GUIDELINES (JSH 2014)

Chapter 2. Measurement and clinical evaluation of blood pressure

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POINT 2A

Blood pressure measurement/assessment

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. (Evidence level: VI)
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. (Evidence level: VI)
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. (Evidence level: IVa, III)
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, the blood pressure value should be used as a level on the occasion. (Evidence level: VI)
5. Criteria for hypertension differ among clinical blood pressure, 24-h ABP and home blood pressure. A clinic blood pressure of > 140/90 mm Hg, a home blood pressure of > 135/85 mm Hg and a mean 24-h ABP of > 130/80 mm Hg are regarded as indicators of hypertension. (Evidence level: E-Ia)
6. When there is a discrepancy of diagnosis between clinic blood pressure and home blood pressure, a home blood pressure-based diagnosis should have priority.
7. In treating hypertension, attention must also be given to the pattern of diurnal blood pressure changes (non-dipper, riser and dipper), nighttime blood pressure, early-morning blood pressure and blood pressure at the workplace. (Evidence level: E-Ib)

White coat hypertension

1. Patients with a systolic clinic blood pressure of 140 mm Hg or more and/or a diastolic blood pressure of 90 mm Hg or more in whom systolic and diastolic home blood pressures

are < 135 and < 85 mm Hg, respectively, or the mean 24-h systolic and diastolic blood pressures on ABPM are < 130 and < 80 mm Hg, respectively, are regarded as having white coat hypertension. (Evidence level: E-Ia)

2. White coat hypertension is observed in 15–30% of hypertensive patients. In the elderly, the percentage increases. (Evidence level: E-II)
3. White coat hypertension may deteriorate to hypertension and diabetes in the future. (Evidence level: E-Ib)

Masked hypertension

1. Patients with a mean systolic clinic blood pressure of < 140 mm Hg and a diastolic blood pressure of < 90 mm Hg who show a systolic home blood pressure of 135 mm Hg or more and/or a diastolic blood pressure of 85 mm Hg or more, or a mean 24-h systolic blood pressure of 130 mm Hg or more and/or a diastolic blood pressure of 80 mm Hg or more on ABPM, are regarded as having masked hypertension. (Evidence level: E-Ia)
2. Masked hypertension is classified into three types: early-morning hypertension (early-morning blood pressure: $\geq 135/85$ mm Hg), nocturnal hypertension (nighttime blood pressure: $\geq 120/70$ mm Hg) and daytime hypertension (daytime blood pressure: $\geq 135/85$ mm Hg). (Evidence level: E-Ia)
3. Masked hypertension is observed in 10–15% of the general population with a normal-range blood pressure and in ~30% of hypertensive patients during antihypertensive therapy in whom systolic and diastolic blood pressure levels are maintained at < 140/90 mm Hg, respectively. (Evidence level: E-II)
4. The risk of cardiovascular morbidity from untreated masked hypertension is similar to that from persistent hypertension. Masked hypertension should be regarded as a subtype of hypertension. (Evidence level: E-Ia)

1. BLOOD PRESSURE MEASUREMENT

1) Blood pressure measurement at the outpatient clinic

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 by using an automatic sphygmomanometer that has been calibrated by the auscultation method. However, the use of a mercury sphygmomanometer

is also often avoided in Japan because of the possibility of environmental pollution by mercury. Table 2-1 shows the standard procedure for sphygmomanometry by the auscultation method. The clinical value of clinic blood pressure measurement 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 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.^{66,67} However, blood pressure is rarely measured in accordance with such a guideline in a screening or clinical setting.⁶⁸ In addition, the accuracy of measurement is often

disregarded or ignored.⁶⁹ Nowadays, clinic blood pressure measurement is usually taken with an automatic sphygmomanometer. Furthermore, an automatic rolling-type sphygmomanometer is used in the waiting room of the clinic, and the blood pressure value obtained is often adopted as a clinic 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 upper arm with thick clothing should not be inserted into the cuff area; and the arm-cuff position should be maintained at the heart level.

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, and auscultation gap exist.

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 $\geq 40\%$ of the brachial girth and a length sufficient to cover at least 80% of the brachial girth are recommended.

A problem encountered in blood pressure measurement is the presence of false hypertension related to incomplete compression of the brachial artery through an increase in arterial stiffness. The presence of incomplete compression of the brachial artery through an increase in arterial stiffness can be predicted, based on Osler's sign.

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 is commonly taken.

In patients with arrhythmia (premature beats), systolic blood pressure is overestimated and diastolic blood pressure is underestimated by the auscultation method.⁶⁹ Therefore, the effects of arrhythmia must be excluded by repeating the measurement three or more times. In patients with atrial fibrillation, accurate sphygmomanometry is often difficult, but proportionate values of systolic and diastolic blood pressures can be obtained by the cuff-oscillometric method unless the patients have bradycardia.⁶⁹ In this case, the measurement must also be repeated three or more times.

In pregnant women, Korotkoff sounds are occasionally heard at 0 mm Hg. 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.⁶⁹

As blood pressure can be extremely variable, a diagnosis of hypertension should be made on the basis of blood pressure measurements taken on two or more different occasions.

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 possible ^a . (b) A cuff with a bladder 13 cm wide and 22–24 cm long is used. (A cuff for children is used in children with 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/cafeine consumption should be avoided before measurement.
Measurement methods	The arm cuff is maintained at the heart level. The cuff is rapidly inflated. The rate of cuff deflation is 2–3 mm Hg per beat or second. 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 as the diastolic blood pressure.
Frequency of measurement	Measurement is performed two or more times at 1- to 2-min intervals in one clinic visit. When two measurements differ markedly, additional measurement is performed.
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.
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 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.

^aRecently, 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.

^bStable values mean that the difference between measurements is <5 mm Hg.

2) Blood pressure measurement in a nonclinical setting

Self-measurement of blood pressure at home (home blood pressure measurement) and ABPM are methods for blood pressure measurement in a nonclinical setting. Home and ABPs are often considered to have clinical values comparable to, or greater than, that of clinic blood

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

	<i>Clinic blood pressure</i>	<i>Home blood pressure</i>	<i>Ambulatory blood pressure</i>
Frequency of measurement	Low	High	High
Measurement standardization	Possible ^a	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) ^b	Impossible	Possible ^b	Possible
Evaluation of changes between 2 days	Impossible	Possible	Impossible
Evaluation of long-term changes (seasonal variation and so on)	Possible	Possible	Impossible

The Guidelines for Home Blood Pressure Measurement (2nd version) were modified.

^aStandardized measurement increases the clinical value of clinic blood pressure. In clinical practice, standardized measurement is not performed in many cases. Standardized clinic blood pressure measurement is strongly recommended.

^bHome blood pressure-measuring devices that can monitor blood pressure during sleep at night are available.

pressure. These blood pressure measurements also have value as blood pressure information differing in nature (Table 2-2).

(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).⁷⁰ Home blood pressure measurement is also useful for the diagnosis of white coat or masked hypertension and for making a diagnosis of resistant hypertension and deciding the therapeutic strategy.⁷¹ As home blood pressure can be measured multiple 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.⁷² Home blood pressure measurement is widely prevalent in Japan.^{73,74} Guidelines for home blood pressure measurement have been proposed by the Japanese Society of Hypertension.^{75,76} 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. According to the conditions presented in Table 2-3, the measurement is performed.

The clinical value of home blood pressure increases through standardized measurement, as indicated for clinic blood pressure. On the other hand, according to a report from the patient population, guidance on conditions for home blood pressure measurement varies among clinicians in clinical practice; it should be standardized. 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 consensus as to which of the measured values should be used for the clinical evaluation of home blood pressure. In the JSH2009 Guidelines⁷⁷ and Guidelines for Home Blood Pressure Measurement in 2003⁷⁵/2011,⁷⁶ the frequency of measurement on each occasion was recommended as once or more (one to three times). Thereafter, many clinicians and hypertension investigators claimed that the frequency of measurement in guidelines was vague and should be standardized. Blood pressure markedly changes in a short period, and home blood pressure is no exception. In many cases, an initially measured value on each occasion is higher than subsequent values, whereas some studies reported that the second value increased in 10% or more of occasions.^{78,79} In brief, in the guidelines, a previous recommendation of once or more (one to three times) on each

occasion was changed to 'twice as a rule' on each occasion from the following clinical perspective: subjects may become anxious about only one measurement on each occasion and may measure blood pressure several times regardless of the blood pressure level. It is recommended that the mean should be used as a blood pressure level on the occasion. On the other hand, it is described that, 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.⁸⁰ 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.

To evaluate hypertension, normal blood pressure and the effects of antihypertensive drugs based on home blood pressure, the mean of the values measured 5 to 7 days per week should be used.

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 in hydrostatic pressure between the heart level and wrist level, and because of the difficulty in completely compressing arteries due to anatomical issues with the wrist.⁸¹ At present, therefore, a blood-pressure-measuring device with an upper-arm cuff is used for home blood pressure measurement.^{82,83} 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 in <http://www.dablededucational.org> or <http://www.bhsoc.org/>.

Home blood pressure has been reported to be a more reliable predictor of prognosis compared with clinic blood pressure.^{47,84–87} Clinical data regarding the relationship between home blood pressure and the incidence of cardiovascular disease (CVD) or prognosis have been gathered.^{88–93} Such favorable properties of home blood pressure are associated with the reproducibility of the mean of home blood pressure levels.⁹⁴

(2) *Ambulatory blood pressure monitoring.* As automatic devices based on the cuff-oscillometric method have commonly been used,^{95–97} blood pressure measurement outside the clinic during

Table 2-3 Methods/conditions/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 ^a . (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, after 1–2-min resting in a sitting position; evening (before retiring): 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, before alcohol consumption. Others (if necessary): in the presence of symptoms, during the daytime on holidays, during sleep at night ^b
Frequency of measurement and handling of values	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.
Measurement period	As long as possible
Recording	All values should be recorded
Values to be evaluated	Mean of morning values obtained for 5 days (five times) or more. Mean of evening values obtained for 5 days (five times) or more. All individual values.
Evaluation ^c	Hypertension: mean morning and evening values $\geq 135/85$ mm Hg Normal-range blood pressure: mean morning and evening values $< 135/85$ mm Hg

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.

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

The Guidelines for Home Blood Pressure Measurement (2nd version) were modified.

^aIn 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.

^bHome sphygmomanometers that facilitate automatic blood pressure measurement during sleep at night are available.

^cMany measurements should not be requested.

activity (ambulatory subjects) has become possible through the use of noninvasive 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 in 2010 have been published.⁹⁸ 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 clinic blood pressure, and that it is closely associated with the regression of target organ damage mediated by antihypertensive medication.^{66,99,100} Moreover, ABPM allows more accurate prediction of the incidence of CVD than clinic blood pressure in the general population, elderly population and in hypertensive patients.^{49,50,67,101–104}

Table 2-4 Indications for ambulatory blood pressure monitoring

When ambulatory blood pressure monitoring is possible in patients meeting one of the following indications, this should be performed if necessary:

1. When a home blood pressure of fluctuates around 135/85 mm Hg or a clinic blood pressure of fluctuates around 140/90 mm Hg makes diagnosis of hypertension difficult.
2. When a high-normal value (125–134/80–84 mm Hg) 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 clinic blood pressure levels markedly change.

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.⁹⁴

2. DIAGNOSIS OF HYPERTENSION

1) Classification of blood pressure levels

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

In the Hisayama Study in Japan, the cumulative mortality rate due to CVD was lowest when the systolic and diastolic blood pressures were < 120 and < 80 mm Hg, respectively, and the risks of stroke and CVD increased significantly when the systolic blood pressure was ≥ 140 mm Hg compared with < 120 mm Hg, and when the diastolic blood pressure was ≥ 90 mm Hg compared with < 80 mm Hg, including in elderly individuals.^{105,106} Moreover, according to the Tanno/Sobetsu Study, an 18-year prospective epidemiological study in Hokkaido, Japan, a systolic blood pressure of ≥ 140 mm Hg and a diastolic blood pressure of ≥ 90 mm Hg were considered significant risk factors for cardiovascular and total mortality.¹⁰⁷ Similarly, in NIPPON DATA80, a significant increase in the mortality rate due to CVD was observed at a blood pressure of $\geq 140/90$ mm Hg.¹⁴ Therefore, in the JSH 2014 Guidelines, the criterion for grade I or higher hypertension was established as systolic/diastolic blood pressure levels of 140/90 mm Hg or more (Table 2-5), as described in conventional criteria. Previously, individuals with a clinic blood pressure of $< 140/90$ mm Hg 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. As there is confusion between normal blood pressure in this subclassification and

Table 2-5 Classification of blood pressure levels in adults (mm Hg)

<i>Classification</i>	<i>Systolic blood pressure</i>		<i>Diastolic blood pressure</i>
<i>Normal-range blood pressure</i>			
Optimal blood pressure	<120	and	<80
Normal blood pressure	120–129	and/or	80–84
High-normal blood pressure	130–139	and/or	85–89
<i>Hypertension</i>			
Grade I hypertension	140–159	and/or	90–99
Grade II hypertension	160–179	and/or	100–109
Grade III hypertension	≥180	and/or	≥110
(Isolated) systolic hypertension	≥140	and	<90

a normal clinic blood pressure of <140/90 mm Hg, a clinic blood pressure range of <140/90 mm Hg was expressed as normal-range blood pressure in the JSH 2014 Guidelines, and normal blood pressure (120–129/80–84 mm Hg) in the subclassification was expressed as normal blood pressure (Table 2-5). The results of observational studies in Europe and the United States^{108,109} and studies in Japan have shown that the incidences of CVD in individuals with a normal blood pressure of 120–129/80–84 mm Hg and those with a high-normal blood pressure of 130–139/85–89 mm Hg are higher than in those with an optimal blood pressure of <120/80 mm Hg.^{29,110} 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.¹¹¹

Recently, a diagnosis of hypertension has increasingly been made on the basis of home blood pressure measurements. In most international guidelines including those in Japan, 135/85 mm Hg (Table 2-6) is adopted as a criterion for the diagnosis of hypertension on the basis of worldwide cross-sectional studies and a prospective study in Ohasama, Japan.^{112–115} As the home 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,¹¹⁶ the JSH2004 Guidelines adopted 135/85 mm Hg as a criterion for hypertension based on home blood pressure to make it consistent with the guidelines in other countries.^{77,115} Recently, the results of a meta-analysis,¹¹⁷ with a median follow-up of 8.3 years, of 6470 persons from the International Database of Home blood pressure in relation to Cardiovascular Outcome, involving the Ohasama Study and Tsurugaya Study in Japan, also support that 135/85 mm Hg should be adopted as a criterion for hypertension and that 125/80 mm Hg should be adopted as a criterion for normal blood pressure. Therefore, a home blood pressure level of <135/85 mm Hg was established as a normal-range blood pressure, that of 125–134/80–84 mm Hg as a high-normal blood pressure and that of <125/80 mm Hg as a normal blood pressure. These are criteria for mean morning or evening home blood pressure, or both.

In the JNC-VI and JNC7 Guidelines, it is proposed that patients with a daytime blood pressure of 135/85 mm Hg or more and a nighttime blood pressure of 120/75 mm Hg or more on ABPM should be regarded as having hypertension.^{112,113} According to the World Health Organization/International Society of Hypertension Guidelines in 1999¹¹⁸ and European Society of Hypertension-European Society of Cardiology 2003 Guidelines,¹¹⁴ a mean 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

Table 2-6 Criteria for hypertension in different measurement methods

	Systolic blood pressure		Diastolic blood pressure
Clinic blood pressure	≥ 140	and/or	≥ 90
Home blood pressure	≥ 135	and/or	≥ 85
<i>Ambulatory blood pressure</i>			
24 h	≥ 130	and/or	≥ 80
Daytime	≥ 135	and/or	≥ 85
Nighttime	≥ 120	and/or	≥ 70

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.¹¹⁹ Following these reports, a mean 24-h ABP of ≥130/80 mm Hg should be regarded as hypertension (Table 2-6). The Subcommittee of Public Education of the American Heart Association Council on High Blood Pressure Research⁶⁸ and European Society of Hypertension-European Society of Cardiology 2013 Guidelines¹²⁰ 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.

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.

The frequency of isolated systolic hypertension increases in elderly people because systolic blood pressure increases, whereas diastolic blood pressure often decreases owing to a reduced compliance of the large elastic arteries caused by atherosclerosis. Several studies, including the Framingham Study,¹²¹ Hisayama Study and Ohasama Study, showed that isolated systolic hypertension was an important risk factor for cerebral or myocardial infarction in elderly people.^{88,106,122,123} 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.

2) Blood pressure measurement and procedures for hypertension diagnosis

Currently, in Japan, 77% of hypertensive patients have a sphygmomanometer for taking home blood pressure measurement. Reportedly, 40% of non-hypertensive individuals possess a home sphygmomanometer.⁷⁴ In Japan, ~40 000 000 home sphygmomanometers may be in use, corresponding to 1 sphygmomanometer per household.¹²⁴ This value is consistent with that reported from the National Health and Nutrition Survey of Japan in 2010.¹ On the other hand, in Japan, ~50 000 000 individuals (1997) undergo a health checkup or screening.¹²⁵ Therefore, individuals without a history of hypertension notice the presence of hypertension on a health checkup or on self-measurement of blood pressure/home blood pressure and consult a clinic (Figure 2-1).

In clinics, clinic blood pressure is measured. Simultaneously, the home blood pressure measured by patients is reported to the clinic, 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' clinic and home blood pressure levels. In this case, when

Figure 2-1 Blood pressure measurement and procedure for hypertension diagnosis. *¹When a clinic blood pressure-based diagnosis differs from a home blood pressure-based diagnosis, the latter should be predominantly adopted. 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. *²Criteria for hypertension regarding ambulatory blood pressure (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 ambulatory blood pressure monitoring (ABPM) is possible, patients meeting one of the above 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. Indication for ABPM is shown in Table 2-4. *³Although this diagnostic procedure is applicable for untreated hypertensive subjects, it must be considered that masked hypertension is also present in hypertensive individuals receiving treatment. A full color version of this figure is available at the *Hypertension Research* journal online.

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 clinic blood pressure. Furthermore, blood pressure measurement in a nonclinical setting has already had priority over clinic blood pressure for the diagnosis and treatment of white coat or masked hypertension.

The JSH2014 Guidelines differ from those in England, Europe and the United States in that the clinical availability, feasibility and diagnostic value of home blood pressure are highly appraised.

In Japan, 40 000 000 home sphygmomanometers are in use, whereas only 20 000 ABPM devices are being used.¹²⁴ Actually, the clinical application of ABPM is not easy. 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 the Guidelines, it is recommended that ABPM should be performed, if available, as a complementary measure for hypertension diagnosis by home/clinic blood pressure measurement (Table 2-4).

3. HYPERTENSION BASED ON HOME BLOOD PRESSURE AND ABPM

The clinic blood pressure level is not always consistent with the nonclinic, 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. It is calculated by subtracting the nonclinic blood pressure level from the clinic blood pressure level.

For the diagnosis of hypertension, the condition can be classified into four types based on clinic and nonclinic blood pressure levels: normal blood pressure, white coat hypertension, masked hypertension and persistent hypertension. Diagnostic procedures are presented in Figure 2-1.¹²⁶

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 within the normal range (Figure 2-1).¹²⁶ As for nonclinic blood pressure measurement, the daytime and nighttime home blood pressure measurements should be recorded in addition to usual morning and evening measurement, and ABPM must also be performed if necessary. This term should be essentially used in untreated patients, but the state of white coat hypertension in hypertensive patients receiving treatment is expressed as white coat hypertension under treatment. White coat hypertension accounts for 15–30% of patients, with a clinic blood pressure of 140/90 mmHg or more, diagnosed with hypertension. The frequency increases in the elderly.¹²⁶ When comparing white coat hypertension with persistent 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.^{101,126,127} However, the white coat phenomenon is not always benign. It is sometimes associated with a stress-related increase in blood pressure. In some patients with white coat hypertension, the condition may deteriorate to persistent hypertension in the future, leading to the risk of cardiovascular events as a long-term outcome.^{48,128–130} High-risk groups include a group in which the blood pressure level in a nonclinical setting is within the normal range, but is slightly high, and groups with other cardiovascular risks, such as obesity-/metabolic syndrome-related factors, and organ damage such as microalbuminuria.¹³⁰ In addition, white coat hypertension with impaired glucose tolerance or dyslipidemia is frequently observed, becoming a risk factor for the onset of diabetes in the future. Therefore, other risk factors and organ damage must also be evaluated in the treatment of white coat hypertension.

2) Masked hypertension

Masked hypertension is a condition in which the blood pressure level measured in a clinical setting is within the normal range, but that measured in a nonclinical setting is at a hypertensive level

(Figure 2-1).^{126,131} This term is used in untreated patients in the ESH2013 Guidelines,¹²⁰ but in both untreated patients and those diagnosed with hypertension (including those receiving treatment) in the guidelines. Masked hypertension in patients receiving treatment is described as masked hypertension under treatment. Masked hypertension is defined on the basis of clinic and nonclinic 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 general population with a normal-range blood pressure level and in ~30% of hypertensive patients undergoing antihypertensive therapy in whom the blood pressure level is controlled at <140/90 mm Hg.¹³¹ The risks of organ damage and cardiovascular events in patients with masked hypertension are significantly higher than in those with a normal-range blood pressure level or white coat hypertension, being similar to those in patients with persistent hypertension. According to previous clinical studies, in patients with masked hypertension metabolic errors are more frequent than in individuals with a normal-range blood pressure level, and hypertensive organ damage, such as left ventricular hypertrophy (LVH) and thickening of the carotid artery/asymptomatic cerebrovascular disorders, progresses regardless of the presence or absence of treatment for hypertension.^{132,133} In follow-up studies of untreated subjects,¹³⁴ community residents^{48,130} and hypertensive patients receiving treatment,¹³⁵ the relative risk for CVD in patients with masked hypertension was similar to that in patients with persistent hypertension.¹³¹

For the treatment of masked hypertension, the home blood pressure level should be initially measured. A high-risk group for masked hypertension consists of all hypertensive patients receiving antihypertensive therapy, those with a high-normal blood pressure level (130–139/85–89 mm Hg), smokers, individuals consuming a large amount of alcohol, those with high-intensity mental stress (workplace, home), those with high-level physical activities, those with a high heart rate, those with abnormal orthostatic blood pressure variations (orthostatic hypertension, orthostatic hypotension), patients with obesity/metabolic syndrome or diabetes and those with organ damage (especially LVH) or CVD. In these subjects, it is important to measure home and ABP levels regardless of the clinic blood pressure level. In some cases, the type of hypertension diagnosed differs between home blood pressure measurement and ABPM.¹³⁶ To detect masked hypertension, daytime and nighttime home blood pressure measurements should be taken in addition to usual morning and evening measurements, and ABPM must also be performed if necessary.

(1) *Morning hypertension.* Patients with a clinic blood pressure of <140/90 mm Hg and a mean home blood pressure measured early in the morning of 135/85 mm Hg or more are regarded as having morning hypertension. Diurnal variations of blood pressure include an increase during nighttime to early in the morning. Morning hypertension is classified into two types: non-dipper/riser and morning surge types. Both of these types may become risk factors for CVD. Between night and early morning, autonomic nerve/blood pressure variability most markedly increases under the influence of the baroreceptor reflex. In addition to a high blood pressure level early in the morning, an increase in blood pressure variability and a morning surge in blood pressure, which refers to a rise during the nighttime to early in the morning, also become risk factors for cardiovascular events^{137–139} and organ damage such as LVH, carotid arteriosclerosis and asymptomatic cerebral infarction, independent of the 24-h blood pressure level.^{137,139} 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. In addition, early in the morning, platelet hyperaggregability and a thrombus tendency exist, in addition to the enhancement of the neuroendocrine system such as the sympathetic nervous and renin–angiotensin systems. Respective risk factors may additively or synergistically deteriorate organ damage, increasing the risk for cardiovascular events.¹⁴⁰ A morning surge in blood pressure is associated with aging, orthostatic hypertension and an increase in vascular stiffness. It is modified by coldness, mental/physical stress, alcohol consumption, smoking and occlusive apnea syndrome-related night hypoxia (Figure 2-2).^{139,141}

Morning hypertension is significantly associated with brain/heart/kidney and all cardiovascular risks. Organ damage is more advanced than in the presence of hypertension defined based on clinic blood pressure, increasing the risks for stroke^{142,143} and nursing required in late-phase elderly people.⁹¹ The morning blood pressure level can be measured using a home sphygmomanometer. However, morning hypertension characterized by a specifically higher morning blood pressure level than during other hours (cases in which the bedtime blood pressure level is within the normal range but the morning blood pressure value is at a hypertensive level, and cases in which the morning blood pressure level is 15 mm Hg or more than the bedtime blood pressure level) becomes a risk factor independent of the mean morning and nighttime blood pressures.^{91,142–144}

In hypertensive patients receiving antihypertensive therapy, the antihypertensive effects are most markedly reduced immediately

Figure 2-2 Conditions classified as masked hypertension and its factors. A full color version of this figure is available at the *Hypertension Research* journal online.

before taking the drug, that is, early in the morning, despite favorable control of clinic blood pressure, raising a clinically important issue.

(2) *Nighttime hypertension.* Patients with a mean nighttime blood pressure level measured by ABPM or using a home sphygmomanometer of 120/70 mm Hg or more are regarded as having nighttime hypertension. In addition, in risers in whom the nighttime blood pressure level is higher than the daytime blood pressure level as a diurnal variation of blood pressure, the risk of CVD is high, and the condition is regarded as highly specific nighttime hypertension. For nighttime blood pressure measurement and the evaluation of abnormal diurnal variations of blood pressure such as the 'riser' pattern, ABPM, which has been covered by health insurance since April 2008, is used. However, recently, the nighttime blood pressure level and its variations can also be measured using a home sphygmomanometer.^{145–147} The nighttime blood pressure measured using a home sphygmomanometer is associated with organ damage, as described for that measured by ABPM.¹⁴⁷ 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 CVD and a reduction in cognitive/physical functions.^{148,149} 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 CVD is high.¹⁵⁰

(3) *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 mm Hg or more, with favorable reproducibility, despite normal-range clinic/home blood pressure levels, are regarded as having daytime hypertension. Mental/physical stress influences ABP (Figure 2-2). As a type of daytime hypertension, 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 present. It is common among obese individuals and among those with a family history of hypertension. As daytime hypertension is overlooked based on clinic blood pressure or home blood pressure routinely measured early in the morning and at bedtime, ABPM or blood pressure measurement at the workplace is necessary for the detection of daytime hypertension. Diurnal variations in blood pressure in shift workers depend on a waking/sleep-related personal behavior pattern rather than the time (daytime, night). However, during sleep in the daytime, a reduction in sympathetic activity is less marked than during sleep at night; therefore, a fall in blood pressure may not occur, and most shift workers show abnormal non-dipper-type diurnal variations of blood pressure.

3) 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.^{151–153} When sleep time is shortened in risers, the risk for CVD synergistically increases.¹⁵⁴ 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 show a non-dipper pattern, the risk increases markedly.¹⁵⁵ In addition, even when clinic and 24-h blood pressure levels are within the normal range, the cardiac load or risk of cardiovascular mortality increases in patients with nighttime hypertension or non-dippers/risers.^{150,153} In these patients, sleep disorder such as sleep apnea syndrome, an increase in the circulating blood volume such as heart/renal failure and autonomic neuropathy such as diabetes, especially orthostatic hypotension, are etiologically involved (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.^{151,152} 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 elderly hypertensive patients with an extreme dipper pattern, asymptomatic brain disease is advanced,^{151,156} and the risk of stroke is also high.¹⁵² 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).^{157–159} 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.¹⁶⁰ 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.

4. BLOOD PRESSURE VARIABILITY

Blood pressure variations include a variation per beat, respiration-/autonomic output-related changes in a relatively short interval, variations at 10- to 30-min intervals obtained by ABPM, 24-h changes (diurnal variations) and daily/weekly/annual (seasonal) variations obtained based on home blood pressure. Clinically, morning hypertension, morning-evening differences, morning surge, nighttime blood pressure fall and variations between consultations are also classified as a phenotype of blood pressure variability.

Hata *et al.* in Japan^{161,162} and Rothwell *et al.*¹⁶³ have indicated the relationship of blood pressure variations between clinic visits with prognosis. Others suggested that short-term blood pressure variability on ABPM reflects the prognosis of target organ damage or CVD.^{164–166} The relationship between diurnal variations of blood pressure and prognosis has been established (see Chapter 2, Measurement and clinical evaluation of blood pressure and Chapter 3, Principles of treatment). Thereafter, the Ohasama Study¹⁶⁷ and Fin-Home Study in Finland¹⁶⁸ reported that day-by-day variability of blood pressures based on home blood pressure has a prognostic significance for CVD.

To use blood pressure variability as a parameter for diagnosis and treatment of hypertension, the definition of blood pressure variability and analytical methods should be established, and evidence regarding the influence of intervention on blood pressure variability, as well as that regarding blood pressure variability-targeting therapeutic intervention, must be gathered.

5. PULSE RATE

Much evidence that an increase in pulse rate is associated with cardiovascular morbidity and mortality and total mortality has been collected.^{169,170} In particular, the prognostic value of pulse rate on ABPM¹⁷¹ or based on home blood pressure measurement is high.¹⁷² According to recent studies, a drug intervention-related decrease in

pulse rate improves the prognosis of CVD.^{173,174} However, there is no evidence that the establishment of an optimal pulse rate and control of pulse rate improve the prognosis. The optimal pulse rate has not been established.

6. EXAMINATION AND DIAGNOSIS

POINT 2B

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 chronic kidney disease (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 (diabetes: 130/80 mm Hg or more) in high-risk patients with diabetes mellitus, urinary protein-positive CKD or a history of CVD.
4. Echocardiography, carotid ultrasonography and brain magnetic resonance imaging (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.

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 metabolic syndrome and CKD) and (4) the underlying lifestyle should be clarified, and the severity of hypertension should be evaluated considering (5) concurrent CVD and hypertensive target organ damage as well as (6) home blood pressure.

1) History

The time of detecting hypertension and its circumstances (health screening, examination and self-measurement), duration, severity and course of treatment should be established (Table 2-7). 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 medical history, 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 CVD 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).

Hypertension alone does not cause any specific symptoms. However, patients with secondary hypertension and those with complica-

Table 2-7 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 CVD (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	Nonsteroidal anti-inflammatory drugs, Chinese traditional herbal drugs, oral contraceptives
Pheochromocytoma	Paroxysmal blood pressure increase, palpitation, sweating, headache
Primary aldosteronism/renovascular hypertension	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

tions/organ damage sometimes show specific symptoms. Therefore, in patients with these symptoms, secondary hypertension screening should be performed to investigate complications and organ damage. 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 use of nonsteroidal anti-inflammatory drugs, Chinese traditional herbal drugs and oral contraceptives should be confirmed.

Inquiries should be made into a history of target organ damage and CVD. 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 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 should be investigated.

2) Examination (physical findings)

In addition to resting blood pressure and heart rate in a sitting position, left–right differences and orthostatic changes in pulse (beat) and blood pressure should be checked during initial examination (Table 2-8).

Height and body weight are measured, and the degree of systemic obesity is evaluated by calculating the body mass index (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 CVD 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, cervical vascular murmurs (if findings are present, the presence or absence of orbital murmurs

is checked), 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/directions of their projection, a pulsating phyma on palpation, liver enlargement/tenderness 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, increased tendon reflex and so on.

Table 2-8 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, 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	

Table 2-9 Clinical examination

1. General examinations	General examinations should be performed on initial consultation and a few times a year during follow-up.
Hematology	Blood cell tests, hemoglobin, hematocrit, creatinine (Cre or cystatin C), uric acid, sodium (Na), potassium (K), fasting triglyceride (TG), HDL cholesterol, total cholesterol (or LDL cholesterol), fasting plasma glucose, ALT, γ-GT, eGFR (calculated from serum Cre or cystatin C)
Urinalysis	Qualification of urinary protein, qualification of urinary glucose, urinary sedimentation
Chest X-ray	Cardiothoracic ratio
Electrocardiography	
2. Items recommended for organ damage and risk assessment	
1) Brain and fundus	Cognitive function test, depression assessment, brain MRI, MR angiography
2) Blood vessels	Funduscopy (Scheie's classification, Keith–Wagener classification), carotid ultrasonography (vascular wall thickness: intima-media complex thickness, plaque: plaque score), ankle-brachial index (ABI)
3) Heart	Chest X-ray (cardiothoracic ratio), electrocardiography (Sokolow–Lyon voltage criteria, Cornell voltage criteria, Cornell product, stress electrocardiography, ST-T changes), echocardiography (left ventricular myocardial weight coefficient, left ventricular relative wall thickness, left ventricular blood inflow waveform, mitral annular ring motor velocity waveform), coronary CT and multi-detector row (MD) CT (coronary calcification, stenosis, plaque)
4) Kidney	eGFR, quantification of urinary protein, quantification of urinary microalbumin (patients with diabetes)
5) Assessment of glucose metabolism	HbA1c, 75g oral glucose tolerance test
6) Autonomic nerves	Standing test
3. Screening tests in patients in whom secondary hypertension is suspected	
Blood analysis (renin activity, aldosterone, cortisol, ACTH, three fractions of catecholamine), urine analysis (fractions of metanephrine, 3 fractions of catecholamine)	
Abdominal ultrasonography	
Nighttime percutaneous oxygen partial pressure monitoring	
4. Specific examinations by specialists	
Adrenal gland CT (including contrast-enhanced CT), renal ultrasonography, renal scintigraphy, adrenocortical scintigraphy, adrenal venous sampling and polysomnography	

Abbreviations: ACTH, adrenocorticotrophic hormone; CT, computed tomography; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

3) Laboratory examinations

Laboratory examinations for the overall assessment of cardiovascular risk in individual patients and for the diagnosis of secondary hypertension are performed by considering cost-effectiveness (Table 2-9).

(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, creatinine (Cre) (or cystatin C), uric acid, sodium (Na), potassium (K), fasting triglyceride, high-density lipoprotein cholesterol, total cholesterol (or low-density lipoprotein cholesterol), fasting blood sugar, ALT and γ -GT are measured in view of risk evaluation. The estimated glomerular filtration rate (eGFR) is calculated from the serum Cre or cystatin C level (described below). Considering that measurement of low-density lipoprotein cholesterol using the direct method has not been standardized, non-high-density lipoprotein cholesterol should be used when Friedewald's formula is not used.

(2) *Evaluation of glucose tolerance and inflammatory risk factor.* The glycated hemoglobin level should be examined when appropriate (not covered by health insurance for hypertension alone in Japan), and fasting plasma glucose measurement or a 75-g oral glucose tolerance test should be performed.¹⁷⁵ Although the blood level of high-sensitive C-reactive protein is lower among the Japanese than in western populations, it is related to coronary artery disease and silent cerebral infarction,^{176–178} and is a risk factor for future stroke.¹⁷⁹

(3) *Autonomic nerve function test.* The frequency of orthostatic dysregulation of blood pressure, as a type of autonomic neuropathy, increases in elderly people and diabetics. This disorder is associated with the progression of organ damage and deterioration of long-term prognosis.^{180,181} 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.^{182,183}

(4) *Examinations for secondary hypertension screening.* For the screening of patients suspected 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 plasma aldosterone concentration, cortisol, adrenocorticotrophic hormone and three fractions of catecholamines, urinary examination of two fractions of metanephrine or three fractions of catecholamines, and abdominal ultrasonography are recommended (with respect to details such as measurement conditions, see Section 3 of Chapter 13, ENDOCRINE HYPERTENSION). Examination 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 computed tomography (including contrast-enhanced computed tomography), renal ultrasonography (including the evaluation of the renal blood flow by the Doppler technique), renal scintigraphy, adrenocortical scintigraphy, adrenal venous sampling and polysomnography.

4) Evaluation of hypertensive target organ damage

As various examinations make it possible to diagnose target organ damage in hypertensive patients and estimate the future risk of CVD even in asymptomatic patients, they may become parameters for follow-up (Table 2-10). Such an evaluation of target organ damage should be started at a stage of high-normal blood pressure in high-risk

Table 2-10 Indexes of organ damages

1. Brain, fundus oculi	Head MRI (T1, T2, T2*, FLAIR) MR angiography Cognitive function test Evaluation of depression Funduscopy	Asymptomatic cerebral infarction, deep white matter lesions, cerebral minor bleeds Stenosis at main cerebral or carotid artery, cerebral aneurysm Mini-mental state examination (MMSE) ≤ 26 , Hasegawa dementia scale ≤ 25 Minor depression state (GDS ≥ 10 ; BDI ≥ 10)
2. Heart	Electrocardiogram Echocardiogram Coronary CT, MDCT ^{*1} Cardiac MRI ^{*1}	Exudate, bleeding, papilledema, morphological changes of arterial wall LVH (Sokolow–Lyon voltage criteria, Cornell voltage criteria, Cornell product, strain pattern) Left ventricular mass index, Left ventricular relative wall thickness, LVEF, left ventricular diastolic performance, left atrial dimension Calcific lesion, coronary stenosis, evaluation of plaque LVH
3. Kidney	eGFR (ml min ⁻¹ per 1.73 m ²) Proteinuria Urinary albumin excretion rate ^{*2}	Chronic kidney disease Spot urine protein ≥ 0.15 g per g Cre Spot urine albumin ≥ 30 mg per g Cre
4. Blood vessel	Carotid ultrasound imaging Ankle-brachial index (ABI) Pulse wave velocity (PWV) Augmentation index (AI) Endothelial function test ^{*1} Contrast-enhanced CT, 3DCT	Intima-media thickness (IMT), max IMT (abnormal ≥ 1.1 mm), plaque, stenotic lesion Peripheral arterial disease (ABI ≥ 1.4 , ABI ≤ 0.9) Carotid-femoral (cf)-PWV, brachial-ankle (ba)-PWV, cardio-ankle vascular index (CAVI) Carotid AI, radial artery AI Flow mediated dilation Thoracic-abdominal aortic aneurysm, dissection

Abbreviations: AI, augmentation index; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery imaging; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging.

patients with diabetes mellitus, CKD and a history of cardiovascular events.

(1) *Brain and fundus.* Hypertension is a risk factor for intracerebral microangiopathy and asymptomatic cerebrovascular disorders (silent cerebral infarcts, cerebral white matter lesions and cerebral microbleeds).^{184,185} In addition, asymptomatic cerebrovascular disorders are strong risk factors for stroke and dementia, and are related to depression and falls in elderly people. MRI is superior to computed tomography for the evaluation of these asymptomatic cerebrovascular disorders. Cerebral white matter lesions show light, high signal intensity at the sites of periventricular hyperintensity and deep/subcortical white matter hyperintensity on T2-weighted and proton density-enhanced imaging, as well as a clear, high signal intensity on fluid-attenuated inversion recovery imaging. The judgment of whether a lesion is subacute or is an old infarction is possible only using fluid-attenuated inversion recovery 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 in those without.^{127,186} Deep white matter lesions that are negative on T1-weighted imaging and positive on T2-weighted imaging also increase the risk of stroke about three to five times.¹⁸⁷ In addition, cerebral microbleeds, which can be detected from a low signal intensity by T2-weighted imaging of MRI alone, are a risk factor for future cerebral hemorrhage.¹⁸⁸ Magnetic resonance angiography is useful for the detection of stenotic lesions of the intracranial main cerebral and carotid arteries and cerebral aneurysms.

However, computed tomography and MRI should be performed when cerebral arteriosclerosis-related cerebral infarction or hemorrhage is suspected, based on clinical findings. These procedures should not be conducted as screening tests of organ damage in hypertensive patients.

In elderly hypertensive patients, the evaluation of cognitive impairment 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 and Beck Depression Inventory are also useful for estimation of the risk of future occurrence of dementia and CVD.^{189,190}

On ophthalmoscopy, the vascular orifice diameter, appearance, retinal flexibility, hard vitiligo, hemorrhage and papilledema should be examined as fundus changes. In particular, papilledema is observed in the presence of hypertensive encephalopathy, as one of the hypertensive emergencies, or in the presence of malignant hypertension. Fundus bleeding suggests severe hypertension and is associated with cardiovascular risk. In particular, ophthalmoscopy is essential when hypertension is complicated by diabetes mellitus. Also, sclerosis and narrowing of the fundal 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 CVD.^{191,192}

(2) *Heart.* For the diagnosis of hypertensive organ damage, an interview and physical examination are initially conducted. Subsequently, simple clinical examinations such as chest X-ray, electrocardiography and blood/urine tests are performed. Various examinations are added if necessary.

Among various types of hypertensive organ damage, LVH is most markedly influenced by blood pressure. It is an independent risk factor for CVD.¹⁹³ The regression of LVH reduces the risk of CVD.¹⁹⁴ For the

screening of the presence or absence of LVH, the cardiothoracic ratio is measured on chest X-ray to confirm the presence or absence of enlargement of the cardiac shadow. A cardiothoracic ratio of 50% or higher is regarded as abnormal. The detection of LVH by 12-lead electrocardiography is simple. Its reproducibility/specificity are high, but its sensitivity is low.¹⁹⁵ The Sokolow–Lyon voltage criteria (SV1+RV5 or RV6 $\geq$ 3.5 mV), Cornell voltage criteria (SV3+RaVL, men: $>$ 2.8 mV, women: $>$ 2.0 mV) and Cornell product (Cornell voltage $\times$ QRS width: $>$ 244 mV-msec) are used as diagnostic criteria for LVH.¹⁹⁶ In addition to hypertrophy, the appearance of ‘strain pattern’ is an independent determinant of CVD and mortality.¹⁹⁷ Echocardiography is appropriate for the diagnosis of LVH. The left ventricular mass index is a strong prognostic factor for CVD. Its regression is strongly associated with improvement in the prognosis.¹⁹⁸ In addition, concentric hypertrophy with an increase in relative wall thickness (end-diastolic left ventricular septal thickness+posterior wall thickness/end-diastolic left ventricular internal dimension $>$ 0.42) shows the most unfavorable prognosis among various types of LVH.¹⁹⁹

As a heart function change related to hypertension, a reduction in the left ventricular diastolic function is initially observed. When the reduction is marked, heart failure may occur despite normal left ventricular systolic function. Enlargement of the left atrium through an increase in the left atrial pressure related to a reduction in the left ventricular diastolic function is a risk factor for future CVD.²⁰⁰

The blood levels of brain natriuretic peptide,²⁰¹ which was isolated and identified in Japan, or N-terminal pro-brain natriuretic peptide increase markedly in patients with symptomatic heart failure owing to left ventricular systolic and diastolic dysfunction, and they have been widely used clinically for the diagnosis of this condition and for evaluation of therapeutic effects. 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, 12-lead resting electrocardiography and stress electrocardiography should be initially performed in accordance with the Guidelines regarding the Noninvasive Diagnosis of Coronary Lesions, which were established by the Japanese Circulation Society.²⁰²

(3) *Kidney.* For the diagnosis of CKD, eGFR and urinary protein and microalbumin levels are measured.²⁰³ In Japanese individuals aged 18 years or older, the eGFR is calculated using the following formula.^{204,205}

Men

$$\text{eGFR}_{\text{creat}} (\text{ml min}^{-1} 1.73 \text{ m}^{-2}) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$$

$$\text{eGFR}_{\text{cys}} (\text{ml min}^{-1} 1.73 \text{ m}^{-2}) = (104 \times \text{Cys} - \text{C}^{-1.019} \times 0.996^{\text{age}}) - 8$$

Women

$$\text{eGFR}_{\text{creat}} (\text{ml min}^{-1} 1.73 \text{ m}^{-2}) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$$

$$\text{eGFR}_{\text{cys}} (\text{ml min}^{-1} 1.73 \text{ m}^{-2}) = (104 \times \text{Cys} - \text{C}^{-1.019} \times 0.996^{\text{age}}) \times 0.929 - 8$$

Urinary protein ($\pm$) semiquantified using the test paper method corresponds to 15 mg dl⁻¹ (0.15 g per g Cre) (1+) to 30 mg dl⁻¹ (0.3 g per g Cre) and (2+) to 100 mg dl⁻¹ (1.0 g per g Cre). It must be considered that patients with alkaluria show false-positive reactions. In diabetics, urinary albumin excretion should be measured. A diagnosis of microalbuminuria is made when the excretion of albumin in spot urine is 30–299 mg per g Cre or that in 24-h urine is 30–299 mg per day. Urinary albumin measurement is covered by health insurance only in diabetics. Urinary protein ($\pm$) semiquantified using the test paper method corresponds to $\sim$ 30 mg per g Cre of urinary albumin.²⁰⁶ Thus, when hypertensive patients without diabetes mellitus

show $\pm$ the urine test paper method, urinary protein should be determined.

(4) *Blood vessels.* Vascular abnormalities are classified into morphological and functional abnormalities. Carotid ultrasonography facilitates the simple, noninvasive assessment of morphological abnormalities. On carotid ultrasonography, the intima-media thickness (IMT) and plaque count are measured.²⁰⁷ Increases in IMT and plaque score are predictive of the future risks for stroke and myocardial infarction.^{208,209} These factors are affected by age, blood pressure,²¹⁰ dyslipidemia²¹¹ and diabetes mellitus.²¹² In the Guidelines for Cervical Vascular Ultrasonography, it is recommended that the maximum IMT, involving plaques, and mean IMT should be measured. An area of thickness 1.1 mm or more is regarded as a plaque. Plaques are more useful than IMT as a prognostic factor for CVD.^{213–215}

The ankle-brachial index (ABI) is the ratio of the ankle blood pressure to the brachial artery blood pressure. It is used for the diagnosis of peripheral artery disease. In patients with an ABI of 0.9 or lower, occlusion or stenosis of peripheral artery are suspected. The ABI is a predictive factor for CVD.²¹⁶ In hypertensive patients, peripheral artery disease with a decrease in ABI is frequently observed.^{217,218} In patients with an ABI of 1.4 or higher, the vascular wall is extremely stiff through vascular calcification, and it is impossible to compress blood vessels with cuff pressure, suggesting severe arteriosclerosis.²¹⁹

Pulse wave reflects the transmission of the arterial pulse generated by blood ejected from the heart to the periphery. The rate at which the pulse wave transmits is termed PWV. In the ESH/ESC Guidelines

for Hypertension Treatment, the PWV between the carotid-femoral arteries is used as a parameter of organ damage.²²⁰ In Japan, brachial-ankle PWV measurement is routinely performed. The brachial-ankle PWV is influenced by age, gender, diabetes mellitus, CKD and other risk factors in addition to hypertension.^{221–223} A high brachial-ankle PWV (≥ 1800 cm s⁻¹) is a predictive factor for the onset of CVD.²²⁴ As the PWV is influenced by the blood pressure level at the time of measurement, the cardio-ankle vascular index was developed to eliminate the influence of blood pressure.²²⁵ Currently, vascular function testing parameters, such as the cardio-ankle vascular index, augmentation index, central blood pressure and endothelial function test/flow-mediated vasodilation, are considered to be biomarkers of angiopathy in hypertensive patients.

Among great vessel disorders, thoracic aortic aneurysms and dissection can be detected as aortic dilatation on chest X-ray in some patients. When abdominal aortic aneurysms and dissection are suspected on abdominal palpation/auscultation for vascular murmurs, their presence or absence should be confirmed using abdominal ultrasonography.

Citation Information

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

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253–392.

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