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GUIDELINES (JSH 2009)

Chapter 2. Measurement and clinical evaluation of blood pressure

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POINT 2A
Blood pressure measurement

1. **Clinic blood pressure should be measured by 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 provide stable values (difference in the values <5 mm Hg) should be used. Diagnosis of hypertension should be based on clinic blood pressures measured on at least two different occasions.**
2. **Clinic blood pressure is measured by the auscultation method using a mercury sphygmomanometer, which is the standard procedure, but the use of an automatic sphygmomanometer 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. They should be used as references in daily clinical practice.**
4. **Home blood pressure should be measured with upper-arm devices.**
5. **Criteria for hypertension differ between clinic blood pressure, 24-h ABP and home blood pressure. A clinic blood pressure of $\geqslant$140/90 mm Hg, a home blood pressure of $\geqslant$135/85 mm Hg and a mean 24-h ABP of $\geqslant$130/80 mm Hg are regarded as indicators of hypertension.**
6. **A normal home blood pressure is $<$125/80 mm Hg.**
7. **Masked hypertension and white coat hypertension must always be considered in the management of hypertension. In addition, for the diagnosis and treatment of resistant hypertension, home blood pressure measurement and 24-h ABPM are indispensable.**
8. **In treating hypertension, attention must also be given to the pattern of diurnal blood pressure changes (non-dipper, riser, dipper, extreme dipper), nighttime blood pressure, early-morning blood pressure and blood pressure at the workplace.**

1) BLOOD PRESSURE MEASUREMENT

a. Blood pressure measurement in the outpatient clinic (blood pressure measurement in a clinical setting)

Correct measurement of blood pressure is necessary for the diagnosis of hypertension. In a clinical setting (for example, an outpatient clinic), blood pressure is measured by the auscultation method using a mercury or aneroid sphygmomanometer, or using an automatic sphygmomanometer that has been calibrated by the auscultation method, and maintaining the arm-cuff position at the heart level. Nowadays, the use of a mercury sphygmomanometer is often avoided, especially in Europe, because of the possibility of environmental pollution by mercury. Table 2-1 shows the standard procedure for sphygmomanometry. Although clinic blood pressure measurement is still regarded as a standard for the diagnosis of hypertension, its clinical value has been questioned in various aspects. Clinic blood pressure measurement, in strict accordance with the procedure shown in Table 2-1, is known to more accurately reflect the true blood pressure than data obtained by disregarding this procedure, and is found to have a clinical value at least comparable to that of ambulatory blood pressure (ABP) monitoring (ABPM) or home blood pressure measurement.[40] However, blood pressure is rarely measured in accordance with such a guideline in a screening or clinical setting. In addition, the accuracy of measurement is often disregarded or ignored.

The Guidelines strongly recommend compliance with the procedure shown in Table 2-1 for the measurement of clinic blood pressure. In sphygmomanometry by the auscultation method, however, problems of terminal digit preference, that is, the tendency to round off the reading of the height of the mercury column to 0 or 5, and auscultation gap exist.

The following are other points of caution for the measurement of clinic blood pressure. For blood pressure measurement in adults, cuffs with rubber bags 13 cm wide and 22–24 cm long are usually used. Internationally, however, cuffs with a width of $\geqslant$40% of the brachial girth and a length sufficient to cover at least 80% of the brachial girth are recommended.

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 arteriosclerosis obliterans and aortic coarctation (particularly in young patients). For the measurement of blood pressure in the leg, an arm cuff is applied to the ankle, 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.

In patients with arrhythmia (premature beats), systolic blood pressure is overestimated and diastolic blood pressure is underestimated by the auscultation method.[42] The effects of arrhythmia must be excluded by repeating the measurement three or more times. In

Table 2-1 Measurement of the clinic blood pressure

1. *Device*
a. The auscultation method using a mercury or aneroid sphygmomanometer, of which the accuracy has been validated, is employed. The use of an electronic sphygmomanometer of which the accuracy has been validated is also recommended.[a]
b. A cuff with a bladder 13 cm wide and 22–24 cm long meeting the Japanese Industrial Standard is used.
(A cuff for children is used in children with a brachial girth of <27 cm. When the arms are thick (arm girth: $\geqslant 34$ 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 with the legs not crossed.
c. No conversation.
d. Smoking and alcohol/caffeine consumption should be avoided before measurement.

3. *Measurement methods*
a. The arm cuff is maintained at the heart level.
b. The cuff is rapidly inflated.
c. The rate of cuff deflation is 2–3 mm Hg per beat or second.
d. In the auscultation method, the blood pressure at the first Korotkoff sound is regarded as the systolic blood pressure, and that at the fifth Korotkoff sound as the diastolic blood pressure.

4. *Frequency of measurement*
a. Measurement is performed two or more times at 1- to 2-min intervals in one clinic visit.
b. When two measurements differ markedly, additional measurement is performed.

5. *Evaluation*
a. The mean value of two measurements that provide stable values[b] is adopted as the clinic blood pressure value.
b. Hypertension should be diagnosed on the basis of blood pressures measured on at least two different occasions.

6. *Other points requiring caution*
a. On the initial clinic visit, bilateral brachial blood pressure should be confirmed.
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 elderly persons, the blood pressure should be measured after 1- and 3-min standing to confirm the presence 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.

[a]Recently, it has been recommended that an electronic sphygmomanometer should be used for reasons such as the environmental pollution of mercury, difficulty in managing mercury column accuracy and inaccuracy of the aneroid sphygmomanometer. Furthermore, a hybrid sphygmomanometer with an electronic analogue column is available instead of a mercury sphygmomanometer. When an automatic rolling-type sphygmomanometer is used in the waiting room, measurement should be performed under sufficient guidance and management to avoid errors.
[b]Stable values mean that the difference between measurements is less than 5 mm Hg.

patients with atrial fibrillation, accurate sphygmomanometry is often difficult, but average values of systolic and diastolic blood pressures can be obtained by the cuff-oscillometric method unless the patients have bradycardia and the smoothness of consecutive pressure waves is lost.[42]

In pregnant women, Korotkoff sounds are occasionally heard at 0 mm Hg. In this case, the blood pressure at 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 indirect sphygmomanometry during exercise. Added to this, there are no sufficient grounds for the evaluation of blood pressure during exercise for the general diagnosis of hypertension.[42]

As blood pressure can be extremely variable and can elevate substantially on certain occasions, usually in a clinical setting, a diagnosis of hypertension should be made on the basis of blood pressure measurements taken on two or more different occasions.

b. Blood pressure measurement in a non-clinical setting

ABPM and self-measurement of blood pressure at home (home blood pressure measurement) are methods for blood pressure measurement in a non-clinical setting. Ambulatory and home blood pressures are often considered to have clinical values comparable to, or greater than, that of clinic blood pressure. These blood pressure measurements also have value as blood pressure information differing in nature (Table 2-2).

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 to assess the duration of the drug effect (for example, morning effect/evening effect ratio (M/E ratio)).[43] Home blood pressure measurement is also useful for the diagnosis of white coat, morning and masked hypertension. Home blood pressure measurement is extremely useful for the diagnosis of resistant hypertension and for deciding the therapeutic strategy.[44] On account of these merits, home blood pressure measurement has been reported to have a very high efficiency in medical economics.[45] Home blood pressure measurement is widely prevalent in Japan. According to a nation-wide survey in 2004–2005 in Japan, 90% of clinicians recommended home blood pressure measurement and 77% of hypertensive patients have a sphygmomanometer at home. Guidelines for home blood pressure measurement have been proposed by The Japanese Society of Hypertension.[49] An upper-arm-cuff device based on the cuff-oscillometric principle that has been confirmed in an individual to yield differences within 5 mm Hg compared with those of the auscultation method is used for home blood pressure measurement. It is recommended to measure blood pressure within 1 h of waking, after urination, after 1–2-min rest in a seated position, before taking antihypertensive drugs and before breakfast in the morning, and before retiring and after 1–2-min rest in a seated position in the evening (Table 2-3). Blood pressure measured before retiring is sometimes affected by alcohol consumption as well as bathing. However, these conditions are not prohibitive for blood pressure measurement before retiring, as prohibition of alcohol consumption and/or bathing before measurements can lower compliance for measurement. When measurements are taken under these conditions, subjects should record this information in addition to the actual blood pressure values. Measurements before dinner and before taking drugs in the evening may also be indicated for the evaluation of drug effects. The clinical value of home blood pressure measurement is sufficient even when conducted only once each morning and each evening if this is continued over a long period. Patients often perform multiple measurements on each occasion,[47] but adherence to measurement decreases if too many measurements are requested on each occasion.[47] In daily practice, the values of multiple measurements on one occasion, their mean and variability must also be evaluated if necessary; therefore, all values measured are recommended to be recorded and reported.[46,47] There is no consensus as to which of the measured values should be used for the clinical

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

	Clinic blood pressure	*Ambulatory blood pressure*	*Home blood pressure*
Frequency of measurement	Low	High	High
Measurement standardization	Difficult	Unnecessary	Possible
Evaluation of short-term variability	Impossible	Possible	Impossible
Evaluation of diurnal changes (evaluation of nocturnal blood pressure)[a]	Impossible	Possible	Possible[a]
Drug efficacy assessment	Possible	Appropriate	Optimal
Evaluation of the duration of drug efficacy	Impossible	Possible	Most favorable
Evaluation of long-term changes	Impossible	Impossible	Possible
Reproducibility	Unfavorable	Favorable	Most favorable
White coat phenomenon	Present	Absent	Absent

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

Table 2-3 Measurement of home blood pressure

1. Devices based on cuff-oscillometric method using upper arm cuff.
2. Measurement conditions
   Essential conditions
   a. Morning: within 1 h after waking up, after urination, before dosing in the morning, before breakfast, after 1- to 2-min resting in a sitting position.
   b. Night: before retiring, after 1- to 2-min resting in a sitting position.
   Selection conditions
   a. According to instructions: before dinner, before dosing in the evening, before bathing, before alcohol consumption.
   b. Others (if necessary): in the presence of symptoms, during the daytime on holidays; in some devices, measurement during sleep at night is possible.
3. Frequency of measurement: one to three times per occasion.[a]
4. Measurement period: as long as possible.
5. Recording: all values should be recorded.

[a]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 emotionally overcome by individual values.
Note 3: Patients should be instructed not to self-modify the treatment regimen based on self-measurements.

evaluation of home blood pressure. However, in the guidelines for the treatment of hypertension in various countries, which are described later, reference values of home blood pressure were derived from epidemiological studies where home blood pressure was measured once on each occasion and were averaged over a certain period. Also, a study in Japan showed that the mean of the values obtained on one occasion is highly reproducible, and that there was only a slight difference between the average of a single value and the average of the mean value of multiple measurements on each occasion over a certain period.[48] Moreover, even single home blood pressure measurement has been shown to have a better predictive power than a clinic blood pressure measurement.[49]

The Guidelines of The Japanese Society of Hypertension recommend that 'the mean value of the first measurement on each occasion of the morning and evening measurements over a long period should be used' for common clinical evaluation.[46] The JSH Guidelines assert that using the mean value of the first measurement taken each morning and evening over a certain period (5-7 times per week) is the basic principle for defining hypertension and normotension, while each value, as well as the mean of all values obtained by multiple measurements on a single occasion (1-3 times per occasion), provide valuable clinical information. Therefore, the Guidelines emphasize the importance of recording all values measured. As the interval between hospital visits is usually 2–4 weeks, it is practical to calculate the mean home blood pressure every 2–4 weeks, but clinical evaluation is also possible using the mean value of the measurements taken over the 5–7 days immediately preceding the visit.[46] For the short-term evaluation of drug effects and evaluation of the blood pressure at a certain point of time, calculation of the mean of all values obtained by multiple measurements on each occasion increases the number of available data and enhances the clinical value of home blood pressure. As the home blood pressure can be measured many times 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.[50]

The finger-cuff device for blood pressure measurement is inaccurate. 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 of hydrostatic pressure between heart level and wrist level, and because of the difficulty in completely compressing arteries due to anatomical issues with the wrist.[51] At present, therefore, a blood-pressure-measuring device with an upper-arm cuff is used for home blood pressure measurement. The accuracy of upper-arm-cuff devices for home blood pressure measurement using the cuff-oscillometric method is generally acceptable as long as they are the products of Japanese companies. The results of tests of the accuracy of various home blood-pressure-measuring devices are provided at www.dableducational.org or http://www.bhsoc.org/blood_pressure_list.stm.

Home blood pressure has been reported to be a more reliable predictor of prognosis than clinic blood pressure.[52,53] As clinical data regarding the relationship between home blood pressure and the incidence of cardiovascular disease or prognosis have been accumulated,[54–59] its clinical application is expected to widen further. Home blood pressure tends to be lower than clinic blood pressure. Recently, diagnosis of hypertension has increasingly been made on the basis of home blood pressure measurements. According to the JNC VI,[60] JNC7[38] and 2003 ESH-ESC Guidelines,[61] 135/80 mm Hg is adopted as a criterion for the diagnosis of hypertension on the basis of worldwide cross-sectional studies and the prospective study in Ohasama, Japan. The WHO/ISH Guidelines published in 1999 reported that a home blood pressure of 125/80 mm Hg is equivalent to a clinic blood pressure of 140/90 mm Hg.[62] Therefore, a blood pressure $<125/80$ mm Hg is considered to be normal. In the Ohasama Study, the criterion for hypertension, tentatively defined as the home blood pressure at which the relative risk of death increases by 10% compared with the home blood pressure at which total mortality is lowest, was 137/84 mm Hg.[63] Added to this, in the Ohasama Study, as the home

Table 2-4 Criteria for hypertension in different measurement methods

	Systolic blood pressure (mm Hg)	*Diastolic blood pressure (mm Hg)*
Clinic blood pressure	140	90
Home blood pressure	135	85
Ambulatory blood pressure		
24-h	130	80
Day	135	85
Night	120	70

Table 2-5 Expected target blood pressure levels of antihypertensive treatment

	Clinic blood pressure	*Home blood pressure*
Young/middle-aged persons	<130/85 mm Hg	<125/80 mm Hg
Elderly persons	<140/90 mm Hg	<135/85 mm Hg
Diabetics		
Patients with kidney disease	<130/80 mm Hg	<125/75 mm Hg
Patients after myocardial infarction		
Patients with cerebrovascular disorders	<140/90 mm Hg	<135/85 mm Hg

Note: As the criteria for hypertension include a clinic blood pressure of 140/90 mm Hg and a home blood pressure of 135/85 mm Hg, the differences between clinic blood pressure and home blood pressure (5 mm Hg) were simply applied to the clinic blood pressure in each condition and derived provisional target home blood pressure levels.

blood pressure at which the relative risk of cardiovascular mortality is lowest is 120–127/72–76 mm Hg, and as the relative risk increases significantly at ⩾138/83 mm Hg,[64] the JSH2004 Guidelines adopted 135/85 mm Hg as the criterion for hypertension based on home blood pressure[65] to make it consistent with the guidelines in other countries. On the other hand, the 2007 ESH-ESC Guidelines proposed 130–135/85 mm Hg as the criterion for hypertension based on home blood pressure, with flexibility in the systolic blood pressure.[66] However, as the criterion used in the JSH2004 Guidelines is being increasingly recognized, the Guidelines have adopted 135/85 mm Hg as the criterion for hypertension (Table 2-4) and have regarded values <125/80 mm Hg as normal blood pressure. Therefore, a blood pressure of ⩾125/80 mm Hg and <135/85 mm Hg should not be considered normal, and should be recognized as being high-normal.

The criterion for normal home blood pressure differs from the target blood pressure level for antihypertensive treatment. The establishment of such target levels will not be possible until the results of an intervention study based on home blood pressure become available,[67] but provisional target control levels based on home blood pressure obtained from the relationship between clinic and home blood pressures are shown in Table 2-5. (See Figure 3-1 in Chapter 3 for details of target blood pressure control levels based on clinic blood pressure.)

Ambulatory blood pressure monitoring. As accurate automatic devices based on the cuff-oscillometric method have been developed,[68–70] blood pressure measurement outside the clinic during activity (ambulatory subjects) has become possible through the use of non-invasive ABPM devices at intervals of 15–30 min over 24 h. The ABPM can provide a 24-h blood pressure profile and blood pressure information over 24 h as well as during specific periods, for example, in the daytime, nighttime and early morning. In Japan, ABPM is widely used and the practice guidelines for ABPM have been published.[71] 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 hypertensive target organ damage than with clinic blood pressure, and that it is closely associated with the regression of target organ damage mediated by antihypertensive medication.[72,73] Moreover, ABPM allows more accurate prediction of the incidence of cardiovascular disease than clinic blood pressure in the general population, elderly population and in hypertensive patients.[40,74–79]

ABPM is particularly useful for the diagnosis of white coat hypertension and masked hypertension (see below). The indications for the use of ABPM are diagnosis of white coat hypertension, poorly controlled hypertension and resistant hypertension. The normal ABP has not been defined, but the mean ± s.d. of the 24-h ABP measured in 634 normotensive Japanese aged 18–93 years was 119 ± 9/70 ± 6 mm Hg in men and 110 ± 10/64 ± 7 mm Hg in women.[80] The JNC VI and JNC7 propose a blood pressure during waking hours of ⩾135/85 mm Hg and during sleep of ⩾120/75 mm Hg to be indicative of hypertension.[38,60] According to the 1999 WHO/ISH Guidelines[62] and 2003 ESH-ESC Guidelines,[61] a 24-h ABP of 125/80 mm Hg is equivalent to an outpatient blood pressure of 140/90 mm Hg. Also, the International Database including the Ohasama Study proposed an ABP of 130/80 mm Hg over 24 h, 140/85 mm Hg during the daytime and 120/70 mm Hg during the nighttime as criteria for hypertension.[81] Following these reports, a mean 24-h ABP of ⩾130/80 mm Hg should be regarded as hypertension (Table 2-4). The 2007 ESH-ESC Guidelines also adopted a mean daytime ABP of ⩾135/85 mm Hg and a mean nighttime ABP of ⩾120/70 mm Hg as criteria for hypertension.[66]

Recently, an increase in short-term variation in ABP has been shown to be a risk factor for cardiovascular disease, adding a new clinical significance to ABPM.[82] As ABPM has been covered by medical insurance since April 2008 in Japan, it is expected to be used more widely and to contribute to the diagnosis and treatment of hypertension.

Information obtained by clinic blood pressure measurements, home blood pressure measurements, 24-h ambulatory blood pressure monitoring and other methods.

White coat hypertension/white coat phenomenon (effect). White coat hypertension is a condition in which blood pressure measured in a clinical setting (for example, at an outpatient clinic) is always at a hypertensive level but that measured in a non-medical setting (for example, home blood pressure, ABP) is always normal. Therefore, home blood pressure measurement or ABPM is indispensable for the diagnosis of white coat hypertension or the white coat phenomenon (effect). This definition of white coat hypertension applies to untreated patients. The differences between blood pressure measured in the clinical setting and that measured in the non-clinical setting are also observed in patients being treated, a finding called the white coat phenomenon (effect). If blood pressure measured in a clinical setting is hypertensive, and that measured in a non-clinical setting is normal in patients who are undergoing treatment, such a condition must be specified as 'white coat hypertension under treatment'. Whether white coat hypertension is harmful remains to be clarified, but white coat hypertension is known to develop into true sustained hypertension in a high percentage of patients,[83] and the risk of stroke in patients with

white coat hypertension was shown to be comparable to that in patients with true sustained hypertension in a 9-year follow-up.[84]

Masked hypertension. Masked hypertension is a condition opposite to white coat hypertension—that is, the blood pressure measured in a clinical setting is normal, but that measured in a non-clinical setting is always at a hypertensive level. It is observed in both treated and untreated patients. This phenomenon is called masked hypertension, because hypertension is undetectable in the clinic. It is related to a rise in blood pressure in the morning as part of physiologic and pathophysiologic changes in diurnal variation of the blood pressure[85,86] (for example, non-dipper, riser and morning surge) and morning hypertension as a result of the insufficient duration of drug effect, allowing the blood pressure to return to a hypertensive level before the next administration.[87] This condition can be detected by home blood pressure measurement as well as ABPM. The prognosis of masked hypertension is clearly poor.[88,89] Workplace hypertension is a cause of masked hypertension.[90]

Morning hypertension. Although there is no strict definition of morning hypertension, a hypertension specifically observed shortly after waking may be defined as morning hypertension. In terms of the absolute values observed by home blood pressure measurement or ABPM, those measured in the morning of $\geqslant$135/85 mm Hg may be regarded as morning hypertension, but, to be faithful to the definition of high blood pressure observed specifically in the morning, measurements taken in the morning must be shown to be higher than those taken before going to bed. Morning hypertension is associated with two types of circadian blood pressure variation. One is the morning surge; that is, a rapid increase in blood pressure after waking from a low level overnight. The other is morning hypertension observed in non-dippers; that is, those who show no nocturnal dip in blood pressure, or risers, that is, those who show a nocturnal increase in blood pressure. Both of these types are considered to be possible risk factors for cardiovascular disease.[85,87,91–94]

Nighttime blood pressure. Blood pressure measured during sleep by ABPM is referred to as nighttime blood pressure. Recently, it has become possible to automatically measure blood pressure during sleep using a home blood-pressure-measuring device.[95] A decrease of 10–20% in the blood pressure during the night compared with the daytime level is classified as a dipper (normal), a decrease of 0–10% as a non-dipper, an increase in the blood pressure during the night compared with the daytime level as a riser, and a decrease of $\geqslant$20% as an extreme dipper. The prognosis is poor in non-dippers and risers.[79,85,96–99] Hypertensive target organ damage such as asymptomatic lacuna infarction, left ventricular hypertrophy (LVH) and microalbuminuria are observed more frequently in non-dippers and risers than in dippers.[96–98] Also, prospective studies have shown that the risk of cardiovascular events is higher in non-dippers than in dippers.[79,85,99] However, in the J-MUBA, evaluating more than 600 Japanese hypertensive patients, many non-dippers were found even among patients showing no target organ damage.[100] According to the results of the Ohasama Study, the risk of cardiovascular events was also high in non-dippers among normotensive individuals.[99] As a result of these findings, the clinical significance of nighttime blood pressure is attracting attention. Although it has been reported that asymptomatic cerebral infarction is observed more frequently in elderly extreme dippers,[101] the risk to extreme dippers is comparable to that of dippers in the general population.[85] Both large-scale intervention study[76] and an international joint study[102] have also suggested that an increase in nighttime blood pressure is linearly related to an increase in the risk of cardiovascular disease; therefore, a low nighttime blood pressure is considered to be associated with a more favorable prognosis.

Central blood pressure. The blood pressure at the root of the aorta is generally called the central blood pressure. Central blood pressure is determined indirectly and noninvasively by converting the radial artery pressure waveform recorded by applanation tonometry into an aortic pressure waveform using a transfer function,[103] or by recording the carotid artery pressure waveform as a substitute for the aortic pressure waveform and correcting it for brachial blood pressure.[104] A method to estimate central blood pressure from the late (second) peak pressure in the radial artery pressure waveform using a linear function is also being evaluated.[105] Central blood pressure is known to show different values from conventional brachial blood pressure due to the variable superimposition of incoming and reflected pressure waves along the arterial tree. Central blood pressure and augmentation index (AI), an index of wave reflection, both of which increase in the presence of cardiovascular risk factors and reflect pressure loads on major organs including the heart, are estimated to be related more closely to hypertensive target organ damage than brachial blood pressure.[65] Antihypertensive drugs exhibit different blood-pressure-lowering effects on the central and brachial blood pressures, and the measurement of central blood pressure may help identify the differential effects of drugs, which are not observed in the measurement of brachial blood pressure.[106] Recent studies have suggested that central blood pressure and AI are related to cardiovascular events independently of brachial blood pressure and may serve as markers of the regression of target organ damage associated with antihypertensive treatment.[107,108] However, the prognostic value of central blood pressure must still be validated by future large-scale observational and interventional studies. In Japan, a device for measuring central blood pressure and AI from radial artery pulse waves (Omron Healthcare, HEM7000AI) is used.

Pulse rate. Extensive evidence that pulse rate is related to cardiovascular morbidity and mortality and total mortality has been accumulated.[109–112] In particular, pulse rates derived from ABPM[113] and home blood pressure measurement have a high predictive value for prognosis.[114] However, there is as yet no convincing evidence that the control of pulse rate at an optimal level improves outcome; therefore, no optimal pulse rate has been determined.

Isolated systolic hypertension and pulse pressures. Isolated systolic hypertension is a strong risk factor for cardiovascular disease in middle-aged and elderly individuals.[54,115,116] Therefore, pulse pressure is known to be a strong predictive factor for the occurrence of cardiovascular disease.[117,118] However, in Japan, systolic and mean blood pressures have a greater predictive power for the occurrence of stroke than pulse pressure.[23,24]

These facts are revealed more clearly by home blood pressure measurement and ABPM.[24,54]

POINT 2B
Definition and classification of blood pressure levels and evaluation of risk factors

1. **Blood pressure is classified into optimal, normal and high-normal, and the corresponding levels are classified into grade I, grade II and grade III hypertension, respectively.**
2. **Hypertensive patients are stratified into low-, moderate- and high-risk groups according to the presence or absence of risk**

factors other than blood pressure, hypertensive target organ damage and cardiovascular disease. In particular, the presence of diabetes mellitus and chronic kidney disease increases the risk. Attention to metabolic syndrome including a high-normal blood pressure as a component is also necessary.

3. **Hypertension is classified into primary (essential) and secondary hypertension. Secondary hypertension is suggested by medical history, physical findings and results of general laboratory tests, and specific tests are performed to confirm the diagnosis if necessary.**
4. **The treatment program should be prepared according to stratification of the risk; all patients must be guided to modify their lifestyle, and antihypertensive medication should be started if necessary to achieve the target blood pressure level.**

2) DEFINITION AND CLASSIFICATION OF BLOOD PRESSURE LEVELS AND EVALUATION OF RISK FACTORS

a. Classification of blood pressure levels

Although a positive correlation is observed between blood pressure and risk of cardiovascular disease, blood pressure values are distributed continuously and hypertension is defined artificially. In the 1999 WHO/ISH Guidelines,[62] the diagnostic criteria for hypertension were combined, in principle, with the JNC VI diagnostic criteria to avoid confusion.[60] Thereafter, the guidelines were revised in the JNC7 in 2003,[38] 2003 ESH-ESC Guidelines,[61] 2003 WHO/ISH Statement[119] and 2007 ESH-ESC Guidelines,[66] all of which defined a blood pressure of $\geqslant$140/90 mm Hg as indicative of hypertension.

In the Hisayama Study in Japan, the cumulative mortality rate due to cardiovascular disease was lowest when the systolic and diastolic blood pressures were $<$120 mm Hg and $<$80 mm Hg, respectively, and the risk of cardiovascular disease increased significantly when the systolic blood pressure was $\geqslant$140 mm Hg compared with $<$120 mm Hg, and when the diastolic blood pressure was $\geqslant$90 mm Hg compared with $<$80 mm Hg, including in elderly individuals.[109] Moreover, according to the Tanno/Sobetsu Study, an 18-year prospective epidemiological study in Hokkaido, Japan, a systolic blood pressure of $\geqslant$140 mm Hg and a diastolic blood pressure of $\geqslant$90 mm Hg were considered significant risk factors for cardiovascular and total mortality.[120] Similarly, in NIPPON DATA 80, a significant increase in mortality rate due to cardiovascular disease was observed at a blood pressure of $\geqslant$140/90 mm Hg.[6]

The JSH 2004 Guidelines classified hypertensive blood pressure levels into mild, moderate and severe hypertension, but they have been expressed as grade I, grade II and grade III hypertension, respectively, in the Guidelines to avoid confusion, because even a mild hypertension may be high-risk hypertension. In the Guidelines, hypertension of grade I or above was also defined as a blood pressure of $\geqslant$140/90 mm Hg, as in the earlier guidelines, and the same criteria for the classification of blood pressure levels have been adopted as those of the 1999 WHO/ISH Guidelines,[62] 2003 ESH-ESC Guidelines[61] and 2007 ESH-ESC Guidelines.[66]

However, according to the results of the meta-analysis of data from approx 1 million people obtained from observational studies in various countries, including the epidemiological data from Japan, the risk of cardiovascular disease increased linearly with blood pressure higher than 110–115/70–75 mm Hg.[9] Similar to observational studies conducted in Western countries[121,122] the results of Japanese studies[17,21,123] have shown the mortality rate from cardiovascular disease to be higher in people with a high-normal blood pressure (130–139/85–89 mm Hg) than in those with a normal or optimal blood pressure. The fact that an optimal blood pressure was defined as $<$120/80 mm Hg indicates that a normal pressure of 120–129/80–84 mm Hg is already above the optimal range. Furthermore, the evidence from the Framingham Study indicated that in individuals with a normal or a high-normal blood pressure, the chances of developing hypertension are higher than in those with an optimal blood pressure at all ages (Table 2-6).[124]

Table 2-6 Definition and classification of blood pressure levels (mm Hg) in adults

Classification	*Systolic blood pressure and diastolic blood pressure*
Optimal blood pressure	$<$120 and $<$80
Normal blood pressure	$<$130 and $<$85
High-normal blood pressure	130–139 and/or 85–89
Grade I hypertension	140–159 and/or 90–99
Grade II hypertension	160–179 and/or 100–109
Grade III hypertension	$\geqslant$180 and/or $\geqslant$110
Isolated systolic hypertension	$\geqslant$140 and $<$90

These classifications of blood pressure levels are criteria for diagnosis based on observational studies, and do not necessarily indicate a level at which antihypertensive medication should be started or a target level of blood pressure control. The diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions over a period of time. Systolic and diastolic blood pressures are mutually independent risk factors, and if they belong to different blood pressure categories, the individual is classified by the higher category.

b. Risk factors for cardiovascular disease

Although hypertension is the most important risk factor for stroke, it is only one of the risk factors for cardiovascular disease. The prognosis of hypertensive patients is markedly affected not only by blood pressure but also by risk factors other than hypertension, the severity of target organ damage secondary to hypertension and the presence or absence of cardiovascular complications (Table 2-7). For the diagnosis and treatment of hypertension, blood pressure, risk factors for cardiovascular disease (Table 2-7A) and the presence or absence of target organ damage/cardiovascular disease (Table 2-7B) are evaluated in addition to the differential diagnosis between primary and secondary hypertension.

c. Risk stratification for evaluation of the prognosis

In addition to blood pressure, the presence or absence of other risk factors—smoking, diabetes mellitus, dyslipidemia such as high low-density lipoprotein (LDL) cholesterol and low high-density lipoprotein (HDL) cholesterol, obesity (particularly abdominal obesity), chronic kidney disease (CKD), old age, family history of premature cardiovascular disease—hypertensive target organ damage and cardiovascular disease should be evaluated. As the risk for cerebrovascular and cardiovascular disease increases with prolongation of the follow-up period even in low- and moderate-risk patients, attention must also be paid to the duration of hypertension.[125]

Metabolic syndrome based on the diagnostic criteria for the Japanese[126] was added as a risk factor for cardiovascular disease in the Guidelines. However, in Tables 2-7A and 2-8, metabolic syndrome is mentioned from a preventive point of view. As established diabetes

Table 2-7 Prognostic factors for risk stratification to use in planning hypertension management

A. *Risk factors for cardiovascular disease*
Advanced age
Smoking
Systolic/diastolic blood pressure levels
Dyslipidemia
Low-HDL-cholesterol (<40 mg per 100 ml)
High-LDL-cholesterol (⩾140 mg per 100 ml)
High triglyceride (⩾150 mg per 100 ml)
Microalbuminuria
CKD
Obesity (BMI⩾25) (especially, abdominal obesity)
Metabolic syndrome[a]
Family history of premature cardiovascular disease
Diabetes
Fasting plasma glucose: ⩾126 mg per 100 ml or glucose tolerance test: 2-h value ⩾200 mg per 100 ml
B. *Target organ damages/cardiovascular disease*
Brain
Cerebral hemorrhage/cerebral infarction
Asymptomatic cerebrovascular diseases
Transient ischemic attack
Heart
Left ventricular hypertrophy (electrocardiogram, echocardiogram)
Angina pectoris/myocardial infarction/coronary revascularization
Heart failure
Kidney
Proteinuria (including microalbuminuria)
Decreased eGFR[b] (<60 ml per min per 1.73 m^2)
CKD, established kidney disease (diabetic nephropathy/renal failure)
Blood vessels
Atheromatous plaque
Carotid intima–media thickness >1.0 mm
Aortic disease
Arteriosclerosis obliterans (decreased ABI<0.9)
Ocular fundus
Advanced hypertensive retinopathy

Abbreviations: ABI, ankle-brachial index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Metabolic syndrome: Patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level, and/or impaired glucose tolerance that does not lead to diabetes) and/or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ⩾85 cm, females: ⩾90 cm).
[b]The eGFR is calculated using the following formula for Japanese:
$eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ ($\times 0.739$; females).

mellitus is a strong independent risk factor, it is mentioned separately in Tables 2-7A and 2-8. In these Tables, metabolic syndrome is defined as a condition with a high-normal or higher blood pressure, and obesity (particularly abdominal obesity) as an essential factor concurrent with abnormal glucose level (an impaired fasting glucose level or an abnormal glucose tolerance below the diabetic level) or dyslipidemia.

In addition, CKD was added to these Guidelines as a new risk factor. CKD is known to represent hypertensive target organ damage, as well as to be a risk factor for cardiovascular disease.[11,127–132] The risk is particularly high when diabetes mellitus and/or CKD are present, and the JNC7[38] and 2007 ESH-ESC Guidelines[66] recommend aggressive antihypertensive treatment on the basis of the results of many interventional studies.[130,133-136] The Hisayama Study also showed that diabetes mellitus is a major risk factor for cerebral infarction and ischemic heart disease.[137] Recently, the number of patients developing chronic renal failure from diabetic nephropathy has increased markedly in Japan.[138]

In patients with both hypertension and diabetes mellitus, the outcome has been shown to be improved by strict antihypertensive medication.[134–136,139,140] As treatment for hypertension has also been shown to be important in controlling the progression of renal diseases, including diabetic nephropathy,[134,136,140–142] the aggressive management of hypertension is important, particularly when diabetes mellitus or renal diseases are complicating factors.

The 1999 WHO/ISH Guidelines[62] classified hypertension into four risk levels (low, medium, high and very high) according to the 10-year absolute risk of cardiovascular disease in individuals aged 45–80 years (mean: 60 years) from the Framingham Study. The JNC7[38] emphasized the population strategy and attached the blood pressure level *per se*, but the earlier JNC VI[60] worked out the high-risk strategy by stratifying hypertensive patients into three levels depending on risk factors.

Although the 1999 WHO/ISH Guidelines,[62] 2003 ESH-ESC Guidelines[61] and 2007 ESH-ESC Guidelines[66] stratified hypertensive patients into low-, middle-, high- and very high-risk groups according to risk factors, they proposed the same therapeutic strategy for high- and very high-risk groups.

As the high-risk strategy as well as population strategy is considered to be extremely effective in Japan, the Guidelines classify hypertensive patients into low-, medium- and high-risk groups according to blood pressure category and presence or absence of risk factors, hypertensive target organ damage and cardiovascular disease (risk strata), as shown in Table 2-8. In the Guidelines, the risk is considered to be high even in patients with a high-normal blood pressure if they have diabetes mellitus, CKD, three or more risk factors, target organ damage or cardiovascular disease, and appropriate antihypertensive therapy must be initiated. On the basis of the current state of antihypertensive therapy in Japan, patients with grade II hypertension as well as 1–2 risk factors or metabolic syndrome (risk stratum-2) were classified as a high-risk group.[143] Cardiovascular risk stratification is essentially based on the evidence of the Framingham Study, in which cardiovascular events in the untreated population have been recorded since the 1940s. At present, there is no study in which absolute cardiovascular risk has been evaluated in untreated patients with grade II hypertension as well as risk stratum-2. In the Ohasama Study, although many patients with grade II hypertension were treated with antihypertensive drugs, those with grade II hypertension as well as risk stratum-2 had a very high absolute risk for stroke.[143] As this absolute risk is similar to that in patients with risk stratum-3 or grade III hypertension, it is reasonable to assume that those with grade II hypertension as well as risk stratum-2 have a high risk.

d. Typing of hypertension

About 90% of hypertension is essential hypertension. The diagnosis of essential hypertension is made by the exclusion of secondary hypertension. Essential hypertension includes white coat hypertension (clinic hypertension), in which hypertension is observed only in a

Table 2-8 Stratification of cerebrovascular/cardiovascular risk in four categories on the basis of (clinic) blood pressure classification and risk strata

Blood pressure classification / *Risk strata (risk factors other than blood pressure)*	*High-normal blood pressure 130–139/85–89 mm Hg*	*Grade I hypertension 140–159/90–99 mm Hg*	*Grade II hypertension 160–179/100–109 mm Hg*	*Grade III hypertension ⩾180⩾110 mm Hg*
Risk stratum-1 (no other risk factors)	No additive risk	Low risk	Moderate risk	High risk
Risk stratum-2[a] (one to two risk factors (other than diabetes) or metabolic syndrome)[b]	Moderate risk[c]	Moderate risk	High risk	High risk
Risk stratum-3[a] (three or more risk factors, diabetes, CKD, target organ damage/cardiovascular disease)	High risk[c]	High risk	High risk	High risk

Abbreviation: CKD, chronic kidney disease.
[a]When obesity and dyslipidemia are present in the absence of other risk factors, risk factors other than the blood pressure level are counted as two, and the risk is classified as the risk stratum-2. However, when other risk factors are present, the total of risk factors is calculated as three or more, and the risk is classified as the risk stratum-3.
[b]Metabolic syndrome in risk stratum-2 indicates patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level of 110–125 mg dl^{-1} and/or impaired glucose tolerance that does not lead to diabetes), or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ⩾85 cm, females: ⩾90 cm).
[c]Treatment in moderate- and high-risk groups with high-normal blood pressure values is based on the algorithm for treatment of hypertension at initial visit. The management of common cardiovascular risks is important here.

medical setting (for example, in outpatient clinics). The diagnosis of white coat hypertension is made by home blood pressure measurement and ABPM, as well as by measurement of blood pressure at the clinic. The frequency of isolated systolic hypertension increases in elderly people, because systolic blood pressure increases whereas diastolic blood pressure often decreases due to a reduced compliance of the aorta caused by atherosclerosis. Several studies, including the Framingham Study, Ohasama Study and Hisayama Study,[54,109,110,115,116] showed that isolated systolic hypertension is a strong risk factor for cerebral and myocardial infarction in elderly people. Isolated systolic hypertension in the elderly is classified into the burned-out type, caused by a decrease in diastolic blood pressure in essential hypertension, and the *de novo* type, caused by a novel elevation of systolic blood pressure in old age.

POINT 2C
Examination and diagnosis

1. **For the examination of hypertension, the overall evaluation of 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 CKD and hypertensive target organ damage are evaluated in addition to blood pressure, including home blood pressure.**
3. **The evaluation of target organ damage should be started from the high-normal blood pressure range in high-risk patients with diabetes mellitus or a history of cardiovascular disease.**
4. **Echocardiography, carotid ultrasonography and brain MRI are representative, special methods of examination for evaluating target organ damage, and the recommended method should be performed appropriately.**
5. **If secondary hypertension is suspected from history taking, physical examination and general laboratory investigation, special screening tests should be performed.**

3) EXAMINATION AND DIAGNOSIS

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

a. History (Table 2-9)

The time of detecting hypertension and its circumstances (health screening, examination, self-measurement, and so on), duration, severity and course of treatment should be established. Particularly, if hypertension has been treated, the types of antihypertensive medications used and their effectiveness and adverse effects should be verified.

With regard to family history, the presence or absence of hypertension, diabetes mellitus and cardiovascular disease, age of onsets, low birth weight or overweight in childhood, and, in women, whether they have had hypertension, diabetes mellitus and proteinuria during pregnancy should be ascertained.

Lifestyle 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, and so on), intake of alcohol or soft drinks and smoking (amount and period), personality and psychological state (anxiety and depressive tendency) and severity of stress (workplace, home).

Hypertensive patients are usually asymptomatic, but whether they have specific symptoms suggesting secondary hypertension or hypertensive complications and target organ damage should be clarified. 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 suggestive 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, history of hematuria, proteinuria and nocturnal pollakiuria, and the use of non-steroidal anti-inflammatory drugs, *kampo* drugs, oral contraceptives, and so on, should be verified.

Inquiries should be made into history of target organ damage and cardiovascular disease. The presence or absence of symptoms 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

Table 2-9 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	
Family history	Parents' histories of hypertension, diabetes and cardiovascular disease (onset and age at onset)
Birth weight/weight gain during childhood	
Pregnancy	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	Course of weight gain
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	Non-steroidal anti-inflammatory drugs, *kampo* drugs, oral contraceptives
Pheochromocytoma	Paroxysmal blood-pressure increase, palpitation, sweating, headache
Primary aldosteronism/renovascular hypertension	Weakness, periodic paralysis of the limbs, polyuria, hypokalemia
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

Table 2-10 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 mass index: body weight (kg)/{height (m)}^{2}]	Obesity, BMI $\geqslant 25\,kg\,m^{-2}$
Waist circumference (standing-position measurement at the umbilical level)	Abdominal obesity, male>=85 cm, female>=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	
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 (radial artery, dorsal artery of the foot, posterior tibial artery, femoral artery) on palpation (disappearance, attenuation, laterality), coldness, ischemic ulcers, edema
7. Nerves	Dyskinesia of the limbs, sensory disturbance, increased tendon reflex

chest pain related to heart disease; pollakiuria, nocturia, hematuria and proteinuria related to kidney disease; and intermittent claudication and coldness of the lower limbs related to peripheral artery disease should be investigated.

b. Examination (physical findings) (Table 2-10)

In addition to resting blood pressure and heart rate in a sitting position, the left–right difference in blood pressure and orthostatic changes in blood pressure and heart rate 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, heart failure, atherosclerosis and cerebrovascular or cardiovascular disease is examined. The skin is examined for abdominal striae and hirsutism (Cushing's syndrome); the face and neck region is examined for anemia/jaundice, thyroid goiter, carotid artery murmurs, jugular vein dilation 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 and rales in the lung fields are performed.

The abdominal region is examined for vascular murmurs and directions of their projection, liver enlargement and tenderness and kidney enlargement (polycystic kidney); the limbs are examined by palpation (disappearance, weakening and lateral difference) of arterial pulse (radial, dorsalis pedis, posterior tibial and femoral arteries), cold sensation, ischemic ulcer, edema, motor disturbances, sensory disturbances, increased tendon reflex, and so on.

c. Laboratory examinations (Table 2-11)

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

Table 2-11 Clinical examination

1.	General examinations (essential on initial consultation, at least once a year during antihypertensive treatment):	
	Hematology	Blood cell counts, hemoglobin, hematocrit, urea nitrogen (BUN), creatinine, uric acid, Na, K, Cl, fasting plasma glucose, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, GOT, GPT, γGTP, eGFR (ml per min per 1.73 m^2)=$194\times Cr^{-1.094}\times age^{-0.287}$ (female: $\times 0.739$)
	Urinalysis	Proteinuria (−, +, ++, +++), hematuria, cast
	Chest X-ray	Cardiothoracic ratio
	Electrocardiography	Left ventricular hypertrophy, ST-T change, arrhythmia such as atrial fibrillation
	Home blood pressure measurement (every day if possible)	
2.	Recommended specific examinations (if necessary on initial consultation/during antihypertensive treatment):	
	Evaluation of hypertensive target organ damage	
	Funduscopy (essential in the presence of diabetes)	
	Brain	Cognitive function test, depression assessment, brain MRI (T1, T2, T2*, FLAIR), MR angiography
	Kidney	Urinary albumin excretion [urinary albumin level (mg g^{-1} creatinine correction)]
	Heart	Echocardiography
	Blood vessels	Carotid ultrasonography, ankle-brachial pressure index (ABI), pulse wave velocity (PWV), augmentation index (AI)
	Glucose metabolism	Hemoglobin A_{1c}, 75 g oral glucose tolerance test (if the fasting plasma glucose >100 mg per 100 ml)
	Inflammation	High-sensitive CRP
	Measurement of 24-h ambulatory and nocturnal home blood pressures	
	Secondary hypertension screening, plasma renin activity, blood aldosterone, cortisol, 3 fractions of catecholamine (blood collection at rest early in the morning), casual urinary metanephrine fraction (Cr), catecholamines in 24-h urine, nighttime percutaneous oxygen partial pressure monitoring, abdominal ultrasonography (kidney, adrenal gland)	
3.	Specific examinations by specialists:	
	Diagnosis of secondary hypertension	Adrenal gland CT (including contrast-enhanced CT), renal ultrasonography (including the evaluation of the renal blood flow by the Doppler technique), renal scintigraphy, adrenocortical scintigraphy, iodine 131-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, adrenal venous sampling and polysomnography

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Examinations that are not covered by health insurance under a diagnosis of hypertension alone are included.

General laboratory examinations. General examinations that should be performed during the initial examination of hypertensive patients and at least once a year during antihypertensive treatment are general urinalysis, blood cell tests, blood chemistry tests concerning blood urea nitrogen (BUN), creatinine (Cr), uric acid, sodium (Na), potassium (K), chlorine (Cl), fasting triglyceride level, HDL-cholesterol, total cholesterol, LDL-cholesterol, glucose, total bilirubin, glutamic oxalacetate transaminase (GOT), glutamic pyruvic transaminase (GPT), and gamma-glutamyl transpeptidase (γGTP), chest X-rays (cardiothoracic ratio), and ECG (LVH, ST-T change and arrhythmias such as atrial fibrillation). In addition, the estimated glomerular filtration rate (eGFR) is calculated from the serum Cr level. Home blood pressure should also be monitored.

Evaluation of glucose tolerance and inflammatory risk factor. The Hb A_{1c} level should be examined when appropriate (not covered by insurance for hypertension alone in Japan), and, if the fasting plasma glucose level is >100 mg per 100 ml, a 75-g oral glucose tolerance test should be performed for the diagnosis of diabetes mellitus or impaired glucose tolerance.[144] Although the blood level of high-sensitive C-reactive protein (CRP) is lower in Japanese than in Western populations, it is related to the progression of carotid artery atherosclerosis and silent cerebral infarct[145–147] and is a risk factor for future stroke.[147]

Examinations for secondary hypertension screening. For the screening of patients suggested to have secondary hypertension on the basis of the results of history taking, physical examinations and general laboratory investigations, examination of the plasma renin activity and hormone levels, including aldosterone, cortisol, ACTH and three fractions of catecholamines in blood sampled after 30-min bed rest in the morning, examination of three fractions of metanephrine or three fractions of catecholamine in 24-h collected urine samples and abdominal ultrasonography are recommended. (See the section on endocrine hypertension in Chapter 12). Examinations such as nighttime pulse oxymetry may be performed for the diagnosis of sleep apnea syndrome.

Special examinations performed by experts for the definitive diagnosis of secondary hypertension include adrenal gland CT (including contrast-enhanced CT), renal ultrasonography (including the evaluation of the renal blood flow by the Doppler technique), renal scintigraphy, adrenocortical scintigraphy, iodine 131-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, adrenal venous sampling and polysomnography.

Evaluation of hypertensive target organ damage. It is now possible to diagnose target organ damage in hypertensive patients, estimate the future risk of cardiovascular disease even in asymptomatic patients by various examinations and use the findings for antihypertensive treatment (Table 2-12). Such an evaluation of target organ damage should be started at a stage of high-normal blood pressure in high-risk patients with diabetes mellitus, chronic kidney disease, and a history of cardiovascular events.

Brain and eyegrounds. Asymptomatic cerebrovascular disorders (silent cerebral infarcts, deep white matter lesions and cerebral microbleeds) are strong risk factors for stroke and dementia and are related to depression and falls in elderly people. MRI is much more effective than CT for the evaluation of these asymptomatic cerebrovascular disorders. The judgment of whether a lesion is subacute or is an old infarction is possible only using fluid-attenuated inversion recovery (FLAIR) images of MRI. The silent cerebral infarcts detected by MRI are the strongest specific predictors for stroke, and, according

to the results of follow-up studies in Japan, the relative risk of stroke in patients positive for this finding is 5–10 times higher than those without.[148,149] Deep white matter lesions that are negative on T_1-weighted imaging and positive on T_2^*-weighted imaging also increase the risk of stroke about 3–5 times.[150] In addition, cerebral microbleeds, which can be detected by T_2-weighted imaging of MRI alone, are a risk factor for future cerebral hemorrhage.[151] Magnetic resonance angiography is useful for the detection of stenotic lesions of the intracranial main cerebral and carotid arteries and cerebral aneurysms.

In elderly hypertensive patients, the evaluation of mild cognitive impairment[152] through cognitive function tests (the mini-mental state examination or Hasegawa dementia scale) and evaluation of depression on the basis of the Geriatric Depression Scale (GDS) and Beck Depression Inventory (BDI) are also useful for estimation of the risk of future occurrence of dementia and cardiovascular disease.

Papilledema, observed in hypertensive encephalopathy as one of the hypertensive emergencies, and eyeground bleeding, a finding of severe hypertension, can be confirmed by ophthalmoscopy. These severe eyeground findings are related to cardiovascular risk. In particular, ophthalmoscopy is essential when hypertension is complicated by diabetes mellitus. Also, sclerosis and narrowing of the eyeground arteries progress with the remodeling of resistance vessels (a possible cause of hypertension), precede the occurrence of hypertension and diabetes mellitus, are related to asymptomatic cerebral infarction and increase the risk of future cardiovascular disease.[153]

Heart. LVH detected by ECG is related to the prognosis of stroke as well as heart disease, including heart failure. The Sokolow–Lyon voltage (Sokolow–Lyon-ECG-LVH: SV_1+RV_5 [RV_6] >35 mm; RV_5 [RV_6] >26 mm), the Cornel voltage (Cornel voltage-ECG-LVH: $RaV_L+SV_3>28$ mm in men; $RaV_L+SV_3>20$ mm in women) and the Cornel Product (Cornel voltage$\times$QRS width >2440 mm ms) are often used for the diagnosis of LVH. LVH accompanied by 'strain type' (ST) depression is observed in about 20% of patients with resistant hypertension, is often concurrent with ischemic heart disease and CKD as well as the 24-h systolic blood pressure or maximum corrected QT interval (QTc) duration, and increases the risk of cardiovascular disorders.[154] The QT duration is prolonged, and variation in the QT duration among leads (QT dispersion) increases with the progression of LVH; both are determinants of a poor cardiovascular prognosis. The Sokolow–Lyon voltage and the Cornel Product significantly decrease on antihypertensive treatment, and the degree of this decrease is related to the decrease in the risk of major cardiovascular diseases, including atrial fibrillation, heart failure and sudden cardiac death.[155] Therefore, intensive antihypertensive treatment aimed at the regression of ECG-LVH in addition to blood pressure control is effective for hypertensive patients showing ECG-LVH.

Atrial fibrillation may occur over the course of the progression of hypertensive heart disease, and non-valvular atrial fibrillation is a very strong risk factor for cerebral infarction, with a relative risk greater than five times. According to the results of a follow-up study of local residents, metabolic syndrome increases the risk of the new occurrence of atrial fibrillation three times.[156] Therefore, in hypertensive patients with metabolic syndrome, antihypertensive therapy must be conducted while paying attention to the appearance of new atrial fibrillation during examinations, in addition to the history of paroxysmal atrial fibrillation.

Echocardiography is superior to ECG for the quantitative evaluation of the cardiac load due to hypertension. It also facilitates evaluation of the cardiac function as well as calculation of left ventricular mass, and is useful for the diagnosis of hypertensive heart failure. The left ventricular mass index is the strongest determinant of stroke and cardiovascular disease, including heart failure. Furthermore, concentric hypertrophy accompanied by relative wall thickening (left ventricular wall thickness/lumen >0.42) in addition

Table 2-12 Examination parameters for hypertensive target organ damage

1. Brain	Cephalic MRI (T1, T2, T_2^*, FLAIR)	Silent cerebral infarcts, deep white matter lesions, cerebral microbleeds
	MR angiography[a]	Stenosis of the main cerebral/carotid arteries, cerebral aneurysms
	Cognitive function test	Mild dementia MMSE score $\leqslant$26 points, Hasegawa dementia scale score $\leqslant$25 points)
	Depression assessment test	(Mild) depression (GDS score $\geqslant$10 points; BDI $\geqslant$10 points)
2. Heart	Electrocardiography	Left ventricular hypertrophy (Sokolow–Lyon voltage, Cornel voltage criteria, Cornel product, strain type), prolongation of the QT duration, increases in QT dispersion, abnormal Q waves, atrial fibrillation
	Echocardiography	Left ventricular mass index, left ventricular relative wall thickness, left ventricular ejection fraction, left ventricular diastolic function, atrial dimension
	Coronary MDCT[a]	Evaluation of calcified lesions, coronary stenosis, and plaque
	Cardiac MRI[a]	Left ventricular hypertrophy, left atrial hypertrophy
3. Kidney	eGFR (ml per min per 1.73 m^2) Proteinuria	
	Urinary excretion of albumin [urinary albumin level ($mg\,g^{-1}$ creatinine correction)][b]	Microalbuminuria (spot urine) $>30\,mg\,g^{-1}$ creatinine
4. Blood vessels	Carotid ultrasonography	IMT, max IMT (abnormal: >1.0 mm), plaque, stenoses
	ABI	Peripheral arterial disease (ABI <0.9)
	PWV	Carotid/femoral artery (cf)-PWV, brachial/ankle (ba)-PWV
	AI[a]	Carotid artery AI, tibial artery AI
	Endothelial function test[a]	Blood flow-dependent vasodilation
5. Autonomic nerves	Standing test	Orthostatic hypotension, orthostatic hypertension
	24-h ABPM	Nocturnal blood-pressure-fall attenuation (non-dipper type), nocturnal blood-pressure increase (riser type)

Abbreviations: ABI, ankle-brachial pressure index; ABPM, ambulatory blood pressure monitoring; AI, augmentation index; BDI, Beck Depression Inventory; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; IMT, intima–media thickness; MMSE, mini-mental score examination; PWV, pulse wave velocity.
[a]Special test.
[b]The urinary excretion of albumin is not covered by health insurance under a diagnosis of hypertension alone in Japan.

to an increase in the left ventricular mass index is a pattern of hypertensive left ventricular geometric remodeling with the poorest cardiovascular prognosis, and improvement in the left ventricular remodeling due to antihypertensive treatment improves the cardiovascular prognosis.[157] Diabetes mellitus as well as hypertension affects the left ventricular remodeling. An increase in the 24-h systolic blood pressure increases the left ventricular mass index, the presence of diabetes mellitus increases the relative wall thickness, and the frequency of concentric hypertrophy increases in diabetic hypertensive patients.[158] Regarding cardiac function, diastolic function decreases before reductions in the values of parameters of the left ventricular systolic function, such as the ejection fraction. This decrease in the left ventricular diastolic function may precede the progression of LVH and cause heart failure with an intact left ventricular systolic function, which is observed in more than 50% of elderly patients with heart failure. In addition, the left atrium dilates with a decrease in the left ventricular diastolic function, and left atrial dilation is a risk factor for future atrial fibrillation.

The blood level of brain natriuretic peptide (BNP),[159] which was isolated and identified in Japan, increases markedly in patients with symptomatic heart failure due to left ventricular systolic and diastolic dysfunction, and it has been widely used clinically for the diagnosis of this condition and evaluation of therapeutic effects. Clinically, it is useful for the screening of hypertensive patients with dyspnea for heart failure.

Multidetector-row CT (MDCT) is useful for the noninvasive screening of hypertensive patients with chest pain for coronary artery diseases.

Kidney. In Japan, CKD has also been shown to be a risk factor for cardiovascular disease.[11,160] CKD is defined as kidney damage or estimated glomerular filtration rate (eGFR) <60 ml per min per 1.73 m^2 for $\geqslant 3$ months.[161] A formula prepared for the calculation of the eGFR in Japanese is as follows:[162] eGFR (ml per min per 1.73 m^2)$=194\times Cr^{-1.094}\times age^{-0.287}$($\times 0.739$, if female).

A diagnosis of microalbuminuria is made when the urinary albumin excretion in spot urine is 30–300 mg g^{-1} Cr or that in 24-h urine is 30–300 mg day^{-1}. However, there is no threshold of cardiovascular risk even in the normal range (<30 mg g^{-1} Cr), and the risks for cardiovascular death and total death decrease with decreased levels of urinary albumin excretion. Microalbuminuria appears under the influence of many risk factors, including those related to metabolic syndrome and inflammation as well as hypertension, and it is related to the future occurrence of hypertension and, in particular, increases in nighttime blood pressure even in normotensive individuals.[163]

The disappearance of microalbuminuria during the course of antihypertensive treatment is related to a decrease in the risk of cardiovascular disease independently of a reduction in blood pressure.[164] Therefore, decreased levels of urinary albumin excretion and the disappearance of microalbuminuria are factors for the evaluation of the effectiveness of antihypertensive treatment in high-risk hypertensive patients showing microalbuminuria.

Blood vessels. For more appropriate prevention and treatment of cardiovascular disease, it is important to evaluate the functional and structural changes in the arterial system noninvasively in the asymptomatic stage.

Carotid ultrasonography facilitates evaluation of the degree of atherosclerosis on the basis of the intima–media thickness (IMT), plaques and stenoses. These vascular echo indices are affected by hypertension and risk factors related to metabolic syndrome and are predictive of the future risk of cerebral and myocardial infarction. In addition, as their values improve through the treatment of hypertension, diabetes, hyperlipidemia, and so on, they are useful as indices for the evaluation of therapeutic effects.

Regarding the IMT, the measurement site and method for the calculation of the mean vary, but the max IMT, which includes the plaque thickness, can be determined with high reproducibility, and the Japanese Academy of Neurosonography recommends the max IMT (IMT-C_{max}) in the distal wall of the common carotid artery as an index of atherosclerosis.[165] The IMT increases when hypertension, diabetes and dyslipidemia are present. The risks of cerebrovascular disorders and coronary artery disease increase linearly with increases in the IMT,[165] which is considered to be abnormal when it exceeds 1.0 mm. Elevated lesions with a height of $\geqslant 1.1$ mm are called plaques, and increases in the height and number of plaques are related to elevations in cardiovascular risk.[166] The risk of symptomatic cerebral infarction is particularly high if plaques show ulceration on the surface and low irregular internal echo levels. The quantitative evaluation of plaque properties has also been attempted.[167] Plaques and stenoses occur frequently at the origin of the internal carotid artery, and carotid artery stenosis $\geqslant 70\%$ may be regarded as as an indicator of carotid endarterectomy and carotid artery stent dilation.

The ankle-brachial pressure index (ABI) is the ratio of the systolic blood pressure between the lower and upper limbs. Its decrease suggests not only the presence of peripheral artery disease but also risk of the future occurrence of stroke and dementia.[168] An ABI of <0.9 is considered to be abnormal and to suggest the presence of peripheral artery disease.

The pulse wave velocity (PWV) is an index based on increases in the velocity of pulse wave transmission through blood vessels with increasing arterial stiffness. The PWV is affected most notably by age and hypertension, but it also increases in the presence of risk factors such as smoking, diabetes mellitus and dyslipidemia. The PWV is related to the risk of occurrence of cardiovascular diseases even after correction for the other risk factors. The PWV between the carotid and femoral arteries (cf-PWV) has been used world-wide and has been shown to be correlated with cardiovascular outcome. Recently, a device to automatically measure the PWV between the brachial and ankle arteries (ba-PWV) simultaneously with the ABI has been developed, and simpler and more reproducible measurement of the PWV has become possible.[169] The results of follow-up studies on the relationship between the ba-PWV and the occurrence of cardiovascular events have not been reported, but it is closely correlated with cardiovascular risk factors and the stage of hypertensive target organ damage, similar to the cf-PWV.[170,171] In addition, as it is a good predictor of the future occurrence of hypertension among patients with a high-normal blood pressure,[172] it may be an alternative to the cf-PWV as an index of arterial stiffness. Although the PWV is reduced by antihypertensive treatment, the decrease is partly due to functional changes caused by a decrease in blood pressure and does not necessarily reflect structural improvements in arterial stiffness.

The arterial pressure pulse wave is derived from ejection waves from the left ventricle and reflection waves from peripheral vessels, and the AI is considered to represent reflection waves. As the AI is affected not only by arterial stiffness of elastic vessels, which determines the time of arrival of reflection waves via the PWV, but also by arterioles, which reflect ejection waves, it is expected to be useful as an index of the function and structure of the entire arterial system. The AI is correlated with cardiovascular risk but is also affected by heart rate, height and cardiac function. Following the recent development of a device that allows not only easy measurement of the AI in the radial or

common carotid artery but also estimation of the central arterial pressure, the clinical significance of the AI is being investigated.[173]

The endothelial flow-dependent vascular dilation, an index of the vascular endothelial function, decreases under the influence of various cardiovascular risk factors and improves through exercise and drug therapies. In patients with coronary artery disease, impairment of the endothelial function has been reported to worsen prognosis. As many clinical studies have shown the usefulness of endothelial function tests, the establishment of a simple standard procedure for its measurement and reference values is awaited.

Autonomic nervous system. Autonomic nervous system disorders are causes of hypertension, promote the progression of hypertensive target organ damage and are involved in the induction of cardiovascular disease. Therefore, impairment of the autonomic nervous system itself may be regarded as a form of target organ damage.

Orthostatic blood pressure dysregulation, a disorder of the autonomic nervous system, is observed more frequently in elderly people and diabetic patients and is related to the progression of target organ damage and adverse long-term survival.[174,175] The head-up tilting test using a tilted table is necessary for the detailed evaluation of orthostatic hypotension, but the active standing test is a simple method that can be used in daily practice. In this test, the blood pressure measured 1–3 min after standing up is compared with that measured 1–2 times after a 5-min rest in a seated (or recumbent) position, and the change in blood pressure is evaluated. Many patients with orthostatic hypotension show abnormal diurnal changes in blood pressure,[176] classified as non-dippers with reduced nocturnal depression of blood pressure, or as risers with nocturnal elevation of blood pressure. Clinically, examination of blood pressure during the nighttime by ABPM is recommended for patients with orthostatic hypotension, particularly if they have target organ damage. Conversely, orthostatic hypertension or an increase in blood pressure on standing has also been reported to be related to large vessel disorders, target organ damage such as asymptomatic cerebral infarction, LVH and microalbuminuria, as well as morning hypertension.[175–177]

Non-dipper- and riser-type abnormalities of diurnal blood pressure changes are related to autonomic nervous system disorders.[176]

Citation Information

We recommend that any citations to information in the Guidelines are presented in the following format:

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