Introductions to the Revised Guidelines

Purpose of the Guidelines
The Guidelines for the Clinical Use of 24 Hour Ambulatory Blood Pressure Monitoring (ABPM) was first released as a 1998–1999 Japanese Circulation Society (JCS) report to describe the results of clinical research and clinical findings based on clinical experience and provide guidance on the clinical use of 24 hour ABPM, which had begun to be used widely in the clinical settings. In 2008, ABPM was endorsed in the National Health Insurance (NHI) in Japan, and has been used as a tool in general practice. The present guidelines are an update of the previous guidelines of 1998–1999.

I Standardization of ABPM Procedures

1. Accuracy Evaluation of ABPM Devices

ABPM is performed using either an auscultatory technique that uses a microphone placed over the artery to detect Korotkoff's sounds (the Korotkoff microphone [KM] method), or an oscillometric technique that measures oscillation in cuff pressure caused by the pulse (the OS method). As compared with direct measurement of atrial pressure, these indirect measurements have limitations such as (1) systolic blood pressure values tend...
to be lower, and diastolic blood pressure values tend to be higher, than the actual values; (2) the upper arm with the cuff must be kept still during measurement; (3) only approximately 100 measurement time points/day are possible; and (4) daytime values in the waking state tend to be lower, and nighttime values during sleep higher, than the actual values.1

The accuracy of ABPM devices is evaluated by comparing measurements of ABPM devices with those obtained via auscultatory blood pressure measurement by a trained healthcare professional, and the difference should be within ±8 mmHg (mean±standard deviation [SD]). The accuracy is evaluated according to the Association for the Advancement of Medical Instrumentation (AAMI) SP-10 standard (2002 revision) or the recommendations of the British Hypertension Society (BHS; 1993 revision) or the European Society of Hypertension (ESH; 2010 revision).2-8 All ABPM devices currently used in Japan are ranked as grade A or B, which represent sufficiently high levels of accuracy (Table 1).

### Table 1. ABPM Devices Currently Used in Japan

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product name</th>
<th>Method of measurement</th>
<th>Weight (kg)</th>
<th>Method of compression</th>
</tr>
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<tbody>
<tr>
<td>A&amp;D</td>
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<td>KM/OS</td>
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<td>O3 3MZ2</td>
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<td>Welch Allyn</td>
<td>ABPM 6100</td>
<td>OS</td>
<td>0.27</td>
<td>P</td>
</tr>
</tbody>
</table>

ABPM, ambulatory blood pressure monitoring; KM, Korotkoff microphone method; OS, oscillometric method; P, automatic pumping.

|M*Multi-biomedical recorder. |

### 2. Methods of Measurement

ABPM devices are programmable allowing for users to set the time to start monitoring, interval of measurements, and duration of monitoring (24 to 48 hours). Before starting ABPM measurement, values with the ABPM device should be compared with values with the auscultatory blood pressure measurement at least three times. It is preferable that the mean difference between the ABPM device and the conventional technique be within 5 mmHg. Since movement of the cuff and microphone may cause errors, they should be fixed with adhesive tape or other appropriate supporting material. Before ABPM, patients should be instructed to keep still the upper arm during measurement. ABPM should be discontinued when patients feel upper arm pain or numbness during cuff inflation.

Some patients may experience numbness of the upper arm, because ABPM devices inflate the cuff up to 280 mmHg, the cuff pressure can be high in patients with severe hypertension, and devices require repeat measurement when an error due tobody movement occurs. It has also been reported that patients wearing ABPM devices cannot sleep well due to the cuff compression, which may cause high systolic blood pressures.9 Physicians should explain to patients in advance the possible problems associated with ABPM and how to discontinue...
ABPM. After wearing the cuff, a test run should be performed in the clinic. ABPM should not be performed in patients who drive a car or operate any other potentially dangerous machinery. Although this is not a safety-related concern, patients often hesitate to wear an ABPM device outside the clinic. It is therefore also important to provide advice on clothing that can cover the device during monitoring.

ABPM may start at any time of the day. However, it is preferable that patients who undergo ABPM for the first time start several hours before going to bed because ABPM may pose mental and physical stress. Also the data in the first one hour should be excluded from analysis since the values are often higher than those in the normal condition due to nervousness. The interval of measurement should be 10 to 30 minutes during daytime and 30 minutes at night. An interval of one hour or longer is not recommended since only several measurements will be available at night and the number of evaluable measurements may be insufficient when errors occur. Patients should be provided with an activity diary to record the times of going to bed, getting up, meals, voiding and defecation, medication and other daily activities. Blood pressure measurements during daytime are lower in non-working days than in working days (weekday).

### 3. Detection of Errors

Since ABPM is performed during usual daily activities, errors may be caused by noise due to activity, movement to the elbow or looseness of the cuff, body position, or other factors. Especially when the center of the cuff is higher or lower than the heart by $h$ cm, the hydrostatic pressure in the arm will affect the results (error $\Delta$ mmHg = $h \times 10 \times 1.055/13.6$). Although it is difficult to avoid errors due to hydrostatic pressure during nighttime sleep because patients may change their position during measurement, patients should be careful to position the cuff appropriately during daytime waking.

These errors should be excluded from the analysis. Unlikely measurements that do not satisfy the conditions in Table 2 should be excluded from the analysis.

### II Analysis and Evaluation of ABPM Data

#### 1. Significance of ABPM Measurements

The fundamental characteristic of ABPM is the large number of measurements. Even in home blood pressure monitoring, a stochastic reliable value may be obtained when patients measure their blood pressure several times a day to obtain the mean of the day or month using a large number of measurements. Such value will correspond with the daytime mean of ABPM measurements. A mean value of several blood pressure measurements is considered to fairly reflect the blood pressure level of the individual. In fact ABPM values may predict the risk of target organ damage in cardiovascular disease and prognosis of the patient. Information obtained with ABPM is essential in the treatment of white coat hypertension in which blood pressure is normal outside the doctor’s clinic. ABPM also provides specific information on blood pressure during nighttime sleep, morning surge (the acute increase in blood pressure from sleeping to waking in the early morning), and blood pressures during daytime activities or exertion. Circadian rhythm and variability of blood pressure may be analyzed using periodic ABPM measurements. Researchers are interested in the association between hypertension-associated target organ damage with various blood pressure parameters such as nighttime blood pressure during sleep, decline in blood pressure at night, severity of morning hypertension and short-term variability in blood pressure (expressed as the SD of daytime blood pressure measurements), which can provide such data, is more suitable than casual blood pressure measurement to evaluate the efficacy of antihypertensive drugs throughout the day. However, ABPM has a definite limited reproducibility because measurements under unrestricted activities may vary day to day. Table 2 lists appropriate indications of ABPM.

#### 2. Reference Values of ABPM

ABPM provides various blood pressure measurements with different clinical implications such as daytime blood pressure during activities and nighttime blood pressure during sleep. Analysis of ABPM data during daytime and nighttime with fixed clock-time periods may cause substantial errors. Although some researchers use short-windows to extract daytime and nighttime data such as data from 8:00 to 21:00 as daytime and...
data from 0:00 to 5:00 as nighttime in order to minimize the error, changes in blood pressure at the time of getting up such as morning surge cannot be evaluated by analyzing data during fixed clock-time periods. So, daytime and nighttime data should be specified with the patient’s diary or actigraph data. Generally, in 24-hour ABPM, the interval of measurements is short during the day and long at night. Therefore, the simple mean value of all measurements underrepresents nighttime blood pressure values. In order to obtain an appropriate average, a weighted mean is calculated using a formula of “mean 24-hour ABPM = (mean daytime value × hours of waking + mean nighttime value × hours of sleeping) / 24”, or other appropriate formula.

Reference values of ABPM may be obtained by calculating statistics from measurements of all individuals including patients with hypertension and patients on antihypertensive treatment who underwent ABPM in a particular community or occupation; by estimating the correlation between casual blood pressure measurements and ABPM measurements in individuals in a particular community or occupation to obtain reference values of ABPM corresponding to established reference casual blood pressure values such as 140/90 mmHg; or by obtaining reference values of ABPM according to the results of long-term prospective studies. The investigators of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) including the data of prospective cohort studies using ABPM calculated that high blood pressure (140/90 mmHg) on office measurement corresponds to 131.0/79.4, 138.2/86.4, and 119.5/70.8 mmHg for 24 hours, daytime and nighttime ABPM, respectively, in terms of the risk of cerebral and cardiovascular diseases. In the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009), high blood pressure is defined as a reading above 130/80 mmHg, 135/85 mmHg and 120/70 mmHg for 24 hour, daytime and nighttime blood pressures, respectively, which are similar to those defined in the 2007 Guidelines for the Management of Arterial Hypertension of the ESC and of the European Society of Cardiology (ESH-ESC 2007 Guidelines) according to the reports in Japan, Europe and the United States (Table 4).

### III Subtypes of Hypertension Identified by ABPM Measurements

#### 1. White Coat Hypertension

White coat hypertension is defined as consistently high blood pressure with reproducibility on different days in the healthcare setting, while blood pressure during daily activities is normal. It has been estimated that white coat hypertension is observed in about 15% of all patients visiting clinic and thus is not a rare condition. The healthcare setting includes hospitals, clinics and health check-up centers where physicians, nurses or other healthcare professionals measure blood pressure. An increase in blood pressure in the healthcare setting is often observed among patients with not only white coat hypertension but also borderline or sustained hypertension, and this is called the white coat phenomenon or white coat effect. White coat hypertension can be thus defined as the white coat phenomenon observed in individuals with normal blood pressure outside the healthcare setting. White coat hypertension is diagnosed when a patient has a mean clinic blood pressure of ≥140/90 mmHg in at least 3 visits but has a mean home blood pressure or daytime blood pressure of <135/85 mmHg, or a mean 24 hour blood pressure of <130/80 mmHg. In the outpatient setting, white coat hypertension or white coat phenomenon is suspected when the following conditions are observed:

1. Target organ damage is mild or totally absent even when casual blood pressure values suggest moderate or severe hypertension.
2. Increased heart rates are observed during blood pressure measurement.
3. The patient does not respond to conventional antihypertensive treatment.
4. The patient is female.
5. The patient is elderly.

It has been reported that the relative risk of patients with white coat hypertension for progression to sustained hypertension was approximately twice as high as patients with sustained normotension. Although no consensus has been reached on the prognosis of white coat hypertension, the prognosis is considered better than that of sustained hypertension. However, since it is unclear whether the prognosis, especially long-term prognosis of patients with white coat hypertension may be considered similar to normotensive individuals or not, such patients should be observed carefully for progression to sustained hypertension and development of target organ damage to ensure prompt diagnosis and be managed with nonpharmacological treatment (life style improvement). Patients with white coat hypertension who have substantially high casual blood pressure, additional risk factors for arteriosclerosis, or established target organ damage should be treated appropriately after careful consideration of the benefits and risks of antihypertensive treatment. Aggressive antihypertensive treatment is not always necessary in patients with white coat hypertension not associated with target organ damage.

#### 2. Masked Hypertension

Masked hypertension is defined as a clinic blood pressure of <140/90 mmHg with elevated ABPM or home blood pressure (≥135/85 mmHg). It has been reported that masked hypertension is about 10% of the general population and about 40% of the patients who are receiving antihypertensive treatment and show normal blood pressure in the clinic. Many reports have described that the severity of target organ damage and long-term prognosis are severer and poorer than normotensive individuals and identical to those with sustained hypertension. So, ABPM and home blood pressure measurements are necessary to detect masked hypertension in patients receiving antihypertensive treatment, and it is preferable that patients with masked hypertension receive antihypertensive treatment to achieve <135/85 mmHg outside the clinic. There are few evidence-based diagnostic and treatment strategies for patients with masked hypertension who are not receiving antihypertensive treatment.

Masked hypertension is classified into the following subtypes:

1. Non-dipper type hypertension in which nighttime blood pressure is higher than daytime blood pressure
2. Morning surge type hypertension in which blood pressure immediately after wake-up is substantially high
(3) Workplace hypertension in individuals who are active or have substantial mental stress during the daytime

(4) Smokers

(5) Masked hypertension associated with duration of action of antihypertensive drugs

ABPM is the only way to measure nighttime blood pressure during sleep. Nighttime blood pressures are not always consistent with blood pressure during sleep. Individuals who stay up for hours at night show nighttime blood pressure significantly higher than that of during sleep. Nighttime blood pressure may vary with the depth of sleep as well. Nighttime blood pressure levels depend on the total peripheral resistance index, and in patients with salt-sensitive hypertension, nighttime blood pressure level is also related to salt intake.49 Nighttime blood pressure during sleep reflects the severity of hypertension more accurately than daytime blood pressure does. A recent analysis of the IDACO data indicated that only nighttime blood pressure was associated with the development of cardiovascular diseases in patients receiving antihypertensive treatment, and blood pressure during waking could not predict the development of cardiovascular diseases.50

Workplace hypertension is defined as a normal blood pressure during health check-ups and in the clinic while high blood pressure during work. A survey in public officials working in a local government office has reported that about one-quarter of antihypertensive drugs have workplace hypertension, which was significantly associated with age, body mass index (BMI) and family history of hypertension.51 The pattern and severity of stress at workplace are related to 24 hour blood pressure and target organ damage. Blood pressure is substantially affected by mental stresses such as family problems, workplace relations, and spouse’s health conditions and whether they need care or not. Since stresses affect the hypothalamus and cause increases in blood pressure and heart rate by activating the sympathetic nervous system, β-blockers are often effective in the treatment of workplace hypertension.

Since many antihypertensive drugs reduce blood pressure in relation to the drug concentration in the blood, insufficient blood pressure control at night and in the early morning are often caused by low blood drug concentrations. Patients with masked hypertension with morning hypertension may be controlled by (1) changing the antihypertensive regimen (take drugs twice a day in the morning and before bed even when the drugs may be administered once daily or take their once-daily drugs before bed rather than in the morning); (2) adding diuretics to their regimens; and (3) using long-acting antihypertensive drugs having a high trough/peak (T/P) ratio, among other methods.

### 3. Morning Hypertension

Morning hypertension, defined as a mean morning blood pressure of ≥135/85 mmHg, is classified into two subtypes, those with the “morning surge” pattern and the “riser/non-dipper” pattern (nocturnal hypertension).52 The morning surge pattern is characterized with an abrupt increase in blood pressure in the early morning, while the riser/non-dipper pattern with sustained high blood pressure at night and in the early morning. Both patterns of morning hypertension are cardiovascular risk factors. ABPM can differentiate these two patterns of morning hypertension.

An increased morning surge is caused by sleep disorder, aging, hypertension, abnormal blood glucose levels, drinking, smoking in the early morning, and increased mental/physical stress through a reduction in endothelial function in the early morning, progression of remodeling in small vessels, increased stiffness of large vessels, reduced baroreceptor sensitivity, activation of the sympathetic nervous system or the renin-angiotensin (RA) system, or other causes.53 The most common causes of the riser/non-dipper pattern of morning hypertension include an increase in the circulating blood volume due to heart failure, chronic kidney diseases, increased salt sensitivity or excessive salt intake; especially autonomic failure including diabetes mellitus associated with orthostatic hypotension; and sleep disorders including sleep apnea syndrome.

Non-specific treatment of morning hypertension is basically performed with long-acting antihypertensive drugs that are effective for 24 hours. When high morning blood pressure is observed during treatment with once-daily antihypertensive drugs (morning), twice-daily treatment (morning and evening) or other modification of the dosage regimen should be considered. Specific treatment of morning hypertension is performed using drugs inhibiting the sympathetic nervous system or RA system that are activated in the early morning. It has been demonstrated that treatment with sympatholytic drugs (eg, α-blockers, α, β-blockers, and central sympatholytic drugs) before bedtime is effective in the treatment of morning hypertension and morning surge.54–56 Bedtime administration of RA inhibitors is also used as a specific treatment of morning hypertension. It is expected that drugs inhibiting the RA system, which is activated at night and in the early morning, not only reduce blood pressure but also protect target organs.56 Antihypertensive chronotherapy using different classes of drugs given at different timings may also be required to ensure strict control of morning hypertension. Addition of long-acting calcium channel blockers to RA inhibitors is effective in suppressing morning surge and reducing blood pressure variability. It is preferable that patients be also treated with low-dose diuretics to reduce nighttime blood pressure, although diuretics may not reduce the risk of morning blood pressure surge.

### 4. Circadian Variation of Blood Pressure

Circadian variation of blood pressure is determined by the relationship between daytime blood pressure during activities and nighttime blood pressure at rest and during sleep. This is affected by extrinsic factors such as sleep-wake cycle and intrinsic factors such as circadian clock in the body. Specifically the circadian variation of blood pressure is defined as the rate of change in mean blood pressures at nighttime and daytime. Although the circadian variation of blood pressure is commonly observed in both normotensive individuals and essential hypertensives, patients with some specific cause of hypertension, or a small number of patients with essential hypertension may show disturbance, disappearance or even inversion of the circadian variation. Table 5 lists different conditions that may affect the circadian variation of blood pressure. The change in circadian variation of blood pressure observed in each condition is an important model for clarifying the components of circadian variation of blood pressure.

Patients are classified as “dippers” when the mean nighttime blood pressure is ≥10% lower than the mean daytime blood pressure or as “non-dippers” when the reduction is <10%. Dippers with ≥20% reduction are referred to as “extreme-dippers”, and non-dippers with the mean nighttime blood pressure higher than the mean daytime blood pressure are defined as “risers”. In the pooled analysis of a large international database including the data of several thousand normotensive or hyper-
tensive subjects, the mean decrement of blood pressure during nighttime was 16.7±11.0/13.6±8.1 mmHg ie, 13% (systolic blood pressure), 17% (diastolic blood pressure) lower than the mean blood pressure during daytime in all subjects. Using the cutoff point described above, the prevalence of non-dippers was about 30% in hypertensive patients. In an analysis of the reproducibility of dipping status, about 70% of the subjects undergoing ABPM measurements on two successive days were classified into either dippers or non-dippers repeatedly, while in the remaining about 30% of the subjects the dipping status differed between the two occasions. When the circadian variation of blood pressure is analyzed, each patient should be interviewed whether he or she could sleep well during ABPM to assess possible effects of ABPM on quality of sleep.

There are many causes and mechanisms that could lead to abnormal circadian variation of blood pressure. It is apparent that dippers are normal since many studies have reported that the risk for target organ damage and cardiovascular events are lowest in dippers. However, studies to investigate the relationship between abnormal circadian variation of blood pressure and the risks of target organ damage and cardiovascular events have not established which of the two is the cause and which is the consequence. It has probably been suggested that they affect each other via different mechanisms to form a vicious circle. When patients with salt-sensitive hypertension undergo salt loading, the nighttime blood pressure does not reduce, and the prevalence of non-dippers is increased. On the other hand, it has been reported that non-dippers undergoing salt restriction, diuretic treatment and potassium supplementation become dippers. This is explained by compensated nocturnal hypertension developed during nighttime in patients with excessive salt intake and trying to excrete excessive salt via pressure diuresis, and this may be a mechanism of non-dipper pattern of circadian blood pressure rhythm. Also increased circulating blood volume due to heart failure and renal failure may specifically increase nighttime blood pressure via mechanisms similar to that noted in salt-sensitive hypertension.

Hyperactivity of the sympathetic nervous system is also one of the important mechanisms proposed for abnormal circadian blood pressure rhythm. It has been found that the reduction in the sympathetic activity and the increase in the parasympathetic activity during nighttime are smaller in non-dippers than in dippers. Reports have described that α-blockers may reduce nighttime blood pressure only in non-dippers, and that administration of α-blockers before bedtime significantly reduced nighttime blood pressure only in non-dippers and risers. On the other hand, given that non-dippers are also common in patients with autonomic failure in whom the activities of the sympathetic and parasympathetic nerves are quite low, it is suggested that the essential cause and mechanism of abnormal circadian blood pressure rhythm may be the autonomic nervous system dysfunction per se rather than reduced activity of sympathetic nerve at nighttime.

### IV Short-Term Blood Pressure Variability

Short-term blood pressure variability should essentially be assessed on the basis of change in blood pressure per pulse during continuous blood pressure monitoring. However, continuous blood pressure monitoring is rarely used in the ambulatory setting, and changes in ABPM measurements obtained every 15 to 30 minutes are evaluated instead. It is nearly impossible to evaluate short-term blood pressure variability using casual blood pressure or home blood pressure monitoring. Short-term blood pressure variability by ABPM is generally described with SD or coefficient of variance (CV) of blood pressure values during the 24 hour period, daytime and nighttime. Since SD of 24 hour blood pressure strongly correlates with the decline in nighttime blood pressure, this parameter is considered to represent the circadian blood pressure variation. Therefore in order to describe short-term variation of blood pressure, it is recommended that SD or CV of the daytime and nighttime blood pressures be calculated. When ABPM is performed every 15 minutes, SD of blood pressure is correlated with that of continuous monitoring, however, such correlation is no longer observed when blood pressure measurements are performed every 30 minutes or longer.

In a study evaluating blood pressure measurements obtained every 30 minutes, blood pressure level, age, pulse pressure and BMI were determinants of variability of blood pressure. It is believed that high pulse pressure suggest increased stiffness of large vessels and reflect impairment of baroreceptor reflex function. Recently, researchers are interested in short-term blood pressure variability as a cause of hypertension-related target organ damage, and cerebral and cardiovascular complications. Many cross-sectional study reports have described a significant relationship between short-term blood pressure variability and the presence of target organ damage. Also, many studies have reported that 24 hour blood pressure variability by ABPM is a predictive factor, which is independent of blood pressure levels, for development of target organ damage. In the antihypertensive treatment, physicians should consider not only to control blood pressure levels but also reduce short-term variability in blood pressure.

### Table 5. Disease Conditions That May Affect Circadian Blood Pressure Rhythm

<table>
<thead>
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<th>Disease Conditions That May Affect Circadian Blood Pressure Rhythm</th>
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<tbody>
<tr>
<td>1. Cerebrovascular disease</td>
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<td>2. Myocardial infarction, heart failure</td>
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<tr>
<td>3. Chronic renal disease</td>
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<tr>
<td>4. Diabetes mellitus</td>
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<tr>
<td>5. Renovascular hypertension associated with atherosclerotic renal artery stenosis</td>
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<tr>
<td>6. Arteriosclerosis obliterans</td>
</tr>
<tr>
<td>7. Sleep apnea syndrome</td>
</tr>
<tr>
<td>8. Elderly male patients</td>
</tr>
<tr>
<td>9. Bedridden patients</td>
</tr>
<tr>
<td>10. Malignant hypertension, hypertensive encephalopathy</td>
</tr>
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<td>11. Eclampsia, preeclampsia</td>
</tr>
<tr>
<td>12. Secondary hypertension (eg, primary aldosteronism, Cush-ing’s syndrome)</td>
</tr>
</tbody>
</table>
V ABPM in Special Conditions

1. Secondary Hypertension

Circadian blood pressure variability is disturbed in patients with secondary hypertension. However, there are no specific findings of disturbed circadian blood pressure rhythm. Abnormal circadian blood pressure variability suggests the presence of a disease condition, but it does not serve as the basis for diagnosis. The changes in circadian blood pressure variability in different disease conditions have attracted interest as models to clarify the mechanism for the circadian blood pressure variability. Since disturbed circadian blood pressure variability in patients with secondary hypertension may play a role in the progression of hypertension-associated target organ damage and cause hypertensive complications, it is important to understand circadian blood pressure variation in this patient population to design appropriate antihypertensive treatment strategies.

2. Hypotension

ABPM is very useful in diagnosing not only hypertension but also hypotension. Especially elderly patients who often have autonomic failure may have hypotensive attacks while standing, after meals or bath, which may cause dizziness and syncope. Hypotension is classified into essential hypotension and secondary hypotension. Essential hypotension is often observed in women, and often reduces the quality of life (QOL) of the patients. However, since essential hypotension causes fewer vascular disorder, treatment is rarely performed for this condition in the light of long-term prognosis. On the other hand, secondary hypotension is caused by underlying disease or condition, and is often associated with hazardous symptoms such as syncope and dizziness, and treatment or prevention of secondary hypotension is required. Therefore, ABPM is useful in diagnosing secondary hypotension.

3. Elderly Patients

Elevated blood pressure variation is a typical finding in elderly patients. Progression of aortic sclerosis will reduce arterial compliance, causing impairment of baroreceptor reflex function. This will increase systolic blood pressure, pulse pressure and short-term variation of blood pressure, which may promote the development of white coat hypertension and morning surge. Pressor response may be increased as a result of reduction in the function of the α receptors and a relative increase in the function of the β receptors in autonomic nervous system, which may further increase blood pressure variability. In elderly patients, the degree of such transient increase in pressor response varies widely among individuals. The decline in nighttime blood pressure becomes smaller and the prevalence of non-dipper is increased. Elderly patients are prone to transient hypotensive attacks such as orthostatic hypotension, postprandial hypotension and hypotension during urination. The ambulatory arterial stiffness index (AASI), a marker of arteriosclerosis, is related to the development of white coat phenomenon, hypotensive attacks and suppression of white coat phenomenon in the function of the α receptors in autonomic nervous system, which may further increase blood pressure variability. In elderly patients, the degree of such transient increase in pressor response varies widely among individuals. The decline in nighttime blood pressure becomes smaller and the prevalence of non-dipper is increased. Elderly patients are prone to transient hypotensive attacks such as orthostatic hypotension, postprandial hypotension and hypotension during urination. The ambulatory arterial stiffness index (AASI), a marker of arteriosclerosis, is related to the development of white coat phenomenon, hypotensive attacks and suppression of white coat phenomenon in the function of the α receptors in autonomic nervous system, which may further increase blood pressure variability. However, there are no specific findings of disturbed circadian blood pressure rhythm. Abnormal circadian blood pressure variability suggests the presence of a disease condition, but it does not serve as the basis for diagnosis. The changes in circadian blood pressure variability in different disease conditions have attracted interest as models to clarify the mechanism for the circadian blood pressure variability. Since disturbed circadian blood pressure variability in patients with secondary hypertension may play a role in the progression of hypertension-associated target organ damage and cause hypertensive complications, it is important to understand circadian blood pressure variation in this patient population to design appropriate antihypertensive treatment strategies.

4. Children

ABPM is indicated for children to evaluate for white coat hypertension, masked hypertension, efficacy of antihypertensive drugs, and hypotensive attacks. It has been reported that nocturnal hypertension and non-dippers are common in children with secondary hypertension, and daytime diastolic blood pressure level is usually higher than that in patients with essential hypertension. Hypotension is very rare in children, but blood pressure monitoring is important in this population. When a child is suspected to have hypotension, especially the blood pressure variability is large, and white coat hypertension must be excluded, he/she should undergo home blood pressure monitoring or ABPM to evaluate actual blood pressure levels and possible secondary hypertension, and then consider for diet and lifestyle modification. Since reference values of 24 hour blood pressure differ among ethnic groups and geographic areas, reference values for Japanese population should be established.

5. Pregnant Women

ABPM devices can be applied for pregnant women. Mean 24 hour blood pressures of normal pregnant women in each trimester is 100/70 mmHg, upper normal limit is 130/80 mmHg, and blood pressure tends to increase in the third trimester of pregnancy. ABPM data should be analyzed carefully in the diagnosis of white coat hypertension in pregnant women. ABPM is established in part as a method to evaluate high-risk pregnant women complicated with hypertension or diabetes mellitus, but its benefits in diagnosing pregnancy-induced hypertension syndrome in previously normotensive women have not been established yet.

VI Therapeutic Applications of ABPM

1. Overview

ABPM is an excellent tool for detailed evaluation of blood pressure during daily life and especially circadian blood pressure variation including nighttime blood pressure, and is also considered useful in the treatment of hypertension. Usually, pharmacological treatment is not necessary for patients with resistant hypertension in whom blood pressure cannot be controlled even with several types of antihypertensive drugs. ABPM is also useful in selecting appropriate antihypertensive drugs and timing of the drug administration based on the mean blood pressure values and circadian blood pressure variation. Patients with resistant hypertension in whom blood pressure cannot be controlled even with several types of antihypertensive drugs are good candidates for ABPM, because...
their mean 24 hour blood pressures are sometimes not very high.\(^\text{83}\) There are not a few patients who seem to be well controlled on the basis of office blood pressure but actually have high 24 hour blood pressure, which is so-called “masked hypertension”.\(^\text{84,85}\) It has been demonstrated that ABPM is useful because improvement of target organ damage such as left ventricular hypertrophy and cardiovascular prognosis after initiation of antihypertensive treatment is more closely related with change in 24 hour blood pressure than with office blood pressure. Studies on cost-effectiveness of antihypertensive treatment have suggested that treatment using ABPM is better than treatment based on casual blood pressure in controlling blood pressure with fewer drugs.\(^\text{86}\)

Problems associated with clinical application of ABPM include insufficient reproducibility of mean blood pressure levels and nighttime blood pressure dipping, since physical and mental activities frequently affect blood pressure levels and variation. Physicians should be aware that single ABPM measurement may not precisely evaluate individual blood pressure during daily living. ABPM is not always indicated for all patients with hypertension, but it is preferable to perform in patients with good indication.

### 2. ABPM in Clinical Studies

Since ABPM is an excellent tool to evaluate circadian blood pressure variation and mean blood pressures, which enable physicians to investigate the duration of action of test drugs and their effects on nighttime blood pressure, ABPM is considered useful in clinical studies of antihypertensive drugs. Although placebo effects on casual blood pressure are commonly observed, those on ABPM data are usually absent or very small if present. ABPM may show a reduction in blood pressure during placebo treatment.\(^\text{87,88}\)

The reproducibility of ABPM is relatively good, and overall mean blood pressures obtained by repeated ABPM measurements are generally stable. However blood pressure level may reduce during repeated ABPM measurements when patients get accustomed to the monitoring. Possible regression to the mean effect should be considered when ABPM data are analyzed. ABPM is superior to casual blood pressure monitoring in terms of reproducibility and reliability of mean values, and is demonstrated to enable physicians to evaluate efficacy of the test drugs in a smaller number of patients. Since ABPM enables physicians to diagnose white coat hypertension, they may exclude patients with white coat hypertension to evaluate patients with sustained hypertension only, so it is considered that the sample number required for clinical studies could be further less. ABPM is therefore expected to reduce the sample number required for clinical studies, although the minimum number of patients required to evaluate the efficacy of antihypertensive drugs has not been established.\(^\text{89}\)

Placebo-controlled double-blind studies are the most reliable method to evaluate the efficacy of antihypertensive drugs, but it is expected that open-label studies may provide reliable results if investigators employ ABPM, which is rarely affected by placebo effects and measurement bias.

### 3. Methods for Evaluating Antihypertensive Drugs

When the efficacy of antihypertensive drugs is evaluated with ABPM, a variety of parameters including mean 24 hour, daytime and nighttime values are used. However, it is preferable that clinically significant, easily obtainable parameters be used to allow them to be used widely (Table 6).

#### 1. Mean Blood Pressures in the 24 Hour Period or Other Time Periods

Mean blood pressures in the 24 hour period or other time periods are readily obtainable parameters and are used most widely. It has been demonstrated that mean 24 hour blood pressure value is more strongly associated with the severity of hypertension-related target organ damage and prognosis than casual blood pressure value. Mean daytime (waking) and nighttime (sleeping) blood pressure value are useful in differentiating dippers and non-dippers and evaluating the efficacy of antihypertensive drugs. They are also considered suitable for the evaluation of morning surge and other important factors.

#### 2. Trough/Peak Ratio

The effects of antihypertensive drugs inevitably vary with time, but abrupt changes in antihypertensive effects should be avoided in the clinical setting. The T/P ratio is a time-related index on the efficacy of antihypertensive drugs, and is calculated as a ratio between the minimum (trough) effect of the drug at the end of dose interval and maximum (peak) reduction in blood pressure observed after administration of drug adjusted for placebo effects.\(^\text{90}\) The Food and Drug Administration (FDA) of the United States recommends that antihypertensive drugs with a T/P ratio of ≥50% are preferable (or a T/P ratio of ≥66% for drugs providing modest reduction [about 5 mmHg] in diastolic blood pressure).\(^\text{91}\)

#### 3. Smoothness Index

The smoothness index (SI) has been proposed as an index of stability of the blood pressure reduction induced by antihypertensive treatment over 24 hours.\(^\text{92}\) The SI is calculated by the average blood pressure values for each hour of the 24 hour monitoring period, both before and during treatment, and all hourly changes in blood pressure induced by treatment (ΔH) is divided by its SD, which represents the dispersion of the antihypertensive effect over the 24 hourly values (SDΔH).

\[SI = \frac{\Delta H}{SD\Delta H}\]

A higher SI represents a more stable antihypertensive effect. However the SI has not been widely used, and target values have not been established.

#### 4. Hyperbaric Index and Blood Pressure Load

The hyperbaric index (or hyperbaric area) is defined as the area above the reference blood pressure (upper normal limit)
in the 24 hour blood pressure curve (mmHg × hr). The most commonly used reference value is 140/90 mmHg. The blood pressure load is defined as the percentage of blood pressure readings above the cutoff point, which is considered appropriate to use 140/90 mmHg during daytime and 120/80 mmHg during nighttime.

4. Effects of Different Antihypertensive Drugs on Circadian Blood Pressure Variation

The effects of antihypertensive drugs on circadian blood pressure variation are different depending on the duration and mechanism of action, time of dosing and condition of patients. In a meta-analysis of the effects of calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and β-blockers on circadian blood pressure variation, these different drug classes provided a similar degree of antihypertensive effects although the reduction at night was 1 to 3% lower than that of during daytime.

Long-acting calcium channel blockers exert antihypertensive effects lasting for 24 hours without affecting the circadian blood pressure rhythm. The antihypertensive effects of RA inhibitors such as ACE inhibitors and angiotensin receptor blockers (ARB) are prominent even at night, and are also observed in patients with relatively low blood pressure. The antihypertensive effects of β-blockers are not dependent on blood concentration as calcium channel blockers do, and β-blockers exert a significant reduction in morning blood pressure. Since sympathetic nerve activity mediated by α receptor plays a role of the increase in morning blood pressure, α-blockers effectively inhibit it. Although α-blockers do not reduce nighttime blood pressure significantly, these drugs do reduce nighttime blood pressure in non-dippers and risers.

Although diuretics are believed to exert their antihypertensive effects only slowly and do affect modestly the circadian blood pressure variation, diuretics reduce nighttime blood pressure in salt-sensitive non-dippers to shift their pattern to the dipper type. It has been reported that bedtime administration of antihypertensive drugs is more effective than morning doses in achieving effective antihypertensive effects lasting for 24 hours. In patients with resistant hypertension, significant reduction in 24 hour blood pressure, especially nighttime blood pressure, were observed in patients who took at least one of their drugs at bedtime as compared with patients receiving drugs once daily in the morning, and the prevalence of non-dippers was also reduced by the treatment regimen.

5. Effects of Antihypertensive Drugs on ABPM Findings in Patients With Various Phenotypes of Hypertension

It has been demonstrated that the effects of antihypertensive drugs on ABPM findings are different depending on baseline blood pressure value, circadian blood pressure variation and other phenotypes of hypertension.

1. White Coat Hypertension and Sustained Hypertension

Antihypertensive effects of drugs are generally more pronounced in patients with higher blood pressure and modest in normotensive individuals. In clinical studies of antihypertensive effects using ABPM, the reduction of blood pressure in 24 hours was smaller in patients with white coat hypertension with a normal 24 hour blood pressure than in patients with sustained hypertension. The relationship between antihypertensive effect and baseline blood pressure somewhat differs among different classes of antihypertensive drugs. In patients receiving calcium channel blockers, the reduction in 24 hour blood pressure is larger in patients with higher baseline blood pressure, while no such relationship was observed in patients receiving ACE inhibitors. Similarly, the antihypertensive effects of calcium channel blockers and β-blockers were observed in patients with a baseline daytime systolic blood pressure of ≥120 mmHg and were prominent in patients with higher baseline value, while that of ACE inhibitors was observed even in patients with a low baseline daytime systolic blood pressure, and were with a less significant relationship between the reduction of blood pressure during treatment and baseline blood pressure.

2. Dippers and Non-Dippers

The effects of antihypertensive drugs on daytime and nighttime blood pressure in hypertensive patients differ depending on the circadian blood pressure variation at baseline. In dippers who show a reduction in blood pressure at night, a variety of antihypertensive drugs reduce both daytime and nighttime blood pressures with a more pronounced effect on daytime blood pressure. On the other hand, in non-dippers who do not significantly show a nocturnal reduction in blood pressure, antihypertensive treatment reduce both daytime and nighttime blood pressures and the nighttime blood pressure reduction is similar to that during the daytime, and larger than the effect observed in dippers.

6. ABPM in Patients Receiving Non-Pharmacological Antihypertensive Treatment

Since ABPM provides reliable mean values and can detect relatively small changes in blood pressure, it is also suitable in evaluating the effects of non-pharmacological antihypertensive treatment (lifestyle modification). Different non-pharmacological strategies affect the 24 hour blood pressure and circadian blood pressure variation in different ways in terms of quality and quantity. Weight reduction in obese patients reduces 24 hour blood pressure, with similar extents on the daytime and nighttime blood pressures. Regular exercise also reduces blood pressure using ABPM. It is reported that many patients with salt-sensitive hypertension are non-dippers, and salt restriction in this patient population reduces nighttime blood pressure more substantially than daytime blood pressure and normalizes the circadian blood pressure variation.

Studies for the effects of potassium, magnesium and calcium supplementation using ABPM have revealed that potassium and magnesium reduced 24 hour, daytime and nighttime blood pressure significantly but modestly by 2 to 4 mmHg in systolic blood pressure and 1 to 2 mmHg in diastolic blood pressure, while the effects of calcium supplementation was not significant.

The effect of alcohol restriction may vary among ethnic groups and individuals. In Japanese, alcohol restriction reduces casual blood pressure but does not cause any noticeable effects on mean 24 hour blood pressure. Alcohol consumption causes a reduction in nighttime blood pressure and an increase in daytime blood pressure, while alcohol restriction causes opposite effects. The effects of smoking cessation on nighttime blood pressure is modest, but smoking cessation is expected to reduce daytime and 24 hour blood pressures unless it is accompanied by body weight gain.
In April 2008, ABPM was endorsed in the NHI as a procedure at a NHI price of 2,000 Japanese yen on the basis of the domestic and foreign evidence demonstrating the favorable predictive effect of ABPM on the development of cerebral and cardiovas-
cular complications that is superior to casual blood pressure measurements, and the results of such as Ohhasama study describing the excellent cost-effectiveness of ABPM.108-116

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**Appendix**

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