful; therefore, long-term reasonable weight control should be individually promoted.

(4) Reduction of alcohol intake Physicians should instruct patients routinely taking a moderate or larger amount of alcohol to restrict alcohol intake.

(5) Smoking cessation Physicians should instruct smokers to quit smoking.

3) Subjects to be treated with antihypertensive drugs and target levels of blood pressure

(1) Subjects to be treated Concerning lifestyle modifications, positive guidance is recommended, as described for non-older patients. With respect to patients to be treated with drugs, in 3 of the randomized controlled trials (RCTs) adopted in a systematic review (SR), which was conducted to determine the target of blood pressure control in patients aged ≥75 years, the subjects included those undergoing treatment. Of these patients, approximately 90% had received antihypertensive drugs. Of 3 trials involving untreated hypertensive patients, the mean SBP was ≥160 mmHg in 2, and it was ≥150 mmHg in 1; therefore, among patients aged ≥75 years, there is only evidence involving those with a SBP of ≥150 mmHg (see CQ13). On the other hand, a study indicated that Ca channel blockers (CCBs) reduced cardiac hypertrophy, improving the QOL in a population in which subjects aged ≥65 years accounted for 49%, with a mean age of 66±6.8 years and a mean blood pressure of 149/83 mmHg at the time of registration [1292].

The guidelines recommend a blood pressure of ≥140/90 mmHg as a general criterion to start antihypertensive drugs in the older population, considering the high incidence of stroke as a complication of hypertension in Japanese, which is closely associated with blood pressure. As a consensus, the Guidelines recommend that the introduction of antihypertensive drugs should be individually evaluated in persons, aged over 75 years, with a SBP of 140–149 mmHg or older persons who are unable to consult an outpatient clinic by themselves [1293]. However, because age- or physical activity-based categorization criteria are not well defined, indication for antihypertensive drugs should be comprehensively assessed considering those categorizations, complications, and target blood pressures.

(2) Target blood pressure in older persons In the CQ13, recommendations for the target of blood pressure control are presented based on the results of an SR [92, 1294]. This SR involved older hypertensive patients who were able to consult an outpatient clinic by themselves based on the patient registration criteria for RCTs or patient background. Of 8577 subjects participating in the RCTs adopted, Japanese patients accounted for 43%, and Asians accounted for 52%; this SR is appropriate for determining recommendations in guidelines in Japan.

In 2017, three SRs for establishing the target of blood pressure control in older persons were published: one described by Weiss et al. [485], which was the basis of the "Pharmacologic Treatment of Hypertension in Adults Aged 60 years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) in 2017" [1295], one described by Garrison et al. [1296] (Cochrane Library), and one described by Reboussin et al. [487], which was the basis of the "2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" [111]. Two RCTs involving Japanese patients (JATOS [498], VALISH [501]) were adopted in all SRs. Among these 3 SRs, the RCTs adopted, analytical methods, and interpretation of the results differed, and, as a result, recommendations markedly differed. Briefly, Weiss et al. recommended a target blood pressure of <150/90 mmHg for patients aged ≥60 years [485], and Garrison et al. concluded that the target of blood pressure control could not be recommended for hypertensive patients aged ≥65 years [1296]. Reboussin et al. recommended a target SBP of <130 mmHg for older persons based on sensitivity analysis regarding RCTs with a mean subject age of ≥60 years [487]. In the "2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" [111], blood pressure control targeting <130/80 mmHg is recommended, considering that the risk of cardiovascular diseases over 10 years is ≥10% in all Americans aged ≥75 years or that cardiovascular diseases is present. However, whether this applies to Japanese patients aged ≥75 years is unclear.

Furthermore, there was no RCT sufficient for conducting a meta-analysis to investigate the usefulness of establishing a target SBP as <130 mmHg in hypertensive patients aged ≥75 years in an SR for CQ13 or the above 3 SRs. The VALISH study involving Japanese patients aged ≥70 years showed that the incidence of adverse events in a group with a SBP of 130–144 mmHg during the treatment period was the lowest in comparison with groups with a SBP of <130 mmHg or ≥145 mmHg, and that the incidence of composite cardiovascular events was lower than in the other two groups, although the results were obtained by a post-analysis [412]. However, apart from the results of such a meta-analysis or post-analysis, the presence of evidence that the incidence of events was significantly lower in the <120-mmHg-targeted group even among patients aged ≥75 years from the SPRINT trial comparing two targets of blood pressure control (SBP: <120 mmHg and <140 mmHg) [92, 1294] is important.

Diastolic blood pressures (DBPs) may reduce with the progression of atherosclerosis, and it is difficult to establish the target of blood pressure control based on the results of a meta-analysis. In addition, there is no direct evidence; therefore, a target DBP has been established as <90 mmHg in accordance with a criterion for hypertension.

With respect to patients aged 65–74 years, the RCTs adopted in the SR for CQ3 involved many subjects of this age. We recommend a target blood pressure of <130/80 mmHg, as described for non-older patients.

Thus, the present guidelines recommend that blood pressure control should be increased step by step in older patients who are able to consult an outpatient clinic by themselves if it is tolerable, that the same target of blood pressure control as recommended for non-older patients should be achieved in patients aged 65–74 years, and that a target blood pressure of <140/90 mmHg should be achieved in patients aged ≥75 years in principle. In addition, after SBP reaches 130–139 mmHg, a target level of <130 mmHg may be considered by individually evaluating tolerability, drug interactions, adherence, and drug expenditure.

(3) Gradual reduction in blood pressure In older patients with hypertension, particular attention must be paid to the speed of blood pressure reduction for intensive blood pressure control because of the high incidence of impairment of vital organ perfusion or autoregulation. In particular, the risks of falling and fracture increase at the start of antihypertensive drug therapy [1297, 1298], and antihypertensive drugs should be started generally at half the regular dose, and the dose should be increased at an interval of 4 weeks-3 months by evaluating the presence or absence of signs of brain ischemia, such as dizziness and orthostatic dizziness, symptoms of angina pectoris, electrocardiographic changes indicating myocardial ischemia and a decline in the QOL. In HYVET, in which the participants were hypertensive patients aged over 80 years, whether the dose should be increased was evaluated every 3 months [1299].

(4) The target of blood pressure control in the presence of concomitant diseases Even if a target SBP of <130 mmHg is recommended for non-older patients due to concomitant diseases, a SBP of <140 mmHg should be initially achieved. If patients are tolerable, a level of <130 mmHg should be targeted, considering the onset of adverse events, number of drugs, interactions between drugs and drug expenditure individually. Concerning patients with an estimated glomerular filtration rate (eGFR) of <45mL/min/1.73m^2, a post hoc analysis of the SPRINT study showed that there were no marked preventive effects on events in the intensive blood pressure control group, and that the incidence of acute kidney damage was high; caution is needed [1164].

(5) Circumstances requiring individualized evaluation in the establishment/achievement of a target level Circumstances requiring individualized evaluation in the establishment/achievement of a target level, as shown at the top (POINT) of Chapter 8, are described in the Guidelines for the Management of Hypertension in Older Patients in 2017 [1290], CQ13, and other chapters of these guidelines. In this chapter, stenosis of the bilateral carotid arteries, coronary stenosis, orthostatic hypotension, a postprandial decrease in blood pressure, and orthostatic hypertension, which are described in the "POINT", are explained.

In patients with ≥75% stenosis of the bilateral carotid arteries, a decrease in blood pressure increases the risk of stroke [900]. In patients with carotid murmurs, those in whom the progression of atherosclerosis in other sites is clear, and those with symptoms suggestive of a reduction in cerebral blood flow after the start of antihypertensive drug therapy, carotid ultrasonography or MRA should be positively performed. If stenosis can be reduced, positive antihypertensive treatment should be conducted.

As the basis of our proposal on an individualized evaluation of significant coronary stenosis, a post-analysis of an interventional study with an antihypertensive drug indicated that the incidence of cardiovascular events was high in a group in which a low blood pressure level was reached. A post hoc analysis of the INVEST involving hypertensive patients with coronary artery disease showed that, among patients aged ≥70 years, the incidence of events increased in the <135/70 mmHg-reached group [1300], and that the incidence of events was lowest at a blood pressure of 125/55 mmHg in patients who underwent coronary bypass [951]. Assuming a mechanism by which a reduction in coronary blood flow related to a decrease in DBP causes ischemia-induced arrhythmia or

heart failure, leading to the onset of events, intensive blood pressure control may be recommended if ischemia is reduced by coronary revascularization. Thus, stress electrocardiography should be performed in patients with a history of coronary artery disease, those with abnormal electrocardiographic findings, and those with effort-related changes in symptoms. If coronary stenosis remains, it must be considered that the risk of cardiac events may increase when DBP reaches <70 mmHg with the achievement of a target SBP.

In patients with orthostatic hypotension or a postprandial decrease in blood pressure, blood-pressure fall is not related to a single etiological factor, and etiology-matched management should be performed. Generally, the magnitude of the decrease is greater at a higher blood pressure and symptoms more frequently occurred. In those with orthostatic hypotension, the magnitude of the decrease in blood pressure on standing is often reduced by decreasing blood pressure [1301]. Furthermore, in the SPRINT study, there was no difference in the incidence of orthostatic hypotension between the positive and standard blood pressure control groups consisting of patients aged ≥75 years [1294]. While paying attention to fall and a decline in the QOL, blood pressure should be gradually reduced. In principle, α-blockers should not be used. Loop diuretics may also exacerbate postprandial hypotension. Diuretics may promote a decrease in blood pressure by a reduction in the circulating plasma volume [1302].

The incidence of orthostatic hypertension also increases in older patients. This disorder is associated with organ damage, a poor prognosis, an excessive decrease in blood pressure at night, and a morning surge of blood pressure. Composite factors are involved in the etiology: baroreceptor reflex disorder, enhancement of sympathetic nerve activity, increased vascular stiffness, asymptomatic cerebrovascular disorder, and chronic kidney disease (CKD) [1303]. Thus, orthostatic hypertension is associated with hypertensive organ damage; therefore, antihypertensive treatment may be necessary. However, there is little evidence regarding the influence of therapeutic intervention on organ damage or prognosis, and we cannot recommend any specific antihypertensive drug to be selected or target of blood pressure control.

4) Selection of antihypertensive drugs

(1) Compelling indication in the presence of complications As older patients often have complications, it is necessary to establish the target blood pressure and select antihypertensive drugs in accordance with the complications. Although there is no older-specific evidence, antihypertensive drugs should be selected as described for non-older patients.

Three conditions, characteristic of older patients, which influence the selection of antihypertensive drugs are explained below. These are not based on evidence regarding a decrease in the incidence of cardiovascular diseases. Therefore, the presence or absence of other compelling indications should be considered concurrently.

In older patients with repeated aspiration pneumonia, the administration of ACE inhibitors should be particularly considered as a first-choice drug. ACE inhibitors have been reported to reduce the frequency of aspiration pneumonia in older patients by enhancing the cough reflex [1304, 1305]. If coughing is tolerable as a side effect, ACE inhibitors should be used in older patients with a history of aspiration pneumonia (including latent pneumonia).

In older patients with the risk of fracture, thiazide-type diuretics should be particularly considered as a first-choice drug. On the other hand, loop diuretics may increase the risk of fracture; therefore, caution is needed. In the HYVET involving hypertensive patients aged over 80 years, a thiazide-like diuretic (indapamide) was used as a first-line drug, and an ACE inhibitor (perindopril) was combined with in 3/4 of the patients in the active-treatment group. There was a significant decrease in the incidence of fracture in the active-treatment group in comparison with the placebo group [1289].

In patients with frequent urination or nocturia, loop diuretics or CCBs may exacerbate nocturia; therefore, caution is needed. On the other hand, thiazide-type diuretics may not exacerbate nocturia even if they are combined with other antihypertensive drugs [1290].

(2) Selection of antihypertensive drugs in the absence of compelling indications As first-choice drugs, we recommend drugs of which the usefulness was demonstrated in comparison with a placebo in older hypertensive patients or those with systolic hypertension, as well as drugs that were shown to be as useful as or more useful than these drugs for preventing cardiovascular diseases in controlled trials. Drugs of which the preventive effects on cardiovascular diseases were less marked than those of other drugs on the comparison between drug groups are excluded from recommendations even when their usefulness was demonstrated in comparison with a placebo. Concerning the details, see the Japanese Society of Hypertension (JSH) 2014 Guidelines for the Management of Hypertension [108]. Thus, CCBs, ARBs, ACE inhibitors, and thiazide-type diuretics are recommended for older and non-older patients. Furthermore, β-blockers should be considered as a first-choice drug in post-myocardial-infarction patients and those with heart failure with reduced ejection fraction (HFrEF), in whom their prognosis-improving effects were demonstrated. In addition, β-blockers are also recommended for patients with tachycardia or effort angina from

the viewpoint of symptom relief. Individual drugs should be selected primarily to achieve the target blood pressure, considering individual background factors, adverse effects, and health expenditure.

An SR and network meta-analysis conducted by Rebousin et al. [487] indicated that diuretics markedly reduced the risk of various outcomes, although the subjects were not limited to older patients. In particular, it is described that diuretics are more useful than CCBs for preventing the onset of heart failure in the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111]. At a more advanced age, heart failure with preserved ejection fraction (HFpEF) is frequent. We propose that diuretics should be positively used.

(3) Combination therapy Even in older patients, combination therapy with several antihypertensive drugs is often required to achieve the target of blood pressure control. The following RCTs prospectively compared combination regimens in hypertensive patients, and presented data from older patients: an age-stratified analysis of ACCOMPLISH (international study) [753], a subanalysis of the COPE trial, which was conducted in Japan, involving older patients [1306], OSCAR [702] and COLM [704].

In the ACCOMPLISH study, ACE inhibitor (benazepril)+ CCB (amlodipine) therapy was compared with ACE inhibitor+ diuretic (hydrochlorothiazide) therapy. Overall, the incidence of composite cardiovascular events was lower in the CCB-combined group. In addition, similar results were also obtained in two subgroups: patients aged ≥65 years (n = 7640) and those aged ≥70 years (n = 4703) [753]. In the COLM study, ARB (olmesartan)+CCB therapy was compared with ARB+diuretic therapy in patients aged ≥65 years. Overall, there were no differences between the two groups [704]. An age-category (border: 75 years)-based analysis showed no interaction related to the age category, but the incidence of events was significantly lower in the CCB-combined group among patients aged ≥75 years. As the mechanism, a reduction in blood pressure variability in the CCB-combined group among patients with systolic hypertension, which is frequently observed in older persons, may be involved [1307]. In addition, in the OSCAR Study, the efficacy of an ARB (olmesartan) at a maximum dose was compared with that of a combination of the ARB at a standard dose and a CCB, and there was no difference in the incidence of cardiovascular events between the two groups [702]. These results suggest that a CCB is more appropriate than a diuretic for combination therapy with a renin–angiotensin (RA) system inhibitor at a more advanced age.

Internationally, evidence regarding CCB-based combination therapy is limited to the COPE trial alone [1306]. In this trial, the results were compared among three combinations, a CCB (benidipine) + a diuretic, benidipine + an ARB and benidipine + a β-blocker. A subanalysis involving older patients showed that there were no differences in the incidence of composite cardiovascular events, as a primary endpoint, among the three groups. However, in the diuretic-combined group, the incidence of stroke was lower than that in the β-blocker-combined group.

Thus, when selecting a combination regimen, blood pressure control to a target level should be primarily

Table 8-4 Precautions for hypertension treatment based on the specificity of older persons

Precautions associated with the prevention of falling/fracture

- Falls/fracture in older persons accounts for more than 10% of the causes of primary nursing care requirement.
- An inquiry on a history of falling within 1 year should be conducted. If such history is present, causing factors should be examined.
- When antihypertensive drug therapy is newly started or changed, the risk of fracture may increase.
- Osteoporosis should be evaluated and treatment should be performed according to guidelines.
- If there is no particular antihypertensive drug to be aggressively indicated, thiazide-type diuretics should be used for patients with osteoporosis.

Dehydration- or environmental change-matched guidance for pharmacological therapy

- Excessive salt restriction or dehydration (diarrhea, fever, excessive sweating in the summer, a decrease in dietary intake) sometimes enhances the responses to antihypertensive drugs. With respect to management under a poor condition related to these symptoms or on a decrease in home blood pressure, patients must be instructed in advance so that they can understand whether they should contact the attending physician or whether the dose-reduction or discontinuation of antihypertensive drugs is possible.
- Blood pressure sometimes changes with environmental changes such as admission to a nursing home (including salt restriction related to meals in the nursing home). Dose reduction or discontinuation must always be considered if necessary.

Precautions for drug adherence management

- Factors involved in a reduction in adherence (continuation of treatment)
  - Insufficient understanding of treatment by the patient (final target of antihypertensive treatment, dosage, drug efficacy, and side effects)
  - Cognitive impairment
  - Impairment of the visual function or coordinated movement (e.g. opening the drug container)
  - Polypharmacy
  - Complex prescription, recent switching of the prescription
- Precautions for the management of drug adherence with antihypertensive drugs
  - Informed consent with supporting the understanding of treatment by the patient
  - Simplification of prescriptions (use of long-acting antihypertensive drugs or fixed-combination drugs)
  - One-dose packaging
  - Utilization of pill calendars/cases
  - Compliance management by the patient's family or nursing care staff

considered, but it is also necessary to consider adverse events such as side effects and health expenditure; the regimen must be individually selected.

5) Other precautions based on the specificity of older patients

(1) Precautions associated with the prevention of falls/fracture Falling and fracture are important factors for being bedridden in older persons. General matters regarding prevention of falls/fracture and matters related to hypertension treatment are presented in Table 8-4. In older persons, an inquiry on a history of falling within at least 1 year should be conducted. If such history is present, management must be performed by dividing causing factors for falls into intrinsic and extrinsic factors. Intrinsic factors are patient's physical factors, including the muscular/skeletal and central nervous systems, which are involved in motor ability/transferability, sensory/nervous system, which is involved in equilibrium function, and cardiovascular systems such as orthostatic hypotension and arrhythmia. Extrinsic factors are primarily associated with the living environment. In addition, sleep-promoting drug (especially benzodiazepine)-/psychotropic drug-/antihistamine drug-induced falls/fracture must also be considered.

With respect to the association of falls/fracture with antihypertensive drugs, a study indicated that the risk of fracture within 45 days after the start of prescription in older patients in whom antihypertensive drug therapy was newly started was 1.43 times higher than that before prescription or 90 days or more after prescription; caution is needed [1297]. In patients receiving treatment, attention must also be paid when increasing the dose of antihypertensive drugs.

(2) Dehydration- or environmental change-matched guidance for pharmacological therapy In older patients, dose-reduction or discontinuation (including temporary discontinuation) is sometimes required due to dehydration, a reduction in dietary intake, or environmental changes related to admission to a nursing home. In older patients in whom the reserve of various organs is reduced, fluctuation of blood pressure is large, and their responses to antihypertensive drugs may increase. Individualized management, such as guidance for pharmacological therapy before its start and prescription changes on blood-pressure reduction, is necessary (Table 8-4).

(3) Evaluation of drug adherence and precautions for drug adherence management Factors involved in a reduction in adherence (continuation of pharmacological therapy) in older patients are presented in Table 8-4 [1308]. The drug adherence-managing ability should be assessed by evaluating the family background, cognitive function, communicating ability and ADL. In particular, a routine inquiry confirming that there is no change in physical condition cannot evaluate cognitive function. The inquiries to exclude cognitive function decline or the history taking from people around the patient might have to be conducted. There may be cases in which the patient intentionally excludes some drugs. The reasons vary, and treatment based on physician-patient concordance is important. Drug adherence should be evaluated based on the patient's and his/her family's/nursing care staff's reports (residual drugs and drug non-adherence associated with the dosing method).

Points of compliance management in older patients are shown in Table 8-4. In particular, one-dose packaging has been reported to maintain older patients' drug adherence and improve pressure-lowering effects [443]. However, there is a limitation: the doses of drugs cannot be regulated during the course. An increasing number of patients require comprehensive care involving the nursing care staff. For drug adherence management by the nursing care staff, prescriptions must be prepared, considering the number and time of visits. The target of treatment should be reviewed in accordance with the nursing care state, and drug adherence management such as priority ranking of the prescription contents is necessary in some cases. It is also important to cooperate with the pharmacist. It was indicated that the involvement of pharmacists in pharmacological therapy for older patients contributed to the avoidance of drug-related adverse events, a reduction in health expenditure, simplification of prescriptions, an improvement in adherence, and a decrease in the frequency of readmission [1309].

For polypharmacy in older patients, attention must be paid from the viewpoints of a reduction in adherence, drug interactions, and an increase in the incidence of adverse events. Generally, therapy with 5 to ≥6 drugs is regarded as polypharmacy. The number of drugs should be minimized, considering adherence, adverse events, and health expenditure. However, concerning antihypertensive drugs, the first aim is to achieve the target of blood pressure control, and there is no upper limit of the number of drugs in combination therapy with antihypertensive drugs. Considering that polypharmacy is a factor for poor adherence, switching to a single drug with a strong titer or a fixed-combination drug, one-packaging, or the simplification of dosing methods should be attempted.

CQ13 WHICH BLOOD PRESSURE LEVEL SHOULD BE TARGETED IN PATIENTS AGED ≥75 YEARS? DOES IT DEPEND ON CONCOMITANT DISEASES OR THE PRESENCE OR ABSENCE OF FRAILTY?

►1. In hypertensive patients aged ≥75 years, blood pressure should be lowered to <140 mmHg if tolerated.

Recommendation grade: 1 Evidence level: A

►2. If a target SBP is recommended as <130 mmHg due to concomitant diseases, a SBP of <140 mmHg should be initially achieved, and a value of <130 mmHg should be targeted by individualized evaluation if patients are tolerable.

Recommendation grade: 2 Evidence level: C

►3. In older patients with frailty or those requiring nursing care, the target of blood pressure control should be individually determined.

Recommendation grade: 2 Evidence level: D

►4. There is no clinical indication of antihypertensive drugs for improving the prognosis in older patients at the end of life. Discontinuation must be positively considered.

Recommendation grade: 2 Evidence level: D

SUMMARY OF EVIDENCE

In hypertensive patients aged ≥75 years, blood pressure control targeting a SBP of <140 mmHg did not reduce the incidence of composite cardiovascular events in comparison with that targeting ≥140 mmHg but prevented all-cause deaths and cardiovascular deaths. In all RCTs, a SBP of <150 mmHg was reached in control groups, suggesting that the preventive effects of blood pressure control targeting <140 mmHg on deaths in patients aged ≥75 years are more marked than those of blood pressure control targeting <150 mmHg. On the other hand, it must be considered that there was variation in the rate of patients with diabetes mellitus or lacunar infarction in some RCTs analyzed.

Although there was no RCT to investigate whether the target of blood pressure control should be changed with respect to the presence or absence of CKD, we examined whether the target of blood pressure control differs between patients with and without CKD based on the criteria for patient registration, mean eGFR and serum creatinine level in the above RCTs. As a result, there was no necessity of recommending different target levels.

We investigated whether the target of blood pressure control differs with respect to the presence or absence of diabetes mellitus, history of stroke, and frailty based on the corresponding RCTs. Blood pressure control targeting <140 mmHg slightly decreased the incidence of composite cardiovascular events in hypertensive patients with diabetes mellitus aged ≥75 years in comparison with that targeting ≥140 mmHg, although its difference was not statistically significant. It should be considered that this analysis involved a small number of patients participating in 2 RCTs, but there was no necessity of establishing different target levels. Furthermore, it must be considered that some RCTs were excluded from the SR because no data from patients aged ≥75 or ≥70 years could be extracted despite the presence of data from those aged ≥65 years. Similarly, some RCTs were excluded with respect to data from patients with a history of stroke. Concerning older patients with frailty, the evidence is limited, and there are several definitions of frailty; therefore, individualized evaluation is appropriate.

There was no RCT from which the target of blood pressure control in older patients requiring nursing care or end-of-life patients could be examined.

INTERPRETATION

1) SR regarding the target of blood pressure control in older patients with hypertension

Among older patients, attention must be particularly paid to those aged ≥75 years and those aged <75 years with frailty or requiring nursing care. In Japanese persons aged ≥65 years, approximately 10-year rejuvenation is demonstrated from various perspectives [1281]. We conducted an SR regarding evidence applicable for hypertensive patients aged ≥75 years [1310]. For a population consisting of persons aged ≥75 years, a target SBP of <150 mmHg is recommended in the JSH2014 Guidelines [108], but the purpose of our SR was to investigate whether lower target levels, <130 mmHg or <140 mmHg, can be recommended.

There were only two studies from which the usefulness of blood pressure control targeting <130 mmHg in patients aged ≥75 years could be investigated: the SPRINT [1294] trial excluding patients with diabetes mellitus and those with a history of stroke and the SPS3 [466] study involving patients with lacunar infarction. It is not appropriate to apply the results of the two studies to patients aged ≥75 years overall from the viewpoint of patient background; therefore, we considered it impossible to examine whether a target SBP of <130 mmHg can be recommended for patients aged ≥75 years.

To examine whether a target SBP of <140 mmHg can be recommended for patients aged ≥75 years, RCTs in which the results were compared between different target levels, with a target level of <140 mmHg in the intensive blood pressure control group, were adopted as evidence. In addition, RCTs in which the target of blood pressure control was 140 mmHg in the standard blood pressure control group, such as the SPRINT [1294] trial, were adopted in our SR, considering the significance of investigating the usefulness of blood pressure control to a lower level. Comparative studies using a drug and placebo, such as the ADVANCE [1311] trial, were also adopted in our SR, considering that conditions including a blood pressure of ≥140 mmHg at the time of registration and a mean blood pressure of <140 mmHg achieved in the drug group are similar to antihypertensive treatment targeting <140 mmHg in clinical practice.

We extracted RCTs to be analyzed in the SR in reference to the JSH2014 Guidelines [108] and two SRs [485, 1296] regarding the target of blood pressure control in older

Table CQ13-1 Outline of 6 RCTs used in an SR regarding intensive blood pressure control targeting <140 mmHg in patients aged ≥75 years

Study	ADVANCE subanalysis [1311]		JATOS [498]		SPRINT subanalysis [1294][*1]		SPS3 subanalysis [466]		VALISH [501][*2]		Wei et al. [502]	
Treatment group	Intensive blood pressure control	Standard blood pressure control	Intensive blood pressure control	Standard blood pressure control	Intensive blood pressure control	Standard blood pressure control	Intensive blood pressure control	Standard blood pressure control	Intensive blood pressure control	Standard blood pressure control	Intensive blood pressure control	Standard blood pressure control
Number of subjects (persons)	483	525	935	934	1317	1319	248	246	925	921	363	361
Target blood pressure (mmHg)	Drug [*3]	Placebo	<140	140–159	<120	<140	<130	130–149	<140	140–149	<140	<150
Blood pressure achieved (mmHg)	137/72	144/74	135.9/74.8	145.6/78.1	123/62	135/67	125/-	137/-	136.6/74.8	142/76.5	135.7/76.2	149.7/82.1
Subject age (years)	≥75		≥75		≥75		≥75		≥75		≥70	
Age at the registration (years)	77		No description		79.9		79.9		76.1		76.6	
Subjects (mmHg)	Diabetes mellitus		Hypertension (SBP≥160)		Hypertension[*4] (SBP≥130)		Lacunar infarction (SBP≥130 or during treatment)		Solitary systolic hypertension (SBP≥160 and DBP<90)		Hypertension(SBP≥150 and/or DBP≥90)	
Percentage of hypertensive patients	79% (patients receiving antihypertensive drugs)		100%		>90% (patients receiving antihypertensive drugs)		87.7% (patients receiving antihypertensive drugs)		100%		100%	
Percentage of patients with diabetes mellitus	100%		11.8% (patients aged ≥65 years overall)		0%		26.9%		13%		23.3%	
Registration criteria for renal function	No criterion		Cr<1.5mg/dL		eGFR≥20 mL/min/1.73 m^2		eGFR≥40 mL/min/1.73 m^2		Cr<2.0mg/dL		Cr<3.0 mg/dL	
Renal function at the time of registration	eGFR 66 mL/min/1.73 m^2 (quartile: 55-76)		eGFR approximately 56 mL/min/1.73 m^2 (eGFR<60: 63%)[*5]		eGFR 63 mL/min/1.73 m^2 (eGFR <60: 44%)		eGFR 66 mL/min/1.73 m^2		No description		Cr 0.98 mg/dL	
Primary endpoint other than cardiovascular disease-related death, myocardial infarction and stroke	(Primary endpoints include diabetic nephropathy and diabetic retinopathy, but they were excluded in this analysis.)		Angina pectoris requiring admission, heart failure, aortic dissection, arterial occlusion, renal failure		Acute non-compensatory heart failure		(Heart disease-related death and myocardial infarction are accessory endpoints.)		Unexpected admission due to cardiovascular diseases, renal failure		No addition	
Follow-up period (years)	4.3		2		3.3		3.7		2.85		4	
Blood pressure at the time of registration (mmHg)	151/78		171.6/89.1		142/71		144.4/-		169.6/81.4		159.5/84.2	
Differences in blood pressure achieved between groups (mmHg)	7/2		9.7/3.3		12/5		11/-		5.4/1.7		14/5.9	
Year of article publication	2010		2008		2016		2013		2010		2013	

[*1] In the SPRINT study, blood pressure was measured by automatic office blood pressure (AOBP) monitoring, and it may be lower than normal office blood pressure.

[*2] The VALISH data on blood pressure and age are derived from patients aged ≥70 years overall.

[*3] Perindopril at 4 mg/indapamide at 1.25 mg

[*4] No diabetes mellitus, no history of stroke, no orthostatic hypotension (SBP one minute after standing up: ≥110 mmHg)

[*5] Subanalysis regarding CKD [1312]

Table CQ13-2 Outline of an SR regarding intensive blood pressure control targeting <140 mmHg in patients aged ≥75 years

	Number of studies	Intensive blood pressure control		Standard blood pressure control		Odds ratio	95%CI	*P*-value for the effects of intensive blood pressure control	*P*-value for study heterogeneity
		Number of events	Number of subjects	Number of events	Number of subjects				
Composite cardiovascular events	6	333	4271	417	4306	0.83	0.64–1.07	0.14	0.03
All-cause deaths	5	273	3956	368	3985	0.73	0.61–0.86	0.0002	0.19
Cardiovascular deaths	5	100	3956	169	3985	0.59	0.45–0.76	<0.0001	0.57
Stroke	5	126	4408	142	4394	0.88	0.69–1.12	0.30	0.10
Serious adverse events	4	739	3593	731	3624	1.02	0.89–1.17	0.75	0.70

patients with hypertension, which were published in 2017. In an SR described by Weiss [485] et al., which was reflected by the Pharmacologic Treatment of Hypertension in Adults Aged 60 years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the ACP and the American Academy of Family Physicians (AAFP) in 2017 [1295], RCTs involving prospective comparison between different target levels, as well as RCTs in which the blood pressures achieved differed between groups, were analyzed. Garrison et al. [1296] (Cochrane Library) analyzed three RCTs in which blood pressure control targeting <140 mmHg was compared with that targeting a lower level: the JATOS [498] study, VALISH [501] study, and study conducted by Wei et al. [502].

Based on the above concept, we extracted 5 RCTs in which the target of blood pressure control was established as <140 mmHg in the intensive blood pressure control group (JATOS [498], SPRINT [1294], SPS3 [466], VALISH [501], and Wei et al. [502]) and 1 in which a drug was compared with a placebo, and a mean blood pressure of <140 mmHg was achieved in the drug group (ADVANCE [1311]) among RCTs for which analysis (including subanalysis) involving patients aged ≥70 or ≥75 years was reported with respect to the target of blood pressure control in older patients with hypertension. In these RCTs, composite cardiovascular events, all-cause deaths, and cardiovascular deaths were considered as outcomes.

In the SR for this CQ, decreases in the incidence of composite cardiovascular events, total mortality rate, cardiovascular mortality rate, and incidence of stroke were assessed as the advantages of the outcome. The incidence of serious adverse events was evaluated as the disadvantage of the outcome.

2) Principle of establishing the target of blood pressure control in older patients with hypertension

In patients aged ≥75 years (RCT [502] conducted by Wei et al.: subjects aged ≥70 years), blood pressure control targeting/achieving a SBP of <140 mmHg (123-137 mmHg) significantly prevented all-cause deaths and cardiovascular deaths in comparison with that targeting/achieving a higher level, <150 mmHg (135- 149.7mmH), although there were no significant decreases in the incidences of composite cardiovascular events or stroke. Furthermore, there was no increase in the incidence of serious adverse events.

The outline of 6 RCTs adopted in the SR is summarized in Table CQ13-1. The following points should be considered: the patient background markedly differed among the studies adopted in the SR, and the definition of composite cardiovascular events was different among the studies. On the other hand, evidence regarding patients with diabetics or stroke, who were excluded from the SPRINT

trial, was complemented in the ADVANCE and SPS3 studies. We consider that a target blood pressure of <140 mmHg can be indicated for patients who are able to consult an outpatient clinic by themselves and participate in an RCT. Furthermore, caution is needed when calculating the number needed to treat (NNT) in a meta-analysis using studies among which the patient background and follow-up period are different, but the NNT required for the prevention of cardiovascular deaths is 59, and there was no increase in the incidence of serious adverse events; therefore, the results are clinically significant. However, in the JATOS and VALISH studies involving Japanese patients, in which the results were compared between different target level groups, there were no preventive effects of blood pressure control targeting <140 mmHg on composite cardiovascular events, although this may have been related to statistical detection power insufficiency. Based on these results, we recommend blood pressure control targeting <140 mmHg for patients, aged ≥75 years, who are able to consult an outpatient clinic by themselves if they are tolerable.

The primary results are summarized in Table CQ13-2. These results were also reproduced by analyses excluding an analysis involving only RCTs using a target SBP of <140 mmHg or lower (ADVANCE [1311]) or an analysis excluding an RCT by Wei et al. [485] excluded as a high risk of bias in the SR conducted by Weiss et al. [502]. In particular, the results of the latter showed that blood pressure control targeting <140 mmHg significantly prevented composite cardiovascular events.

3) Is the target of blood pressure control different among concomitant diseases?

When examining the necessity of changing a target SBP of <140 mmHg to a higher or lower level with respect to the presence or absence of concomitant diseases, we initially investigated whether a target level of <140 mmHg can be recommended. When a target level of <140 mmHg was regarded as recommendable, we investigated whether a target level of <130 mmHg could be recommended.

We recommend a target SBP of <140 mmHg if CKD (G3a or lower), diabetes mellitus, or a history of stroke is present as a concomitant disease. Even when a lower target level, <130 mmHg, is recommended for non-older patients, including those with other concomitant diseases, there is no evidence to positively support this for patients aged ≥75 years. However, as specialists' opinions, we recommend that, if patients are tolerable, a lower blood pressure level (<130 mmHg) should be targeted while paying much attention to adverse events and individually considering the number of drugs, drug interactions, and drug expenditure. Individual concomitant diseases are explained below.

(1) CKD Concerning older hypertensive patients with CKD, this SR may involve a large number of patients with CKD G3a (eGFR: 45–59mL/min/1.73m^2) based on the registration/exclusion criteria adopted in each RCT (Table CQ13-1) [1312]. Indeed, the rates of patients with an eGFR of <60mL/min/1.73m^2 in RCTs in which the eGFR at the time of registration was clear were 63 (JATOS) and 44% (SPRINT), respectively. The mean eGFRs in the ADVANCE, JATOS, SPRINT and SPS3 studies were 66, 56, 63 and 66mL/min/1.73m^2, respectively. Therefore, it is appropriate to apply the target of blood pressure control as a principle in older hypertensive patients, as recommended in the above section, to CKD G3a or higher patients. However, the subjects of this SR may include a low rate of patients with an eGFR of <45mL/min/1.73m^2 (more advanced than G3b); therefore, we cannot present a recommendation that there is no necessity of changing the target of blood pressure control. There was no RCT appropriate for an SR involving patients, aged ≥75 years, with CKD G3a or higher.

(2) Diabetes mellitus To the CQ "Is it necessary to change the target of blood pressure control in older hypertensive patients with diabetes mellitus from that in a generally older population, we conducted an SR to examine the efficacy of blood pressure control targeting a SBP of <140 mmHg. Of the RCTs used in the SR for establishing the target of blood pressure control in patients aged ≥75 years overall, the ADVANCE (≥75 years) [1311] and VALISH (≥70 years) [501] investigated the onset of events with respect to the presence or absence of diabetes mellitus. In the ADVANCE trial, the mean age in the ≥75-year-old group was 77 years, and blood pressures of 137 and 144 mmHg were achieved in the drug and placebo groups, respectively. In the VALISH trial, the subjects' ages ranged from 70 to 84 years, (mean age: 76 years), and the results were compared between different target levels, <140 and 140–149 mmHg. In an SR using the two RCTs, the odds ratio of composite cardiovascular events in the <140 mmHg-targeted group was 0.76 (95%CI: 0.58–1.01, P=0.06); the onset of events was slightly inhibited, although this may have been related to statistical power insufficiency. However, the tendency toward a reduction in the incidence of composite cardiovascular events at a target level of <140 mmHg was consistent; it is not necessary to change the target of blood pressure control in hypertensive patients, aged ≥75 years, with diabetes mellitus. There is no evidence to recommend a target SBP of <130 mmHg for older patients.

(3) Stroke In the SR published by Weiss et al. [485], the PROGRESS [676] and SPS3 [466] trials were adopted as studies, regarding the secondary prevention of stroke, available to examine the target of blood pressure control in patients with a history of stroke or transient cerebral

ischemic attacks. The mean age of the subjects of these studies was <65 years, but there was no upper limit of age. Although this was not an age-specific analysis, it is weakly recommended that a SBP of <140 mmHg should be targeted in hypertensive patients, aged ≥60 years, with a history of stroke or transient cerebral ischemic attacks (moderate-level evidence-based recommendation) in the 2017 ACP/AAFP Guidelines [1295] based on this SR. In this CQ, we consider that this recommendation applies to patients aged ≥75 years because there was no upper limit of age in the PROGRESS or SPS3 studies. There is no evidence to recommend a target SBP of <130 mmHg for older patients.

(4) Others There is no evidence regarding hypertension in older patients appropriate for investigating whether the target of blood pressure control depends on the patient background, such as a history of myocardial infarction, concomitant heart failure, and therapy with antithrombotic drugs. Therefore, no SR-based recommendation can be presented.

4) The target of blood pressure control in older patients with frailty

Concerning older patients with frailty, the HYVET [1313] and SPRINT [1294] studies were published, and there is weak evidence that it is not necessary to change the target of blood pressure control in older patients with frailty. However, there are several definitions of frailty. Most patients regarded as having frailty in these two studies may be classified as strong to pre-frailty according to other criteria [1314]. Furthermore, there was a marked difference in the blood pressure value achieved under intensive blood pressure control between the HYVET and SPRINT studies. Currently, there is little evidence to establish the target of blood pressure control in older patients with frailty. We propose an individualized evaluation.

5) The target of blood pressure control in older patients requiring nursing care or at the end of life

As there is no interventional study of hypertension treatment involving older patients requiring nursing care or at the end of life, a target level should be established based on observational studies. However, many studies indicated that the prognosis of patients with low blood pressure was unfavorable. However, the prognosis may be poor due to cardiovascular diseases in patients in whom antihypertensive treatment reduces blood pressure (reversion of causality). Based on these, it is recommended that the target of blood pressure control should be individually established in patients requiring nursing care in the Guidelines for the Management of Hypertension in Older Patients in 2017 prepared by the Japan Geriatrics Society [1290]. Furthermore, it is described that the discontinuation of antihypertensive drugs should be positively considered rather than antihypertensive treatment to improve the prognosis in older end-of-life patients receiving antihypertensive drugs.

Chapter 9. Dementia and hypertension

POINT 9

1. **Hypertension in middle age is a risk factor for cognitive impairment in later life, and it should be aggressively treated from the perspective of dementia prevention.**
2. **The prevention of dementia by antihypertensive medication in older persons has not been proved, but no study has suggested that antihypertensive drugs reduce the cognitive function. Accordingly, antihypertensive drug therapy should be performed.**
3. **There is little evidence about the effects of antihypertensive drugs on cognitive function in hypertensive patients with dementia, but antihypertensive medication should be considered for the prevention of cardiovascular diseases.**

Hypertension is a risk factor for vascular dementia [111, 1315–1317]. Alzheimer's disease is also complicated by cerebrovascular disease or cerebral microangiopathy [1315–1317]. Its association with hypertension has been reported [111, 1315–1317].

1. BLOOD PRESSURE AND COGNITIVE DYSFUCNTION / DEMENTIA

Hypertension induces cerebrovascular structural and functional abnormalities, but various factors including age, the duration of hypertension, and antihypertensive drugs, are closely involved in the relationship between the blood pressure and cognitive function or dementia [1315, 1318]. In particular, age has profound effect on this relationship. One study has shown that hypertension at a young age is a risk factor for cognitive impairment in middle life [1319] and many studies have reported that hypertension in middle life is a risk factor for cognitive impairment in later life [25, 111, 1315–1317].

A study in 2011 on potentially modifiable risk factors for dementia showed that the population–attributable risk fraction of mid-life hypertension for dementia was about 8% [1320]. On the other hand, the adjusted population-attributable risk fraction of hypertension calculated in 2017 based on the data of the National Institute for Health and Care Excellence (NICE) in England and National Institute of Health (NIH) in the US was 2.0% [1321]. In this study,

mid-life hypertension was a risk factor for dementia, but later-life hypertension (≥ 65 years old) was not a risk factor [1321]. The Hisayama Study also reported that mid-life hypertension was a significant risk factor for vascular dementia in later life [25]. Hypertension in middle-aged persons should be aggressively treated from the perspective of dementia prevention [111, 1315–1317].

On the other hand, the relationship between dementia and blood pressure in older persons is inconclusive. Not only hypertension but also hypotension has been shown to be associated with dementia [1322, 1323]. A possible explanation of inconclusive relationship between the blood pressure and cognitive function in late life could be the interaction between the middle-age and late-life blood pressures [1317, 1324]. In the presence of mid-life hypertension, a low blood pressure was related to cognitive impairment as well as brain atrophy in late life [1317, 1324]. However, without mid-life hypertension, such a relationship was not observed.

Studies have also shown possible associations between abnormal blood pressure variability and cognitive impairment or mild cognitive impairment (MCI). Cognitive decline or the onset of dementia has been shown to be associated with orthostatic hypotension [1325] or inter-day blood pressure variability (the Ohasama study [202] and the Hisayama study [57]).

2. ANTIHYPERTENSIVE MEDICATION AND COGNITIVE FUNCTION, PREVENTION OF DEMENTIA

Whether antihypertensive medication could prevent dementia and preserve cognitive function in older patients with hypertension is addressed in CQ14. A meta-analysis of long-term prospective observational studies showed no effects of antihypertensive medication on cognitive decline in older patients [1326]. Another meta-analysis of randomized controlled trials (RCTs) using a placebo in hypertensive older patients without a prior stroke showed significant protective effects of antihypertensive medication on cognitive decline [1327]. On the other hand, a meta-analysis of RCTs using a placebo in high-risk patients, such as those with a stroke or a history of cardiovascular diseases, showed no significant effects [1328].

The preventive effects of antihypertensive medication on dementia were observed in the above meta-analysis of observational studies [1326] but not in the meta-analysis of RCTs using a placebo in older patients without a prior stroke [1327]. The prevention of dementia by an intensive vascular care (preDIVA) trial, in which the usefulness of a 6-year intensive intervention targeting cardiovascular risk factors including hypertension was evaluated in subjects aged 75–79 years, revealed no difference in the incidence of dementia between the intensive intervention and usual care groups [1329].

Among antihypertensive drug classes, several studies showed the effectiveness of renin–angiotensin (RA) system inhibitors. A meta-analysis of cohort studies showed significant preventive effects of both angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors on the development of dementia [1330] but in RTCs both ARBs or ACE inhibitors had no effect on dementia prevention [1330] Another meta-analysis showed that episode memory is improved by ARBs but not by other antihypertensive drugs [1331]. On the other hand, another meta-analysis of 15 studies revealed diuretic use relates lower risk of dementia [1332]. Thus, the results of previous studies have been inconsistent.

Since the incidence of dementia is low, it needs many cases and long-term observational period for the confirmation of the preventive effects of antihypertensive drugs on dementia [1321]. The involvement of many factors in dementia may be the reason why no conclusion has been reached in most studies [1321].

Therefore, there is no conclusive evidence that antihypertensive medication prevents dementia or preserves cognitive function in older patients with hypertension. However, there have been no study reported that antihypertensive medication deteriorated cognitive function in older patients without dementia. Therefore, antihypertensive medical treatment should be performed [111].

3. ANTIHYPERTENSIVE MEDICATION IN PATIENTS WITH COGNITIVE IMPAIRMENT

There is little evidence about the effect of antihypertensive drugs in hypertensive patients with cognitive impairment. Two meta-analyses in which the progression risk factors from MCI to dementia was evaluated showed that hypertension was not a significant risk for progression [1333, 1334]. However, in a cross-sectional study in China, the prevalence of MCI was high in hypertensive patients, however it was significantly low in patients receiving antihypertensive medication as well as those with well controlled blood pressure [1335]. An observational study indicated that antihypertensive drugs prevented the conversion of MCI to Alzheimer's disease [1336]. In a study on the possible effects of ginkgo biloba on cognitive function, sub-analysis of subjects with MCI at baseline showed a significantly low incidence of progression to dementia in patients receiving a diuretic [1337]. In addition, in an observational study in MCI patients receiving antihypertensive drugs, a significantly low rate of progression to dementia and preventive effects on cognitive decline were observed in patients receiving centrally acting ACE inhibitors or ARBs [1338]. Although evidence is scarce, strict control of risk factors for arteriosclerosis, including hypertension, should be considered.

About 70% of hypertensive patients with dementia were reported to use antihypertensive drugs [1339]. Only a few studies have investigated the effect of antihypertensive treatment on the cognitive function in hypertensive patients with dementia, especially Alzheimer's disease. Control of risk factors for atherosclerosis, including using antihypertensive drugs, was reported to be associated with a slower cognitive decline in patients with Alzheimer's disease [1340]. In an observational study in patients with Alzheimer's disease, the decrease in cognitive function was less marked in patients receiving antihypertensive drugs than in those not receiving them [1341]. Clinical trials in Japan have shown that RA system blockers slow cognitive decline in patients with Alzheimer's disease [1342–1344].

There is little evidence for the optimal blood pressure level in hypertensive patients with dementia. An observational study in patients with MCI or Alzheimer's disease showed a significant progression of cognitive decline in the low daytime blood pressure group (daytime systolic blood pressure [SBP] ≤ 128 mmHg) receiving antihypertensive medication [1345]. A decrease in cerebral perfusion associated with an excessive pressure fall has been suggested to reduce cognitive function [1346, 1347], but discontinuation of antihypertensive medication resulted in no improvement in cognitive function [1348]. SPRINT-MIND as a subanalysis of SPRINT showed a significant lower rate of new MCI cases in the intensive antihypertensive treatment group, suggesting the effectiveness of intensive antihypertensive treatment [1349]. However, the results of this analysis cannot be used to determine the blood pressure target in patients with dementia.

At present, in patients with dementia, attention should be paid to avoid excessive blood pressure lowering and to improve adherence, and antihypertensive medication for the prevention of cardiovascular diseases should be considered.

CQ14 IS HYPERTENSIVE TREATMENT EFFECTIVE FOR MAINTAINING COGNITIVE FUNCTION IN OLDER PATIENTS WITH HYPERTENSION?

►Antihypertensive medication has been suggested to maintain cognitive function in older hypertensive patients, but there is no conclusive evidence. There has been no report that antihypertensive medication has adverse effects on cognitive function.

Recommendation grade No recommendation Evidence level C

SUMMARY OF EVIDENCE

A meta-analysis of long-term longitudinal observational studies showed that antihypertensive medication reduced the risk of developing dementia, but was not associated with the reduction of development of cognitive impairment or decline. A meta-analysis of RCTs using a placebo revealed significant improvement in cognitive function by antihypertensive treatment in hypertensive patients without a prior cerebrovascular disease, while a meta-analysis in patients including those with a prior cerebrovascular disease revealed no significant effects. A meta-analysis of RCTs using a placebo showed no preventive effects of antihypertensive drugs on the development of dementia.

INTERPRETATION

1) Long-term longitudinal observational studies

In 2017, a meta-analysis of 10 long-term prospective longitudinal observational studies was reported [1326]. In 6 studies evaluating the development of dementia, the risk of developing dementia was low in patients receiving antihypertensive drugs (relative risk [RR], 0.86; 95% confidence interval [CI], 0.75–0.99; $P = 0.033$). However, antihypertensive medication had no protective effects on the onset of Alzheimer's disease (RR, 0.83; 95%CI, 0.64–1.07; $P = 0.15$). Antihypertensive medication also had no preventive effects on cognitive decline in 2 studies on evaluating cognitive impairment (RR, 1.11; 95%CI, 0.86–1.43; $P = 0.415$) and 4 studies on cognitive decline (RR, 0.89; 95%CI, 0.57–1.38; $P = 0.60$) [1326].

2) RCT: Cognitive function

In a meta-analysis published in 2013, the effects of antihypertensive medication on cognitive function were evaluated in hypertensive patients without a prior cerebrovascular disease [1327]. This meta-analysis of both 7 RCTs using a placebo and 12 RCTs comparing effects among antihypertensive drugs showed significant improvement in general cognitive function from the baseline after antihypertensive medication irrespective of the antihypertensive drug class [1327]. In the 7 RCTs using a placebo alone, similar effects were observed. All cognitive functions except language (executive function, immediate memory, episodic memory, processing speed, and attention) improved. Similar results were obtained in analysis of 3 RCTs using the Mini-Mental State Examination (MMSE) [1327].

A meta-analysis of RCTs using a placebo in subjects including those withcerebrovascular diseases showed no effects of antihypertensive medication in 8 RCTs on its effects on cognitive impairment (odds ratio [OR], 0.97; 95% CI, 0.92–1.03; $P = 0.34$) [1328] or in 6 RCTs on effects on cognitive decline (OR, 0.97; 95% CI, 0.92–1.01; $P = 0.17$) [1328].

A meta-analysis of 7 RCTs comparing between intensive and standard antihypertensive treatments revealed no

adverse effects of intensive treatment on cognitive function [485].

3) RCT: Onset of dementia

The meta-analysis of hypertensive patients without a prior cerebrovascular disease published in 2013 showed no significant preventive effects of antihypertensive medication on the development of all-cause dementia in 4 RCTs using a placebo (OR, 0.89; 95% CI, 0.74–1.07) [1327].

In the meta-analysis of RCTs using a placebo in subjects including those with cerebrovascular disease, effects of antihypertensive medication on dementia subtype were evaluated [1328]. In 3 RCTs, antihypertensive medication had preventive effects on the onset of vascular dementia (OR, 0.76; 95% CI, 0.57–1.00; P=0.05). However, PROGRESS markedly contributed to this result; the preventive effects on the onset of dementia were associated with stroke recurrence. In 2 RCTs, antihypertensive medication had no effects on the development of Alzeheimer's disease (OR, 0.79; 95% CI, 0.53–1.18; P=0.25).

Intensive antihypertensive treatment compared with standard treatment also had no adverse effects on the development of dementia [485]. In SPRINT-MIND, the rate of new MCI cases was reduced in the intensive antihypertensive treatment group [1349].

Thus, several results have shown usefulness, however there is no conclusive evidence that antihypertensive medication has effects for maintaining cognitive function in older hypertensive patients. The clinical trials have methodological problems such as inadequate statistical power, an inadequate follow-up period, and inappropriate dementia assessment methods to show clinical usefulness [111]. However, there have been no results showing the adverse effects of antihypertensive medication on the development of dementia or cognitive function. To prevent complications, such as cardiovascular events, standard antihypertensive treatment for general older hypertensive patients should be performed.

Q7 IS THE DISCONTINUATION OF ANTIHYPERTENSIVE DRUGS OR A REDUCTION IN THE DOSE USEFUL IN OLDER HYPERTENSIVE PATIENTS WITH COGNITIVE IMPAIRMENT?

- There is little evidence for the discontinuation of antihypertensive drugs or the determination of the blood pressure value requiring a reduction in the dose. The possibility that an excessive fall in the blood pressure due to antihypertensive medication unfavorably affects cognitive function cannot be excluded. In older patients, the dose of antihypertensive drugs should be adjusted so as not to reduce the blood pressure markedly below the target value.

INTERPRETATION

A decrease in the blood pressure in older people could readily reduce blood flow due to impaired autoregulation of blood flow, which can aggravate cognitive function in dementia patients. In an observational study evaluating the blood pressure level and cognitive changes in 172 older patients (mean age, 79 years) with dementia or MCI, tertile analysis of the daytime SBP (9:00–21:00) determined using ambulatory blood pressure monitoring (ABPM) showed a significant decrease in the MMSE score after 9 months in the lowest tertile group (systolic BP≤ 128 mmHg) than in the intermediate (129–144 mmHg) or highest tertile group (≥ 145 mmHg) [1345]. This association was only observed in older patients treated with antihypertensive medication. There was no significant association between the office blood pressure and a decrease in the MMSE score.

A study in which 385 older hypertensive patients (≥ 75 years) with MCI (MMSE score, 21–27) free from severe cardiovascular diseases who were receiving antihypertensive medication were randomly allocated into the antihypertensive drug discontinuation and continuation groups, and cognitive function was compared after 16 weeks.Blood pressure showed a 5.4/1.3 mmHg increase from 148.8/82.3 mmHg in the discontinuation group and a 2.0/1.3 mmHg increase from 147.0/80.0 mmHg in the continuation group. However, there was no improvement in cognitive function in the discontinuation group [1348]. In this study, cerebral blood flow was also measured using the MRI pCASL method, but no difference was observed after 16 weeks between the continuation and discontinuation groups [1350]. A per protocol analysis showed improvement orthostatic prevalence in the discontinuation group (61%) compared with the continuation group (38%) [1351]. The possibility that an excessive decrease in the blood pressure due to antihypertensive medication could deteriorate cognitive function cannot be excluded. Therefore, it is important to adjust antihypertensive drugs using ABPM or home blood pressure measurement so that the blood pressure would not markedly decrease below the target value in older persons.

Chapter 10. Hypertension in women

POINT 10

1. **Hypertension (≥140/90 mmHg) during pregnancy is called "hypertensive disorders of pregnancy (HDP)." HDP is classified into pre-eclampsia, gestational hypertension, superimposed pre-eclampsia and chronic hypertension.**

2. **Methyldopa and labetalol are recommended as first-choice drugs for treatment of hypertension (chronic hypertension) at gestational age less than 20 weeks. At gestational age 20 weeks and over, nifedipine may also be used. If no other drug can be chosen and nifedipine is used at gestational age less than 20 weeks, informed consent needs to be obtained from the patient prior to the drug use.**
3. **For treatment of gestational hypertension, hydralazine may be used as a first-choice drug in addition to the three drugs.**
   It is recommended that nifedipine should be administered regardless of the dosage form only when the advantage of treatment exceeds its risk (for pregnant women after Week 20 of pregnancy). Basically, a long-acting preparation should be used. The sublingual administration of capsule preparations should not be performed.
4. **In patients with gestational hypertension, antihypertensive treatment should be started soon after recording of systolic blood pressure (SBP) ≥180 mmHg or diastolic blood pressure (DBP) ≥120 mmHg.**
   If an urgent decrease in blood pressure is necessary, drugs for intravenous injection (nicardipine, nitroglycerin, or hydralazine) should be used.
5. **If eclampsia is present or suspected, $MgSO_4$ should be intravenously administered.**
6. **In pregnant women, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors (DRIs) should not be used.**

The primary purpose of this chapter is to facilitate understanding of the strategy for treatment of gestational hypertension extensively by internists who often encounter hypertensive patients under the current upward trend of the mean age of pregnant women in Japan.

In Japan, the rapid aging of society is advanced, and pregnant women are not exceptional. Currently, the mean age of pregnant women on delivery is approximately 32 years. The number of pregnant women with hypertension or diabetes mellitus (complication pregnancy) is also gradually increasing. In such cases, various risks for maternal and fetal conditions must also be sufficiently explained. In the management of hypertension, renin–angiotensin (RA) system inhibitors have recently been used in many patients, but it is also important to repeatedly explain that pregnancy should always be avoided while taking these drugs.

This chapter was prepared in a form tailored to the current status in Japan, with reference to the guidelines issued from the professional societies related to hypertension or obstetrics across the world [1352].

1. PREGNANCY-ASSOCIATED HYPERTENSION

The information on pregnancy-associated hypertension was summarized in 2018 by the Japan Society for the Study of Hypertension in Pregnancy and the Japan Society of Obstetrics and Gynecology as shown in Table 10-1 [1353]. HDP have been classified into 4 types. This chapter will describe gestational hypertension and chronic hypertension.

Gestational hypertension refers to a condition in which SBP is ≥140 mmHg or DBP is ≥90 mmHg after Week 20 of pregnancy, and it returns to a normal value before 12 weeks after delivery (this type refers to cases in which the SBP reaches 140 mmHg or higher or the DBP reaches 90 mmHg or higher for the first time at gestational age 20 weeks or later and the elevated pressure returns to normal by 12 weeks after delivery). In patients with this type of hypertension, the blood pressure during normal pregnancy begins to decrease immediately at the very early stage of pregnancy and begins to rise gradually around the gestational age of about 20 weeks, returning to a level close to the pre-pregnancy level around gestational age 35 weeks (i.e., immediately before delivery). An approximately similar course of change has been reported also in analysis of home blood pressure data [1354, 1355]. In patients with HDP, blood pressure usually begins to rise around the gestational age 20 weeks.

Recently, the pathogenesis of HDP has been rapidly clarified. Although various theories have been proposed, it is assumed that vascular dysplasia may occur on placentation due to some etiological factor, increasing blood pressure through the release of several cytokines and tyrosine kinase from the dysplasia-affected area into maternal blood. Among these, soluble fms-like tyrosine kinase 1 has been emphasized, and a high soluble fms-like tyrosine kinase 1/placental growth factor (PlGF) ratio is useful for the diagnosis of HDP [1356].

1) Diagnosis

Numerous reports on office blood pressure measurement, home blood pressure measurement and 24-h ambulatory blood pressure monitoring (ABPM) are available also concerning pregnant women. Some studies have suggested that home blood pressure measurement and ABPM are useful for the early detection of HDP [1357–1360], as indicated for hypertension in the general population. These parameters should be adopted in addition to the blood pressure measurement in the clinic; however, currently, a diagnosis should be usually made, according to the criteria for office blood pressure measurement.

However, because cases of white coat HDP and masked HDP are present like the cases of white coat hypertension and masked hypertension, a diagnosis of HDP based on home blood pressure during pregnancy should be made if

Table 10-1 Definition and classification of HDP (Japan Society for the Study of Hypertension in Pregnancy, Japan Society of Obstetrics and Gynecology, 2018)

1. **Name**

English name Hypertensive disorders of pregnancy (HDP)

2. **Definition**

Hypertension during pregnancy is called "hypertensive disorders of pregnancy (HDP)." HDP is classified into pre-eclampsia, gestational hypertension, superimposed pre-eclampsia and chronic hypertension.

Method for blood pressure measurement:

1. After the subject has remained still for 5 min or more and confirming that the cuff around the upper arm is at the heart level, blood pressure is measured twice at an interval of 1–2 min in the sitting position. The average of two measurements is adopted.

If the second blood pressure reading differs by 5 mmHg or more from the first one, measurement is repeated several times until the reading becomes stable. The subject should be prohibited to take caffeine or smoke within 30 min before measurement.

2. During the first session of measurement, blood pressure is measured on both of right and left upper arms. If the reading differs by 10 mmHg or more between two sides, the higher reading is adopted.

3. Measurement should use an automated sphygmomanometer of precision comparable to that of a mercury sphygmomanometer.

Proteinuria: Positive urinary protein (urinary protein excretion 300 mg/day or more, or protein/creatinine ratio in random urine sample 0.3 mg/mg.Cr or higher)

3. **Subtyping by symptoms**

① **Severity**

HDP is rated as severe if it falls under any of the following criteria. The category "mild" is not used, as a rule, because it can be misunderstood as indicating HDP without high risk.

1. Cases of pre-eclampsia, gestational hypertension, superimposed pre-eclampsia or chronic hypertension in which blood pressure satisfies any of the criteria given below:
SBP ≥160 mmHg DBP ≥110 mmHg

2. Cases of pre-eclampsia or superimposed pre-eclampsia in which maternal organ damage or uteroplacental dysfunction is present

* Severity classification based on intensity of proteinuria is avoided.

4. **Disease typing**

① **Pre-eclampsia (PE)**

1. Hypertension with proteinuria occurring for the first time after week 20 of pregnancy but resolving within 12 weeks after delivery.

2. Hypertension having developed for the first time after week 20 of pregnancy, without proteinuria but having any of the below-listed problems resolving within 12 weeks after delivery

i) Hepatic impairment without underlying disease (hepatic enzyme increased [ALT or AST>40 IU/L], right hypochondrial or epigastric pain of persisting severity not responding to treatment and not allowing any other diagnosis)

ii) Progressive nephropathy (serum creatinine >1.0 mg/dL, other renal diseases ruled out)

iii) Stroke, neuropathy (intermittent convulsion, eclampsia, visual field defect, headache excluding primary headache)

iv) Coagulopathy (HDP-associated thrombocytopenia [<150000/μL], disseminated intravascular coagulation, hemolysis)

3. Hypertension having developed for the first time after week 20 of pregnancy, without proteinuria but associated with uteroplacental dysfunction (fetal growth retardation [FGR], abnormal umbilical artery flow pattern, still birth)

② **Gestational hypertension (GH)**

Hypertension occurring for the first time after week 20 of pregnancy but resolving within 12 weeks after delivery and not falling under the definition of pre-eclampsia

③ **Superimposed pre-eclampsia (SPE)**

1. Hypertension occurring before pregnancy or by week 20 of pregnancy, along with any of hepatic/renal impairment (without proteinuria or underlying disease), stroke, neuropathy or coagulopathy emerging after week 20 of pregnancy.

2. Aggravation of pre-existing (before pregnancy or before week 20 of pregnancy) hypertension and proteinuria after week 20 of pregnancy. Either one or both aggravations are acceptable.

3. Hypertension emerging after week 20 of pregnancy in patients with pre-existing renal diseases that manifest solely as proteinuria.

4. Hypertension occurring before pregnancy or by week 20 of pregnancy, associated with uteroplacental dysfunction after week 20 of pregnancy

④ **Chronic hypertension (CH)**

Hypertension occurring before pregnancy or by week 20 of pregnancy, without accompanying superimposed pre-eclampsia

Notes

1. **Pregnancy-induced proteinuria**

Refers to proteinuria first detected after week 20 of pregnancy and resolving within 12 weeks after delivery, but not included in disease typing.

2. **Diagnosis of hypertension**

Office blood pressure sometimes does not reflect the real blood pressure, as seen in cases of white coat hypertension or masked hypertension. Particularly in cases of chronic hypertension, it is advisable to conduct home blood pressure measurement or ABP monitoring for diagnosis of white coat hypertension or masked hypertension and distinction from other accidental complications.

3. **Related conditions**

① **Eclampsia**

Convulsive seizure occurring after week 20 of pregnancy. Exclusion of epilepsy and secondary convulsion is essential. Eclampsia is classified into three types: eclampsia gravidarum, intrapartum eclampsia and puerperal eclampsia based on the timing of convulsive seizure. Eclampsia is considered as convulsive seizure due to reversible angiogenic edema of the cerebral cortex, but edema can develop also in the occipital lobe or brainstem, resulting in various disorders of the central nervous system (CNS).

② **HDP-associated CNS disorders**

Includes cortical blindness, posterior reversible encephalopathy syndrome (PRES), hypertension-associated cerebral hemorrhage and cerebrovascular spasm.

③ **HELLP syndrome**

Develops during pregnancy or during or after delivery, associated with signs of hemolysis (LDH increased), hepatic impairment (AST increased) and thrombocytopenia but not attributable to any other accidental complication. Conditions presenting with only one of these signs/symptoms are not described as HELLP syndrome.

The diagnosis of HELLP syndrome should be based on the diagnostic criteria of Sibai.*

④ **Lung edema**

HDP involves increased vascular permeability due to vascular endothelial dysfunction, often leading to edema. In severe cases, lung edema is also noted.

⑤ **Perinatal cardiomyopathy**

Women having no history of heart disease can develop heart failure suddenly during pregnancy or puerperium, resulting in a fatal outcome in severe cases. HDP is an important risk factor for this condition.

*Hemolysis: Serum indirect bilirubin>1.2 mg/dL, serum LDH>600 IU/L, appearance of pathologic erythrocytes
Hepatic function: Serum AST (GOT)>70 IU/L, serum LDH>600 IU/L
Thrombocytopenia: Platelet count <100000/mm^3

the blood pressure exceeds 135/85 mmHg, consistent with the generally used criteria for diagnosis of hypertension. In this way, white coat HDP and masked HDP are ruled out. There is a report demonstrating that the home blood pressure was 102/60 mmHg in week 20 of pregnancy, 130/80 mmHg in week 30, 110/68 mmHg in week 38–39 and 126/80 mmHg in week 40 [1361].

2) Treatment

The basic treatment for HDP is the interruption of pregnancy, and maternal protection must be predominantly considered with respect to antihypertensive therapy for gestational hypertension. Considering the two points, the contents of treatment should be explained to patients, and the treatment of gestational hypertension should be performed. Simultaneously, it is important to establish a close cooperative relationship with an obstetrician. Particularly after week 20 of pregnancy, it is advisable to assign the patient management (including child delivery) to obstetricians.

In the field of obstetrics, it is essential to be concerned not only with treatment of hypertension but also with the reported questions/issues about which type of blood pressure course is likely to result in pre-eclampsia [1362].

Gestational hypertension can induce maternal organ damage if it becomes severe. In addition, excessive blood pressure fall can induce fetal dysfunction due to reduced fetoplacental circulation. To date, however, no definite level for start of treatment has been set in the management of gestational hypertension.

In the systemic review of Cochrane Library in 2014, no significant influence of antihypertensive drug use was shown on any of maternal mortality, eclampsia, proteinuria, maternal adverse reactions, progression to pre-eclampsia, cesarean section, fetal/neonatal mortality, premature labor (<37 weeks), low birth weight, or admission to special care baby unit (SCBU) [1363]. The review of the data conducted this time yielded approximately similar results. Taken together, these findings suggest that antihypertensive treatment is less effective at least in cases of gestational hypertension (SBP <160 mmHg and DBP <110 mmHg). According to the recently reported CHIP [1364], in which the target level of DBP control in non-severely sick pregnant women was set at two levels (100 and 85 mmHg), there was no difference between the two groups in terms of pregnancy-related complications (including maternal mortality), admission to SCBU or other outcome indicators. However, progression into severe maternal hypertension was significantly prevented in the group with the target level set at 85 mmHg. This result is noteworthy if we consider that more than 50% of the subjects of this study were cases of chronic hypertension.

About lifestyle modifications (particularly salt reduction) which are attempted during treatment of ordinary hypertension, reference should be made to CQ15. The other measures related to nutrition or weight reduction should be taken carefully, bearing in mind that patients may have other complications such as obesity, diabetes mellitus and dyslipidemia [1365, 1366].

(1) Chronic hypertension Adequate data which can serve as evidence are not available concerning which type of antihypertensive treatment should be performed in cases of chronic hypertension or which target levels of blood pressure control should be adopted. These are open issues to be addressed from now on. Recently reported meta-analyses suggested the possibility that the incidence of pre-eclampsia is 8-fold or higher in women with chronic hypertension [1367, 1368].

(2) Severe hypertension In patients with severe hypertension, prompt antihypertensive treatment to prevent maternal organ damage (cerebrovascular, heart or kidney damage) is necessary [1369]. At present, therefore, antihypertensive drug therapy for GH should be indicated for patients with a blood pressure exceeding criteria for severe hypertension. Some studies have indicated that, if the pregnancy period is prolonged with continued antihypertensive treatment in the immature fetal phase, the fetal prognosis may be improved while avoiding the maternal risk. However, the volume of available data does not appear to be large enough to be called "established evidence." [1370]

With respect to concrete criteria for the start of drug therapy, there are slight differences among investigators: SBP, 160–170 mmHg and DBP, 105–110 mmHg [1368, 1371]. However, if precursor symptoms for the onset of eclampsia are present, drug therapy must be promptly initiated [1372].

(3) Emergency If SBP is ≥180 mmHg or DBP is ≥120 mmHg in pregnant or post-partum women, treatment with hypotensive drugs should be promptly started under a diagnosis of hypertensive emergency, to achieve blood pressure reduction to the target level rapidly.

3) Target of blood pressure control in antihypertensive drug therapy

The target level of blood pressure control in patients with severe hypertension has been set at less than 160/110 mmHg. To what extent the blood pressure should be reduced is to be judged on the basis of the maternal/fetal situations based on close linkage to obstetricians.

4) Selection of antihypertensive drugs

As first-choice oral antihypertensive drugs, methyldopa, labetalol, and nifedipine (at gestational age 20 weeks and

over) should be used. The features and adverse effects of individual antihypertensive drugs, described later, should be taken into consideration so that drugs tailored to individual patients may be selected. For combination therapy, a combination of two drugs with different antihypertensive action mechanisms is desirable, as methyldopa and labetalol are classified as sympatholytic drugs, and hydralazine and sustained-release nifedipine as vasodilators. Before week 20 of pregnancy (chronic hypertension), a combination of methyldopa and hydralazine or that of labetalol and hydralazine is recommended. After week 20 of pregnancy (gestational hypertension), monotherapy with a sympatholytic drug (either methyldopa or labetalol) or a vasodilator (either hydralazine or nifedipine) or combination therapy with the two drugs should be performed.

For intravenous injection, nicardipine, nitroglycerin, or hydralazine should be used. These drugs should be used to reduce blood pressure in the case of hypertensive emergency on delivery if blood pressure control with oral drugs is inappropriate. In such cases, particular attention should be paid to the fetal condition of the fetus, and fetal heart rate monitoring should be performed.

5) Various antihypertensive drugs

(1) Methyldopa This is a centrally acting sympatholytic drug, and is still the most commonly used to treat HDP [1373–1375]. Although there is no evidence, this drug has been in use for 40 years or more. No serious adverse effect on maternal or fetal conditions has been reported. Side effects, such as sleepiness, dry mouth, general malaise, hemolytic anemia, and hepatopathy, are observed.

(2) Ca channel blockers (CCBs) According to the package inserts in Japan, CCBs other than use of nifedipine at gestational age 20 weeks and over are contraindicated for pregnant women or those who may be pregnant. Regarding the use of CCBs other than nifedipine in cases in which antihypertensive treatment with any other drug is difficult because of the nature of illness and the mother/child is at increased risk, it is acceptable to consider their use in accordance with the physician's evaluation and responsibility after explaining their necessity for treating the condition and obtaining appropriate informed consent, although this approach is not recommended in guidelines because of insufficient supporting evidence. There appears to be few problems with the safety of CCBs at least in pregnant women (gestational age 20 weeks and over) or newborns [1376].

(3) β-blockers The $\alpha_1\beta$-blocker, labetalol, has been relatively commonly used in Europe and the United States, and there may be no sufficient problems regarding its safety. In addition, a meta-analysis has shown that labetalol was more useful than hydralazine with respect to adverse effects on the maternal condition [1377].

Most β-blockers are contraindicated for pregnant women (attached inserts). Therefore, if the administration of other β-blockers is necessary, informed consent must be obtained after explaining the contents of treatment, as described for CCBs other than nifedipine.

(4) Hydralazine This is a vasodilator and frequently causes side effects. Usually, this drug is not normally used for hypertension treatment. Although we are aware of the fact that this drug is now used by relatively many obstetricians, according to a recently reported meta-analysis, this drug was less effective than labetalol for HDP from all aspects [1377].

(5) Diuretics Diuretics may deteriorate hemoconcentration/a reduction in the circulating plasma volume related to pre-eclampsia, reducing placental blood flow. Therefore, diuretics should be avoided in patients with pre-eclampsia, as a rule, if pulmonary edema or heart failure signs are absent. In patients who had taken an antihypertensive diuretic before pregnancy, continued treatment may not markedly reduce placental blood flow [1352].

(6) α-blockers According to the attached of α-blockers inserts, these drugs are not contraindicated for pregnant women or those who may be pregnant. However, generally, they are not used, and should be avoided. Only one study has reported the use of these drugs in pregnant women with pheochromocytoma [1378].

(7) RA system inhibitors In Japan, RA system inhibitors are classified into three types: ACE inhibitors, ARBs and DRIs. The administration of ACE inhibitors during pregnancy may induce oligohydramnios, teratogenicity, or renal dysplasia; these drugs are therefore contraindicated [1379, 1380]. At present, this type of drug is judged to contraindicated during pregnancy from the standpoint of safety and its use during pregnancy should be avoided, although a report denying universal validity of such a policy was recently published [1381, 1382]. If women using this drug are found to be pregnant, its use should be discontinued immediately [1383]. For women found to be pregnant during use of RA system inhibitors, the Pregnancy and Drug Information Center of the National Center for Child Health and Development has opened the consultation unit [1384], and consultation to this unit is recommended.

(8) $MgSO_4$ As a drug used to treat eclampsia, $MgSO_4$, exhibits mild hypotensive effects, although it is not an antihypertensive drug. Furthermore, its preventive effects on the onset of eclampsia have also been demonstrated in

Table 10-2 Antihypertensive drugs during the nursing period

	Generic name	Assessment by Pregnancy and Drug Information Center	Assessment by LactMed (National Institutes of Health)	RID (%)*
CCB	Nifedipine	Possible	Possible	1.9
	Nicardipine	Possible	Possible	0.07
	Amlodipine	Possible	Possible	1.4
	Diltiazem	Possible	Possible	0.87
αβ-blocker	Labetalol	Possible	Possible, but other drugs are recommended for premature infants	0.2–0.6
β-blocker	Propranolol		Possible	0.28
Central agonist	Methyldopa	Possible	Possible	0.11
Vasodilator	Hydralazine	Possible	Possible	
ACE inhibitor	Captopril	Possible	Possible	0.02
	Enalapril	Possible	Possible	0.17

* If the relative infant dose (RID) is 10% or less, lactation is possible. If it is 1% or less, administration is not problematic.

LactMed: Website primarily utilized in North America.

severe pre-eclampsia patients with impending symptoms of eclampsia [1385]. This drug is commonly used under high-risk circumstances regarding the onset of eclampsia, such as the delivery induction and a 24-h period after delivery. Currently, the use of this drug for the prevention of eclampsia is also approved. When using Magsent R (magnesium sulfate hydrate at 10 g per 100 mL), as an initial dose, 40 mL (4 g as magnesium sulfate hydrate) of this preparation should be intravenously administered over 20 min or more. Subsequently, continuous intravenous administration should be performed from a rate of 10 mL (1 g) per hour. The dose should be increased by 5 mL (0.5 g) per hour in accordance with symptoms, and the maximum dose of this preparation should be 20 mL (2 g) per hour. This preparation should be administered using a pump for continuous infusion, excluding initial-dose administration. Care is needed because this preparation can reinforce the activity of CCBs and, when used in combination with nicardipine or the like, can cause excessive blood pressure reduction.

6) Precautions immediately after delivery

HDP is considered to subside after the completion of pregnancy. However, symptoms of severe/early-onset HDP do not promptly decrease, and eclampsia or hemolysis, elevated liver enzymes and low platelets counts (HELLP) syndrome are frequently observed immediately to 48 h after delivery. In patients with severe HDP, strict blood pressure management is necessary particularly for 3 days after delivery.

7) Antihypertensive drugs during the nursing period

In Japan, the Pregnancy and Drug Information Center of the National Center for Child Health and Development [1384] is providing consultation over breast-feeding, and its utilization is recommended. Sufficient linkage to pediatricians is also required. Table 10-2 was prepared on the basis of recent findings and the assessments generally employed at present.

2. POSTMENOPAUSAL BLOOD PRESSURE

Cardiovascular diseases are more frequently responsible for woman deaths than cancer [1386, 1387]. During menopause, risk factors for atherosclerosis, such as centric obesity, elevation in total cholesterol and reduction in HDL-cholesterol, accumulate and, if they are combined with poor blood pressure control, onset of cardiovascular diseases may result in older women.

The recent increase in the prevalence of hypertension is sharper among women than in men, and this trend is more marked among older women [138, 1386, 1388, 1389]. This difference is associated with the global tendency for aging of the population, particularly the trend of longer life expectancy for women than for men. There is a report that the prevalence of hypertension after menopause is twice as high as that before menopause, and the influence of weight gain and abnormal lipid profile has also been pointed out [1390, 1391]. In meta-analysis, no evident gender-related difference was shown about the usefulness of blood pressure control or antihypertensive drugs [373].

1) Mechanism for postmenopausal blood pressure elevation

Changes in the activity of estrogen and progesterone have been shown as a possible cause [1390, 1391]. Estrogen has been reported to induce vasodilation, suppress vascular remodeling, reduce reactivity to angiopathy, protect the kidneys and reduce sympathetic nerve activity. Progesterone has been reported to exert endothelium-dependent vasodilative activity.

Vascular endothelial dysfunction can be typically characterized by reduced NO formation. Estrogen activates NO synthase and stimulates NO formation mediated by elevation of intracellular calcium level [1392]. Estrogen has antioxidative activity as well.

Estrogen has been reported to reduce AT1 receptor and ACE [1393, 1394], thus suppressing stimulation of the RA system. This means that activation of the RA system can occur after menopause.

Women often become obese after menopause, although differences among races have also been reported [1390, 1391, 1395]. Obesity involves accumulation of various risk factors (insulin resistance, diabetes mellitus, dyslipidemia, hyperleptinemia) as metabolic syndrome and is involved also in blood pressure elevation [1395]. There is a report that the fat distribution pattern shifts from subcutaneous fat to visceral fat even when obesity does not develop [1396].

Weight gain, hyperleptinemia and aging are known to increase the sympathetic nerve activity [1397]. The relationship between sympathetic nerve activity and hypertension is evident also from the data of blood pressure fall after renal sympathetic denervation [1398]. Furthermore, higher sympathetic nerve activity after menopause than that before menopause has been reported [1399]. In postmenopausal women, obesity or stimulation of sympathetic nerve activity can serve as a cause for hypertension, but none of them can explain the hypertension in non-obese women.

Women at menopause occasionally show neurosis or depressive tendency. Neurosis and depressive tendency are risk factors for cardiovascular diseases and are seen more frequently in women than in men [1400]. In the presence of neurosis or mental stress, the sympathetic nervous system is stimulated, possibly leading to blood pressure elevation. In addition, there is a report that neurosis and depressive tendency are often seen in hypertensive patients [1401]. Thus, the relationship of neurosis or depressive tendency to the onset of hypertension is not uniform or unilateral.

2) Influence of hormone replenishing therapy on blood pressure

The influence of hormone replacement therapy (HRT) on blood pressure during menopause varies depending on the type of drugs used by individuals or the method employed for blood pressure measurement, and no consensus has been reached yet [1391]. In cases treated with estrogen or progesterone, mild elevation of SBP has been reported [1402]. In a study using drospirenone and estradiol, reduction in 24-h SBP has been reported [1403]. HRT is known to induce adverse reactions, such as carcinogenesis and enhanced coagulation, thus indicating the necessity of monitoring not only blood pressure but also adverse reactions during follow-up.

3) Influence of pregnancy

According to a meta-analysis of more than 3 million parous women, the women having developed pre-eclampsia during pregnancy had an approximately 2.7-fold increase in the incidence of hypertension and an approximately 2-fold increase in the incidence of ischemic heart disease, stroke and venous thrombosis [1404]. It is important during pregnancy to receive health checkup and appropriate guidance/treatment. The information carried in the mother-child pocketbook, describing the course of maternal body, may be useful in health management of women.

4) Characteristics of hypertension in women

Hypertension in women is first characterized by a high percentage of therapy-resistant hypertension, possibly because of enhanced sensitivity to edible salt and stimulation of sympathetic nerve activity. As a result, the incidence of cardiovascular diseases tends to be higher in women than in men of the same generation. Next, the influence of changes in sex hormones due to menopause is present. Furthermore, blood pressure can be increased by the drugs taken only by women such as oral contraceptives.

There is a report that the incidence of adverse reactions to antihypertensive drugs in women is twice that in men [1405]. High incidences of dry cough due to ACE inhibitors and peripheral edema during use of diuretics are known [1406]. There is also a report that hypokalemia and hyponatremia develop more frequently in women during use of diuretics [1407].

CQ15 IS SALT REDUCTION RECOMMENDED IN PATIENTS WITH GESTATIONAL HYPERTENSION?

► Salt reduction (less than 6 g/day) is not recommended as a non-drug therapy for gestational hypertension.

Recommendation Grade 1 Evidence Level C

EVIDENCE SUMMARIZATION

This CQ included the following analyses in patients with gestational hypertension aged 18 and over: 1) decrease in maternal mortality, 2) decrease in urinary protein and

pre-eclampsia, 3) decrease in cesarean section, 4) increase in the onset of hypotension, 5) decrease in fetal/neonatal mortality, 6) increase in premature labor, 7) increase in low birth weight infants.

Systematic review (SR) was conducted, including existing SR [1408] and SR based on domestic/overseas papers. With the Cochrane Library, SR had been conducted on the basis of 2 randomized controlled trials (RCTs) derived from 13 papers, and 11 other papers were added to the present SR. In analysis of all outcomes from 1) through 7), no benefit or disadvantage of salt reduction was noted.

ITEM-WISE ANALYSIS

1) Decrease in maternal mortality

Because the number of events was quite small, accuracy is judged to be poor. However, at least a tendency for higher maternal mortality in the intervention (salt reduction) group was noted, making it impossible for us to judge that salt reduction is beneficial.

2) Decrease in urinary protein and pre-eclampsia

Because the differences among papers were large and the confidence interval was wide, we judged it necessary to reduce the recommendation grade. Salt reduction may not reduce urinary protein or pre-eclampsia.

3) Decrease in cesarean section

Because the differences among papers were large and the confidence interval was wide, we judged it necessary to reduce the recommendation grade. Salt reduction did not manifest a benefit of decreasing cesarean section.

4) Increase in the onset of hypotension

Although there were large differences among papers, some papers described the possibility that mild salt reduction would reduce blood pressure in patients with gestational hypertension (140–160/90–110 mmHg). Salt reduction manifested no evident effect (neither a disadvantage of increased onset of hypotension nor a benefit of suppressed onset of hypertension).

5) Decrease in fetal/neonatal mortality

Although there were large differences among papers, no evident association was noted between salt reduction and decease in fetal/neonatal mortality.

6) Increase in premature labor

Although there were large differences among papers, no evident association was noted between salt reduction and increase in premature labor.

7) Increase in low birth weight infants

Although there were large differences among papers, no evident association was noted between salt reduction and increase in low birth weight infants.

COMMENTARY

The amount of salt intake in Japan is generally larger than that in Western countries, and this tendency is seen also in pregnant women. In hypertensive patients, salt reduction usually lowers the circulating blood volume, resulting in blood pressure fall. In pregnant women, however, the circulating blood volume has already been reduced by pregnancy and, if salt intake is restricted, the circulating blood volume will further decrease, possibly leading to decrease in placental blood flow and renal blood flow.

According to the papers reviewed this time, very strict salt reduction (2–3 g/day) was implemented in the intervention group, in contrast to the control group in which the previous dietary style was maintained and the amount of salt intake was about 10 g/day. The amount of salt intake in Japan is 11 g/day or more, in contrast to less than 10 g/day on average in Western countries. When we searched domestic papers on studies involving intervention (low salt diet, 7 g/day), adoption of low salt diet (7 g/day) by patients with gestational hypertension (140–160/90–110 mmHg) resulted in blood pressure fall, indicating usefulness of this intervention. However, in the severe HDP group, this diet did not lower blood pressure but resulted in adverse effects such as elevated hematocrit, elevated uric acid level and reduced renal function. On the other hand, the number of papers published concerning intervention with salt reduction to approximately 7–8 g/day was small [1409, 1410] and we judged it difficult to conduct meta-analysis of these studies. Thus, we reached a conclusion that at least strict salt reduction is not recommended because this CQ did not demonstrate any benefit of strict salt reduction.

Under such circumstances, recent guidelines in Western countries do not usually recommend salt intake restriction during management of gestational hypertension. The latest treatment guidelines prepared by the Japan Society of Obstetrics and Gynecology and the Japan Society for the Study of Hypertension in Pregnancy recommend salt intake restriction to 7–8 g/day.

In case in which salt intake is extremely large (i.e., 15 g/day or more), reducing the salt intake to 10 g/day or less may be useful in preventing a severe course of gestational hypertension. In this sense, careful salt reduction may be of value.

Chapter 11. Hypertension in children

POINT 11

1. **In children, blood pressure should be consecutively measured ≥3 times using an appropriate size cuff, and the mean of two stable measurements should be adopted.**
2. **If the blood pressure values measured at ≥3 different opportunities are above criteria for childhood hypertension, childhood hypertension could be diagnosed.**
3. **A marked increase in blood pressure above criteria should be differentiated from secondary hypertension.**
4. **Childhood essential hypertension is related to obesity in many cases, and it may have complication, such as left ventricular hypertrophy. As essential hypertension in children can track into adult essential hypertension, lifestyle modifications should be primarily performed.**
5. **For drug therapy, new antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and Ca channel blockers (CCBs) are recommended.**
6. **Obese children with low-birth weight should be measured blood pressure, because they have a high risk of hypertension.**

1. INCIDENCE AND SECULAR TRENDS OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

On blood pressure screening for healthy children in Japan, hypertension is detected in approximately 0.1–3% of elementary and junior high school students [1411]. A meta-analysis of epidemiological studies regarding hypertension in children also showed that the prevalence of hypertension was approximately 3% [1412]. Concerning secular trends in blood pressure in Japanese children, slight decreases in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) from 1994 until 2010 were reported [1413].

2. BLOOD PRESSURE MEASUREMENT IN CHILDREN AND CRITERIA FOR HYPERTENSION

Accurate blood pressure measurement is essential for the diagnosis of hypertension. Even in children, right brachial blood pressure should be measured in a sitting position. In small children, blood pressure should be measured in a seated position on the lap of a parent. The selection of an appropriate size cuff is also important. Cuffs of 7-cm width for children aged 3 to 6 years, 9-cm width for those aged 6 to 9 years and 12-cm width (adult size) for those aged ≥9 years are commercially available. However, the cuff should be selected according to the size of the child's upper arm rather than their age, and one with an inflatable bladder width exceeding 40% of the arm circumference at a point midway between the olecranon and acromion and a length sufficient to cover 80% or more of the arm circumference should be used. Although blood pressure measurement by auscultation is ideal, children are often unable to rest for a specific time; therefore, the use of an automatic blood pressure meter by oscillometric methods is unavoidable. However, it must be considered that DBP tends to be lower than that measured by auscultation [1414]. Blood pressure should be consecutively measured ≥3 times, and, as a rule, the mean of two stable measurements should be adopted. However, a study adopted the value obtained on the third session of measurement [1415].

Table 11-1 Criteria for hypertension in children with respect to age and sex

		SBP (mmHg)	DBP (mmHg)
Pre-school children		≥120	≥70
Elementary school	First to third graders	≥130	≥80
	Fourth to sixth graders	≥135	≥80
Junior high-school	Boys	≥140	≥85
	Girls	≥135	≥80
High-school		≥140	≥85

Concerning criteria for childhood hypertension, detailed diagnostic criteria according to sex, age and height were established based on oscillometric methods in the United States [1416]. However, the criteria are complex, and a study reported that the use of simple diagnostic criteria: 6 to 11 years of age, ≥120/80 mmHg; and 12 to 17 years of age, ≥130/85 mmHg facilitated adult cardiovascular disease risk screening [1417]. To make a diagnosis of hypertension, values exceeding the reference value on ≥3 sessions of blood pressure measurement at different opportunities are necessary. According to a meta-analysis regarding the incidence of childhood hypertension, 12.1% of children had been diagnosed with hypertension at a single opportunity, 5.6% at two opportunities, and 2.7% at three opportunities [1412]. It is important to confirm hypertension at ≥3 different opportunities.

In Japan, there are few reports on blood pressure in children. In the Japanese Society of Hypertension (JSH) 2014 Guidelines for the Management of Hypertension, criteria for hypertension were established based on the data obtained on blood pressure screening using an automatic blood pressure meter by oscillometric methods [1418]. In the JSH2019 Guidelines, the reference values were also

adopted as criteria for childhood hypertension (Table 11-1). When analyzing the blood pressure levels of ~40,000 elementary-school and junior-high-school students measured by Tokyo Health Service Association, the prevalence of hypertension calculated according to the criteria is consistent with that previously reported, suggesting the usefulness of the criteria for evaluation on blood pressure screening that are conducted in various areas. On the other hand, a study reported criteria for hypertension (95 percentile value) based on the age-category-based blood pressure values obtained on reliable blood pressure measurement using an automatic blood pressure meter in a total of ≥10,000 Japanese children [1419, 1420]. The reference values of hypertension are regarded as criteria for management. The reference values for management are 10- to 15-mmHg lower than those for screening. In children, with underlying diseases, such as diabetes mellitus and chronic kidney disease (CKD), requiring strict blood pressure control, the criteria for management should be adopted. However, if the criteria for management are used on blood pressure screening, too large number of children may be regarded as having hypertension, making post-screening management difficult.

3. PATHOLOGICAL FEATURES OF HYPERTENSION IN CHILDREN

Hypertension detected on blood pressure screening is mostly essential hypertension. A diagnosis of childhood essential hypertension is made based on the absence of symptoms suggestive of secondary hypertension, age (adolescence), degree of hypertension (mild), obesity, family history and low birth weight. Children under 10 years old should be excluded from the diagnosis of essential hypertension. The mechanism of essential hypertension in children involves insulin resistance [1421] and excessive salt ingestion [1422], as reported for adults.

The possibility of secondary hypertension increases with a younger age or higher blood pressure. Hypertension related to renal diseases accounts for 60–80% of children with secondary hypertension, and scarred kidney (reflux nephropathy) associated with vesicoureteral reflux or chronic renal failure related to congenital renal/urinary tract abnormalities requires particular attention.

4. OBESITY AND HYPERTENSION IN CHILDREN

Hypertension is observed more frequently in obese children from the fourth to ninth grade (3–5%) than in those with a standard body size (0.5%) [561]. The prevalence of hypertension increases with the degree of obesity. Isolated systolic hypertension, which is a characteristic of obese children, is observed in 1.6% of boys and 3.1% of girls with mild obesity but in 8.3% of boys and 12.5% of girls with severe obesity [561]. Insulin resistance and hyperinsulinemia related visceral fat accumulation are associated with increase in blood pressure in obese children. Furthermore, an increase in the leptin level is associated [1421]. As hypertension and obesity [562] in children frequently track into essential hypertension and obesity in adulthood, they should be managed since childhood.

5. NUTRITION OF THE FETAL PERIOD AND HYPERTENSION

It has been shown that nutrition during embryonic and fetal development is closely associated with the occurrence of essential hypertension. According to results of studies in Japan, blood pressure at the age of 3 years was higher with lower birth weight and higher body weight at the age of 3 years [1423]. Moreover, in a 20-year follow-up of 4626 individuals from birth, a lower birth weight and a smaller rate of increase in height from 3 until 20 years of age were independently associated with increases in the blood pressure and serum cholesterol level at the age of 20 years, respectively [1424].

A study of severe obese children reported that those with a lower birth weight has a tendency to become metabolic syndrome with hypertension [1425]. The number of nephrons is smaller in children with a lower birth weight, leading to insulin resistance [1426]. If these children become obese after birth, they are thought to be hypertensive [1427].

6. PROBLEMS WITH ESSENTIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

Problems with essential hypertension in children and adolescents include complications (target organ damage) and the tracking into adult essential hypertension. As complications, left ventricular hypertrophy (an increase in left ventricular myocardial weight), carotid intima/media complex thickness, renal dysfunction (urinary albumin excretion) and changes in the fundic arterioles were reported, with an incidence of 14–42% [1428].

Transition to adult essential hypertension is a more important issue. According to the results of comparison of blood pressure at junior-high-school age and after 20 years in Japan, 20.9% of hypertensive junior-high-school students were still hypertensive after 20 years, whereas 5.5% of normotensive individuals became hypertensive [1429]. In a study in which college students were re-examined after 8–26 years, hypertension was observed in 44.6% of the hypertensive group but in only 9.2% of the normotensive group [1430]. In an overseas large-scale study that followed-up 1505 children aged 5–14 years for 15 years or longer (Bogalusa Heart Study) [1431], 40% for SBP and 37% for DBP of children with the highest quintile in blood

pressure still belonged to the highest quintile 15 years later. The morbidity rate of adult hypertension in the highest SBP group was 3.6 times higher than in the other 4 groups (18 *vs*. 5%, respectively). In the highest DBP group, it was 2.6 times higher than in the other 4 groups (15 vs. 5.8%, respectively). Therefore, nonpharmacological treatments involving therapeutic lifestyle changes and health-related behaviors are highly recommended in children and adolescents with essential hypertension in the early stage.

7. LIFESTYLE MODIFICATIONS DURING CHILDHOOD

According to a follow-up survey regarding blood pressure in children, childhood hypertension is correlated with adult hypertension, and there is a stronger correlation in late elementary school children and adolescents [1432]. Therefore, early lifestyle modifications are important. For early detection, it is necessary to introduce blood pressure measurement to a health checkup system for children. As the reason for this, asymptomatic hypertension cannot be detected unless blood pressure is measured, and no management strategy can be performed, although blood pressure measurement is difficult in young children. Opportunities to detect hypertension include follow-up outpatient clinics by the neonatal intensive care unit (NICU), obesity outpatient clinics, health checkups for 3-year-old children established in the Maternal and Child Health Act, school kidney examination established in the School Health and Safety Act, and heart examination.

Furthermore, the morbidity rate of childhood hypertension increases with chronic conditions, such as obesity, sleep disorder, a low birth weight and CKD [1416]. These conditions should be initially evaluated, and preventive dietary/exercise management should be conducted in accordance with the conditions.

1) Dietary therapy

In children with a body mass index (BMI of >99 percentile, the incidence of obesity-related hypertension is 4 times higher than in those with a normal BMI. In children with a BMI of 95–98 percentile, it is 2 times higher [1433]. Dietary therapy for obese children consists of energy intake restriction, adequate nutrient distribution, and correction of incorrect eating activities such as overeating. To correct such eating activities, therapeutic intervention involving the patient's family is effective [1434]. Furthermore, as indicated in adults, an excessive salt intake may be involved in an increase in blood pressure even in children. Salt restriction practiced from the neonatal period suppresses increases in blood pressure in childhood [1435]. A study involving children/adolescents (8–18 years) indicated that there was a positive correlation between salt intake and blood pressure/the risk of hypertension, and that this tendency was more marked in obese children [1436]. In addition, low-birth-weight neonates (birth weight: <2500 g) account for approximately 10% of neonates overall despite a recent further decrease in the number of children in Japan (demographic statistics in 2017: men, 8.4%; women, 10.5%) [1387]. In such children, weight gain is a higher risk factor, and early therapeutic intervention should be performed [1437].

Salt restriction and K intake should be promoted in accordance with guidelines for adults. In children, positive vegetable/fruit consumption and bean- or plant-derived diet

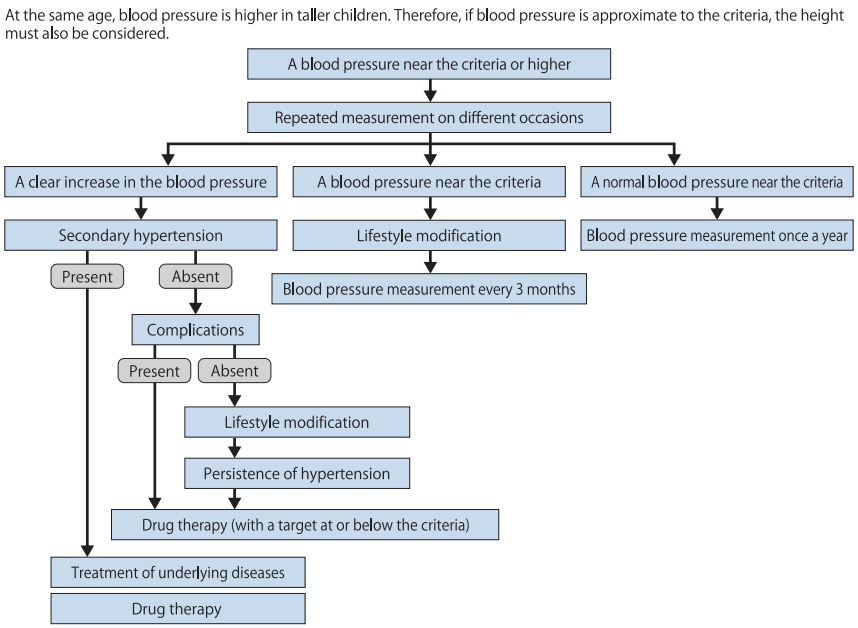


Fig. 11-1 Procedure for hypertension management in children

Table 11-2 Antihypertensive drugs approved for the treatment of hypertension in children (once-a-day oral administration)

Generic name	Proprietary name (standard unit)	Dosage (daily dose)	Remark
ACE inhibitor* Enalapril	Renivace (2.5, 5, and 10 mg tablets)	Infants aged 1 month or older: 0.08 mg/kg	
Lisinopril	Zestril, Longes (5, 10 and 20 mg tablets)	Children aged 6 years or older: 0.07 mg/kg (maximum dose: 20 mg)	
ARB Valsartan	Diovan (20, 40, 80 and 160 mg tablets)	Children aged 6 years or older (Body weight of <35 kg: 20–40 mg, Body weight of ≥35 kg: 40 mg)	
Candesartan	Blopress (2, 4, 8, and 12 mg tablets)	Children aged 1 to 6 years: 0.05–0.3 mg/kg, children aged 6 years or older: 2–8 mg (maximum dose: 12 mg). If nephropathy is present, administration should be started at a low dose, and the dose may be increased up to 8 mg if necessary.	Under public knowledge-based application
CCB Amlodipine	Norvasc and Amlodin (2.5 and 5 mg tablets/OD tablets)	Children aged 6 years or older: 2.5 mg	

The doses of these drugs should be increased/decreased in accordance with age and symptoms if necessary.

*ACE inhibitors are not recommended for children with renal hypofunction as a rule. If administration is required, it should be started at a low dose, and the dose should be carefully increased while checking the renal function.

or low-fat food ingestion are also associated with a decrease in blood pressure.

2) Exercise therapy

There is no evidence that exercise reduces blood pressure in children, but moderate to intense exercise for 30 to 60 min per session should be conducted 3 to 5 times per week based on previous studies.

3) Sleep

Even in children, sleep disorder is associated with hypertension. In particular, the risk of hypertension increases with the severity of obstructive sleep apnea syndrome (OSAS), and therapeutic intervention for hypertension is necessary.

8. MANAGEMENT OF HYPERTENSION

Figure 11-1 shows the procedure for managing hypertension in children. If blood pressure exceeds the reference value, it should be measured two more times after an appropriate interval for confirmation. At different opportunities, similar measurement should be repeatedly conducted. Thus, if blood pressure always exceeds the reference value, home blood pressure measurement or 24-h ambulatory blood pressure monitoring (ABPM) should be performed to rule out the possibility of white coat hypertension. As secondary hypertension is suggested in the absence of white coat hypertension or moderate to severe obesity, close examination, primarily of the kidneys, should be performed. By these measurements, children should be regarded as having hypertension or showing a borderline blood pressure. Management should be performed according to the procedures shown in the figure. The target of blood pressure control should be established as <90 percentile or <130/80 mmHg (a lower value should be adopted) [1416].

1) Nonpharmacological interventions

As hypertension in children and adolescents is often mild, lifestyle (diet/exercise) modifications, as described above, should be primarily performed. Concerning diet, salt intake should be initially reduced. Excessive salt ingestion causes hypertension, and excessively enhances appetite. In children with obesity-related hypertension, it is important to restrict energy intake and introduce exercise to their lifestyle [1438].

2) Drug therapy

Drug therapy is indicated for children with hypertension meeting the following criteria: persistent hypertension despite non-drug therapy involving lifestyle modifications, symptomatic hypertension, secondary hypertension requiring drug therapy, the concomitant development of target

organ damage, the presence of CKD, and the presence of diabetes mellitus.

Internationally, over the past ≥10 years, the effects of relatively new antihypertensive drugs, such as ACE inhibitors, ARBs and CCBs, in children have been evaluated, and their effects have been validated. In Japan, the assessment of antihypertensive drugs in children has also been promoted. In particular, the effects of ACE inhibitors and ARBs on proteinuria in children with CKD have been evaluated. In children with CKD, the renal prognosis can also be improved by maintaining blood pressure within the normal range using ACE inhibitors [1439]. In order to treat left ventricular hypertrophy, ACE inhibitors or ARBs are used, and strict blood pressure control with ACE inhibitors reduces left ventricular hypertrophy [1440, 1441]. However, ACE inhibitor is generally not recommended to the infants with reduced renal function, caution is needed. The administration of these drugs should be started at a low dose as monotherapy, and their effects must be evaluated at 2- to 4-week intervals. The dose should be increased until blood pressure is normalized (<90 percentile) (or until it reaches a maximum or an adverse reaction appears). Drugs that are currently available in children are listed in Table 11-2. Concerning antihypertensive drugs that have been used over many years, such as captopril, propranolol, sustained-release nifedipine and furosemide, no trial will be conducted in the future; [1439] these drugs are handled as "not applicable".

Chapter 12. Hypertension under special conditions

POINT 12A

[Hypertensive emergencies and urgencies]

1. **In patients suspected of having a hypertensive emergency, the diagnosis and evaluation of the pathological condition must be made by prompt examination, and treatment must be initiated without delay.**
2. **As target organ damage progresses rapidly, patients with complications of hypertensive encephalopathy, acute aortic dissection, acute heart failure with pulmonary edema related to severe hypertension, acute coronary syndrome with severe hypertension, pheochromocytoma crisis and pregnancy with eclampsia or with severe hypertension must be admitted, and intravenous (i.v.) antihypertensive treatment must be started immediately. In principle, treatment should be conducted in facilities with specialists for associated organs, such as cardiologists, nephrologists and neurologists, and by hypertension specialists. The same approach as for hypertensive emergency would be taken for accelerated-malignant hypertension.**
3. **Regarding sustained marked hypertension (usually ≥180/120 mmHg) not associated with the progression of acute organ damage or in which acute organ damage may not progress as an urgency, antihypertensive treatment with oral preparations should be performed.**

Table 12-1 Hypertensive emergencies

Accelerated-malignant hypertension (hypertension with retinal hemorrhages and/or papilledema)
Hypertensive encephalopathy
Severe hypertension associated with acute organ damage
Brain hemorrhage
Subarachnoid hemorrhage
Atherothrombotic brain infarction
Head trauma
Acute aortic dissection
Acute heart failure
Acute myocardial infarction and acute coronary syndrome
Acute or rapidly progressive renal failure (including that after kidney transplantation)
Severe hypertension after thrombolytic therapy for brain infarction*
Excess circulating catecholamines
Pheochromocytoma crisis
Interactions of monoamine oxidase inhibitors with foods or drugs
Use of sympathomimetic drugs
Rebound hypertension after sudden cessation of antihypertensive drugs
Automatic hyperreflexia after spinal cord injury
Pregnant women with a SBP of ≥180 mmHg or a DBP of ≥120 mmHg
Eclampsia
Hypertensive emergencies related to surgery
Severe hypertension in patients requiring emergency surgery*
Postoperative hypertension
Postoperative bleeding from vascular suture lines
After coronary bypass
Severe body burns
Severe epistaxis

Accelerated-malignant hypertension, perioperative hypertension, rebound hypertension, burns and epistaxis are classified as urgencies if they are not severe.

*Concerning 'Severe hypertension' in this line, a blood pressure level at which emergency blood pressure control is required in accordance with each condition is considered.

Table 12-2 Check items for evaluating conditions suspected to be hypertensive emergencies

History, symptoms
History of diagnosis and treatment of hypertension, state of use of sympathomimetic drugs and other drugs, headache, visual impairment, neurological symptoms, nausea/vomiting, chest/back pain, cardiac/respiratory symptoms, oliguria and body weight changes
Physical findings
Blood pressure: repeat measurements (DBP is often ≥120 mmHg), laterality
Pulse, respiration and body temperature
Evaluation of the body fluid volume: tachycardia, dehydration, edema and measurement of the blood pressure in the standing position
Central nervous system: disturbance of consciousness, convulsion and hemiparesis
Ocular fundus: linear or flame-shaped hemorrhage, soft exudate, retinal edema and papilledema
Neck: jugular vein distension and bruit
Chest: cardiac enlargement, heart murmur, III/IV sounds and moist rales of the lung field
Abdomen: hepatomegaly, bruit and (pulsatile) mass
Limbs: edema and arterial pulsation
Emergency examinations
Urinalysis and blood cell count (including smears)
Blood chemistry (urea nitrogen, creatinine, electrolytes, glucose, LDH and creatine kinase)
ECG, chest X-ray (two directions), arterial blood gas analysis as indicated
Cardiac and abdominal ultrasonography, brain CT scan or MRI and chest/abdominal CT scan, as indicated
Blood sampling for the measurement of the plasma renin activity, aldosterone, catecholamine and BNP concentrations, as indicated

1. DIAGNOSIS AND TREATMENT OF HYPERTENSIVE EMERGENCIES AND URGENCIES

1) Definition, classification and outline

A hypertensive emergency is not simply a condition in which the blood pressure level is abnormally high but that in which acute damage of target organs such as the brain, heart, kidney and large vessels, progresses due to marked hypertension (usually ≥180/120 mmHg). This condition must be diagnosed promptly, and antihypertensive treatment must be started immediately.

Hypertensive emergencies include hypertensive encephalopathy, hypertension complicated by acute aortic dissection, acute heart failure with pulmonary edema related to severe hypertension, acute coronary syndrome (acute myocardial infarction, unstable angina) associated with marked hypertension, pheochromocytoma crisis and pregnancy with eclampsia or with severe hypertension (Table 12-1) [1442, 1443]. In principle, treatment should be carried out in facilities with specialists for associated organs such as cardiologists, nephrologists and neurologists, and hypertension specialists.

Marked hypertension with no rapid progression of organ damage is regarded as a hypertensive urgency. In these cases, there is no evidence of improvement in outcome with emergency antihypertensive treatment. Whether the condition is an emergency cannot be judged solely on the basis of blood pressure levels. Emergency antihypertensive treatment is not indicated only with an abnormal high blood pressure if there is no acute or progressive organ damage. However, in patients with hypertensive encephalopathy related to a rapid increase in blood pressure, eclampsia or aortic dissection, emergency treatment is often necessary even when blood pressure is not abnormally high. This pathological condition must be clarified promptly (Table 12-2), the judgment of whether it is an emergency case must be made promptly, and antihypertensive drugs to be used, administration methods, a target level of blood pressure control, and the time until the target level is reached should be determined. The initiation of treatment for emergencies must not be delayed by spending time on a detailed evaluation.

2) Principles for treatment

Hypertensive emergencies must, in principle, be treated by hospitalization. In the intensive care unit or under an environment in accordance with it, antihypertensive drugs should be intravenously administered to decrease blood pressure. For blood pressure control, invasive monitoring of blood pressure is necessary. Due to the presence of organ damage or vascular abnormalities in patients with hypertensive emergencies, an unnecessarily rapid and excessive decrease in blood pressure is likely to cause ischemic organ damage, such as brain infarction, myocardial infarction and progression of renal dysfunction, because of a decrease in organ perfusion pressure. Therefore, drugs that facilitate the prediction of the level or time of decrease in blood pressure and prompt regulation of these factors should be selected, and intravenously administered.

General targets of blood pressure control are a decrease in mean blood pressure of no more than 25% during the first 1 h and to a level of 160/100 mmHg within the next 2–6 h. Subsequently, blood pressure should be carefully decreased to <140/90 mmHg over 24–48 h [3]. However, in patients with aortic dissection, acute coronary syndrome or hypertensive encephalopathy related to a rapid increase in blood pressure (acute glomerulonephritis and eclampsia), a blood pressure level at which treatment should be initiated, as well as the target control level, should be set lower. In the acute phase of cerebral hemorrhage, systolic blood pressure (SBP) should be promptly decreased to <140 mmHg (See Chapter 6: "1. Cerebrovascular disease"). Furthermore, there is no evidence to clarify whether antihypertensive treatment prevents

Table 12-3 Parenteral drugs (antihypertensive drugs) for the treatment of hypertensive emergencies

Drug		Dosage/regime	Onset of action	Duration of action	Adverse effects/points requiring caution	Special indications
Vasodilators	Nicardipine	i.v. infusion 0.5–6 μg/kg/min	5–10 min	60 min	Tachycardia, headache, flushing and local phlebitis	Most emergencies. Caution with high intracranial pressure or acute coronary syndrome
	Diltiazem	i.v. infusion 5–15 μg/kg/min	Within 5 min	30 min	Bradycardia, AV block and sinus arrest.	Most emergencies excluding heart failure with reduced ejection fraction (HFrEF)
	Nitroglycerin	i.v. infusion 5–100 μg/min	2–5 min	5–10 min	Headache, vomiting, tachycardia, methemoglobinemia and tolerance with prolonged use. This drug must be protected from light	Acute coronary syndrome
	Sodium nitroprusside	i.v. infusion 0.25–2 μg/kg/min	Immediate	1–2 min	Nausea, vomiting, tachycardia and cyanate poisoning at a high concentration or related to prolonged administration. This drug must be protected from light	Most emergencies. Caution with high intracranial pressure or renal dysfunction
	Hydralazine	i.v. injection 10–20 mg	10–20 min	3–6 h	Tachycardia, flushing, headache, exacerbation of angina pectoris and sustained hypotension	Eclampsia (not the first choice)
Sympatholytic drugs	Phentolamine	i.v. injection 1–10 mg infusion at 0.5–2 mg/min after an initial bolus injection is also possible	1–2 min	3–10 min	Tachycardia and headache	Pheochromocytoma and excess circulating catecholamines
	Propranolol	i.v. injection 2–10 mg (1 mg/min) → 2–4 mg every 4–6 h			Bradycardia, AV block and heart failure	Inhibition of tachycardia induced by other drugs

If pulmonary edema, heart failure or body fluid retention is noted, furosemide or carperitide should be used concomitantly.

In the package inserts, it is described that nicardipine and diltiazem may be indicated for “hypertensive emergencies” in Japan.

eclampsia in pregnant women with pregnancy-induced hypertension related to a marked increase in blood pressure. However, if a SBP of ≥180 mmHg or a diastolic blood pressure (DBP) of ≥120 mmHg is observed, patients should be diagnosed with hypertensive emergencies regardless of the presence or absence of convulsion [1353]. Antihypertensive treatment should be started immediately, and SBP should be decreased to <140 mmHg within 1 h [111].

Once the initial target of blood pressure control has been reached and oral medication has been started, i.v. treatment is gradually reduced until discontinuation. The doses and administration methods of parenteral drugs available in Japan, interval until the appearance of efficacy/duration of action, adverse reactions/precautions and main indications are shown in Table 12-3. With nitroprusside, the rate and degree of decrease in blood pressure are easy to adjust because of the rapid onset and short duration of its action. Cyanate poisoning is unlikely to occur at doses <2 μg/kg/min. In Japan, however, because of the lack of enough experience with the use of nitroprusside and anxiety regarding the restriction of diseases for which this drug is indicated or adverse reactions described in the package inserts, Ca channel blockers (CCBs) have been used more frequently. If no drug is indicated for the disease, nicardipine may be administered. However, CCBs require a slightly long interval until the appearance of action, and the duration of action is relatively long; therefore, the dose should be carefully regulated.

In patients with hypertensive urgencies, a long history of hypertension and chronic organ damage is often observed. This suggests that the lower limit of autoregulation of organ blood flow is high. Although antihypertensive treatment should be started within a few hours after diagnosis, blood pressure should be reduced relatively slowly to about 160/100 mmHg over 24–48 h thereafter. In many patients with hypertensive urgencies, blood pressure can be controlled using oral drugs. The oral administration of the capsule contents of nifedipine or bolus i.v. injection of the CCB, nicardipine, should be avoided, as it can cause an excessive decrease in blood pressure and reflex tachycardia. CCBs with a relatively rapid onset of action (intermediate-type CCBs), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), the αβ-blocker, labetalol or β-blockers should be administered orally, or loop diuretics may be used concomitantly depending on the condition. Dose adjustment is easy with captopril because of the relatively rapid onset and short duration of its action, but it should be started at a low dose (6.25–12.5 mg), as it may cause an excessive decrease in blood pressure in patients with malignant hypertension and in a dehydrated state, in which the RA system are activated. Caution should be paid in patients with renal dysfunction because hyperkalemia is most likely to occur 1–2 days after commencing treatment with ACE inhibitors or ARBs. ACE inhibitors or ARBs should not be used in patients suggested to have bilateral renovascular hypertension (RVHT) or RVHT with a functionally solitary kidney, as they may cause renal failure. If they are used, monitoring of the serum creatinine and potassium levels is necessary. In patients with hypertensive urgencies, initial treatment is possible at the outpatient clinic, but careful observation in the facility for 5–6 h after the beginning of administration and on an outpatient basis for 2–3 days thereafter with adjustment of the regimen is necessary. However, treatment by hospitalization is also necessary for a hypertensive urgency in high-risk patients such as those with a history of cardiovascular diseases. Furthermore, there are many patients with organ damage or resistant patients, and they should be referred to hypertension specialists or treated in consultation with such specialists.

3) Hypertensive encephalopathy

Hypertensive encephalopathy refers to a condition in which the blood pressure level exceeds the upper limit of cerebral blood flow autoregulation caused by a rapid or marked increase in blood pressure. The cerebral blood volume increases to an unusual level, impairing the blood-brain barrier and causing vasogenic brain edema. It is most likely to occur when blood pressure increases to ≥220/110 mmHg in chronically hypertensive patients and to ≥160/100 mmHg in normotensive individuals [1444]. Some patients show no proteinuria or hypertensive retinopathy. Hypertensive encephalopathy is the most severe hypertensive emergency leading to brain hemorrhage, disturbance of consciousness, coma and death without appropriate treatment. It is associated with exacerbating headache, nausea/vomiting, visual disorder, disturbance of consciousness and convulsions, but focal neurological symptoms are relatively rare. As rapid reduction of blood pressure must, in principle, be avoided in patients with brain infarction, its diagnostic exclusion is important. On MRI, findings of posterior reversible encephalopathy syndrome (PRES) reflecting vasogenic edema involving the white matter of the parietal to occipital lobes are frequently observed.

As the autoregulation of cerebral blood flow is disturbed, a rapid and marked decrease in blood pressure is most likely to cause brain ischemia. Treatment should be started with i.v. preparations (continuous i.v. infusion). The rate of decrease in blood pressure should be adjusted by monitoring blood pressure and neurological symptoms. Treatment should be conducted to achieve an ~25% decrease in blood pressure over the first 2–3 h. The i.v. injection of nicardipine does not decrease brain tissue oxygen supply, and is useful for treating hypertensive emergencies with neurological signs [1445]. Diltiazem

and nitroprusside can also be used. If extracellular fluid volume is increased, furosemide should be used concomitantly. As hydralazine increases intracranial pressure, it should not be used in such condition.

4) Cerebrovascular disease

See Section 1 Chapter 6, "CEREBROVASCULAR DISEASE".

5) Acute heart failure

In acute heart failure patients with pulmonary edema related to severe hypertension, treatment should be started immediately. Treatment with vasodilators is primarily applied. The sublingual, trans-spray, or intravenous administration of nitrate drugs (nitroglycerin, isosorbide dinitrate) is effective in reducing pulmonary congestion [716]. Carperitide (α-type human atrial natriuretic polypeptide preparation) exhibits both vasodilative and diuretic actions, and the continuous intravenous infusion of nicorandil or carperitide is also useful [716, 1446]. If the body fluid volume is increased, furosemide should be combined with these drugs.

Although no clear target level of blood pressure has been set, blood pressure should be reduced (usually ~10–15% decrease in SBP) by examining the symptomatic improvements. After blood pressure has been reduced to an appropriate level, treatment should be shifted to oral medication using RA system inhibitors, such as ACE inhibitors and ARBs, combined with CCBs.

6) Severe hypertension complicating acute coronary syndrome (acute myocardial infarction and unstable angina)

To treat anginal attacks associated with an increase in blood pressure, nitrites should be administered sublingually or sprayed intra-orally first. If hypertension complicates acute coronary syndrome, nitroglycerin should be administered by continuous i.v. infusion to reduce the myocardial oxygen demand and increase the coronary blood flow as well as lower blood pressure. However, if the concomitant development of right ventricular infarction is suspected due to inferior wall infarction, administration should be avoided, considering a nitroglycerin-related reduction in preloading. A β-blocker can be used concomitantly if there is no contraindication such as marked bradycardia. If a β-blocker cannot be used, or blood pressure cannot be reduced sufficiently, diltiazem should be used. For blood pressure control, a target SBP should be <140 mmHg. In patients with myocardial infarction, the administration of β-blockers in the acute stage and ACE inhibitors from the early stage is reported to be useful [1447].

7) Aortic dissection

See Section 4 of Chapter 6, "VASCULAR DISEASES".

8) Pheochromocytoma crisis

Pheochromocytoma crisis refers to a rapid increase in blood pressure related to an excessive secretion of catecholamines. The initial target of blood pressure control is to control a paroxysmal increase in blood pressure [1448], and SBP should be decreased to <140 mmHg within 1 h after the start of treatment [111]. The mortality rate on the onset of crisis is reportedly 15%; therefore, it is necessary not only to control blood pressure but also to manage systemic hemodynamic conditions [1449].

Phentolamine at 2–5 mg should be intravenously injected at a rate of 1 mg/min every 3–5 min while monitoring the response of blood pressure. After intravenous injection at an initial dose, continuous intravenous infusion may be performed. Oral medication using drugs, such as the selective α-blocker doxazosin, should be started simultaneously. Although β-blockers are effective for tachycardia, they should be used after the administration of α-blockers at a sufficient dose. Monotherapy with β-blockers exaggerates α-receptor-mediated vasoconstriction, causing a further increase in blood pressure; therefore, it must be contraindicated [1448]. As the body fluid volume is reduced, a sufficient volume of physiological saline should be infused after α-blocker administration to prevent hypotension.

For intraoperative blood pressure control, the continuous i.v. infusion of phentolamine is sometimes performed in accordance with the patient's blood pressure level. However, the continuous i.v. infusion of nicardipine or nitroglycerin, which less frequently cause side effects, and whose doses can be readily regulated, can also be selected.

9) Accelerated-malignant hypertension

In patients with accelerated-malignant hypertension, DBP is ≥120–130 mmHg, and renal dysfunction progresses rapidly if left untreated; the general condition rapidly deteriorates and cardiovascular complications, including heart failure, hypertensive encephalopathy and brain hemorrhage, occur, leading to a poor prognosis. Its pathological characteristics are fibrinoid necrosis and proliferative intimitis following arteriolar endothelial damage and the infiltration of plasma components into the vascular wall due to prolonged, marked hypertension; pathological findings in the kidney are called malignant nephrosclerosis. In this condition, a vicious cycle of progressive renal dysfunction and an increase in blood pressure is established. Ophthalmoscopic findings include retinal hemorrhage, soft exudates, retinal edema and/or papilledema. In the brain, the autoregulation of blood flow is disrupted by vascular damage, and if brain edema occurs hypertensive encephalopathy may result. Malignant hypertension associated with papilledema (grade IV according to the Keith–Wagener classification) and accelerated hypertension associated with retinal hemorrhage and exudative lesions (grade III) are used to be

distinguished. However, as there is no difference between them in the progression of organ damage or survival rate, they have been combined as accelerated-malignant hypertension. Internationally, these conditions are sometimes expressed as "hypertension with retinal hemorrhage and/or papilledema" [1442, 1450].

Increased blood pressure at the time of hypertension diagnosis, interruption of antihypertensive treatment and long-standing psychological/physical stress are involved in the development of malignant hypertension [1451]. Not only essential but also secondary hypertension, such as renal parenchymal or RVHT, may lead to accelerated-malignant hypertension.

Its incidence has recently decreased because of the spread of antihypertensive treatment and improvements in social and living environments, However, according to admission statistics in the United States after 2000, there is no decrease in the incidence of this disease [1452]. According to results from a single facility in Japan, fundic findings at the time of onset, left ventricular hypertrophy and organ damage, such as renal dysfunction in patients treated between 1984 and 1999, were less marked than in those treated between 1971 and 1983 [1453, 1454]. In addition, a study in England indicated that the 5-year survival rate had markedly improved from 32.0 to 91.0% in patients treated between 1997 and 2006 in comparison with those treated before 1977 [1455]. Another study reported that the severity of renal dysfunction at the time of onset was a prognostic factor for 5-year mortality/dialysis [1456]. On the other hand, according to a study, renal dysfunction progressed to end-stage kidney disease (ESKD) in 31% of patients, with a mean interval of 5.6 years from onset; the renal prognosis remains poor [1457]. Long-term blood pressure control is important in addition to that immediately after onset.

Although accelerated-malignant hypertension is regarded as an urgency, it promotes the progression of arteriole lesions, and should be treated in accordance with emergencies [236, 1450]. In many cases, treatment with oral drugs is possible. As many patients have a long history of hypertension, a rapid decrease in blood pressure is associated with the risk of ischemia of important organs. Blood pressure should be reduced to no less than a diastolic pressure of 100–110 mmHg during the first 24 h [1458]. ACE inhibitors and ARBs may be effective because body fluid is reduced due to pressure diuresis, and because hyperactivity of the RA system is closely involved in the pathogenesis in patients with this condition resulting from essential hypertension [1453] or the renal crisis of collagen diseases. However, as these drugs may cause an excessive decrease in blood pressure, their administration should be started at a low dose, and attention must be paid so that there may be no deterioration of renal function. If a decrease in the body fluid volume is marked, fluid replacement with physiological saline may be necessary. On the other hand, loop diuretics should be used if sodium/water retention is present.

Table 12-4 Conditions that may exhibit marked transient increases in blood pressure

- Impairment of the baroreflex mechanism
- Hyperventilation associated with anxiety
- Panic attacks (panic disorder)
- Pseudopheochromocytoma
- Pheochromocytoma

POINT 12B

[TRANSIENT INCREASES IN BLOOD PRESSURE]

1. **If a marked temporary increase in blood pressure is not associated with progressive organ damage, emergency antihypertensive treatment is unnecessary except in cases of pheochromocytoma.**
2. **If a marked increase in blood pressure persists, antihypertensive drugs may be used, considering the age and systemic condition, but the administration of short-acting antihypertensive drugs, such as the contents of nifedipine capsules, may cause cerebral or cardiac ischemia by a rapid, excessive decrease in blood pressure; therefore, it is contraindicated.**
3. **If the involvement of psychological factors is suggested, patients should be treated in cooperation with mental health care specialists in accordance with the necessity.**

2. TRANSIENT INCREASES IN BLOOD PRESSURE

Marked transient increases in blood pressure, except those caused by pheochromocytoma, do not require emergency antihypertensive treatment unless there is progressive or chronic organ damage (Table 12-4). In patients with impairment of the baroreflex mechanism such as older patients and those with autonomic neuropathy, blood pressure markedly changes, and hypertension (≥180/110 mmHg) is observed in some patients. Causes of an increase in blood pressure, such as pain and urinary retention, should be resolved. There is no criteria for the use of antihypertensive drugs, but, if a blood pressure of ≥180/110 mmHg is noted on repeated measurements, antihypertensive drugs may be used, considering the age and systemic condition. Whether antihypertensive drugs should be used must be determined, considering that resting alone gradually decreases blood pressure. Even when adopting

antihypertensive drugs, it is not necessary to promptly normalize blood pressure, and a blood pressure level of approximately 160/100 mmHg may be targeted, avoiding excessive decrease in blood pressure. The administration of short-acting antihypertensive drugs, such as nifedipine capsule contents, may cause ischemia of the main organs, such as the brain and heart, by a rapid and excessive decrease in blood pressure; therefore, these drugs are contraindicated.

Pheochromocytoma is a type of secondary hypertension characterized by physical symptoms, such as paroxysmal headache, chest pain, dizziness, nausea, palpitation, flushing and diaphoresis, as well as a marked increase in blood pressure. For the diagnosis and treatment of pheochromocytoma, see Section 3 of Chapter 13, "4) Pheochromocytoma / paraganglioma". On the other hand, 'pseudopheochromocytoma' is a condition in which diagnostic imaging does not show any tumors despite clinical symptoms resembling those of pheochromocytoma, with only a slight increase in the catecholamine level. The involvement of psychological factors in this condition is suggested [1459]. Similarly, a paroxysmal increase in blood pressure with symptoms, such as tachycardia, palpitation, and dyspnea, is observed in patients with panic disorder (panic attacks) or hyperventilation. Panic disorder is associated with hypertension and is reported to be a risk factor for cardiovascular diseases such as myocardial infarction and stroke [1460, 1461].

As antihypertensive drugs, αβ-blockers and centrally acting antihypertensive drugs are appropriate for patients with hypertension in whom the involvement of stress or psychological factors is marked, but it is difficult to control blood pressure using antihypertensive drugs alone in many cases. In addition to the use of anxiolytic drugs/antidepressants, psychological approaches by mental health care specialists for psychiatry or psychosomatic medicine, such as psychotherapy and behavioral therapy, should be considered (see Q8) [1462].

POINT 12C

[PREOPERATIVE AND POSTOPERATIVE BLOOD PRESSURE MANAGEMENT]

1. **For the prevention of perioperative complications in hypertensive patients, a differential diagnosis of secondary hypertension, such as pheochromocytoma, and evaluation of hypertensive organ damage/complications are important.**
2. **If blood pressure is ≥180/110 mmHg at the time of elective surgery, blood pressure control should be predominantly performed.**
3. **Blood pressure should be controlled by continuous oral or i.v. antihypertensive treatment throughout the perioperative period, including the administration on the morning of surgery.**
4. **On the day of surgery, β-blocker administration should not be newly started, but administration should be continued in patients chronically treated with the drug. In high-risk patients regarding coronary artery disease (excluding patients with vasospastic angina pectoris or bronchial asthma), the start of β-blocker administration in the early phase before surgery (≥7 days before surgery) should also be considered.**
5. **In patients taking diuretics, ARBs or ACE inhibitors, much attention should be paid to intra-/postoperative hypotension, a decrease in the body fluid volume and renal dysfunction.**
6. **Elimination of pain/anxiety and excitation is also important for controlling the increase in blood pressure.**

3. PREOPERATIVE AND POSTOPERATIVE BLOOD PRESSURE MANAGEMENT

1) Preoperative evaluation of hypertension

Elective surgery is a good opportunity to assess hypertension and evaluate the therapeutic approach. In patients with untreated hypertension, perioperative risk assessment by the evaluation of hypertensive organ damage and complications, as well as a differential diagnosis of secondary hypertension, is important. In particular, it is necessary to examine the presence or absence of conditions in which ischemic complications due to perioperative blood pressure decreases are most likely to occur such as cerebrovascular disease, carotid artery stenosis, left ventricular hypertrophy, coronary artery disease and renal dysfunction.

If there is a risk of ischemic complications, consistent blood pressure management from the preoperative period is necessary to avoid excessive perioperative changes in blood pressure. In patients suspected of having pheochromocytoma, examinations should be performed by postponing surgery, and, if a definitive diagnosis is made, the tumor must be removed before the intended surgery. Conditions, such as RVHT, primary aldosteronism (PA) and Cushing's syndrome, pose few problems if blood pressure is controlled to a level below 160/100 mmHg before surgery, but manageable secondary hypertension should be treated before elective surgery.

Hypertension (<180/110 mmHg) is not an independent risk factor for perioperative cardiovascular complications, but preoperative blood pressure should be controlled below a target blood pressure. If blood pressure prior to elective surgery is ≥180/110 mmHg, the postponement of surgery

should be considered [111]. When conducting endoscopic surgery or invasive examinations in patients with a blood pressure of ≥180/110 mmHg or high-risk patients, the usefulness of those procedures must be considered individually by evaluating their risks and merits.

2) Use of antihypertensive drugs in the perioperative period

In patients receiving long-term antihypertensive treatment, antihypertensive drugs should be administered until the day of surgery, in principle, and be resumed as soon as possible after surgery. The perioperative use of β-blockers in patients undergoing cardiac surgery reduces the risk of ventricular or supraventricular arrhythmia [1463]. However, the start of β-blocker administration before non-cardiac surgery decreased the incidence of nonfatal myocardial infarction, but increased the risks of stroke, death, hypotension and bradycardia [1464]. Therefore, treatment should be continued in patients chronically treated with β-blockers before surgery, but administration should not be newly started on the day of surgery [1465]. However, the onset of nonfatal myocardial infarction may be prevented in high-risk patients regarding coronary artery disease; therefore, indications involving the timing of starting administration must be carefully considered. Administration should be started ≥7 days before surgery, and attending physicians should consult cardiologists if necessary (see CQ16).

If there is a risk of intraoperative hypotension, postoperative dehydration or hypokalemia, the preoperative discontinuation of diuretics must also be considered. If the patient is being treated with an ACE inhibitor or an ARB, it may induce a decrease in blood pressure or renal dysfunction associated with a perioperative decrease in the body fluid volume. A study indicated that the continuous administration of ACE inhibitors or ARBs increased the risks of hypotension and serious cardiovascular events (death, stroke, myocardial damage) [1466]. Whether preoperative administration should be discontinued in high-risk patients including older patients must be evaluated, considering the condition or surgical invasiveness. If administration is discontinued before surgery, it should be promptly resumed after surgery [1465].

Increases in blood pressure during an emergency or elective surgery should be controlled by the continuous i.v. infusion of CCBs, nitroglycerin or nitroprusside. As hemodynamics remain unstable after surgery, antihypertensive treatment should be started as early as possible, intravenously if oral administration is impossible. Appropriate treatment is also necessary for factors that increase blood pressure such as postoperative pain, anxiety and excitation. Administration of the contents of nifedipine capsules must be avoided.

3) Dental surgery and blood pressure management

As cardiovascular diseases, such as stroke, may also occur during dental treatment, evaluation of the presence or absence of hypertension and the state of blood pressure is also necessary before dental treatment. If blood pressure is ≥180/110 mmHg, medical consultation and referral to an internist should precede dental treatment except for emergency procedures [1467]. Patients receiving antihypertensive medication should be advised to take their medication on the day of dental treatment so that blood pressure before treatment may be controlled. Dental procedures that involve pain or anxiety or require a prolonged time induce an increase in blood pressure [1468]. Local anesthetics including adrenaline (epinephrine) increase the plasma adrenaline concentration, but, if the dose is low, there may be no influence on blood pressure [1469]. Their doses should be carefully determined while ensuring that there is sufficient anesthesia for pain control [1468, 1469]. Prescription of anxiolytic drugs can be considered in patients complaining of intense anxiety.

CQ16 IS THE PERIOPERATIVE USE OF B-BLOCKERS RECOMMENDED WHEN PERFORMING NON-CARDIAC SURGERY IN HIGH-RISK PATIENTS REGARDING CARDIOVASCULAR DISEASES?

►When performing non-cardiac surgery in high-risk patients regarding cardiovascular diseases, β-blocker administration should not be newly started on the day of surgery.

Recommendation grade: 2 Evidence level: B

SUMMARY OF EVIDENCE

A meta-analysis of 16 randomized controlled trials (RCTs) including the DECREASE-I and DECREASE-IV showed that the perioperative administration of β-blockers decreased the incidence of nonfatal myocardial infarction, whereas it increased the incidence of nonfatal stroke. There was no difference in the total mortality rate. However, it was indicated that the two DECREASE studies had limitations regarding a part of the study methods; their reliability is controversial. When preparing a recommendation for this CQ, we adopted the results of a meta-analysis of 14 RCTs, excluding the two studies, in which the start of β-blocker administration before surgery was earlier. The results showed that the perioperative administration of β-blockers decreased the incidence of nonfatal myocardial infarction, whereas it increased the risks of nonfatal stroke and all-cause mortality.

INTERPRETATION

Serious perioperative cardiac events related to non-cardiac surgery, such as myocardial infarction, develop in 3.9% of high-risk patients regarding cardiovascular diseases [1470]. The prevention of such events with safety improvements is an important clinical issue. As β-blockers exhibit protective effects on the cardiac muscle by decreasing myocardial oxygen consumption, their perioperative use has been considered to prevent cardiac events. According to several initial-phase studies, which were conducted to examine the effects of perioperative β-blocker administration (Mangano et al. [1471], DECREASE-I [1472]), the use of β-blockers prevented cardiac death and nonfatal myocardial infarction. No serious adverse event has been reported. Based on these results, it had been considered that the start of β-blocker administration in the perioperative phase is effective in preventing cardiac events in high-risk patients regarding cardiovascular diseases [1473]. On the other hand, the POISE study showed that there was a 30% decrease in the incidence of nonfatal myocardial infarction, whereas there were 33% and 2-fold increases in the total mortality rate and incidence of stroke, respectively, which was inconsistent with the results of the initial-phase studies [1474]. Concerning the DECREASE-I study, limitations regarding the study protocol and a part of the study contents were indicated, and the reliability of the data is controversial [1475, 1476]. Furthermore, there was a dissociation in the results between the DECREASE [1472, 1477] and other subsequent studies, and perioperative β-blocker handling involving systematic review (SR) methods has been extensively discussed.

In the DECREASE-I study, in addition to its limitation regarding the reliability of the data, the timing of starting β-blocker administration (≥1 week before surgery) was different from that in other studies. For this reason, many investigators indicated that statistical analysis should be performed, excluding the DECREASE studies [1476]. In 2014, the American College of Cardiology (ACC)/American Heart Association (AHA) published the results of a SR on perioperative β-blocker administration [1464], but, thereafter, no report from RCTs establishing cardiovascular events and death as outcomes could be extracted on the PubMed. In this CQ, the perioperative use of β-blockers was examined based on the results of the ACC/AHA meta-analysis [1464].

According to an analysis involving the DECREASE-I and DECREASE-IV studies, the onset of nonfatal myocardial infarction was prevented (odds ratio [OR]: 0.68, 95% confidence interval [CI]: 0.57–0.81), but the incidence of nonfatal stroke increased (OR: 1.79, 95%CI: 1.09–2.95). However, there was no significant difference in the total mortality rate, which was markedly influenced by the results of the DECREASE-I and DECREASE-IV studies (OR: 0.96, 95%CI: 0.62–1.47). Next, we evaluated a meta-analysis, excluding these DECREASE studies of which the data/study protocol reliability is controversial. The incidence of nonfatal myocardial infarction decreased (OR: 0.72, 95%CI: 0.59–0.86), but the risks of nonfatal stroke (OR: 1.86, 95%CI: 1.09–3.16) and all-cause death (OR: 1.30, 95%CI: 1.03–1.63) increased. These are consistent with the results of a meta-analysis conducted by Blessberger et al., excluding the DECREASE studies [1463].

Based on these circumstances, in this CQ, we considered it appropriate to adopt analyses excluding the DECREASE studies, of which the limitations regarding a part of the study contents have been indicated, and present recommendations based on their results. For analysis, 14 RCTs were used. However, in these studies, β-blocker administration was newly started within 1 day before surgery (on the day of surgery), resulting in a decrease in the incidence of nonfatal myocardial infarction and increases in the total mortality rate and incidence of nonfatal stroke. Concerning the onset of congestive heart failure, we newly conducted a meta-analysis using the data presented in the articles published by the ACC/AHA. However, there was no β-blocker-related difference (OR: 1.15, 95%CI: 0.91–1.44). The results regarding heart failure were similar even when the DECREASE studies were included. Thus, the start of β-blocker administration on the day of surgery may increase the risks of all-cause death and nonfatal stroke, and it should be avoided. This recommendation is consistent with the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [111].

On the other hand, previous observational studies indicated that β-blockers newly administered within 7 days before surgery or acutely influenced the onset of cardiovascular events involving all-cause death [1478–1480], strongly suggesting the marked influence of perioperative β-blocker initiation on all-cause death and cardiovascular events. The results of these observational studies support the recommendation obtained from a SR on this CQ.

The perioperative administration of β-blockers prevents the onset of nonfatal myocardial infarction, but increases the total mortality rate and incidence of nonfatal stroke. Therefore, how to balance risks and benefits is controversial. The results of observational studies showed that β-blocker administration from the early phase before surgery was useful for preventing all-cause death and cardiovascular events in high-risk patients regarding cardiovascular diseases [1481–1483]. In particular, β-blocker administration may be considered in high-risk patients meeting ≥3 of the Revised Cardiac Risk Index (RCRI) items: high-risk surgery, ischemic coronary heart disease, heart failure, stroke, insulin use, and renal failure

[1484], or those with myocardial ischemia previously diagnosed, taking adverse events, such as death and stroke, into consideration [1465].

Considering the risks and benefits of perioperative β-blocker administration, a surgeon, anesthesiologist, and cardiologist should discuss whether a β-blocker should be administered when starting administration before surgery. In addition, when administering β-blockers, administration should be started ≥7 days before surgery, and the dose must be carefully regulated so that hypotension, bradycardia and excessive administration may be avoided while strictly monitoring blood pressure and heart rate. On the other hand, in patients chronically treated with β-blockers, discontinuation-related rebound phenomena of blood pressure and heart rate may occur, and a perioperative discontinuation-related increase in the total mortality rate was also indicated; [1485] therefore, administration should be continued in the perioperative phase.

It was suggested that the onset of cardiovascular events depends on the type of β-blocker used in the perioperative phase. Several observational studies indicated the possibility that the use of metoprolol may affect cardiovascular outcomes, such as an increase in the incidence of stroke, in comparison with atenolol and bisoprolol [1486–1488]. This may be because the selectivity of metoprolol to β_1 receptors is lower than that of atenolol and bisoprolol, and because the duration of action is shorter. Considering this, atenolol or bisoprolo is recommended as β-blockers to be administered in the perioperative phase in the guidelines for noncardiac surgery prepared by the European Society of Cardiology (ESC)/European Society of Anaesthesiology (ESA) [1489]. The results of this meta-analysis may have been influenced by the POISE study [1474] involving a large number of subjects. In the POISE study, high-dose metoprolol was used, and this may have influenced this CQ. However, the results of the other RCTs, excluding the POISE study, also showed an increase in the total mortality rate; the influence on this recommendation may be limited.

In many RCTs previously reported, a sufficient number of subjects were not analyzed, and, if the DECREASE and POISE studies are excluded, the number of subjects sufficient for statistical analysis cannot be assured. In some studies, high-dose β-blockers were intravenously administered, and excessive administration may have been performed. In the future, conditions for which perioperative β-blocker administration is appropriate and adequate administration methods should be clarified.

LITERATURE SEARCHING

We searched the literature from January 2013 to June 2017 on the PubMed, Cochrane Library and Ichushi-Web. However, the results of searching did not involve any RCT associated with this CQ, and we used a SR published by the ACC/AHA in 2014.

Q8 ARE ANXIOLYTIC DRUGS OR ANTIDEPRESSANTS USEFUL FOR THE PREVENTION OF A TRANSIENT INCREASE IN BLOOD PRESSURE TRIGGERED BY EMOTIONAL/PSYCHIATRIC DISTRESS, INCLUDING PANIC DISORDER AND SO ON?

- In patients with a transient increase in blood pressure triggered by emotional/psychiatric distress including panic disorder and so on, psychological factors are often observed as a background factor, and the administration of anxiolytic drugs/antidepressants or combination therapy with psychological approaches should be considered.

INTERPRETATION

It is well known that blood pressure is markedly influenced by psychological factors such as anger and anxiety. These emotional changes also cause a transient increase in blood pressure. A paroxysmal increase in blood pressure is sometimes observed in normotensive persons, whereas it is often noted in hypertensive patients. No clinical study has shown any evidence regarding the prevention of a paroxysmal increase in blood pressure, and neither international nor domestic guidelines provided recommendation for treatment. However, in clinical practice, there are many opportunities to encounter patients with a paroxysmal increase in blood pressure, and this is an important clinical issue.

Conditions with a transient increase in blood pressure in which psychological factors may be etiologically involved include pseudopheochromocytoma, panic disorder and hyperventilation. In many patients with these conditions, symptoms, such as tachycardia and palpitation, concomitantly occur with an increase in blood pressure. These must be differentiated from pheochromocytoma. Respective disease entities differ, but conditions often overlap by their mutual relationship. A study indicated the presence of psychological factors in many patients with resistant hypertension [1490], but this may reflect that many hypertensive patients have some psychological problems [1491].

The clinical reports on actual treatment is limited, and how to control blood pressure in these patients has not been established. However, a paroxysmal increase in blood pressure may be prevented or relieved by combining antihypertensive drugs (in the case of hypertension), antidepressants/anxiolytic drugs, and psychotherapy adequately, and such combination therapy may be effective in ≥50% of patients [1462, 1492–1494].

The morbidity rate of panic disorder is high, and psychological factors are closely involved. On panic attacks, marked anxiety/fear are present, and this disorder is characterized by repeated onsets [1495]. In patients with panic disorder, selective serotonin reuptake inhibitors (SSRIs) and anxiolytic drugs are useful for prevention [1495]. Therefore, a transient attack-related increase in blood pressure may be inhibited by preventing panic attacks using these drugs. Actually, it has been reported that these drugs are effective to prevent paroxysmal hypertension on clinical experience [1462].

On the other hand, the involvement of psychological factors in the pathogenesis of pseudopheochromocytoma is often unclear [1493], differing from panic disorder. Pseudopheochromocytoma must be differentiated from pheochromocytoma, and an inquiry and follow-up should be carefully performed. Increased adrenal adrenaline secretion and hyperresponsiveness of the cardiovascular system to catecholamines are involved in the mechanism of blood-pressure increase [1496]. Therefore, when adopting antihypertensive drugs, αβ-blockers and central antihypertensive drugs are likely to be appropriate. On the other hand, it is often difficult to control blood pressure using antihypertensive drugs alone in patients in whom stress or psychological factors are closely involved [1459, 1462]. There was a case report in which an antidepressant or anxiolytic drug was effective in preventing a paroxysmal increase in blood pressure [1497]. If the presence of psychological background is suggested, treatment should be performed in cooperation with mental health care specialists for psychiatry or psychosomatic medicine.

Hyperventilation syndrome increases the frequency of respiration, primarily causing symptoms such as paresthesia of the fingers, vertigo, palpitation and headache. A decrease in the blood concentration of carbon dioxide leads to respiratory alkalosis, increasing the intracellular calcium ion concentration and elevating blood pressure by vasoconstriction. Hyperventilation is often complicated by anxiety disorder or panic disorder, making antihypertensive treatment difficult. For the prevention of hyperventilation attacks, psychiatric approaches, such as cognitive behavioral therapy, may be useful [1462], but there is no direct evidence that this prevents a transient increase in blood pressure.

There is no criteria of blood pressure to consider antihypertensive treatment for a transient increase in blood pressure related to these conditions in the absence of organ damage. Usually, antihypertensive treatment is not indicated for patients with such a transient increase in blood pressure. However, if SBP exceeds 180 mmHg as a criteria for urgencies despite resting for ≥30 min, the use of antihypertensive drugs may also be considered [1498]. Even in such cases, it is not necessary to normalize blood pressure immediately, and a blood pressure level of approximately 160/100 mmHg may be targeted. Furthermore, whether antihypertensive drugs should be used must be evaluated, considering that resting alone gradually decreases blood pressure, as described below.

As antihypertensive drugs to be used on a paroxysmal increase in blood pressure, central antihypertensive drugs, such as clonidine, may be effective. However, in Japan, there are few opportunities in which these drugs are used. Considering the mechanism of blood pressure reduction, αβ-blockers may also be appropriate, and a study indicated their efficacy [1499]. In clinical practice, CCBs (excluding short-acting drugs) are also recommended. When administering antihypertensive drugs, attention must be paid so that there may be no excessive decrease in blood pressure. If anxiety is marked, the use of low-dose anxiolytic drugs could also be considered.

Several studies examined the course of blood pressure in patients who consulted the Emergency Outpatient Unit with a marked increase in blood pressure in the absence of organ damage. Grossman et al. reported that the reduction of blood pressure by diazepam at 5 mg were similar to those by sublingually administered captopril at 25 mg [1500]. Yilmaz et al. also indicated that the reduction of blood pressure by alprazolam were similar to those by captopril [1501]. However, a study investigated serial blood pressure changes until 2 h after treatment by randomly dividing patients into two groups: an antihypertensive drug (telmisartan at 40 mg)-treated group and a resting group (patients were rested in a sitting position without administering any antihypertensive drugs), and indicated that there were 32.2- and 32.8-mmHg decreases in SBP after 2 h in the resting and telmisartan-treated groups, respectively, suggesting that the effect of decrease in blood pressure is similar between the two groups. Regarding a 10 to 35% decrease in mean blood pressure as a primary endpoint, a decrease in blood pressure was achieved in 68.5% and 69.1% of the patients, respectively [1502]. These results suggest that the effects of RA system inhibitors or anxiolytic drugs on a paroxysmal blood pressure increase are limited. Otherwise, they suggest the importance of resting and follow-up by anxiety removal in that condition.

Chapter 13. Secondary hypertension

Hypertension related to a specific etiology is termed secondary hypertension, markedly differing from essential hypertension in the condition and therapeutic strategies. Secondary hypertension is often resistant hypertension, for which a target blood pressure is difficult to achieve by standard treatment. However, blood pressure can be

effectively reduced by identifying its etiology and treating the condition. Therefore, it is important to suspect secondary hypertension and make an appropriate diagnosis. Secondary hypertension accounts for ≥10% of all hypertensive patients, and this percentage is higher than previously reported. In particular, according to several studies, primary aldosteronism (PA) accounts for approximately 5–10% of hypertensive patients. Furthermore, a study indicated that sleep apnea syndrome was the most frequent etiological factor for secondary hypertension. The number of patients with secondary hypertension may further increase with the widespread diagnosis of sleep apnea syndrome.

Diseases that cause secondary hypertension, findings suggestive of the condition, and examinations necessary for differentiation are shown in Table 13-1. Initially, it is important to suspect secondary hypertension so that it may not be overlooked. An inquiry should be made while considering differences in the onset and course between essential hypertension and secondary hypertension. Most patients with essential hypertension have a family history of this disorder, and blood pressure is slightly high from 20 to 39 years of age, and it increases with age. Therefore, secondary hypertension should be suspected in young patients with severe hypertension or patients who developed hypertension at the age of >50 years.

Secondary hypertension should be suspected in patients with severe or resistant hypertension and those in whom blood pressure control became difficult despite previous good control. Even if a diagnosis of essential hypertension is made on screening, it may often be complicated by secondary hypertension a few years later. Attention must be particularly paid to the rapid onset of hypertension. If blood pressure rapidly increases in a few weeks, detailed investigation must be conducted, considering the presence of a serious etiology. Furthermore, secondary hypertension should also be suspected in patients with severe organ damage relative to the blood pressure level. In many patients with secondary hypertension, the diurnal rhythm of blood pressure is affected, as represented by nocturnal hypertension. Furthermore, aldosterone exhibits non-blood-pressure-dependent organ-damaging actions. If inter-day or diurnal changes are marked, secondary hypertension should be suspected.

The details of diseases that cause secondary hypertension are described below, but there are some precautions. PA is characterized by hypokalemia or nocturnal polyuria, but such findings are observed in <50% of patients. Attention must also be paid to drugs that are prescribed due to other diseases. Glycyrrhizic acid (hepatoprotective drugs or licorice) and non-steroidal anti-inflammatory drugs (NSAIDs) show vasopressor actions. Licorice is contained in Chinese herbal medicines and stomach medicines including S/M combination granules. Usually, there is no problem, but as they may cause hypokalemia or hypertension in high-sensitivity or older persons, caution is needed. Antidepressants and antiparkinson drugs may cause orthostatic hypotension in addition to vasopressor actions, contributing to marked blood pressure fluctuations. Furthermore, attention must be paid to health foods. Renal dysfunction related to Chinese tea used for folk medicine for obesity is well-known as aristolochic acid-induced nephropathy. As patients do not spontaneously talk about the use of health foods, physicians must make an inquiry.

The possibility of secondary hypertension should be considered in the diagnosis and treatment of all hypertensive patients. It is important to conduct appropriate examinations without overlooking findings of secondary hypertension. If the possibility of secondary hypertension is high, patients should be referred to specialists.

1. RENAL PARENCHYMAL HYPERTENSION

As the kidney plays an important role in the regulation of blood pressure, many patients with chronic kidney disease (CKD) develop hypertension [1503]. Hypertension caused by renal parenchymal disease is termed “renal parenchymal hypertension”, which is different from renovascular hypertension (RVHT) related to stenosis of the renal artery (or a relatively major intra-renal artery). Several factors including an increase in the body fluid volume or the enhancement of the renin–angiotensin (RA) system are involved in its etiology. Renal parenchymal hypertension is one of the most common form of secondary hypertension, accounting for 2–5% of all hypertensive patients [1504–1506]. In the Hisayama Study, which followed up a general population aged over 40 years, autopsy was performed on 131 hypertensive patients during the 20 years after 1961, and renal parenchymal hypertension was observed in 3.1% of hypertensive patients [1505].

However, hypertension in the presence of CKD is not always renal parenchymal hypertension. Briefly, CKD patients with essential hypertension or patients with kidney damage related to hypertension (nephrosclerosis) are not strictly regarded as having renal parenchymal hypertension. For the diagnosis of renal parenchymal hypertension, it is necessary to confirm the presence of kidney damage prior to the onset of hypertension. For this purpose, it is particularly important to evaluate urine findings on regular health checkups and the course of blood pressure. If various urine findings, such as proteinuria, hematuria and the presence of various casts, are observed prior to the onset of hypertension, the presence of renal parenchymal disease should be suspected. When previous laboratory data and their course are unclear, current urine findings are useful for differentiating renal parenchymal hypertension from benign nephrosclerosis. If the urinary protein level is ≥1 g/day (or

≥1 g/gCr), a diagnosis of primary glomerular disease may be made. In patients with nephrosclerosis, the urinary protein level is at most ≤1 g/day (most cases: ≤0.5 g/day), excluding patients with renal failure or malignant hypertension. However, among kidney disease patients, in those with Sjogren's syndrome or drug-induced nephritis, in whom the interstitium is primarily injured, the urinary protein level is often low, and a differential diagnosis should be made based on the presence of urinary concentration disorder or other systemic findings rather than the urinary protein level. Furthermore, macroscopic hematuria is not observed in the case of benign nephrosclerosis. On the other hand, primary glomerular disease frequently causes glomerular hemorrhage. In the case of glomerular hemorrhage (differing from urinary tract hemorrhage), the morphology of urinary erythrocytes is not uniform, or deformity or destruction is often observed. In addition, if erythrocytic casts are observed, glomerular disease may be present. In the presence of glomerular disease, various casts, such as epithelial/granular and hyaline casts, are often observed, but at most hyaline casts are noted in patients with nephrosclerosis. Therefore, urinalysis should be performed in all hypertensive patients, and, if an abnormality persists, kidney morphology must be evaluated using abdominal ultrasonography or CT. As the prognosis of CKD, especially renal parenchymal disease, may be improved by early treatment, it is strongly recommended to promptly refer patients suspected of having renal parenchymal disorders to nephrologists [1507]. Hypertensive nephrosclerosis and diabetic nephropathy are discussed in Section 3 of Chapter 6, KIDNEY DISEASE. Recently, the improvement of diabetes treatment has increased the number of diabetic patients with kidney damage overlapping with nephrosclerosis. The condition has been regarded as diabetic kidney disease, which is a comprehensive entity [1508].

Among patients with CKD, blood pressure may increase from the relatively early phase in those with glomerular disease or polycystic kidney disease (PKD). However, the onset of hypertension follows the progression of renal hypofunction in many patients with interstitial kidney diseases such as drug-induced nephritis and chronic pyelonephritis [1509, 1510]. NSAIDs are primarily involved in the etiology of drug-induced nephritis. In particular, caution is needed in older patients with renal dysfunction. With respect to the mechanism of NSAIDs-related kidney damage and an increase in blood pressure, see Section 7 "1) Non-steroidal anti-inflammatory drugs (NSAIDs)". Hypertension is closely involved in the condition/progression of CKD. Briefly, persistent hypertension further causes kidney damage, leading to the progression of CKD. As a result, the severity of hypertension is also advanced, forming a vicious circle. To avoid this vicious circle, the treatment of renal parenchymal hypertension is extremely important. Antihypertensive treatment strategies for renal parenchymal hypertension should be performed in accordance with Section "3. Kidney disease" of Chapter 6.

1) Chronic glomerulonephritis

Patients with chronic glomerulonephritis frequently develop hypertension from an early stage. Blood pressure is elevated further with the progression of renal dysfunction, and hypertension occurs in nearly all patients with end-stage renal failure [1508]. Hypertension is observed more often in patients with marked tissue damage on kidney biopsy. It may be caused by body fluid expansion due to Na retention (increased salt sensitivity), inappropriate activation of the RA system, and due to an enhancement of the sympathetic nervous activity [1511–1513]. Patients with a high urinary protein level may have glomerular hypertension requiring treatment; therefore, RA system inhibitors that reduce intraglomerular pressure by dilating the efferent arterioles should be selected as a first-choice drug. In patients with more marked renal hypofunction, the renoprotective effects of RA system inhibitors are more potent, and such effects are reflected by a decrease in the urinary protein level. Furthermore, a study indicated that, in glomerular disease with proteinuria, blood pressure variability from the time of consultation until the next occasion of consultation was a risk factor for renal failure [1514]. Thus, blood pressure control in consideration of variability is also important.

2) PKD

PKD is a disease in which a large number of cysts develop in the cortex and medulla of the bilateral kidneys, inducing parenchymal atrophy and fibrosis. Confirmation of the presence of many cysts in the bilateral kidneys by abdominal ultrasonography or CT is necessary for diagnosis [1515]. Genes that cause autosomal dominant polycystic kidney disease (ADPKD), which is the most frequent type of PKD, include *PKD1* (short arm of chromosome 16) and *PKD2* (long arm of chromosome 4). In addition, some patients show the mode of autosomal recessive inheritance. *PKD1* accounts for 80–90% of the disease, with *PKD2* accounting for the rest [1516]. The number of PKD patients visiting medical institutions accounts for 1 in 2000–4000 of the population [1517]. The disease is progressive, and renal function declines gradually, resulting in end-stage renal failure in about 40% of patients in their 50s [1517]. However, its progression in patients with *PKD1* anomalies may be faster than in those with *PKD2* anomalies [1518]. As extra-renal lesions, cysts in other organs, such as the liver and pancreas, intracranial cerebral aneurysms, and valvular disease, such as mitral valve prolapse, may concomitantly develop. PKD-related hypertension more frequently develops at a young age compared with essential hypertension. In

the initial phase of PKD, when renal function is normal, hypertension is observed in approximately 60% of patients [1509, 1519]. When renal function reaches to end-stage renal failure, hypertension develops in most cases [1520]. Cysts displace blood vessels and causes ischemia in local kidney tissues. The resultant increases in renin section and sympathetic nervous activity are involved in the genesis of hypertension [1521]. Currently, no antihypertensive drug to be recommended or target of blood pressure control can be accurately determined. Thus, therapeutic strategies should be conducted in accordance with Section "3. Kidney disease" of Chapter 6. However, untreated hypertension may deteriorate renal function, increase the total renal volume, or increase the risk of valvular heart disease- or cerebral aneurysmal rupture-related death; [1522] therefore, the early detection and treatment of hypertension are important.

In patients with ADPKD, cyclic adenosine monophosphate (cAMP) stimulates the proliferation of cystic epithelial cells. A vasopressin V2 receptor antagonist, tolvaptan, reduces cAMP production by selectively inhibiting vasopressin V2 receptors in the renal collecting duct. Therefore, this drug may inhibit an increase in the size of renal cysts [1523]. An international phase III collaborative study involving patients with ADPKD (TEMPO3/4) was conducted [1524]. The results showed that tolvaptan inhibited an increase in the kidney volume and a decline in renal function in ADPKD patients with sufficient renal function and a bilateral kidney volume of ≥750 mL (measured using MRI). The TEMPO3/4 study involved 177 Japanese patients, and the rates of change in the estimated glomerular filtration rate (eGFR) in the tolvaptan and placebo groups were −3.83 and −5.05 mL/min/1.73m^2/year, respectively, suggesting the efficacy of tolvaptan in inhibiting the decline in renal function in Japanese patients [1525]. Based on these clinical results, health insurance-covered therapy with tolvaptan for ADPKD was started in March 2014 in Japan. Indication criteria include CKD stage 1–4, a bilateral kidney volume of ≥750 mL, and an annual enlargement rate of approximately ≥5%. In the evidence-based guidelines for the management of PKD in 2017, it is also recommended that tolvaptan should be used in ADPKD patients with a creatinine clearance of ≥60 mL/min and a bilateral kidney volume of ≥750 mL [1515].

POINT 13A

[RENOVASCULAR HYPERTENSION (RVHT)]

1. **RVHT is one of secondary hypertension caused by stenosis or obstruction of the renal artery and is observed in about 1% of all hypertensive patients. Its primary cause is atherosclerosis in middle-aged and older patients and fibromuscular dysplasia in younger patients. Atherosclerotic renal artery stenosis is often associated with other vascular diseases such as coronary artery disease and atherosclerotic peripheral arterial obstruction.**
2. **RVHT should be suspected in patients with juvenile hypertension, severe or therapy-resistant hypertension, exacerbating hypertension, abdominal vascular bruit, a difference in kidney size or deterioration of renal function after the administration of an RA system inhibitor, RVHT should be suspected.**
3. **Diagnosis of RVHT should be made on the basis of morphological evaluation involving diagnostic imaging, and functional testing should be performed as an auxiliary procedure. As screening for morphological diagnosis, renal Doppler ultrasonography is useful. If this examination cannot be performed, MRA or CTA should be performed in consideration of renal function.**
4. **To patients with RVHT, combination therapy with RA system inhibitors, Ca channel blockers (CCBs), diuretics and β-blockers should be administered until a target blood pressure is achieved. However, the following precautions for the use of RA system inhibitors must be considered:**
   - **In patients with unilateral renal artery stenosis, administration of RA system inhibitors should be considered because they are effective for decreasing blood pressure, maintaining renal function and improving the prognosis.**
   - **In patients with bilateral renal artery stenosis, administration of RA system inhibitors has a risk to cause renal dysfunction, and are contraindicated as a general rule.**
5. **In patients with fibromuscular dysplasia-related RVHT, percutaneous transluminal renal angioplasty (PTRA) exhibits potent blood pressure decreasing effects, and the long-term outcome is relatively good; therefore, this procedure should be considered.**
6. **In patients with atherosclerotic RVHT, the combination of PTRA and antihypertensive drug therapy could be considered for a limited number of patients.**

2. RVHT

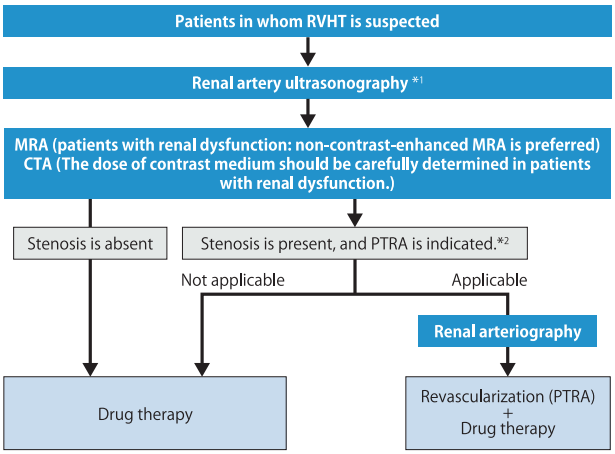
RVHT is caused by stenosis or obstruction of the renal artery, and it is also important as an etiological factor for resistant hypertension or renal dysfunction. Furthermore, progressive renal dysfunction related to stenosis or obstruction of the renal artery is termed ischemic nephropathy, accounting for approximately 10% of underlying

Table 13-1 Underlying disease of secondary hypertension, suggestive findings, and examinations necessary for differential diagnosis

Secondary hypertension in general (suggestive findings) Juvenile hypertension, middle- to advanced-age-onset hypertension, severe hypertension, resistant hypertension, cases in which blood pressure control became difficult despite previous good control, rapid-onset hypertension, cases in which severe organ damage relative to the blood pressure level is present, cases in which there are marked blood pressure fluctuations		
Underlying disease	Suggestive findings	Examinations necessary for differential diagnosis
RVHT	Rapid deterioration of the renal function after the administration of RA system inhibitors, laterality in the kidney size, hypokalemia, abdominal vascular bruit and nocturnal polyuria	Renal artery ultrasonography, abdominal CTA and abdominal MRA
Renal parenchymal hypertension	Increase in the serum Cr level, proteinuria, hematuria and a history of kidney disease	Seroimmunological test, abdominal CT, ultrasonography and kidney biopsy
Primary aldosteronism	Hypokalemia, adrenal incidentaloma and nocturnal polyuria	Plasma renin activity, plasma aldosterone level, load test, adrenal CT and adrenal venous blood collection
Sleep apnea syndrome	Snoring, obesity, daytime sleepiness and morning/nighttime hypertension	Polysomnography
Pheochromocytoma	Paroxysmal/labile hypertension, palpitation, headache, sweating and hyperglycemia	Blood/urinary catecholamines and their metabolites, abdominal ultrasonography/CT and MIBG scintigraphy
Cushing's syndrome	Central obesity, moon face, skin striae, hyperglycemia, hypokalemia and a non-age-matched decrease in the bone mineral density/compression fracture	Cortisol, ACTH, abdominal CT, brain MRI and dexamethasone suppression test
Subclinical Cushing's syndrome	Adrenal incidentaloma, hyperglycemia, hypokalemia and a non-age-matched decrease in the bone mineral density/compression fracture	Cortisol, ACTH, abdominal CT and dexamethasone suppression test
Drug-induced hypertension	Previous drug administration, hypokalemia and labile hypertension	Confirmation of previously administered drugs
Aortic coarctation	Differences in blood pressure between the upper and lower limbs, vascular bruit	Thoracic/abdominal CT, MRI/MRA and angiography
Acromegaly	Acromegaly of the limbs, distension of the brow ridge, hypertrophy of the nose/lips, hyperglycemia	IGF-1, growth hormone, MRI of the pituitary gland
Hypothyroidism	Bradycardia, edema, hypoactivity and increases in the levels of lipids, CK and LDH	Thyroid hormone, TSH, autoantibody and thyroid ultrasonography
Hyperthyroidism	Tachycardia, sweating, weight loss and a decrease in the cholesterol level	Thyroid hormone, TSH, autoantibody and thyroid ultrasonography
Hyperparathyroidism	Hypercalcemia, nocturnal polyuria and thirst	Parathyroid hormone
Brainstem vascular compression	Facial spasm, trigeminal neuralgia	Brain MRI
Others	(Urinary tract abnormalities, nutcracker syndrome, renin-producing tumors)	

Table 13-2 Diagnostic clues to RVHT

- Juvenile hypertension
- Resistant hypertension, malignant hypertension
- Worsening renal function after the start of RA system inhibitor administration
- Unexplained renal dysfunction, atrophic kidney or size discrepancy between kidneys of greater than 1.5 cm
- Unexplained pulmonary edema
- Presence of cardiovascular diseases
- Abdominal vascular bruit
- Nocturia
- Hypokalemia



*1 If it is difficult to perform this procedure, MRA or CTA should be conducted.
*2 Hemodynamically significant stenosis of the renal artery is present in addition to 1) fibromuscular dysplasia, 2) resistant hypertension, 3) exacerbating/malignant hypertension, 4) unexplained or repeated pulmonary edema/heart failure, 5) bilateral renal artery stenosis or unilateral renal artery stenosis in solitary kideny.

Fig. 13-1 Treatment procedures for RVHT

diseases for end-stage kidney disease (ESKD) according to reviews in Europe and the United States [1526].

Frequent etiological factors for RVHT (renal artery stenosis) are atherosclerosis in middle-aged to older patients and fibromuscular dysplasia in young patients. Other etiological factors include Takayasu's arteritis, congenital malformations, aortic dissection, compression of the renal artery by extrarenal masses and thromboembolism. Furthermore, systemic arteriosclerosis is advanced in many patients with atherosclerosis, and coronary artery disease, atherosclerotic peripheral arterial obstruction, renal dysfunction, or proteinuria is concomitantly present in many cases.

Patients with RVHT reportedly account for approximately 1% of all hypertensive patients, but the morbidity rate of renal artery stenosis differs among etiological factors or concomitant diseases. According to a systematic review (SR), the morbidity rates of atherosclerotic stenosis of the renal artery (percent stenosis: ≥50%) in hypertensive patients with coronary artery disease, those with atherosclerotic peripheral arterial obstruction, and those with abdominal aortic aneurysms were 10, 25, and 33%, respectively [1527], and increased with age or the presence of cardiovascular diseases [111, 1528]. The incidence of fibromuscular dysplasia is estimated to be 0.4% of a general population, and is more frequent in women [1529].

Stenosis of the unilateral renal artery is more frequent than that of the bilateral renal arteries, but the incidence of the latter is not low. Frequent sites depend on underlying diseases: the origin of the renal artery in patients with atherosclerosis and the middle to distal sites in those with fibromuscular dysplasia [1530]. Fibromuscular dysplasia has subtypes, such as intimal and medial thickening, and causes stenosis of the coronary artery, carotid artery, or intracranial blood vessels in some cases [1531, 1532].

1) Diagnostic clues

Medical histories and clinical signs suggestive of RVHT or ischemic nephropathy are shown in Table 13-2.

2) Examination for a diagnosis

RVHT is suspected based on the patient's medical history/clinical signs, supported by morphological assessment, and definitively diagnosed based on the treatment response. Therefore, diagnostic procedures should be promoted, considering individual patients' background, the accuracy of institutional examinations, and merits and demerits of each examination method. Diagnostic methods are classified into morphological diagnosis by renal artery ultrasonography, CTA, and MRA (Figure 13-1) and functional diagnosis based on plasma renin activity (PRA), renal scintigraphy findings (renograms) and captopril-loaded PRA.

The diagnostic ability of renal artery ultrasonography is high (sensitivity: 84–98%, specificity: 62–99%) [1528, 1533], and the procedure is inexpensive, noninvasive assessment; therefore, it is considered as a first-choice procedure [1534]. The peak systolic velocity (PSV) of the renal artery and renal/aortic ratio (RAR = PSV at the renal artery/PSV of the abdominal aorta) are measured, and ≥60% stenosis of the renal artery is suspected based on a renal artery PSV of >180–200 cm/second, RAR of >3.5, and waveforms characteristic of renal arterial blood flow [1535, 1536]. However, it was also indicated that the specificity of diagnosis using a PSV of >180 cm/second as a reference value was low [1537]. For this procedure, skills are required, and the accuracy of this procedure depends on clinical technologists' expertise. The examination time is longer than that of other types of ultrasonography. Furthermore, obesity or intestinal gas makes the visualization of the renal artery difficult in some cases [1538].

If renal artery ultrasonography could not be performed, or if a definitive diagnosis of stenosis cannot be made using

this procedure, assessment using MRA or CTA should be considered. Contrast-enhanced MRA is highly accurate [1533], but nephrogenic systemic fibrosis may occur in patients with renal dysfunction (eGFR <30 mL/min/1.73m^2), and it cannot be performed as a rule [1539, 1540]. A study indicated that the accuracy of non-contrast-enhanced MRA was similar to that of contrast-enhanced MRA [1541], but the former requires a specific time, and its accuracy depends on the type of device or clinical technologists' skills. Furthermore, this procedure cannot be performed in patients with metallic prosthetic devices; it is impossible to evaluate the renal artery after stenting. The spatial/temporal resolution of CTA is higher than that of MRA or arteriography [1533], and clearer, high-quality images can be obtained. However, in calcified lesions, stenosis may be overestimated. Furthermore, there are limitations such as renal damage and radiation exposure due to the use of iodine contrast medium or ionizing radiation. Considering renal function, the dose of contrast medium should be determined [1542]. If neither renal artery ultrasonography nor MRA/CTA reveals stenosis, or when examining whether PTRA is considered, renal angiography should be considered.

Although PRA can be simply measured, it is not necessarily high in some patients with bilateral renal artery stenosis. Moreover, PRA is normal in 20% of patients with RVHT, and, in some cases, PRA is increased in essential hypertensive patients [1543]. The diagnostic capability of captopril-loaded PRA (sensitivity: 61%, specificity: 86%) and captopril renography (sensitivity: 45–94%, specificity: 81–100%) are slightly lower than those of MRA and CTA [1528], but, captopril renography is useful for evaluating a right and left renal function as well as intrarenal blood flow. These conventional functional diagnostic methods are not appropriate for screening test based on the results of comparing their accuracy with that of image-based morphological diagnosis; [111] they should be used as secondary methods [1528].

3) Treatment

Treatments for RVHT include antihypertensive drugs, revascularization by PTRA or bypass, and nephrectomy. Concerning PTRA for atherosclerotic renal artery stenosis, no previous randomized controlled trial (RCT) [1544–1546] or meta-analysis [1547, 1548] has shown its established therapeutic effects in comparison with drug therapy alone. Treatment methods should be decided in accordance with individual patients' conditions and comorbid diseases. Even if any treatment method is decided, changes in the serum creatinine level and renal Doppler ultrasonography findings must be periodically checked.

(1) Drug therapy Effective drug treatment strategy for RVHT has not been established, but previous RCTs [1545, 1546] applied the combination therapy including antihypertensive drug, statin and aspirin. These medications in combination with smoking cessation and blood glucose control may be effective [111].

RVHT is often resistant to antihypertensive treatment, and several antihypertensive drugs, such as RA system inhibitors, CCBs, diuretics and β-blockers, are often required to achieve the target of blood pressure control. Although no RCT has conducted a comparison test between antihypertensive classes, many observational studies found the effectiveness of RA system inhibitors (angiotensin converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) in terms of cardiorenal protection. ACE inhibitors use were reported to improve the prognosis and renal prognosis regardless of PTRA treatment [1549], and RA system inhibitors were reported to decrease the incidence of heart failure-related admission, end-stage renal failure requiring regular hemodialysis and mortality rates in comparison with other antihypertensive drugs [1550]. Therefore, in RVHT patients with unilateral renal artery stenosis, RA system inhibitors use should be considered. However, other study found the association between RA system inhibitors use and acute kidney injury (AKI) [1551]. Administration of RA system inhibitors should be started at a low dose, and regular monitoring must be performed. If an excessive decrease in blood pressure, rapid deterioration of renal function, or hyperkalemia is found, administration should be discontinued, or the RA system inhibitor should be switched to another antihypertensive classes. Although some studies indicated the tolerability and/or the efficacy of RA system inhibitors in RVHT patients with bilateral renal artery stenosis [1552, 1553], they have a risk to cause renal dysfunction [1554], and their safety has not been established. As a rule, RA system inhibitors are contraindicated for RVHT patients with bilateral renal artery stenosis.

There is little evidence regarding other antihypertensive drugs, but β-blockers may be effective, considering their pharmacological mechanism. CCBs do not influence the RA system. α-blockers are also available.

(2) Vascular reconstruction In patients with fibromuscular dysplasia, PTRA should be preferentially performed unless it is technically difficult. The initial success rate of PTRA is high [1555], and its blood pressure decreasing effects are more marked than in those with atherosclerotic renal artery stenosis [1556]. In addition, PTRA treatment may result in the dose-reduction or discontinuation of antihypertensive drugs. A meta-analysis showed blood pressure decreasing effects of PTRA is expected to be better in young patients or those with a short duration of hypertension [1557].

However, postoperative restenosis is frequently observed because angioplasty without a stent is usually performed for fibromuscular dysplasia patients [1558].

The treatment success rate of PTRA without a stent for atherosclerotic renal artery stenosis is slightly low, and the incidence of restenosis is high [1559]. PTRA with a stent may reduce the incidence of restenosis [1560]. Although non-RCTs showed the blood pressure decreasing effects of PTRA [1561, 1562], no RCT has proved any potent beneficial effect in comparison with antihypertensive drug therapy alone [1563–1568]. Similarly, none of three RCTs published after 2009 demonstrated any potent blood pressure lowering, or cardiorenal protective effects [1544–1546]. In contrast, PTRA-related complications may occur, and the results of these RCTs support drug therapy alone. However, limitations on study protocols, such as the selection of subjects, have been indicated [1569, 1570], and we must wait for the results of clinical studies that are being conducted [1571, 1572]. A meta-analysis showed that PTRA decreased diastolic blood pressure (DBP) by 2 mmHg in comparison with drug therapy alone, whereas there was no difference in the prognosis involving renal function [1547]. Several studies examined predictors of the therapeutic effects of PTRA [1573, 1574], and a subanalysis of RCTs suggested that the therapeutic effectiveness of PTRA are expected in patients without albuminuria [1575]. However, a valid biomarker to predict its therapeutic effects after PTA has not been established.

Currently, PTRA for RVHT could be considered in patients with hemodynamically significant stenosis of the renal artery and one of the following conditions: 1) fibromuscular dysplasia, 2) resistant hypertension, 3) exacerbating/malignant hypertension, 4) unexplained or repeated pulmonary edema/heart failure, or 5) bilateral renal artery stenosis or renal artery stenosis in solitary kideny [111, 1528, 1576, 1577].

Internationally, the number of patients for whom surgical procedures, such as nephrectomy and bypass, has decreased, but bypass is an option for patients in whom revascularization by PTRA is difficult or those with repeated restenosis after PTRA. The patency rate and prognosis after bypass are similar to or slightly better than those after PTRA [1578, 1579], but the high surgery-related mortality rate was reported in one study [1580].

POINT 13B

[ENDOCRINE HYPERTENSION]

1. **As appropriate diagnosis and treatment of endocrine hypertension are essential, patients in whom endocrine hypertension is suspected should be referred without delay to the specialists of The Japanese Society of Hypertension (JSH) and/or the Japan Endocrine Society.**
2. **The morbidity rate of PA is high, and it often causes organ damage. Early diagnosis and treatment are therefore important. In hypertensive patients, especially a hypertensive group with a high morbidity rate of PA, screening test should be conducted, and subsequently, confirmatory testing, and unilateral adrenalectomy for unilateral lesion, or medical therapy with mineralcorticoid receptor (MR) antagonists should be performed based on subtype testing results.**
3. **For the diagnosis of Cushing's syndrome, attention should be paid first to characteristic physical findings, followed by measurement of blood cortisol and adrenocorticotropic hormone (ACTH) levels and the dexamethasone suppression test. In cases of adrenal incidentaloma, subclinical Cushing's syndrome should be differentiated.**
4. **Pheochromocytoma/paraganglioma should be suspected on the basis of symptoms such as tachycardia and headache, paroxysmal hypertension and adrenal incidentaloma. A diagnosis should be made by measurement of urinary catecholamines and their metabolites, fractionated metanephrine, and imaging procedures. Potentially, these lesions are malignant, and lesions with non-chromaffin tissue metastasis or local infiltration are definitively diagnosed as malignant.**
5. **Characteristic physical findings are clues to the diagnosis of acromegaly, hyperthyroidism and hypothyroidism. Hypercalcemia with high parathyroid hormone (PTH) levels suggests primary hyperparathyroidism.**

3. ENDOCRINE HYPERTENSION

Endocrine hypertension is a group of diseases in which hypertension is caused by excessive hormone secretion from the endocrine organs, represented by PA, Cushing's

Table 13-3 Hypertension with a high morbidity rate of PA for which a screening test is recommended

- Hypertension complicated by spontaneous hypokalemia (including diuretic-induced hypokalemia)
- Hypertension in young patients
- Grade II or severer hypertension
- Resistant hypertension
- Hypertension with adrenal incidentaloma
- Hypertension with juvenile cerebrovascular disorder
- Hypertension with sleep apnea

Table 13-4 Influence of various antihypertensive drugs on PAC, PRA and ARR

	PAC	PRA	ARR
ACE inhibitors/ARBs	↓	↑↑	↓[*1]
CCBs	→ - ↓	↑	↓[*1,3]
MR antagonists Thiazide diuretics	↑	↑↑	↓[*1]
β-blockers	↓	↓↓	↑[*2]
DRIs	↓	↓↓	↑[*2]

[*1] Possibility of false-negative results

[*2] Possibility of false-positive results

[*3] The influence is less marked than that of ACE inhibitors and ARBs

syndrome and pheochromocytoma/paraganglioma. Although endocrine hypertension can be cured by the treatment of the primary disease, a delay in diagnosis is involved in the progression of organ damage. Early diagnosis and treatment are therefore important. Patients in whom endocrine hypertension is suspected should be referred without delay to the specialists of The JSH and/or the Japan Endocrine Society.

1) Primary aldosteronism (PA)

The morbidity rate of PA in hypertensive patients is reported to be 5–15%. PA represents secondary hypertension, being characterized by the autonomous secretion of aldosterone and suppressed PRA. Hypokalemia is observed only in typical PA patients. The incidences of cerebrovascular disorder, coronary artery disease, arrhythmia, such as atrial fibrillation, and cardiovascular complications, such as peripheral artery disease, are 3 to 5 times higher than in patients with essential hypertension [1581–1585]. In patients with PA, salt-sensitive hypertension, in which the plasma aldosterone concentration (PAC) does not sufficiently decrease despite excessive salt ingestion, is noted. Many patients with PA have resistant hypertension, which cannot be controlled using 3 antihypertensive drugs including a diuretic. The subtypes of PA include unilateral lesions that can be treated by adrenalectomy (aldosterone-producing adenoma: APA) and bilateral adrenal hyperplasia (idiopathic hyperaldosteronism [IHA]), for which drug therapy is indicated. In many patients with unilateral PA, adrenalectomy results in complete biochemical cure, and it is important to detect PA patients in the early stage and provide adequate treatment. Treatment guidelines were published in Japan, the United States and France [1586–1590].

(1) Diagnostic clues Among hypertensive patients, screening is particularly recommended for high-risk patients regarding PA (Table 13-3) [1586–1588]. In the Endocrine Society Clinical Practice Guideline for the Management of

Table 13-5 Type and outline of function-confirming tests in patients with PA

	Methods	Criteria for positive results	Adverse effects
Captopril challenge test	Oral administration of captopril at 50 mg	ARR (60 or 90 min) ≥200[*1]	A decrease in blood pressure
Furosemide-upright postures test	Intravenous injection of furosemide at 40 mg and upright posture for 2 h	PRAmax ≤2.0 ng/mL/h	Orthostatic hypotension, a decrease in the serum K level
Saline infusion test[*4]	Intravenous drip infusion of saline at 2 L/4 h	PAC (4 h) ≥60 pg/mL	A rise in blood pressure, a decrease in the serum K level
Oral salt-loading test[*4]	24-h urine collection at the outpatient clinic[*2]	Urinary aldosterone ≥8 μg/day (urinary Na ≥170 mEq/day[*3])	A rise in blood pressure, a decrease in the serum K level

[*1] ARR is calculated with PAC in the unit of pg/mL.

[*2] In inpatients, salt intake should be maintained at 10–12 g/day for 3 consecutive days.

[*3] It should be confirmed that salt loading is sufficient.

[*4] Neither saline infusion nor oral salt-loading tests should be conducted in patients with heart failure and renal insufficiency. Values obtained in a supine position on a saline infusion test should be used for assessment with criteria for positive results.

Primary Aldosteronism: Case Detection, Diagnosis, and Treatment, which was published in the United States in 2016 [1589], the reference values of systolic blood pressure (SBP) and DBP for screening were reduced to ≥150 and ≥100 mmHg, respectively, and patients with sleep apnea syndrome and PA patients' first-degree relatives with hypertension (type II familial hyperaldosteronism screening) were added as subjects to be screened.

(2) Screening tests For PA screening, the PRA or plasma active renin concentration (ARC) and PAC are measured by simultaneous blood collection early in the morning or before noon, and a PAC (pg/mL)/PRA (ng/mL/hour) ratio (ARR) of >200 [1586–1588] or a PAC (pg/mL)/ARC (pg/mL) ratio of >40–50 [1591] is used as a cut-off value. To prevent false-positive findings related to hyporeninemia, patients with a high ARR or a PAC of >120 pg/mL should be regarded as showing positive findings. However, the possibility of PA cannot be ruled out even in patients with a PAC of ≤120 pg/mL. For measurement, casual blood samples should be collected in a sitting position early in the morning or before noon. If negative findings are obtained, an additional examination under stricter conditions (early in the morning, after fasting, after bed rest) or referral to specialists should be considered. Initially, it is important to conduct a screening test. Firstly, medications with whom patients are taking should be checked. Many antihypertensive drugs influence the renin and aldosterone levels (Table 13-4), but it is not necessary to switch antihypertensive drugs or discontinue them as long as PRA was suppressed (≤1 ng/mL/hour) during treatment with antihypertensive drugs other than β-blockers or direct renin inhibitors (DRIs). On the other hand, if PRA is not suppressed (>1 ng/mL/hour), with an ARR in the boundary zone of the cut-off value, antihypertensive drugs should be switched to CCBs or α-blockers as promptly as possible. Additional examination should be conducted after ≥2 weeks (the influence of MR antagonists may remain for ≥2 months). However, for blood pressure control, antihypertensive drugs should be discontinued or switched, considering their advantages and risks. Furthermore, as a rule, evaluation is performed on a single session of measurement, but, if negative findings are obtained, additional examination should be conducted at an appropriate time, considering antihypertensive drugs or conditions for blood collection. On PAC measurement, the unit of pg/mL or ng/dL is used, which depends on measurement methods. It must be considered that a value expressed in the unit of pg/mL corresponds to a value 10-fold the same value expressed in the unit of ng/dL.

(3) Confirmatory tests If a positive result is detected on screening, it should be confirmed on at least 1 function-confirming test to verify the autonomous secretion of aldosterone (Table 13-5). The superiority or inferiority of each test's performance is unclear. If the PAC/PRA ratio is >1000, with a PAC of >200 pg/mL, a confirmatory test may be omitted [1589]. In some patients with hypokalemia, false-negative findings are observed; therefore, the confirmatory test should be performed after correction with potassium preparations. Captopril challenge and oral salt-loading tests can be performed at the outpatient clinic. The furosemide-upright posture test is physically stressful. A saline infusion test should be conducted in a supine position. The duration of examination is long, and this test is not appropriate in patients with cardiac and renal insufficiency. However, a recent study indicated that the frequency of false-negative findings was reduced by performing this test in a sitting position [1592].

Furthermore, subclinical adrenal Cushing's syndrome is present in approximately 10% of PA patients with adrenal tumors on CT; the dexamethasone suppression test must be conducted.

(4) Subtype testing (Lateralizing diagnosis) Adrenal CT should be performed in all patients to rule out giant adrenal tumors suggestive of malignancy. If patients with positive findings on a function-confirming test wish to undergo adrenalectomy, the adrenal vein should be visualized (contrast-enhanced CT with 1- to 3-mm slices) to improve the success rate of adrenal venous sampling (AVS). Adrenal tumors in PA patients measure ≤5 mm in diameter, and ≥50% of these patients show negative findings on CT. Even if a unilateral adrenal tumor is present, the possibility of a non-functional tumor may increase with aging. Therefore, when considering adrenalectomy, AVS is necessary as a rule. Adosterol scintigraphy is not appropriate for lateralizing diagnosis, because false-positive and -negative findings are frequently detected. The concomitant use of ACTH loading is useful for successfully achieving catheterization and evaluating the location of the lesion site. AVS is invasive, and has the following limitations: criteria for lateralizing diagnosis has not been standardized, and the success rate for the right adrenal vein is low, raising technical issues. Therefore, whether AVS is indicated should be determined, considering the presence or absence of indications for surgery and the patient's wishes. In addition, AVS should be performed in a skilled, special facility.

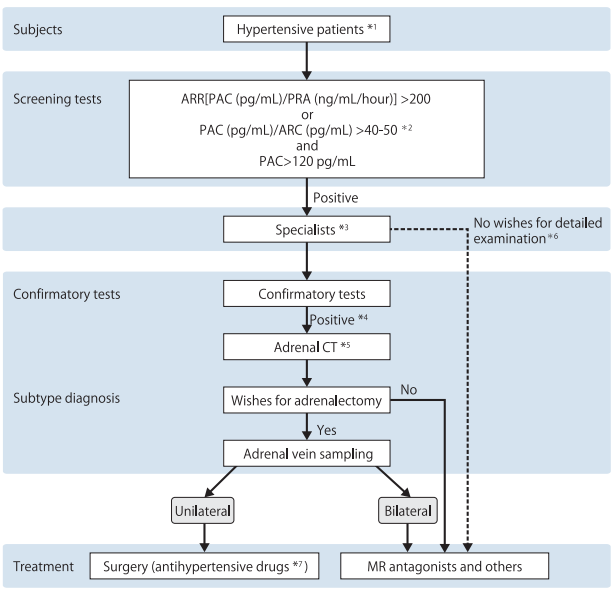
For accurate lateralizing diagnosis, AVS is necessary, but an analysis involving a large number of patients showed clinical features for which AVS may be omitted. These included young patients, aged <35 years, with positive findings on screening. In patients with hypokalemia and typical unilateral tumors (low attenuation) on CT, location diagnosis by CT is often accurate [1589, 1593]. According to the JPAS [1594] study, approximately 94% of patients

with a normal serum potassium level in whom CT did not reveal any adrenal tumor measuring ≥1 cm in diameter had bilateral lesions.

(5) Treatment Treatment methods depend on the subtype of PA (unilateral or bilateral lesions). The prognosis must be separately evaluated as biochemical cure by the alleviation of hyperaldosteronism or hypokalemia and clinical cure by the alleviation of hypertension [1595]. In patients with unilateral lesions, laparoscopic adrenalectomy is a first-choice procedure. After surgery, biochemical cure may be achieved. However, the postoperative blood pressure normalization rate is approximately 30% due to the duration and severity of hypertension and the presence or absence of essential hypertension. In patients with no indication or wish for surgery, or those with bilateral lesions, hypertension and hypokalemia must be treated using MR antagonists. If blood pressure control with an MR antagonist alone is difficult, the drug should be combined with a CCB, a diuretic, or an ACE inhibitor/ARB while monitoring the serum potassium level.

Therapeutic strategies should be determined based on 3 factors: disease characteristics (the severity of hypertension or hypokalemia, sex, age), medical staff's characteristics (therapeutic strategy sharing, skilled radiologists, the presence or absence of clinical data accumulation) and patients' wishes (wishes for adrenalectomy, the understanding of therapeutic strategies, health expenditure). In patients with severe hypertension, severe hypokalemia or severe PA (PAC > 200 pg/mL), the possibility of APA is clinically suggested, and detailed examination is important. In young patients, especially in young females, the number of antihypertensive drugs that can be orally administered during pregnancy in the future is limited; therefore, detailed examination should be promoted. In medical institutions where there are radiologists skilled in AVS as medical staff, detailed examination can be promoted, but patient referral to such institutions should be considered in skilled radiologist-free institutions. To determine future therapeutic strategies, it is also important to accumulate clinical data with respect to therapeutic strategies. Patients' wishes for adrenalectomy should be confirmed after explaining the merits and demerits of this procedure and drug therapy. Patient- and medical-staff-shared therapeutic strategies can be adopted by determining final therapeutic strategies based on these 3 factors. It is unclear whether the long-term outcome differs between adrenalectomy and drug therapy, but several studies indicated that adrenalectomy was superior to drug therapy in the prevention of cardiovascular death or new-onset atrial fibrillation [1596, 1597]. Furthermore, a retrospective cohort study showed that the cardiovascular risk related to the dose-adjustment of MR antagonists targeting blood pressure and serum potassium control in the absence of PRA suppression (≥1 ng/mL/hour) was similar to that in patients with essential hypertension [1598]. Spironolactone has a high affinity for MR, exhibiting potent MR antagonism, but it frequently causes sex-hormone-associated adverse reactions, such as gynecomastia and menstrual irregularity, by androgen receptor antagonism and progesterone receptor-stimulating actions. On the other hand, eplerenone has a low affinity for MR, exhibiting weak MR antagonism. However, its MR selectivity is high, and the incidence of sex-hormone-associated adverse reactions is extremely low. Based on adverse events in a clinical trial, as a rule, MR antagonists are contraindicated for patients receiving potassium preparations or diabetes mellitus with proteinuria.

In the spring of 2019, the manufacturing and sales of a new non-steroidal MR antagonist, esaxerenone, were approved. This drug is contraindicated for patients receiving potassium preparations, as indicated for eplerenone. It must be carefully administered to diabetics with albuminuria or proteinuria and patients with moderate renal dysfunction (eGFR: 30 to 59 mL/min/1.73 m^2), and the risk of hyperkalemia should be considered.



*1 Hypertension groups in which the morbidity rate of PA is particularly high should be investigated.
*2 If the ARR is in the cut-off boundary range, an antihypertensive drug should be switched to a CCB or an β-blocker, and additional examination should be performed after 2 weeks.
*3 Patients should be referred to the specialists of the Japanese Society of Hypertension and/or the Japan Endocrine Society.
*4 Of the tests presented in Table 13-5, a positive reaction should be confirmed on at least one.
*5 If a large tumor suggestive of malignancy is detected, surgery should be considered. In patients in whom contrast medium is available, thin slice CT is useful for visualizing the presence of an adrenal tumor and the bilateral adrenal veins.
*6 In screening-positive patients who do not wish to undergo detailed examination, the administration of an MR antagonist should be considered.
*7 If hypertension persists after adrenalectomy, antihypertensive drugs should be administered.

Fig. 13-2 Algorithm for the diagnosis of PA

(6) Timing of referral to specialists Figure 13-2 shows the procedure for the diagnosis of PA in clinical practice. In hypertensive groups in which the morbidity rate of PA is particularly high, screening should be performed. If a

positive result is detected, the patient must be referred to a specialist.

2) Other conditions associated with mineralocorticoid excess

Patients with other types of mineralocorticoid excess show normal to low PRA and PAC values. Congenital adrenal hyperplasia (17α- and 11β-hydroxylase deficiency) and deoxycorticosterone (DOC)-producing tumors cause hypertension and hypokalemia by the activation of MR by DOC. Pseudoaldosteronism related to the oral administration of Chinese herbal medicines causes hypertension and hypokalemia by MR activation by cortisol accumulated in the kidney with 11β-hydroxysteroid dehydrogenase 2 suppression by licorice (glycyrrhizic acid).

3) Cushing's syndrome

Cushing's signs, hypertension and diabetes mellitus are caused by the autonomous and excessive secretion of cortisol. The disease conditions are classified into ACTH-independent and ACTH-dependent types. The former includes adrenal Cushing's syndrome (narrow-sense Cushing's syndrome) due to adrenal adenoma or bilateral adrenal hyperplasia, whereas the latter includes Cushing's disease due to ACTH-producing pituitary tumors and ectopic ACTH-producing tumors. Complications, such as myocardial infarction, venous thromboembolism and stroke, contribute to an increase in the mortality rate in patients with this disease [1599–1602].

(1) Diagnostic clues Attention must be paid to Cushing's signs such as central obesity, moon face, buffalo humps, red striae, thin skin, hirsutism and acne. Nonspecific findings include hypertension, diabetes mellitus, dyslipidemia, osteoporosis, urolithiasis and nail onychomycosis. On general laboratory tests, considerable attention should be paid to eosinopenia, lymphopenia, neutrophilia and hypokalemia. In the presence of subclinical adrenal Cushing's syndrome, an adrenal tumor is present on CT, and the autonomous secretion of cortisol is observed, but the basic cortisol level is normal, and there is no characteristic Cushing's sign; therefore, if an adrenal incidentaloma is detected, differential diagnosis may be necessary [1603].

(2) Diagnosis Increases in the 24-h urinary free cortisol and midnight serum cortisol levels and the absence of cortisol suppression on the dexamethasone suppression test (overnight method) (cortisol level in the morning the day after the oral administration of dexamethasone at 1 mg: >5 μg/dL) must be confirmed [1599–1602]. Whether the condition is dependent on or independent of ACTH must be differentiated by the presence or absence of plasma ACTH suppression, and adrenal lesions, pituitary lesions and ectopic ACTH-producing tumors should be investigated using adrenal CT and pituitary MRI, respectively. Subclinical adrenal Cushing's syndrome should be diagnosed based on the results of the dexamethasone (1 mg) suppression test [1603].

(3) Treatment First-choice procedures for adrenal adenoma, Cushing's disease and ectopic ACTH-producing tumors are laparoscopic adrenalectomy, trans-sphenoidal hypophysectomy and resection of the causative mass, respectively. If the tumor diameter is 4 cm or larger or there is a slight increase in its size in patients with subclinical adrenal Cushing's syndrome, hypertension, obesity, or impaired glucose tolerance, surgery should be considered [1599, 1602].

(4) Timing of referral to specialists If Cushing's signs, the concurrence of resistant hypertension and diabetes mellitus, or adrenal incidentaloma is detected, patients should be referred to specialists.

4) Pheochromocytoma / paraganglioma

Catecholamine-producing tumors include adrenal medulla-derived pheochromocytoma and paraganglion-derived paraganglioma. These lesions are associated with hypertension and impaired glucose tolerance due to catecholamine excess. Extra-adrenal, bilateral, and multiple lesions account for approximately 10%, and it was shown that patients with gene mutations, who were previously considered to account for approximately 10%, accounted for approximately 40% [1604, 1605]. These lesions should be diagnosed/treated in accordance with the treatment guidelines prepared by the Japan Endocrine Society [1605] and Endocrine Society (United States) [1604]. When metastasis is detected, a diagnosis of malignant pheochromocytoma is made. However, recently, it has been recognized that this tumor may be malignant in all patients.

(1) Diagnostic clues Symptoms including catecholamine excess-related headache, palpitation, hyperhidrosis, and pallor of the face and upper/lower limbs, as well as paroxysmal hypertension, are suggestive of pheochromocytoma/paraganglioma. Hypertensive crisis is caused by exercise, stress or defecation. It may also be caused by oral metoclopramide or intravenous glucagon injection. Recently, pheochromocytoma and paraganglioma have been detected as adrenal incidentaloma in the absence of symptoms rather than the above symptoms related to catecholamine excess in an increasing number of patients.

(2) Diagnosis Screening should be performed using a spot urine metanephrine or normetanephrine excretion of >500 ng/mgCr as a criterion. In patients meeting this criterion,

whether there is an increase in metanephrine or normetanephrine excretion in 24-h urine (threefold the upper limit of the normal range or greater) must be confirmed [1604]. Screening using the plasma concentrations of free metanephrine and normetanephrine became possible (it became covered by health insurance in January 2019). These concentrations can be measured on a single blood test without collecting 24-h urine, which is collected using a complex method. Their sensitivity is high (96–100%), but their specificity is slightly low (85–89%), which is a limitation. Therefore, metanephrine and normetanephrine levels in 24-h urine should be initially measured in a low-risk group regarding pheochromocytoma/paraganglioma (PPGL) (resistant hypertension, excessive adrenaline secretion-related attack symptoms [palpitation, hyperhidrosis, headache, tremor, pallor]). On the other hand, measurement of the plasma concentrations of free metanephrine and normetanephrine is useful for screening in a high-risk group (family history of PPGL, MEN2-related familial PPGL, after surgery for PPGL, adrenal incidentaloma [with a lipid-poor mass]). Provocative (glucagon, metoclopramide) test is contraindicated because of problems with specificity and safety. In some patients with a high blood noradrenaline level, the clonidine suppression test is useful. The location of the tumor is determined by CT. However, the use of contrast medium may cause hypertensive crisis, and it is contraindicated. Tumors have abundant blood vessels, with a low lipid content, causing cysts or calcification in some cases. On MRI, a low signal intensity on T1-weighted and a high signal intensity on T2-weighted images are characteristic findings. If tumor location is unclear, or when investigating multiple tumors or metastatic foci, the whole body should be scanned by iodine-123 metaiodobenzylguanidine (I-123 MIBG) scintigraphy, whole-trunk CT and/or 18F-FDG-PET. Of patients with abdominal/pelvic paragangliomas, malignant lesions account for approximately 40%, and *succinate dehydrogenase subunit B gene (SDHB)* mutations are frequently detected. In the World Health Organization (WHO) classification revised in 2017, the disease code of paraganglioma was changed to that reflecting malignancy. In patients with bilateral adrenal pheochromocytoma, examination should be performed, considering the possibility of multiple endocrine neoplasia type 2 (MEN2) or von Hippel-Lindau disease.

(3) Treatment Resection of the tumor is the treatment of choice. For preoperative blood pressure management, correction of the circulating plasma volume and prevention of intraoperative crises, α_1-blockers, such as doxazosin, should be administered. β-blockers are concomitantly used for the treatment of tachycardia and arrhythmia. However, the administration of β-blockers alone is contraindicated because it enhances α-actions. Furthermore, the manufacturing and sales of a tyrosine hydroxylase inhibitor, metyrosine, were approved, allowing its use for alleviating excessive catecholamine secretion by PPGL. Malignant pheochromocytoma is the most important issue. As it is difficult to differentiate benign from malignant diseases based on histopathological findings, follow-up is necessary over the lifetime even after surgery. Pheochromocytoma crises should be treated by the intravenous injection or drip infusion of an α-blocker, phentolamine, followed by the administration of α_1-blockers.

(4) Timing of referral to specialists If typical symptoms, such as paroxysmal hypertension and pallor of the face or adrenal incidentaloma, are observed, patients should be referred to specialists.

5) Other endocrine hypertension

(1) Acromegaly The diagnosis is suggested by characteristic physical findings, including enlargement of the peripheral parts of limbs and forehead protrusion. Hypertension is noted in about 40% of patients with acromegaly. This disease is diagnosed based on increases in the blood growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, a lack of GH suppression on a 75g oral glucose tolerance test (>0.4 ng/mL), and the presence of pituitary tumors. Acromegaly-related hypertension is characterized by increases in the circulating blood volume and peripheral vascular resistance, the enhancement of renal epithelial sodium channel activity and sympathetic nerve activity, and concomitant development of sleep apnea syndrome. Trans-sphenoidal hypophysectomy is the treatment of choice, and it should be combined with drug therapy with somatostatin derivatives, GH receptor antagonists, or dopamine agonists.

(2) Hyperthyroidism An increase in the blood T3 level enhances sympathetic nerve β-receptor activity, causing systolic hypertension and an increase in pulse pressure by increases in the heart rate and cardiac contractility. Palpitation, finger tremor, increased appetite, weight loss, goiter and exophthalmos suggest the disease. A diagnosis of hyperthyroidism is made by measuring the fT_3, fT_4, thyroid-stimulating hormone (TSH) and TSH receptor antibody (TRAb) levels. The disease is treated by the administration of antithyroid drugs and β-blockers. Patients should be referred to specialists for the differentiation of the disease from thyrotoxic disorders such as painless thyroiditis.

(3) Hypothyroidism Chronic thyroiditis (Hashimoto's disease) is the major cause of hypothyroidism. A decrease in the thyroid hormone level increases peripheral vascular resistance, and reduces endothelium-derived relaxing factor (EDRF) in addition to a reduction in cardiac output/

contractility and bradycardia, causing hypertension in some cases. Nonspecific symptoms, such as malaise, chills and alopecia, goiter and dyslipidemia, are clues to the diagnosis. Levothyroxine replacement therapy should be performed.

(4) Primary hyperparathyroidism Hypertension is noted in 40 to 65% of patients with primary hyperparathyroidism. The enhancement of the renin–angiotensin–aldosterone system, a reduction in the diastolic ability of resistant blood vessels, and enhancement of the reactivity of vasopressor hormones may be involved. However, no study has examined changes in blood pressure after parathyroid adenomectomy. Hypercalcemia, an increase in the intact PTH level and/or urolithiasis are clues to the diagnosis. Resection of the enlarged parathyroid glands should be performed.

POINT 13C

[VASCULAR HYPERTENSION]

1. **Diseases that cause vascular hypertension include Takayasu's arteritis, other forms of vasculitis syndrome (polyarteritis nodosa [PN], progressive systemic scleroderma [PSS]), aortic coarctation and diseases with an increase in cardiac output (aortic valve regurgitation, patent ductus arteriosus and arteriovenous fistula). Treatment should be performed in accordance with the condition of each disease for blood pressure control.**

4. VASCULAR HYPERTENSION

1) Takayasu's arteritis

Takayasu's arteritis refers to idiopathic, nonspecific large-vessel arteritis that causes obstructive or dilating lesions in the aorta, its major branches or pulmonary/coronary arteries [1606]. In Japan, this disease is observed more frequently in women [1607]. This disease is relatively rare, and sometimes requires a long period until a definitive diagnosis can be made. Therefore, common complaints on the initial consultation include vertigo, syncope, vision disorder, numbness of the hands and hypertension, which suggest the progression of vascular lesions. It is important to prevent the progression of vascular lesions by starting the administration of adrenocorticosteroids or immunosuppressive drugs early, for improving the patient's outcome/quality of life (QOL). Even when nonspecific symptoms, such as fever and malaise, are present, this disease should be considered. A study reported the usefulness of FDG-PET for diagnosis [1608], and this procedure is covered by health insurance for the purpose of lesion location or activity assessment. Its primary findings are lateralities in the pulse and blood pressure, neck or abdominal bruit and an enhanced carotid sinus reflex. An aortitis syndrome is an important etiological factor for secondary hypertension, and hypertension is observed in about 40% of patients with this disease, and markedly affects the outcome [1609]. In patients with bilateral subclavian artery stenosis, the upper limb blood pressure is lower than the aortic pressure, leading to underestimation. Advances in noninvasive diagnostic procedures, such as diagnostic imaging and medical treatment, have facilitated early therapeutic intervention. In patients who developed aortitis syndrome after 2000, the incidences of hypertension and aortic valve regurgitation have decreased [1610]. The pathogenesis of hypertension in the presence of this disease varies: (1) RVHT, (2) hypertension due to aortic coarctation (atypical aortic coarctation), (3) aortic valve regurgitation-related hypertension and (4) hypertension due to aortic wall sclerosis [1606, 1607].

RVHT is observed in about 20% of patients with Takayasu's arteritis [1611]. Revascularization is indicated for aortic coarctation and RVHT when (1) antihypertensive drugs have become ineffective for the sufficient control of blood pressure, (2) antihypertensive treatment causes renal dysfunction, (3) congestive heart failure has occurred and (4) the renal artery has narrowed bilaterally [1606]. PTRA for RVHT is selected due to its minimum invasiveness. Its postoperative antihypertensive effects and decreases in the doses of antihypertensive drugs have been reported, but the long-term patency rate is lower than that after bypass, and, when selecting PTRA as a first-line procedure, whether it should be indicated must be carefully evaluated [1612, 1613]. Moreover, aortic valve regurgitation is an important complication that influences the outcome of this disease; hence, under appropriate antihypertensive treatment, aortic valve replacement, including Bentall's operation, should be indicated in accordance with indication criteria for aortic valve regurgitation in general [1614].

Surgical treatment for this disease should be performed after the complete resolution of active inflammation or control of inflammation with adrenocorticosteroids. Although the long-term outcome of Japanese patients with this disease undergoing surgery is generally good, attention must be paid to the occurrence of anastomotic aneurysms and dilation of the rest of the ascending aorta [1615]. Hypertension due to renal artery stenosis or aortic coarctation, congestive heart failure due to aortic valve regurgitation, coronary artery disease, dissecting aortic aneurysms and aortic aneurysm rupture are important clinical conditions that influence the outcome. Therefore, early, appropriate medical treatment, such as steroid therapy, antihypertensive therapy, and appropriate surgery for severe cases may improve the long-term outcome [1612].

Antihypertensive treatment for this disease is basically the same as that for renovascular or essential hypertension.

However, as cerebral blood flow may be reduced in patients with stenotic lesions in the carotid artery, sufficient evaluation for the cerebral blood flow is necessary for conducting antihypertensive treatment.

2) Other forms of vasculitis

Vasculitis syndrome, other than Takayasu's arteritis, such as PN and PSS, contributes to hypertension [1616]. Necrotic arteritis of systemic small- and medium-sized muscular arteries, including the renal artery in PN patients [1617] and spasms of the renal vessels in PSS patients, is involved in the etiology of hypertension. PN is complicated by hypertension (≥160/95 mmHg) in about 30% of patients [1618], and some patients develop rapidly progressing glomerulonephritis. Patients with PSS often show renal crisis, such as malignant hypertension, renal failure. Other than PSS, causes of death in the acute phase are cerebral hemorrhage, myocardial infarction, heart failure and renal failure, all of which are closely related to the hypertension they complicate; therefore, the importance of blood pressure control must be recognized. For conditions other than PSS, steroid pulse and immunosuppressive therapies are performed in combination in the acute phase. The strategy for blood pressure control is the same as that for renal parenchymal or essential hypertension. In PSS patients, a treatment basically the same as that for malignant hypertension is indicated, and ACE inhibitors and CCBs are markedly effective [1619, 1620].

3) Coarctation of the aorta

Coarctation of the aorta is suspected, based on vascular bruit ranging from precordium to back along the descending aorta, a reduction in lower limb artery abnormalities on palpation and differences in blood pressure between the upper and lower limbs. In this condition, blood pressure is increased in the upper limb proximal to the site of stenosis and reduced in the lower limb distal to the site of stenosis, with a SBP difference between the upper and lower limbs of 20–30 mmHg or greater. In patients with this disease, the progression of systemic vascular remodeling, RA/sympathetic nervous systems and mechanical factors, such as an increase in the arterial reflection waves from the site of aortic coarctation, an increase in the peripheral vascular resistance in the upper body and weakening of the Windkessel effect of the aorta, are involved in the etiology of hypertension [1621–1623]. As a rule, the surgical relief of stenosis or angioplasty using a balloon catheter is indicated in childhood, and a better outcome has been reported for earlier treatment [1624]. Postoperative recurrence of hypertension is observed in ~33% of patients [1625], and in this case antihypertensive treatment should be performed in accordance with the condition. Some studies suggest that not only an increase in blood pressure at rest but also that on ambulatory blood pressure monitoring (ABPM) or exercise loading is a prognostic factor for recurrence of hypertension in the postoperative chronic phase [1626, 1627]. Recent studies reported the antihypertensive effects of stenting in the acute and chronic phases [1628, 1629].

4) Vascular hypertension associated with an increase in cardiac output

In patients with aortic valve regurgitation, patent ductus arteriosus or arteriovenous fistula, systolic hypertension may be caused primarily by an increase in stroke volume. Antihypertensive treatment should be performed in accordance with individual conditions. However, radical treatment for the primary disease may reduce hypertension.

POINT 13D

[HYPERTENSION RELATED TO DISEASES OF THE BRAIN OR CENTRAL NERVOUS SYSTEM]

1. **In patients with hypertension related to an increase in intracranial pressure (Cushing's reaction) due to cerebrovascular disorders, brain tumors, encephalitis (myelitis) or brain injury, treatment for each cause should be performed first.**
2. **Compression by arteries around the rostral ventrolateral medulla causes an increase in blood pressure by the enhancement of sympathetic activities (neurovascular compression syndrome). In patients with neurological symptoms, such as unilateral facial spasm, surgical decompression may also be considered.**

5. HYPERTENSION RELATED TO DISEASES OF THE BRAIN OR CENTRAL NERVOUS SYSTEM

Hypertension associated with stroke is described in detail in Chapter 6. In patients with central nervous diseases, such as brain tumors (particularly those in the posterior cranial fossa), encephalitis (myelitis) and brain injury, sympathetic activities are increased by ischemia related to increased intracranial pressure at the brainstem, possibly causing hypertension (Cushing's reaction). Furthermore, the pathogenesis of neurovascular compression syndrome, in which compression of the rostral ventrolateral medulla, which is the vasomotor center of sympathetic activities, by surrounding arteries causes an increase in blood pressure or hypertension by the enhancement of sympathetic activities, and a surgical decompression-related decrease in blood pressure, was reported in the 1980s [1630]. Thereafter, in Japan, it was also reported that this syndrome was an etiological factor for hypertension with the enhancement of sympathetic activities, and that it was related to blood

Table 13-6 Genes involved in congenital blood pressure abnormalities and their clinical features

Hereditary hypertension	Causative genes	Clinical features
Liddle syndrome	Epithelial Na channel β/γ subunits (*SCNN1B*, *SCNN1G*), AD	Low PRA, low PAC, metabolic alkalosis
Gordon syndrome (PHAIIB, IIC, IID, IIE)	Serine-threonine kinase (IIB: *WNK4*, IIC: *WNK1*), ubiquitinated protein (IID: *KLHL3*, IIE: *CUL3*), AD	High K, low PRA, metabolic acidosis, normal PAC, thiazide responsiveness
Apparent mineralocorticoid excess (AME) (New syndrome)	11β-hydroxysteroid dehydrogenase (*HSD11B2*), AR	Low PRA, low PAC, low K, delayed growth, metabolic alkalosis, spironolactone responsiveness
Glucocorticoid-remediable aldosteronism (GRA) (corresponding to type I familial aldosteronism (FH-I))	11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) chimera, AD	Low PRA, low PAC, low K (rare), glucocorticoid/spironolactone responsiveness
Type III familial aldosteronism (FH-III)	G protein-coupled inwardly rectifying potassium channel (*KCNJ5*), AD	Low PRA, low PAC, high 18-oxocortisol, adrenal hyperplasia, high 18-hydroxycortisol
11β-hydroxylase deficiency (11β-OHD)	11β-hydroxylase (*CYP11B1*), AR	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, virilization
11α-hydroxylase deficiency (11α-OHD)	17α-hydroxylase (*CYP17*), AR	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, feminization
Early-onset type hypertension with severe exacerbation during pregnancy	Mineralocorticoid receptor (MR) (*NR3C2*), AD	Onset at <20 years of age, development of eclampsia, blood-pressure increase by the actions of progesterone on mutant MR
Hereditary hypertension with brachydactyly (HTNB)	Phosphodiesterase 3A (*PDE3A*), AD	E-type brachydactyly, severe non-salt-sensitive/aging-related hypertension, onset of stroke at <50 years of age, changes in the baroreceptor reflex
Metabolic defects cluster (hypertension, hypercholesterolemia, hypomagnesemia)	Mitochondrial tRNA, isoleucine (*MTTI*), maternal inheritance	Low Mg, low K, permeability: 50%, onset at <50 years of age
Hereditary hypotension	**Causative genes**	**Clinical features**
Type 1/2 Bartter syndrome	Type 1: Na-K-2Cl cotransporter (*SLC12A1*), AR Type 2: ATP-sensitive K channel (*KCNJ1*), AR	Severe, low K, low Mg, metabolic alkalosis, hyperprostaglandin E_2 syndrome, high PRA, high PAC
Type 3/4 Bartter syndrome	Type 3: kidney Cl channel (*CLCNKB*), AR Type 4: Barttin (*BSND*), AR	Onset during childhood, polyuria, tetanus (rare), low K high PRA, high PAC, hypercalciuria
Gitelman syndrome	Thiazide-sensitive Na-Cl cotransporter (*SLC12A3*), AR	Onset during adolescence, milder than Bartter syndrome, hypocalciuria, high PRA, high PAC, low K, low Mg
Type I pseudohypoaldosteronism (PHA I)	Mineralocorticoid receptor (*NR3C2*), AD (PHAIA), epithelial Na channel α/β/γ subunit (*SCNN1A/B/G*), AR (PHAIB)	Onset during the neonatal period/infancy, high PRA, high K, low Na, age-related amelioration of symptoms (PHAIA), severer than PHAIB

AD, autosomal dominant, *AR*, autosomal recessive

pressure changes and the functional prognosis after the onset of ischemic stroke [1631, 1632]. A prospective survey involving 48 hypertensive patients with unilateral facial spasm and neurovascular compression showed that decompression normalized blood pressure in 14 patients (29%) in the absence of antihypertensive drugs, and that good blood pressure control was achieved in most patients [1633]. Therefore, in patients with neurological symptoms, such as unilateral facial spasm and trigeminal neuralgia, surgical decompression should be considered. On the other hand, neither the efficacy nor safety of decompression in patients without concomitant neurological symptoms has been established. In nonresponders to treatment with antihypertensive drugs, whether this procedure should be indicated must be carefully examined. As antihypertensive drugs, α-blockers, β-blockers and centrally acting sympatholytic drugs are effective from the perspective of their pressor mechanisms. RA system inhibitors and CCBs, especially drugs with sympatholytic actions, are useful [1634, 1635].

POINT 13E

[HEREDITARY HYPERTENSION]

1. **Essential hypertension is a multifactorial disorder in which genetic and environmental factors are involved. Approximately 30–70% of inter-individual differences are influenced by genetic factors. For genetic factors, many common variants have been identified.**
2. **The influence of individual genetic variants on blood pressure in the general population is not marked (~1 mmHg). Despite the potential racial diversity, the frequency of candidate gene polymorphisms for salt sensitivity is high in the Japanese population.**
3. **On the other hand, genetic variants that markedly influence blood pressure have also been reported, although they are rare.**
4. **Hereditary blood pressure abnormalities caused by single-gene disorder exist, but are rare.**

6. HEREDITARY HYPERTENSION

Essential hypertension is a multifactorial disease in which many genetic and environmental factors are involved. The morbidity of hypertension is reported to be ~3.5 times higher in pairs of hypertensive siblings than in the general population [1636], and the contribution of genetic factors is estimated to be approximately 30–70% [1637]. Common inter-individual variations in the nucleotide sequence of the genome observed in the general population are called 'genetic polymorphisms or variants', showing a wide range of frequency, from common to rare. Among genetic factors, common mutations were identified by comprehensive genetic analysis, that is, a genome-wide association study (GWAS), and the total number of hypertension-associated gene loci exceeded 500. However, the influence of individual common variants on blood pressure in the general population is only slight (~1 mmHg) [1638], suggesting that epigenomes, such as DNA methylation, are etiologically involved. The diagnosis of essential hypertension based on genetic variants information alone is considered difficult [1639]. In a GWAS involving different racial groups, while many genetic factors have been identified across the populations, there should be marked racial differences in the rate of genetic variants and their influence on blood pressure [1640]. In addition, a GWAS of salt sensitivity-associated genes was conducted [1641], and a study reported that the frequency of candidate gene polymorphisms for salt sensitivity was relatively high in the Japanese population [1642]. Therefore, information on gene polymorphisms may be useful for recommending lifestyle modifications, including salt reduction [1643], and for selecting antihypertensive drugs [1644].

On the other hand, among the genetic factors, some rare variants markedly influence blood pressure [1645], and diagnosis and treatment may be determined/changed primarily based on such variant information, although it is rare, in a group of individuals. In contrast, rare heritable blood pressure abnormalities caused by single-gene mutation and diagnosed by gene analysis have been reported [1646]. In particular, many such blood pressure abnormalities result from gene mutations of ion channels or cotransporters regulating water and electrolyte balance at the renal tubular level. In clinical practice, genetic analysis is also performed in some cases to make a definitive diagnosis. Table 13-6 shows the genes responsible for and clinical characteristics of hereditary blood pressure abnormalities. In the clinical setting, cases in which genetic analysis is required are rare. However, if patients with early-onset hypertension do not respond to treatment and have a low PRA value, an abnormal serum potassium level and acid-base balance disturbance, the possibility of hereditary hypertension must be considered. When suspecting hereditary hypertension based on family history or clinical characteristics and wishing to perform a detailed analysis, the attending physician should consult a specialist in hypertension, because specialized analytical facilities differ depending on the gene abnormalities. In such cases, currently, the purpose of genetic analysis is limited to research, and it is essential to conduct gene analyses in accordance with the Ethics Guidelines for Human Genome/Gene Analysis Research [1647] from the timing of informed consent regarding blood collection.

Table 13-7 Drugs causing drug-induced hypertension and hypertension treatment

Causative drugs	Etiologies of hypertension	Strategies to treat hypertension
NSAIDs	Water/Na retention and vasodilator suppression by the inhibition of renal prostaglandin production, attenuation of the antihypertensive effects of ACE inhibitors/ARBs/β-blockers/diuretics	Dose reduction/discontinuation of NSAIDs, dose elevation of an antihypertensive drug that has been administered, CCBs
Glycyrrhiza (licorice) Glycyrrhizin-containing drugs for liver disease, drugs for digestive disorders, *kampo* drugs, supplements, cosmetics	Water/Na retention and K reduction by the enhancement of intrinsic steroid actions related to the prolongation of the half-life of cortisol associated with the inhibition of 11β-hydroxylated steroid dehydrogenase	Dose reduction/discontinuation of *kampo* drugs, MR antagonists
Glucocorticoids	Increases in angiotensinogen and erythropoietin productions and the inhibition of NO production may be involved in the mechanism, but it remains to be clarified.	Dose reduction/discontinuation of glucocorticoids, CCBs, ACE inhibitors, ARBs, β-blockers, diuretics, MR antagonists
Cyclosporine, tacrolimus	Nephrotoxicity, activation of the sympathetic nervous system, inhibition of calcineurin, vascular endothelial cell dysfunction	CCBs, combination therapy with CCBs and ACE inhibitors, diuretics
Erythropoietin	Enhancement of blood viscosity, vascular endothelial dysfunction, an increase in the intracellular Na level	Dose reduction/discontinuation of erythropoietin, CCBs, ACE inhibitors, ARBs, β-blockers, diuretics
Estrogen Oral contraceptives, hormone replacement therapy (HRT)	An increase in angiotensinogen production	Discontinuation of estrogen preparations, ACE inhibitors, ARBs
Drugs with sympathomimetic actions Phenylpropanolamine, tricyclic/tetracyclic antidepressants, serotonin/noradrenaline reuptake inhibitors, monoamine oxygenase inhibitors	α-receptor stimulation, inhibition of catecholamine reuptake at the sympathetic nerve terminals	Dose reduction/discontinuation of drugs with sympathomimetic actions, α-blockers
Cancer molecule-targeting drugs Angiogenesis inhibitors (anti-VEGF antibody preparations, inhibitors against several types of kinase)	A decrease in the microvascular floor, a reduction in NO synthesis, renal hypofunction	Dose reduction/discontinuation of molecule-targeting drugs, if possible, treatment with standard antihypertensive drugs

POINT 13F

[DRUG-INDUCED HYPERTENSION]

1. **NSAIDs raise the blood pressure and antagonize the antihypertensive effects of diuretics, β-blockers, ACE inhibitors and ARBs. Their influence is more marked in older patients or those with renal dysfunction; therefore, these drugs must be carefully administered.**
2. **The use of *kampo* drugs containing glycyrrhizin, a major active component of glycyrrhiza, drugs for liver/gastrointestinal diseases, or health foods may cause hypertension associated with hypokalemia (pseudoaldosteronism). Attention is necessary particularly when using *kampo* drugs. If there is an increase in blood pressure, the discontinuation of these drugs must be considered.**
   If the discontinuation of administration is difficult, an MR antagonist should be used.
3. **Massive therapy with glucocorticoids causes an increase in blood pressure. If their administration is unavoidable, CCBs, ACE inhibitors, ARBs, β-blockers, diuretics or MR antagonists should be used.**
4. **The use of cyclosporine or tacrolimus may cause an increase in blood pressure. For antihypertensive treatment, CCBs, ACE inhibitors, ARBs or diuretics should be used.**
5. **The use of erythropoietin, estrogen or sympathomimetic drugs including antidepressants may cause an increase in blood pressure. If blood pressure increases during the use of these drugs, a reduction in the dose or discontinuation of administration should be considered.**
   If they cannot be discontinued, CCBs, ACE inhibitors, ARBs or α-blockers should be used.
6. **Cancer molecule-targeting drugs, primarily, angiogenesis inhibitors (anti-VEGF antibody preparations or inhibitors against several types of kinase), cause hypertension. Its incidence depends on the type of drug or tumor. However, when using these drugs, changes in blood pressure must be monitored. Treatment with routine antihypertensive drugs should be performed.**

7. DRUG-INDUCED HYPERTENSION

Drugs, such as NSAIDs, glycyrrhizin preparations, glucocorticoids, cyclosporine, erythropoietin, oral contraceptives and sympathomimetic drugs, are suggested to have hypertensive effects, to cause hypertension and attenuate the blood pressure-lowering effects of antihypertensive drugs if used concomitantly. Recently, hypertension caused by molecule-targeting drugs has been reported (Table 13-7). Many hypertensive patients also have other diseases and consult multiple medical organizations. Therefore, if the blood pressure management used to be adequate but has become difficult, or in cases of poorly controlled hypertension, the possibility of drug-induced hypertension should be considered. Also, if these drugs are used, attention must be paid to blood pressure control, and their administration simply as routine must be avoided.

1) NSAIDs

NSAIDs inhibit cyclooxygenase (COX) in the process of prostaglandin production by arachidonic acid, suppressing renal prostaglandin production and, thus, reducing water/sodium retention and vasodilation [1648]. In older patients and patients with renal dysfunction, renal prostaglandins maintain the renal function as a compensatory mechanism and contribute to the prevention of an increase in blood pressure. A decrease in the production of prostaglandin related to the use of NSAIDs increases blood pressure by renal hypofunction. COX has two isoforms, COX-1 and COX-2, which are expressed in the presence of inflammation. Although classic NSAIDs nonselectively inhibit both, there are also selective inhibitors of COX-2. The harmful effects of nonselective and selective COX-2 inhibitors on the cardiovascular system are related to the suppression ratio between COX-1 and COX-2 and tissue-specific COX distribution, rather than the selectivity. Therefore, similar caution is necessary when using NSAIDs that are nonselective as well as for selective COX-2 inhibitors [1649–1651].

In older people, NSAIDs often cause acute renal dysfunction, which further aggravates the rise in blood pressure, and they also increase the risk of heart failure if used concomitantly with diuretics compared with diuretics alone. Therefore, if NSAIDs are administered to older hypertensive patients, they should be used at a low dose for a limited period with careful observation and examination of the renal function. If renal hypofunction is observed and the drug cannot be discontinued, switching to acetaminophen should be considered.

Diuretics simultaneously inhibit the reabsorption of NaCl and stimulate prostacyclin production in the renal tubules. Therefore, the antihypertensive effects of diuretics are reduced when they are used with NSAIDs. The antihypertensive effects of ACE inhibitors and β-blockers are also reduced by their concomitant use with NSAIDs. The effects of their concomitant use with ARBs have not been evaluated sufficiently, but ARBs appear to be affected similarly as ACE inhibitors [1652]. There is no influence on

the antihypertensive effects of CCBs in combination with NSAIDs.

2) Glycyrrhiza (licorice), glycyrrhizin

Glycyrrhiza is contained in drugs for liver and gastrointestinal diseases, in many other *kampo* drugs, in supplements and in cosmetics. Glycyrrhizin, a major active component of glycyrrhiza, inhibits 11β-hydroxylated steroid dehydrogenase, which metabolizes cortisol into inactive cortisone, enhances the actions of endogenous steroids by prolonging the half-life of cortisol [1653] and enhances Na/water retention and reduces the potassium level, causing pseudoaldosteronism. The glycyrrhizin dose, administration period and age (≥60 years) are considered to be risk factors for glycyrrhizin-induced hypertension [1654]. Glycyrrhizin-induced hypertension should be suspected if hypokalemia is concurrent with hypertension, and if the plasma renin activity and plasma aldosterone level are reduced (pseudoaldosteronism). As the use of *kampo* drugs or supplements is rarely reported by patients themselves, the possibility of their use must be carefully evaluated. Clinically, glycyrrhizin-induced hypertension is resolved by the discontinuation of glycyrrhiza ingestion for a few weeks (maximum: 4 months) or by combination therapy with an MR antagonist.

3) Glucocorticoids

Glucocorticoids rarely cause hypertension at low doses even in the long-term treatment of asthma or rheumatoid arthritis. However, the long-term administration of glucocorticoids at intermediate doses frequently causes hypertension [1655]. As with other drugs, blood pressure increased more notably in older patients with increases in the dose of prednisolone, and marked increases were observed when the dose was 20 mg per day or higher. Hypertension was observed in 37.1% of these older patients, and hypertensive patients more often had a familial history of hypertension compared with nonhypertensives [1656]. The mechanism of a glucocorticoid-induced increase in blood pressure remains to be clarified, although an increase in the angiotensin II level due to elevated angiotensinogen production [1657], vasoconstriction due to an increase in erythropoietin production [1658], vascular endothelial dysfunction by impairment of nitric oxide (NO) use related to the inhibition of NO production [1659] or excess production of superoxides [1660], and stimulation of mineral corticoid receptors have been suggested. Treatment is primarily a decrease in dose or withdrawal of the glucocorticoid. If this is difficult, blood pressure should be controlled with CCBs, ACE inhibitors, ARBs, β-blockers, diuretics or MR antagonists.

4) Others

Cyclosporine and tacrolimus are used for immunosuppression after organ or bone marrow transplantation. Both of them frequently cause hypertension, although frequency varies with dose, treatment period and pathological conditions. Although the mechanism of the occurrence of hypertension has not been sufficiently clarified, the involvement of nephrotoxicity [1661], stimulation of the sympathetic nervous system [1662], inhibition of calcineurin [1663] and vascular endothelial cell dysfunction [1664] are suspected. CCBs are effective in the treatment of hypertension due to immunosuppressants, and their combination with ACE inhibitors has been reported to be even more effective [1665]. Although diuretics are also effective, caution regarding uric acid metabolism is necessary in patients after kidney transplantation.

As CCBs may increase the blood concentrations of cyclosporine and tacrolimus, measurement of the blood concentrations of these immunosuppressants should be considered if necessary.

Although erythropoietin alleviates renal anemia, it increases the blood pressure. In Japan, an increase in blood pressure was reported in 29% of patients surveyed in postmarketing research [1666]. Its possible mechanism involves increases in the hematocrit and blood viscosity associated with recovery from anemia by erythropoietin treatment and a resultant increase in peripheral vascular resistance, but this possibility has been refuted by one report [1667]. An increase in the intracellular Na concentration [1668], vascular endothelial dysfunction [1669] and genetic predispositions [1670] may also be involved. There is also a report that no increase in blood pressure due to erythropoietin was observed before hemodialysis [1671]. The dose of erythropoietin should be reduced or administration should be discontinued if hypertension develops or if blood pressure increases. However, if the increase is mild, antihypertensive drugs are also useful [1672]. On the other hand, a study indicated that blood pressure control was insufficient despite the administration of antihypertensive drugs in chronic dialysis patients (patients registered at the Japanese Society for Dialysis Therapy), of whom 82% were taking erythropoietin [1673].

Estrogen is used as an oral contraceptive and drug for climacteric disturbance, but has been considered to cause an increase in blood pressure or thromboembolism at a high dose. The details of the mechanism of estrogen-induced hypertension have not been clarified, although an increase in angiotensinogen production in the liver may be involved. An investigation of the relationship between the use of oral contraceptives and health showed that, although the blood pressure and lipid levels in users were slightly higher than in age-matched nonusers, the former's satisfaction with health and QOL was higher, suggesting the safety of oral contraceptives [1674]. Although the rate of increase in blood pressure was dose-dependent, caution is necessary even at a low dose. A sufficient analysis of the relationship

between oral contraceptives and hypertension has not been performed in Japan. When using oral contraceptives, blood pressure should be measured periodically, their use should be discontinued if an increase in blood pressure is observed and other contraceptive measures should be selected. If they cannot be discontinued, the administration of ACE inhibitors or ARBs should be considered. Concerning hormone replacement therapy (HRT), see Section 2 of Chapter 10, POSTMENOPAUSAL BLOOD PRESSURE.

Drugs with sympathomimetic actions may increase the blood pressure. An overdose of phenylpropanolamine, which is contained in drugs for the common cold, may increase the blood pressure. Caution is needed in its concomitant use during treatment with a β-blocker alone, because it may cause a state of dominant α-receptor stimulation and cause a marked increase in blood pressure. Tri- or tetracyclic antidepressants may also inhibit the antihypertensive effects of peripheral sympatholytic drugs by inhibiting catecholamine reuptake at the sympathetic nerve terminals and cause hypertensive crisis [1675] or hypertensive emergencies [1676]. Serotonin/noradrenaline reuptake inhibitors (SNRIs), which are used as antidepressants, reduce pain by inhibiting catecholamine uptake. They are selected to treat neuropathic pain, but may increase blood pressure by sympathomimetic actions.

Monoamine oxidase inhibitors, which are used for the treatment of Parkinson's disease, also cause an increase in blood pressure or orthostatic dysregulation.

A monoamine oxidase inhibitor and a tricyclic antidepressant must not be used simultaneously. The concomitant use of a monoamine oxidase inhibitor with ephedrine or methylephedrine may also increase blood pressure and tachycardia. If hypertension develops by these drugs, a reduction in the dose or discontinuation of administration is necessary, but if discontinuation is impossible α-blockers or central sympatholytic agents should be administered.

As metoclopramide, a dopamine (D2) receptor antagonist used for the treatment of gastrointestinal disorders, β-blockers and tricyclic antidepressants may cause clinical activation of pheochromocytoma as well as hypertensive crisis, caution is needed in their use [1677].

Molecule-targeting drugs inhibiting angiogenesis, which are used for the treatment of malignant tumors or age-related macular degeneration, primarily angiogenesis inhibitors (anti-VEGF antibody preparations and inhibitors against several types of kinase), may cause hypertension, myocardial infarction and cerebral infarction [1678, 1679]. The incidence of hypertension is reportedly approximately from 2–3% to 80%, although it depends on the type of drug or tumor and race [1680]. The pathogenesis of hypertension remains to be clarified, but an increase in peripheral vascular resistance associated with a decrease in the microvascular floor or a VEGF inhibition-related reduction in NO production, as well as renal dysfunction, is suggested [1680–1682]. If hypertension is present before the start of treatment with anti-VEGF antibody preparations, strict blood pressure control should be performed. If hypertension develops, a reduction in the dose of the drug or discontinuation must be considered, and treatment with standard antihypertensive drugs should be performed. However, some studies recommend that, under specific circumstances, renin–angiotensin–aldosterone (RAA) system inhibitors or CCBs should be administered [1680, 1682].

CQ17 IS THERE A DIFFERENCE IN THE PROGNOSIS BETWEEN ADRENALECTOMY AND THERAPY WITH MR ANTAGONISTS FOR PRIMARY ALDOSTERONISM (PA)?

►Affected-side adrenalectomy is recommended for patients with unilateral lesions as the normalization of aldosterone excess and cure/amelioration of hypertension may be achieved.

Recommendation grade: 1 Evidence level: C

►In patients with bilateral lesions, those who do not wish to undergo surgery or in whom surgery is impossible, and those who do not wish to undergo examinations after screening, drug therapy with an MR antagonist, as a first-choice drug, should be performed, and, as a rule, it must be continued over the lifetime.

Recommendation grade: 1 Evidence level: C

SUMMARY OF EVIDENCE

We compared adrenalectomy with therapy with MR antagonists, but there is no evidence regarding the usefulness of the former for improving the long-term outcome in comparison with the latter. There is no article corresponding to a difference in the total mortality rate, and we could not evaluate it. There were no differences in a decrease in the incidence of cardiovascular diseases, a decrease in the incidence of left ventricular hypertrophy, alleviation of hypertension, reduction of hypokalemia or an increase in the incidence of renal dysfunction between the two groups. In the adrenalectomy group, there was a more marked decrease in the number of oral antihypertensive drugs. There is little evidence regarding the comparison of these treatment procedures, and the effects on the prognosis were similar between the two procedures, excluding a decrease in the number of oral antihypertensive drugs.

INTERPRETATION

PA is classified into two disease types: APA and IHA. After a diagnosis of PA is made based on the results of a function-confirming test, its location and disease type are evaluated

by AVS. In patients with APA, aldosterone production is higher than in those with IHA, and an increase in blood pressure, hypokalemia, and cardiovascular events are more frequent. Furthermore, cure is achieved in approximately 45% of APA patients undergoing adrenalectomy, whereas drug therapy must be continued over the lifetime. Therefore, therapeutic strategies depend on the disease type. As a rule, affected-side adrenalectomy has been established for patients with APA, and therapy with MR antagonists for those with IHA. These are recommended in endocrine society guidelines in various countries [1587, 1589, 1683]. Even among APA patients, adrenalectomy is not performed in only a limited number of patients for the following reasons: the poor general condition, making surgery impossible, or patients do not wish to undergo surgery. We conducted a meta-analysis for this CQ, but there was no study comparing adrenalectomy with therapy with MR antagonists for APA or IHA. We should keep in mind that this CQ is based on the literature involving adrenalectomy for APA and therapy with MR antagonists for IHA.

Thus, we compared adrenalectomy with therapy with MR antagonists [1684]. To compare the two groups, we examined the total mortality rate, a decrease in the incidence of cardiovascular diseases, a decrease in the incidence of left ventricular hypertrophy, alleviation of hypertension, reduction of hypokalemia, an increase in the incidence of renal dysfunction, and a decrease in the number of oral antihypertensive drugs. Concerning the total mortality rate, as the number of events was small, and there were no relevant articles, evaluation was impossible. There were no treatment-related differences in a decrease in the incidence of cardiovascular diseases (risk ratio: 0.85, 95%CI: 0.22–3.29), a decrease in the incidence of left ventricular hypertrophy (mean difference: −2.89 g/m$^{2.7}$, 95%CI: −8.77–2.98), a decrease in SBP (mean difference: −1.86 mmHg, 95%CI: −5.20–1.48), reduction of hypokalemia (mean difference: 0.09 mEq/L, 95%CI: −0.08–0.25), or an increase in the incidence of renal dysfunction (mean difference: −1.83 mL/min/1.73m^2, 95%CI: −5.85–2.20). In the adrenalectomy group, there was a significant decrease in the number of oral antihypertensive drugs in comparison with the drug therapy (MR antagonist) group (mean difference: −1.76, 95%CI: −2.01 – −1.52). Overall, there was no marked difference in the prognosis between adrenalectomy and therapy with MR antagonists.

As described above, disease-type-based treatment methods for PA have been established, and it may be difficult to conduct a clinical study comparing treatment methods with respect to the disease type in the future. This meta-analysis involved the comparison of patients who underwent adrenalectomy for APA with those who received treatment with MR antagonists for IHA. There was no difference in the prognosis, excluding a decrease in the number of oral antihypertensive drugs, between the two groups. However, a study reported that the total mortality rate and incidence of cardiovascular diseases in the adrenalectomy group were lower than in the non-surgery group [1596], and a prospective study indicated that there was no difference in the incidence of atrial fibrillation between APA patients undergoing adrenalectomy and patients with essential hypertension, whereas it increased in the IHA drug therapy group (newly published literature) [1597], although these studies were not detected on literature searching. Therefore, if a diagnosis of APA is made, adrenalectomy should be considered. Concerning MR antagonist therapy, it was reported that, when the dose was adjusted so that the suppression of PRA might be reduced (>1 ng/mL/hour), there was no significant difference in the cardiovascular prognosis in comparison with patients with essential hypertension, whereas the cardiovascular prognosis in the presence of PRA suppression was poorer than in patients with essential hypertension. For therapy with MR antagonists, the blood pressure, serum potassium concentration, and PRA should be used as indices [1598].

Q9 HOW SHOULD SECONDARY HYPERTENSION SCREENING DURING ANTIHYPERTENSIVE DRUG THERAPY BE PERFORMED?

- Renin–angiotensin system
  As a rule, the administration of ARBs, ACE inhibitors, diuretics, and ☒-blockers should be discontinued for 2 weeks before renin and aldosterone measurement, and the administration of MR antagonists should be

Table Q9-1 Parameters for secondary hypertension screening

Disease	Parameter
RVHT	PRA or active renin level
Primary aldosteronism	PAC
Pheochromocytoma	Blood catecholamine, urinary catecholamine Urinary catecholamine metabolites (metanephrine • normetanephrine)
Cushing's syndrome	Blood ACTH • blood cortisol, urinary free cortisol
Hyper-/hypothyroidism	Thyroid-stimulating hormone • free T4 • free T3
Primary Hyperparathyroidism	Parathyroid hormone, serum Ca, phosphorus level

discontinued for 4 weeks. If the discontinuation of antihypertensive drug administration is difficult, the drug should be switched to a CCB or an □-blocker. If switching to a CCB or an □-blocker alone is difficult, the renin and aldosterone levels may be measured without changing antihypertensive drugs.

- Catecholamines
  On measuring catecholamines and their metabolites, β- and α-blockers may influence measurement values, but it is possible to perform screening tests while continuing the oral administration of antihypertensive drugs.
- ACTH, cortisol

No study has reported the influence of antihypertensive drugs on ACTH or cortisol measurement. These parameters may be measured while continuing the oral administration of antihypertensive drugs. However, dexamethasone, which is used for a function-confirming test, is influenced by CYP3A4, which is a hepatic drug-metabolizing enzyme. Therefore, the ACTH and cortisol levels may be influenced on a dexamethasone suppression test during therapy with diltiazem or nifedipine, which influence CYP3A4 activity.

INTERPRETATION

Parameters to be evaluated on secondary hypertension screening are presented in Table Q9-1. Of these, renin, aldosterone and catecholamines/their metabolites may be influenced by antihypertensive drugs.

Many antihypertensive drugs influence renin and aldosterone. In particular, the influence of MR antagonists is marked. These drugs increase both the renin and aldosterone levels, but their influence on the former is particularly marked, reducing the ARR [1685]. β-blockers increase the ARR by a reduction in plasma renin activity (plasma renin concentration), increasing the number of false-positive findings [1686, 1687]. Diuretics may contribute to false-negative findings by an increase in plasma renin activity. ACE inhibitors and ARBs increase plasma rennin activity, but reduce the aldosterone level; therefore, they may increase the number of false-negative findings [1686]. According to some studies, there is no influence of α-blockers on the ARR [1589, 1686].

Thus, screening should be performed before antihypertensive drug administration or after discontinuation for at least 2 weeks. In particular, the administration of MR antagonists, which may markedly influence the results of screening, should be discontinued for 4 weeks [1589]. However, blood pressure control should be conducted as a first priority even during the examination period. The regimen should be switched to monotherapy with a CCB or an α-blocker or combination therapy with the two drugs, which may not markedly influence the results of screening. In patients with poor blood pressure control in whom switching to these antihypertensive drugs is difficult, the ARR may be measured without changing antihypertensive drugs, considering their influence on the ARR [1688–1693].

In the guidelines for the management of pheochromocytoma/paraganglioma published in the United States, it is indicated that the urinary levels of metanephrine and normetanephrine to be measured for pheochromocytoma diagnosis may increase in patients receiving labetalol, sotalol, or α-methyldopa, which depends on measurement methods [1604]. However, these drugs may not influence the values measured using primary measurement methods in Japan such as high-performance liquid chromatography and liquid chromatography-mass spectrometry. It is possible to measure catecholamines and their metabolites during antihypertensive drug therapy.

No study has reported the influence of antihypertensive drugs on the ACTH or cortisol levels. In patients with Cushing's syndrome, the dexamethasone suppression test is conducted as a function-confirming test. As dexamethasone is metabolized by CYP3A4, the effects of dexamethasone may be potentiated in patients receiving a drug that reduces CYP3A4 activity (diltiazem), enhancing suppression. In contrast, the effects of dexamethasone may be reduced in patients receiving a drug that increases CYP3A4 activity (nifedipine), attenuating suppression. When interpreting the cortisol level on the dexamethasone suppression test, caution is needed [1694].

Chapter 14 Attempts for improving hypertension management and future perspectives

POINT 14

1. **Despite the remarkable progress in the diagnosis/treatment methods for hypertension and preparation of hypertension treatment guidelines, hypertension still remains the greatest cause of death from cardiovascular diseases in Japan.**
2. **Countermeasures against hypertension need to be taken not only at the level of individuals but also at the level of the entire society.**
3. **Approaches with multidisciplinary linkage, with the current status of regional communities taken into account, are needed against hypertension.**
4. **It is essential to set definite goals of antihypertensive treatment by the team consisting of patients/family members and healthcare professionals and to share a concrete plan to achieve the goals.**

5. **Utilization of various databases will enable identification of untreated patients and patients with poor control of hypertension as well as follow-up of the course of their treatment and is thus expected to contribute to improving the treatment rate and the control rate.**
6. **Factors underlying insufficient blood pressure control include clinical inertia in addition to poor adherence to drug intake instructions and inappropriate lifestyle.**
7. **Enforcement of the "Basic Law Concerning Countermeasures against Stroke, Heart Disease and Other Cardiovascular Diseases for Extension of Healthy Lifespan" is expected to accelerate also anti-hypertension measures, which are important in prevention of the onset of cardiovascular diseases, taken by the entire society.**

In Japan, there are as many as 43 million patients with hypertension, and hypertension is the disease with the highest incidence. Due to the development of excellent diagnostic methods and drugs in recent years, management of hypertension has advanced remarkably over the past four decades. There is, however, an important issue related to hypertension, that is, the fact that only 57% (24.5 million) of all hypertensive patients are receiving treatment, and in only about 50% of them (12 million, accounting for less than 30% of all hypertensive patients) is blood pressure being controlled (to less than 140/90 mmHg) (see Chapter 1 "Epidemiology of hypertension"). As a result, hypertension is the leading cause of death related to cardiovascular diseases (stroke, myocardial infarction, heart failure). According to the investigation in 2007, hyptertension is responsible for about 100000 death annually. It is additionally known that the presence of hypertension increases the risk of developing cognitive dysfunction, and it is a major factor leading to the need for nurseing care in daily living, together with the role of sequelae to stroke. Thus,

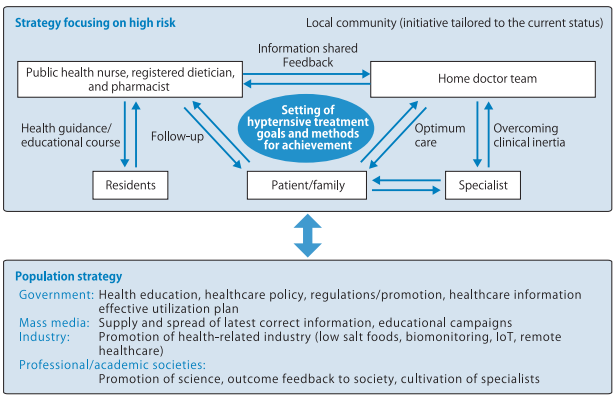


Fig. 14-1 Measures for improvement in hypertension treatment

despite the remarkable advances in the diagnosis/treatment of hypertension, countermeasures against hypertension are still insufficient, and this status is called the "hypertension paradox". In Japan which now faces the the trend of low birth rate and aging of the population, countermeasures against hypertension can be viewed as an urgent topic in extending the healthy lifespan of the nation.

In such diseases like hypertension which is free of subjective symptoms and can have large impacts on the nation's health/welfare and medical economy because of the large number of patients, developing an appropriate method of diagnosis and treatment does not suffice for adequate management. It is additionally important to help individuals become aware of whether they have hypertension and understand the importance of its treatment, and to assure so that treatment is started and blood pressure goal achieveded and maintainted. Hypertension is a disease which is affected markedly by the lifestyle of individuals, and lifestyle is affected largely by social background. Therefore, countermeasures against hypertension need to be taken by the entire society rather than at the level of individuals.

In preceding chapters, the measures for improving hypertensive treatment were described. Chapter 1 "Epidemiology of Hypertension" describes the population strategy and the high-risk strategy as measures against hypertension from the public health point of view. Chapter 3 "Principles of Hypertension Management and Treatment" describes the importance of patient-participating healthcare, concordance, adherence and consideration of quality of life (QOL). In ordr for these measures to be effective, approaches with consideration of the actual status of patients/inhabitants within a local community is needed and, for this purpose, close linkage/cooperation among healthcare providers (home doctors, specialist physicians, affiliated healthcare professionals), public health nurses, registered dieticians, pharmacists, local government agencies and regional industrial organizations is essential. For the population strategy, close linkage/cooperation among governments, mass media, industrial organizations and academics is also important. Effective approaches by a combination of implementation of anit-hypertensive measures in local communities and population strategy is indispensable for extending the healthy lifespan by reducing cardiovascular diseases arising from hyperyension (Figure 14-1). Such comprehensive measures serve as the core of the "Basic Law on Measures against Stroke, Heart Disease and Other Cardiovascular Diseases to be Taken for Extending Healthy Lifespan" (the so-called "Anti-Cardiovascular Disease Basic Law") made public on December 14, 2018. This basic law sets forth the necessity of commitment by all stakeholders related to cardiovascular diseases, including the people, the central government, local governments, healthcare/public health organizations, academia and industrial

organizations. For this purpose, a basic plan for promotion of anti-cardiovascular disease measures will be devised, and incorporate concrete action plans. We may thus expect that measures against hypertension, which is the largest factor responsible for cardiovascular diseases, will be promoted in a comprehensive manner.

What is most basic and important in the management of hypternsion within local communities is creation of sufficient partnership between patients/families and medical teams as well as setting/sharing definite goals of hypertensive treatment and concrete treatment plans towards such goals (Figure 14-1). During such a process, the understanding of hypertension and importance of its treatment among patients and their family members will be deepened and the team organized by patients/families and home doctors can take actions together towards achievement of the goal. Such a treatment plan should not be devised or implemented in a uniform way. Instead, it should be devised in a manner tailored to the view of life, lifestyle, occupation and family profile of individual patients as well as the culture and traditions unique to a given community for achieving maximum efficacy. It is practically impossible for physicians to take all of these actions during their busy practice. Thus, the roles played by affiliated healthcare professionals, such as nurses, pharmacists and registered dieticians involved in hypertension management, will be important. Thus, cultivation of affiliated healthcare professionals having expertise knowledge is needed. In addition, actions and initiatives at local communities are also important in continuation of good blood pressure control for patients. Public health nurses have opportunities of collecting information about the daily living of residents and hypertensive patients at home. Close information exchange between home doctors and public health nurses to provide effective advice on health and medication and follow-up tailored to the features of individual patients is thus important. To facilitate such linkage, it is indispensable to establish a close system of cooperation and linkage among medical associations, administrative/public health agencies, and academic societies.

Another key element of anti-hypertension measures in local communities is how to decrease the number of untreated patients. Such patients with hypertension account for 18.5 million, of whom 14 million are unaware of hypertension and 4.5 million are aware of this illness (see Chapter 1). Although Japan has excellent public health checkup programs, the public health checkup for local residents aged 40–74 was actually implemented for by only 51.4% of the residents covered by the program in 2016 and the health guidance based on such health checkup was given to only 17.0% of those judged as requiring such guidance in the same year. Under such circumstances, it is necessary to promote a population strategy (e.g., educational campaigns to people) and initiatives reflecting the actual status in local communities. If health checkup data are compared with the data contained in the bills to health insurers, it will be possible to identify untreated patients and patients not yet having achieved the treatment goals, and to follow the course of treatment in individual patients, eventually contributing to improving the hypertension treatment rate and control rate. It is essential to develop a system for effective utilization of such data by linkage/cooperation among insurers and administrative agencies.

One of the characteristics of Japan is the high salt intake. Initiatives of the entire society to reduce salt intake are particularly important (see Chapter 1 “Epidemiology of hypertension,” Chapter 4 “Lifestyle Modifications 1. Salt reduction”). To this end, strong commitment by industry, government and academia is indispensable. An example of success in such initiatives is found in the Consensus Action on Salt & Health (CASH) in the United Kingdom. Under the initiative of the British government, the food industry set a voluntary goal of reduction in salt content of products and gradually reduced the salt contained in food products. As a result, the daily amount of salt intake per adult decreased by 15% from 9.5 g in 2006 to 8.4 g in 2011, while the population taking such foods remained unaware of such an initiative. This change was accompanied by reduction in blood pressure by 3.0 mmHg (systolic pressure) and 1.4 mmHg (diastolic pressure) on average. In parallel to these changes, an approximately 40% reduction in the mortality from stroke/heart disease during the 2003–2011 period was reported [1695]. In Japan, as a considerable proportion of salt intake originates from processed food, and low salt products with good taste are being developed and available on the market. We may expect that nation-wide educational campaigns about the importance of salt reduction and the commitment by the government and industrial sectors will stimulate wide-spread use of low salt products at home and promotion of such products during health/nutritional guidance to residents. Furthermore, attempts of developing low salt products unique to local communities, based on awareness of regional dietary style/culture, have also begun to be made by local industrial organizations, and a public system supporting such activiries is now needed. The Japanese Society of Hypertension (JSH) has also made public low salt products evaluated by its own standards on its website.

Close attention has recently been paid not only to poor adherence to drug intake instructions and inappropriate lifestyle but also to clinical inertia (see the Column) [1696] as factors responsible for insufficient anti-hypertension measures despite availability of advanced diagnostic methods/ant-hypertensive drugs and treatment guidelines [1697]. Clinical inertia in the context of hypertension

management includes therapeutic inertia (treatment not yet started despite the presence of hypertension or high blood pressure left as it is without intensifying treatment despite exceeding the target level of antihypternsive treatment) and diagnostic inertia (leaving the cause for intractable/therapy-resistant hypertension unexamined) [1697–1699]. It has been considered that clinical inertia leads to continuation of insufficient blood pressure control, eventually having adverse impact on the prognosis (survival) or the onset of cardiovascular diseases. According to an investigation of general practitioners in the United States, the percentage of untreated hypertensive patients who begin to receive hypotensive drug therapy is 26.4% and the percentage of patients receiving intensified treatment because of unachieved treatment goals despite ongoing antihypertensive drug therapy is 11.2% [1700]. It is pointed out that the factors for clinical inertia on the side of healthcare providers is high patient volume, while those on the patient side includes age and number of comorbidity. Educational programs for general practitioners and patients have been reported as effective countermeasures against clinical inertia [7]. In Japan, it is necessary to clarify the status of clinical inertia and to take actions against it. Because overwhelming majority of hypertensive patietens are managed by physicians not specialized for hypertension, it is essential to promoate linkage between hypertension specialists and general practitioners, to spread hypertension management guidelines, and to improve the social campaign/educational programs for patients/residents and also the education/training programs for physicians, affiliated healthcare professionals (nurses, pharmacists, registered dieticians, laboratory technologists) and public health nurses.

As described above, the measures against hypertension need to be taken not only by medical facilities and professional societies/academic organizations but also by the entire society including the goverments and industrial fields. We expect that the recent publication of the Anti-Cardiovascular Disease Basic Law will accelerate anti-hypertension measures that are critical in preventing the onset of cardiovascular diseases.

COLUMN: CLINICAL INERTIA

In 2001, Phillips et al. reported that clinical inertia is a large factor responsible for insufficient treatment of illness free of subjective symptoms such as hypertension, diabetes mellitus and dyslipidemia [1696]. Clinical inertia involves diverse factors, including factors on the side of healthcare providers, factors on the side of patients and problems with healthcare systems. This new term is emphasized in this guideline for the purpose of disseminating the importance of following the guidelines and pointing out the necessity of addressing this issue (see the main text for details)

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List of Abbreviations

Technical Terms

ABI	ankle-brachial pressure index
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin converting enzyme
ACR	albumin creatinine ratio
ACTH	adrenocorticotropic hormone
ADPKD	autosomal dominant polycystic kidney disease
ADL	activities of daily living
AKI	acute kidney injury
AHI	apnea-hypopnea index
AOBP	automated office blood pressure

APA	aldosterone-producing adenoma
ARB	angiotensin II receptor blocker
ARC	active renin concentration
ARR	aldosterone-to-renin ratio
AVS	adrenal venous sampling
baPWV	brachial-ankle pulse wave velocity
BMI	body mass index
BNP	brain natriuretic peptide
CAVI	cardio-ankle vascular index
CCB	Ca channel blocker
cfPWV	carotid-femoral pulse wave velocity
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CTA	CT angiography
CV	coefficient of variability
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DOC	deoxycorticosterone
DRI	direct renin inhibitor
EDRF	endothelium-derived relaxing factor
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FMD	flow-mediated vasodilatation
GDS	geriatric depression scale
GWAS	genome-wide association study
HDP	hypertensive disorders of pregnancy
HELLP	hemolysis, elevated liver enzymes and low platelets counts
HRT	hormone replacement therapy
ICER	incremental cost-effectiveness ratio
IGF-1	insulin-like growth factor 1
IHA	idiopathic hyperaldosteronism
IMT	intima-media thickness
MCI	mild cognitive impairment
MIBG	metaiodobenzylguanidine
MMSE	mini-mental state examination
MR	mineralocorticoid receptor
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NO	nitric oxide
NSAIDs	non-steroidal anti-inflammatory drugs
OSAS	obstructive sleep apnea syndrome
PA	primary aldosteronism
PAC	plasma aldosterone concentration
PKD	polycystic kidney disease
PRA	plasma renin activity
PSG	polysomnography
PTH	parathyroid hormone
PTRA	percutaneous transluminal renal angioplasty
PWV	pulse wave velocity
QOL	quality of life
RCT	randomized controlled trial
RH-PAT	reactive hyperemia peripheral arterial tonometry
RVHT	renovascular hypertension
SBP	systolic blood pressure
SD	standard deviation
SR	systematic review
TIA	transient ischemic attack
t-PA	tissue plasminogen activator
TSH	thyroid stimulating hormone
UCG	echocardiography
VIM	variability independent of the mean

Organizations

AAMI	Association for the Advancement of Medical Instrumentation
AAFP	American Academy of Family Physicians
ACC	American College of Cardiology
ACP	American College of Physicians
AHA	American Heart Association
ANSI	American National Standards Institute
ACSM	American College of Sports Medicine
BPLTTC	Blood Pressure Lowering Treatment Trialists'Collaboration
ESC	European Society of Cardiology
ESH	European Society of Hypertension
JIS	Japanese Industrial Standards
JSH	Japanese Society of Hypertension
KDIGO	Kidney Disease: Improving Global Outcomes
Minds	Medical Information Network Distribution Service
PMDA	Pharmaceuticals and Medical Devices Agency
ICH-GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice
ISO	International Organization for Standardization
NICE	National Institute for Health and Clinical Excellence
NGSP	National Glycohemoglobin Standardization Program
WHO	World Health Organization