



## Guideline

## 2010 Guidelines of the Taiwan Society of Cardiology for the Management of Hypertension

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Hypertension is one of the most important risk factors for atherosclerosis-related mortality and morbidity. In this document, the Hypertension Committee of the Taiwan Society of Cardiology provides new guidelines for hypertension management. The key messages are as follows. (1) The life-time risk for hypertension is 90%. (2) Both the increase in the prevalence rate and the relative risk of hypertension for causing cardiovascular events are higher in Asians than in Caucasians. (3) The control rate has been improved significantly in Taiwan from 2.4% to 21% in men, and from 5% to 29% in women in recent years (1995–2002). (4) Systolic and diastolic blood pressure (BP)  $\geq$  130/80 mmHg are thresholds of treatment for high-risk patients, such as those with diabetes, chronic kidney disease, stroke, established coronary heart disease, and coronary heart disease equivalents (carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm). (5) Ambulatory and home BP monitoring correlate more closely with end-organ damage and have a stronger relationship with cardiovascular events than office BP monitoring, but the feasibility of home monitoring makes it a more attractive alternative. (6) Patients with masked hypertension have higher cardiovascular risk than those with white-coat hypertension. (7) Lifestyle changes should be encouraged in all patients, and include the following six items: S-ABCDE (Salt restriction; Alcohol limitation; Body weight reduction; Cessation of smoking; Diet adaptation; Exercise adoption). (8) When pharmacological therapy is needed, physicians should consider “PROCEED” (Previous experience of patient; Risk factors; Organ damage; Contraindication or unfavorable conditions; Expert or doctor judgment; Expense or cost; Delivery and compliance) to decide the optimal treatment. (9) The main benefits of antihypertensive agents are derived from lowering of BP *per se*, and are generally independent of

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the drugs being used, except that certain associated cardiovascular conditions might favor certain classes of drugs. (10) There are five major classes of drugs: thiazide diuretics;  $\beta$ -blockers; calcium channel blockers; angiotensin-converting enzyme inhibitors (ACEIs); and angiotensin receptor blockers (ARBs). Any one of these can be used as the initial treatment, except for  $\beta$ -blockers, which are only indicated in patients with heart failure, a history of coronary heart disease, and hyperadrenergic state. (11) A standard dose of any one of the five major classes of antihypertensive drugs can produce an  $\sim$ 10-mmHg decrease in systolic BP (rule of 10) and a 5-mmHg decrease in diastolic BP (rule of 5), after placebo subtraction. (11) Combination therapy is frequently needed for optimal control of BP, and the amount of the decrease in BP by a two-drug combination is approximately the same as the sum of the decrease by each individual drug ( $\sim$ 20 mmHg in systolic BP and 10 mmHg in diastolic BP) if their mechanisms of action are independent, with the exception of the combination of ACEIs and ARBs. (13) An ACEI or ARB plus a calcium channel blocker or a diuretic (A+C or A+D) are reasonable two-drug combinations, and A+C+D is a reasonable three-drug combination, unless patients have special indications for  $\beta$ -blockers. (14) Single-pill (fixed-dose) combinations that contain more than one drug in a single tablet are highly recommended because they reduce pill burden and cost, and improve compliance. (15) Very elderly patients ( $\geq$ 80 years) should be treated without delay, but BP should be reduced gradually and more cautiously. Finally, these guidelines are not mandatory; the responsible physician's decision remains most important in hypertension management.

**Key Words:** blood pressure, disease management, drug therapy, hypertension

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## Preface

Hypertension is the most important risk factor for cardiovascular morbidity and mortality.<sup>1</sup> Since the Seventh Report of the Joint National Committee Guidelines (JNC 7) on hypertension in 2003<sup>2</sup> and the European Society of Hypertension and European Society of Cardiology Guidelines for the Management of Arterial Hypertension in 2007,<sup>3</sup> there have been many new data from

epidemiological studies and randomized control trials. The Hypertension Committee of the Taiwan Society of Cardiology believes it is an appropriate time to provide updated guidelines for the management of hypertension. This report serves as a guide, and the Committee continues to recognize that the judgment of the responsible physician remains paramount.

## Classification

According to the largest meta-analysis of observational data carried out to date, cardiovascular morbidity and mortality have a continuous relationship with both systolic (down to 115 mmHg) and diastolic (down to 75 mmHg) blood pressure (BP).<sup>4</sup> For every 20 mmHg difference in systolic BP, or 10 mmHg difference in diastolic BP, there is a twofold increase in the stroke death rate, and twofold differences in the death rates from coronary heart disease (CHD) and from other vascular causes.<sup>4</sup> However, for descriptive purpose and therapeutic guidance, hypertension needs to be classified. The definition and classification of hypertension in these guidelines is based on office BP, as shown in Table 1. For patients with high Framingham risk ( $\geq 20\%$  in 10 years), such as patients with diabetes, chronic kidney disease, stroke, established CHD, and CHD equivalents (carotid artery disease, peripheral arterial disease, and abdominal aneurysm), a target of  $< 130/80$  mmHg is recommended.<sup>5</sup>

## Epidemiology

Hypertension is one of the most important risk factors for atherosclerosis-related mortality and morbidity. According to the Prospective Studies Collaboration, hypertension produced the greatest mortality burden in 2001, accounting for more than 7 million deaths worldwide, more than any other known risk factors.<sup>1</sup> About 54% of stroke and 47% of ischemic heart disease worldwide are attributable to high BP.<sup>6</sup> Overall, about 80% of the

**Table 1.** Definition and classification of hypertension by office blood pressure\*

Stage	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	$< 120$	and	$< 80$
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	$\geq 160$	or	$\geq 100$
Stage 3 hypertension	$\geq 180$	or	$\geq 110$

\*Systolic BP  $\geq 130$  or diastolic BP  $\geq 80$  is considered hypertension for patients with coronary heart disease, coronary heart disease equivalent (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm), stroke, diabetes and chronic kidney disease. BP = Blood pressure.

attributable burden occurred in low- and middle-income economies.<sup>6</sup>

The life-time risk of having hypertension is about 90%.<sup>7</sup> The prevalence rate of hypertension is also growing. There were 972 million patients (26.4%) with hypertension in 2000 and the number will reach 1.56 billion (29.2%) in 2025, a 60% increase in 25 years.<sup>8,9</sup> The rampant increase in prevalence is most serious in Asia. For men, there will be a 65.4% increase in Asia compared with a 51.2% increase for men in the rest of the world. It is even more severe in women; an 81.6% increase in Asia compared with a 54.4% increase in the rest of the world.<sup>8</sup> In a recent survey in Taiwan, the nationwide prevalence rates of hypertension, defined by systolic BP  $> 140$  mmHg or diastolic BP  $> 90$  mmHg, were 25% in men and 18% in women, and the rate increased to 47% among individuals of age  $\geq 60$  years.<sup>10</sup> The community-based data on a 10-year follow-up cohort in Taiwan have shown that the incidence rates have increased among individuals with prehypertension, obesity and metabolic syndrome.<sup>11</sup> Furthermore, baseline BP categories play an important role in predicting cardiovascular risks; the hazard ratios of prehypertension and hypertension increased from 1.73 to 4.52, compared with baseline normotensive subjects.<sup>11</sup>

The impact of hypertension on cardiovascular events in Asian is higher than that in Caucasian.<sup>12</sup> With the same increase in systolic BP of 15 mmHg, the hazard ratio for CHD and stroke is

higher in Asian than in Caucasian.<sup>12</sup> The hazard ratio of hypertension for fatal vascular events is higher for men in China and Japan, compared to men in Australia and New Zealand.<sup>13</sup> In 6105 patients with a history of stroke or transient ischemic attack, treatment of hypertension resulted in a 38% reduction in the risk of recurrent stroke in Asian patients, compared with a 20% reduction in Caucasian patients with a similar decrease in BP.<sup>14</sup>

In a recent survey from 10 developed countries, the prevalence rate of hypertension was higher in men than in women before the age of 60 years.<sup>8</sup> After that, it was higher in women. An epidemiological study in Taiwan has shown similar findings, in that the age-related rise in systolic BP was steeper in women than in men between ages 40 to 80 years.<sup>10</sup> Despite the mean systolic BP in men being higher than that in women before the age of 60 years, it becomes lower than that in women after 60 years.<sup>10</sup>

The control rate for hypertension, defined by office BP < 140/90 mmHg in non-high-risk patients and < 130/80 mmHg in high-risk patients, is generally low. No single country has an overall control rate > 40%.<sup>2,15</sup> In Taiwan, compared with the national survey in 1993,<sup>16</sup> there was a significant improvement in the awareness, treatment, and control rate in the 2002 survey,<sup>10</sup> a finding that could be attributable to the implementation of the National Health Insurance system since 1995.<sup>10</sup> Hypertension control rate increased from 2.4% to 21% in men, and from 5% to 29% in women.<sup>10</sup> In fact, the control rate in Taiwan is higher than that in Korea (10.7%),<sup>17</sup> Japan (12%)<sup>18</sup> and China (5%).<sup>19</sup> The control rate of hypertension varies in different areas in Taiwan; it reaches about 50% for women in the northern area, but is < 10% for men in eastern parts, which reflects the disparity in medical resources.<sup>20</sup>

## Etiology

Blood pressure is a product of the interaction between genetic determinants and environmental interfering factors, where the causes of hypertension

arise. Currently, the etiology of hypertension is divided into two categories: essential and secondary hypertension.

### *Essential hypertension*

In patients with high BP, essential hypertension is diagnosed after secondary causes of hypertension are excluded.<sup>21</sup> Essential hypertension accounts for nearly 95% of all cases of hypertension. The development of study into human genetics has led to the recognition of several genes that are involved in regulation of BP.<sup>22-24</sup> These associations between common variants and BP and hypertension offer mechanistic insights into the regulation of BP, and point to novel targets for interventions to prevent cardiovascular disease. However, genetic analysis for most patients with hypertension is not practical at present. In contrast, detection of environmental interfering factors is useful for BP control. These factors include: (1) obesity; (2) insulin resistance; (3) high alcohol intake; (4) high salt intake (in salt-sensitive patients); (5) aging; (6) sedentary lifestyle; (7) stress; (8) low potassium intake; and (9) low calcium intake. Many of these factors occur in clusters and the effects are additive, such as obesity, insulin resistance, and sedentary lifestyle.

### *Secondary hypertension*

Secondary hypertension is a potentially curable condition if the cause is eliminated.<sup>25</sup> The most common form is secondary to renal parenchymal disease; the causes of which include acute and chronic glomerulonephritis of varying causes, autosomal dominant polycystic kidney disease, diabetic nephropathy, and hydronephrosis secondary to obstructive uropathy. Renovascular disease is also a common cause of secondary hypertension related to the kidneys, which is due to renal artery stenosis, which is often caused by atherosclerosis in elderly patients. Apart from the kidneys, other common causes of secondary hypertension are endocrine-related, due to either hyperactivity or hypoactivity, depending on the glands involved. Table 2 summarizes the causes of secondary hypertension.

**Table 2.** Causes of secondary hypertension

Acute stress related secondary hypertension	Isolated systolic hypertension due to an increased cardiac output
<b>Diseases of the aorta</b>	Neurological causes
Coarctation of the aorta	Guillain–Barre syndrome
Rigidity of the aorta	Idiopathic, primary, or familial dysautonomia
<b>Drugs and exogenous hormones</b>	Increase intracranial pressure
<b>Endocrine</b>	Quadriplegia
Acromegaly	Obstructive sleep apnea
Adrenal cortical	Pregnancy induced hypertension
Apparent mineralocorticoid excess	Renal
Cushing syndrome	Increased intravascular volume
Primary aldosteronism	Primary sodium retention (Liddle's syndrome)
<b>Adrenal medulla</b>	Renal parenchymal disease
Carcinoid syndrome	Renin-producing tumors
Pheochromocytoma	Renal vascular disease
<b>Hyperparathyroidism</b>	
<b>Hyperthyroidism</b>	
<b>Hypothyroidism</b>	

### Office Blood Pressure, Ambulatory Blood Pressure, Home Blood Pressure, and Other Blood Pressure Parameters

Blood pressure can be measured by doctors or nurses in the office or clinic (office BP), by automatic machine over 24 hours (ambulatory BP monitoring; ABPM), or by the patient or a relative at home (home BP monitoring; HBPM). Although office BP is used for staging of hypertension, there is increasing evidence that it might not reflect the true cardiovascular risk for hypertensive patients.<sup>26</sup>

ABPM and HBPM have become increasingly important for the management of hypertension.<sup>26,27</sup> They both make use of automated, validated oscillometric devices, and the BP values are operator-independent.<sup>28</sup> They also eliminate the alarm reaction and the “white-coat” effect associated with office BP measurement, and provide more stable and reproducible readings of BP values.<sup>29</sup> A new electronic device for HBPM, which implements an algorithm for the diagnosis of atrial fibrillation, has an excellent diagnostic accuracy.<sup>30</sup> A much larger number of values than office BP measurements make HBPM and ABPM more accurate estimates of future cardiovascular events.<sup>31</sup>

### Office blood pressure

The measurement of BP is likely to be the clinical procedure of greatest importance that is performed in the sloppiest manner. Blood pressure measurement should follow the guidelines outlined by Pickering et al,<sup>32</sup> and is not mentioned further in this paper. In brief, the diagnosis of hypertension should be based on multiple measurements on separate occasions over a period of time. The patients should be seated with their back supported and both feet lying flat on the floor for at least 5 minutes in a quiet room, with an empty bladder. At least two measurements of BP should be taken each time, separated by at least 1 minute. Blood pressure can be measured by a mercury sphygmomanometer or other noninvasive electronic devices. The latter is becoming an important modality because of its simplicity of use and the progressive banning of the medical use of mercury. For mercury sphygmomanometry, phase I and V Korotkoff sounds are taken to identify systolic and diastolic BP, respectively. The BP should be taken in both arms at first visit and the higher value is used as reference. For follow-up, one only needs to measure the BP in the arm with the higher value.

Although the data from the Framingham Heart Study have shown that diastolic BP is a stronger predictor for future coronary events than systolic BP in patients aged < 50 years,<sup>33</sup> it is generally believed that systolic BP is a more important

predictor for overall cardiovascular risk in elderly patients ( $\geq 65$  years).<sup>2,34</sup> In a 19-year follow-up study of 3779 patients in Japan, elevated systolic BP was an independent risk factor for cardiovascular mortality, whereas elevated diastolic BP was not.<sup>35</sup> Seventy-five percent of people with high BP are aged  $> 50$  years, therefore, the burden of disease is mainly due to systolic BP.<sup>36</sup> The importance of controlling systolic BP has also been shown in a meta-analysis of 28,436 patients, in which antihypertensive drugs improved outcome mainly through lowering systolic BP.<sup>37</sup> Nevertheless, systolic BP is more difficult to control, especially in diabetic patients.<sup>38</sup>

### ***Ambulatory blood pressure monitoring***

ABPM was initially confined to specialized hypertension centers due to its high cost, but over the years its availability has steadily increased. ABPM provides information on 24-hour average BP and mean values of more specific periods, such as daytime and nighttime BP. ABPM correlates more closely with end-organ damage and has a stronger relationship with cardiovascular events than office BP has.<sup>39</sup> In addition, recent studies have suggested that nighttime is better than daytime BP in predicting target-organ damage and future cardiovascular events.<sup>40–42</sup>

Blood pressure thresholds for defining hypertension with ABPM are lower than those from office BP (Table 3).<sup>3</sup> One recent study of ABPM has suggested that optimal 24-hour mean BP is  $< 115/75$  mmHg, daytime BP  $< 120/80$  mmHg, and nighttime BP  $< 100/65$  mmHg.<sup>43</sup> These values are lower

than the thresholds set in the current hypertension guidelines, but intriguingly correspond to the epidemiological observation that the continuous relation between cardiovascular risks and BP starts from the level of 115/75 mmHg.<sup>4</sup> It needs to be mentioned that ABPM should not be regarded as a substitute for information derived from conventional BP measurements. Although the price of ABPM units has fallen considerably in recent years, the costs of the system and its maintenance remain relatively high; it is unquestionably higher than those of HBPM.<sup>29</sup> In Taiwan, the costs of ABPM measurement have not been reimbursed by the National Health Insurance system. Therefore, the use of ABPM is limited to a research setting, or in the following conditions: when BP is not below target despite receiving appropriate chronic antihypertensive therapy, when symptoms are suggestive of hypotension, or when office BP readings fluctuate. HBPM is an economically feasible substitute for ABPM.<sup>31</sup>

### ***Home blood pressure monitoring***

Self-measurement of BP at home is becoming an important method in assessing future cardiovascular risk of patients and is now regarded as an important additive to the conventional BP measurements. There is rapidly growing evidence that measurements taken by patients at home are often lower than readings taken in the office, and are closer to the averaged BP recorded by ABPM, which are the best predictor of future cardiovascular risk.<sup>27</sup> More readings can be taken by HBPM. HBPM is more reproducible than office reading and can reduce the white-coat effect. There is also convincing evidence to show that HBPM has better correlations with target-organ damage.<sup>28</sup> In studies that have compared the predictability of HBPM with office BP measurement for future cardiovascular events, four out of five were in favor of the former.<sup>27,41,44–46</sup>

Home BP is measured by validated automatic devices, rather than using a mercury sphygmomanometer.<sup>27</sup> An up-to-date list of validated devices is available on the Dabl Educational website<sup>47</sup> and the website of the British Hypertension Society.<sup>48</sup>

**Table 3.** Blood pressure thresholds for definition of hypertension with ambulatory blood pressure and home blood pressure<sup>3,43</sup>

Category	Systolic BP (mmHg)	or	Diastolic BP (mmHg)
Ambulatory BP	$\geq 130$	or	$\geq 80$
Day time	$\geq 135$	or	$\geq 85$
Night time	$\geq 120$	or	$\geq 70$
Home BP	$\geq 135$	or	$\geq 85$

BP = Blood pressure.

The devices that use the brachial artery with a cuff placed on the upper arm are most reliable, and have the additional advantage that the brachial artery pressure is the measure that has been used in all epidemiological studies of hypertension.<sup>27</sup> Wrist monitors are not recommended for routine clinical use.<sup>27</sup> We recommend that measurements should be taken at least twice a day:<sup>49</sup> in the morning and in the evening after 5 minutes rest,<sup>29</sup> with two measurements on each occasion, separated by 1 minute.<sup>50</sup> The morning measurements should be done within 1 hour after waking, after urination, and before morning dosing and breakfast. The evening measurements should be performed before retiring. HBPM devices with a built-in memory function are encouraged for some patients who might tend to make their home readings look better than they really are.

The number of HBPM readings is probably more important than the monitoring schedule.<sup>49</sup> A minimum of 12 measurements and up to 25 measurements over a few days might be desirable.<sup>29</sup> Two morning readings and two evening readings for 7 days immediately before each visit, excluding the readings from the first day, should be measured and stored in devices. Thus 12 readings either in the morning or evening, with a total of 24 readings, are averaged for each visit.<sup>29</sup> Physicians can use separated averages of morning or evening BP to adjust the timing of administration of antihypertensive agents. The threshold of home BP (< 135/85 mmHg, and < 130/80 mmHg for high-risk patients) is lower than that of office BP (Table 3). HBPM is cheaper and easier to perform than ABPM, and provides more information when there is clinical suspicion of white coat hypertension or masked hypertension in cases in which ABPM is not feasible.<sup>27</sup>

HBPM has many features that are not achievable with ABPM. HBPM can be performed repeatedly and regularly over extended periods of time, which is not feasible with ABPM. HBPM also encourages the active involvement of patients, which enables better BP control and improves medication compliance.<sup>51</sup> HBPM is increasingly replacing ABPM in clinical practice. It might also

be the most reasonable option for the initial assessment in untreated hypertensive patients, in patients whose office BP is close to diagnostic threshold, in patients whose out-of-office BP is discrepant from office BP, or in patients with target-organ damage in spite of normal office BP.<sup>31</sup> Therefore, priority should be given to HBPM in most patients when out-of-office BP measurement is needed.

## White Coat Hypertension

White coat hypertension, also called isolated office hypertension, can be diagnosed when: (1) office BP is  $\geq 140/90$  mmHg on at least three occasions; (2) 24-hour mean and daytime BP, measured by ABPM, are below their thresholds; or (3) average home BP, measured by HBPM, is < 135/85 mmHg. It has been estimated that white coat hypertension might be present in about 15% of the general population.<sup>3</sup> The long-term prognostic significance of white coat hypertension is inconsistent.<sup>45,52–55</sup> Nevertheless, it has been reported that white coat hypertension is associated with higher cardiovascular risks than in normotensive subjects,<sup>53</sup> which suggests that lifestyle modification and close follow-up are needed in all patients with white coat hypertension. In case of evidence of target-organ damage, drug treatment should be considered.

## Masked Hypertension

Masked hypertension is defined as individuals with normal office BP (< 140/90 mmHg) but with elevated ambulatory or home BP values. It has been calculated that about one in seven or eight subjects with normal office BP could fall into this category.<sup>53</sup> Masked hypertension is associated with target-organ damage<sup>52,55,56</sup> and increased cardiovascular risks to a similar degree to those with sustained high BP.<sup>45</sup> ABPM or HBPM is useful in the diagnosis and treatment of patients with masked hypertension.

## Central Aortic Blood Pressure

Central aortic pressure can be estimated by a combination of brachial cuff measurement and analysis of the pulse waveform.<sup>57</sup> In a 10-year follow-up study in 1272 Taiwanese patients, central systolic BP was more valuable than other BP variables in predicting cardiovascular mortality.<sup>58</sup> In a recent meta-analysis of 17 longitudinal studies that have evaluated aortic pulse wave velocity and followed up 15,877 subjects for a mean of 7.7 years, an increase of 1 m/s corresponded to an age-, sex- and risk-factor-adjusted risk increase of 15% in all-cause mortality.<sup>59</sup> It remains to be demonstrated if treatment aimed at reducing central aortic pressure is more effective in preventing cardiovascular events than traditional care.<sup>60</sup>

## Physical Examination

Physical examination plays an essential role in assessment of hypertensive patients. The purposes of physical examinations in evaluating patients with hypertension are to document the presence and severity of hypertension, and to search for signs that suggest secondary hypertension and end-organ damage, and evidence of visceral obesity.<sup>3</sup> Initially, an appropriate measurement of BP in both arms, as compared with the BP in the legs, should be carefully taken.<sup>2</sup> Then, the physical examination should include calculation of body mass index (BMI); inspection of Cushingoid appearance including moon face, buffalo hump, truncal obesity, and wide purple striae; evaluation of optic fundi for hypertensive retinopathy; palpation of the thyroid gland for hyperthyroidism; auscultation of carotid, abdominal and femoral bruits for peripheral artery disease and renovascular disease, as well as a loud murmur over the back for coarctation of aorta; comprehensive examination of the heart and lungs for left ventricular hypertrophy with congestive heart failure; examination of the abdomen for enlarged kidneys, masses, and abnormal aortic pulsation; palpation of the lower extremities for edema and pulses; and complete

neurological assessment.<sup>2</sup> The aforementioned evaluation should be undertaken in every patient in the first visit for initial diagnosis of hypertension.

## Laboratory Tests

Laboratory tests aim to provide evidence for additional risk factors, search for secondary hypertension, and the absence or presence of organ damage, shown in Table 4. The younger the patient, the higher the BP and the more severe the target-organ damage, the more detailed the diagnostic work-up should be.<sup>2</sup> Routine laboratory tests recommended before initiating therapy include chest X-ray; electrocardiography; urinalysis complemented by proteinuria via dipstick test; hemoglobin and hematocrit; serum sodium, potassium, calcium, creatinine [or the corresponding estimate creatinine clearance via the Cockcroft–Gault formula or glomerular filtration rate by the abbreviated MDRD (Modification of Diet in Renal Disease) formula:  $186.3 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female})$ ], uric acid; and a 9–12-hour fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides<sup>2,3,58–60</sup> (Table 4).

Recommended studies are shown in Table 4. Measurement of urinary albumin excretion or albumin/creatinine ratio is strongly recommended in Taiwan, which has the highest prevalence of end-stage renal disease in the world.<sup>64</sup> When fasting plasma glucose is  $\geq 100$  mg/dL, a glucose tolerance test is recommended. High-sensitivity C reactive protein (hs-CRP) has been reported to predict the incidence of cardiovascular events in several clinical settings, especially in patients with metabolic syndrome.<sup>3,65,66</sup> In a recent study in apparently healthy persons using hs-CRP levels for risk stratification, statin treatment in those with elevated hs-CRP significantly reduced the incidence of major cardiovascular events.<sup>67</sup> Ultrasound assessment of the heart and carotid walls helps to obtain a more valid assessment of global cardiovascular risk in hypertensive patients without

**Table 4.** Laboratory investigations

Initial tests
1. Hemoglobin and hematocrit
2. Serum creatinine with estimated creatinine clearance (Cockcroft–Gault formula) or glomerular filtration rate (Modification of Diet in Renal Disease formula)
3. Serum sodium, potassium and calcium
4. Fasting glucose
5. Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides
6. Serum uric acid
7. Urinalysis (complemented by microalbuminuria via dipstick test and microscopic examination)
8. Electrocardiogram
9. Chest X-ray
Recommended tests
1. Glucose tolerance test (if fasting plasma glucose higher than 100 mg/dL)
2. High sensitivity C reactive protein (in patients with metabolic syndrome)
3. Quantitative microalbuminuria/proteinuria (if positive dipstick tests)
4. Fundoscopy
5. Echocardiography
6. Carotid ultrasound
7. Renal ultrasound
8. Home and 24 h ambulatory blood pressure monitoring
9. Ankle-brachial index
10. Pulse wave velocity measurement
Extended evaluation (domain of the specialist)
1. Further search for cerebral, cardiac, renal and vascular damage. Mandatory in complicated hypertension
2. Search for secondary hypertension when suggested by history, physical examination or routine tests: measurement of renin, aldosterone, corticosteroids, catecholamines in plasma and/or urine; angiographies; renal and adrenal ultrasound; computer-assisted tomography; magnetic resonance imaging (see content)

evidence of target-organ damage after routine examination.<sup>68</sup>

### Screening of Secondary Hypertension

The causes of secondary hypertension are listed in Table 2. Screening for secondary hypertension can be obtained from clinical history, physical examination and routine laboratory investigations. The complete physical examination has been mentioned above. A secondary form of hypertension is suggested by younger or older onset of hypertension, severe BP elevation, sudden onset or worsening of hypertension, significant target-organ damage, and BP responding poorly to drug

therapy. In these cases, specific diagnostic procedures might become necessary.<sup>2,3</sup>

Renal parenchymal disease is the most common cause of secondary hypertension. The finding of bilateral upper abdominal masses at physical examination is consistent with polycystic kidney disease, and might require abdominal ultrasound examination. Ultrasound is noninvasive and provides all the necessary anatomical data concerning kidney size and shape, cortical thickness, urinary tract obstruction and renal masses. Assessment of the presence of protein, erythrocytes and leukocytes in the urine, as well as measuring serum creatinine concentration, are the appropriate functional screening tests for renal parenchymal disease.<sup>2</sup>

Renovascular hypertension is the second most common cause of secondary hypertension.<sup>2</sup> Renal artery stenosis is mostly due to atherosclerosis in the elderly population. Fibromuscular dysplasia accounts for up to 25% of total cases and is the leading cause in young adults. Abrupt onset before age 30 years or worsening after age 55 years, renal artery bruit, unexplained hypokalemia, resistance to antihypertensive therapy, sustained rise in creatinine after initiation of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), retinal hemorrhages, exudates, or papilledema or flash pulmonary edema suggests the presence of this condition.<sup>69</sup> Determination of the longitudinal diameter of the kidney using ultrasound can be used as a screening procedure. However, a difference of > 1.5 cm in length between the two kidneys, which is usually considered diagnostic for renal artery stenosis, is only found in 60–70% of the patients with renovascular hypertension.<sup>70</sup> Color Doppler ultrasonography can detect stenosis of the renal artery, particularly when localized close to the origin of the vessel. There is evidence that investigation of the renal vasculature by three-dimensional, gadolinium-enhanced magnetic resonance angiography or spiral computed tomography is the diagnostic choice for renovascular hypertension. Once there is strong suspicion of renal artery stenosis, digital subtraction angiography, the gold standard for detection, should be performed.

Hypertension occurs in about 70% of all cases of pheochromocytoma, and is stable or paroxysmal. The clinical symptoms include headache, sweating, palpitations, and pallor. The diagnosis is based on establishing an increase in plasma or urinary catecholamines or their metabolites.

It has been suggested that patients with unprovoked hypokalemia or truly resistant hypertension should be evaluated for primary aldosteronism.<sup>71</sup> Serum potassium level is an important part of screening. The disease can be confirmed by the fludrocortisone suppression test (failure of 4 days administration of the hormone to reduce plasma aldosterone below its threshold value), and measurement of aldosterone and renin under

standardized conditions.<sup>72</sup> A cut-off of aldosterone-renin ratio > 100 ng/dL per ng/mL/hr and plasma aldosterone > 20 ng/dL after captopril differentiates bilateral aldosterone-producing adenoma from bilateral adrenal hyperplasia.<sup>73</sup>

Hypertension is reported in about 80% of patients with Cushing's syndrome. The syndrome is usually suggested by the typical body habitus. The determination of 24-hour urinary cortisol excretion is the most practical and reliable diagnostic test, and a value > 110 mmol (40 mg) is highly suggestive of Cushing's syndrome.<sup>2</sup>

Obstructive sleep apnea is characterized by recurrent episodes of cessation of respiratory airflow caused by upper airway inspiratory collapse during sleep, with a consequent decrease in oxygen saturation. It is important to consider sleep apnea in obese patients. Furthermore, hypertensive patients, who are classified as "non-dippers" on ABPM, should be investigated for obstructive sleep apnea. Signs and symptoms include daytime somnolence, impaired concentration, un-refreshing and restless sleep, choking episodes during sleep, witnessed apneas, nocturia, irritability and personality changes, decreased libido, and increased motor vehicle accidents. The gold standard diagnostic tool for assessing obstructive sleep apnea is polysomnography.

Coarctation of the aorta is a rare form of hypertension in children and young adults. The diagnosis is usually evident from physical examination. A mid-systolic murmur, which might become continuous with time, is heard over the anterior part of the chest and also over the back. The femoral pulse is absent or delayed relative to the radial pulse. Hypertension is found in the upper extremities concomitantly with low or unmeasurable BP in the legs.

Finally, patients should be asked about their medication when their clinical history is taken, and the use of drugs that can raise BP should be monitored carefully. Substances or drugs that can raise BP include licorice (mostly existing in anti-tussive syrup), oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, cocaine and amphetamines, erythropoietin, cyclosporin, tacrolimus, and some pills used to treat colds.

**Table 5.** Therapeutic life style changes for managing hypertension (S-ABCDE)

Changes	Recommendation	Expected benefits in systolic BP reduction
<u>S</u> alt restriction	< 6 g/d salt (< 100 mmol NaCl)	2–8 mmHg
<u>A</u> lcohol limitation	<u>Men</u> < 30 g/d ethanol (< 700 mL/d beer, < 240 mL/d red wine, < 75 mL/d whiskey or brandy) <u>Women</u> < 20 g/d ethanol (< 470 mL/d beer, < 160 mL/d red wine, < 50 mL/d whiskey or brandy)	2–4 mmHg
<u>B</u> ody weight reduction	BMI = 18.5–24.9 kg/m <sup>2</sup>	1 mmHg/kg
<u>C</u> essation of smoke	Complete abstinence	No independent effect
<u>D</u> iet adaptation	<b>DASH</b> diet: rich in fruits and vegetables (8–10 servings/d), rich in low-fat dairy products (2–3 servings/d), and reduced in saturated fat and cholesterol	10–12 mmHg
<u>E</u> xercise adoption	Aerobic, at least 30 min/d, and at least 5 d/wk	3–7 mmHg

BP = blood pressure; BMI = body mass index; DASH = Dietary Approaches to stop Hypertension.

## Lifestyle Changes

Lifestyle changes (modification) should be promoted for all patients with prehypertension, definite hypertension, and those who require drug treatment.<sup>2,3</sup> The purpose is to lower BP, control other risk factors, and reduce numbers or doses of antihypertensive drugs.<sup>3</sup> The lifestyle measures that are widely recommended to lower BP and cardiovascular risks can be summarized as S-ABCDE: Salt restriction, Alcohol limitation, Body weight reduction, Cessation of smoking, Diet adaptation, and Exercise adoption (Table 5). The main problem with lifestyle changes is the low adherence rate. In fact, adherence to a healthy lifestyle pattern has decreased during the past two decades in the United States.<sup>74</sup> Failure to adopt healthy lifestyles has been a crucial factor in the paradoxical increase in the number of people with uncontrolled hypertension despite the enormous advances in antihypertensive drug therapy.<sup>75</sup>

### *Salt restriction*

Epidemiological studies and randomized controlled trials have indicated that dietary sodium restriction is helpful for BP lowering.<sup>76</sup> Reducing dietary sodium intake to < 100 mmol/L could

decrease BP by 2–8 mmHg.<sup>2,76</sup> Recommendation for dietary sodium intake is generally accepted as no more than 2.4 g sodium or 6 g sodium chloride (< 100 mmol NaCl).<sup>2</sup> This threshold is also supported by recent epidemiological data from Taiwan for which a significant J-shape relationship between urinary sodium excretion and risk of hypertension has been observed. Participants who were in the highest quartile of urinary sodium excretion and higher baseline BP had a 2.43-fold increased risk of hypertension (95% confidence interval: 1.72–3.22) compared with those in the lowest quartiles of urinary sodium and lower BP.<sup>77</sup> In the trials of hypertension prevention, patients with prehypertension were randomized to a sodium reduction intervention group or a control group.<sup>78</sup> The risk of a cardiovascular events was 25% lower among those in the intervention group.<sup>78</sup> The risk of high salt intake has been confirmed in a recent meta-analysis of 19 prospective cohort studies of 177,025 patients. High salt intake (about 5 g/d higher than low salt intake) was associated with a 23% higher risk of stroke and 17% higher risk of cardiovascular diseases.<sup>79</sup> A study to estimate the economic benefits of lowering sodium consumption among the American public has found that \$18 billion in

healthcare costs for hypertension could be reduced every year if salt intake were reduced to the amount recommended by health officials.<sup>80</sup> More recently, investigators in the United States, using the Coronary Heart Disease Policy Model, have found that population-wide reduction of dietary salt by 3 g per day (1200 mg/d sodium) is projected to reduce the annual number of new cases of CHD by 60,000–120,000, stroke by 32,000–66,000, and myocardial infarction by 54,000–99,000, and to reduce the annual number of deaths from any cause by 44,000–92,000 in the US.<sup>81</sup> It could save 194,000–392,000 quality-adjusted life-years and \$10–\$24 billion in health care costs annually. Salt restriction is more effective in patients with metabolic syndrome, and the odds ratio of salt sensitivity is positively related to the number of risk factors for metabolic syndrome.<sup>82</sup> Excessive dietary sodium ingestion makes an important contribution to resistance to antihypertensive treatment. Strategies to reduce dietary salt intake substantially should be part of the overall treatment of resistant hypertension.<sup>83</sup> Supplemental calcium, potassium, or magnesium have been proposed to lower BP, but data are not entirely consistent.<sup>76</sup>

### **Alcohol limitation**

Excess alcohol consumption accounts for 5–30% of all hypertension.<sup>84</sup> Alcohol restriction has blood-pressure-lowering effects.<sup>76</sup> Reduction of weekly alcohol intake from 452 to 64 mL was associated with a fall of 5/3 mmHg in 3 weeks.<sup>84</sup> Many studies have shown a U or L shaped association between alcohol consumption and mortality,<sup>3</sup> but this association has been challenged by a recent meta-analysis in which a dose-response relationship was observed between mean percentage of alcohol reduction and mean BP reduction.<sup>85</sup> Alcohol reduction was associated with a significant reduction in mean systolic BP of –3.3 mmHg and diastolic BP of –2.0 mmHg. It is recommended that consumption should be limited to no more than two drinks or 20–30 g per day ethanol for men and no more than one drink or 10–20 g per day ethanol for women.<sup>2,3</sup>

### **Body weight reduction**

There is a direct positive relation between body weight or BMI and BP.<sup>3,86</sup> There is also conclusive evidence that weight reduction lowers BP and reduces cardiovascular risks.<sup>3</sup> Every 10-kg weight reduction is associated with 5–20 mmHg reduction in systolic BP in overweight subjects. In a recent meta-analysis, every 1 kg body weight reduction was associated with a 1.1-mmHg reduction in systolic and 0.9-mmHg reduction in diastolic BP.<sup>87</sup> Maintenance of normal body weight (BMI, 18.5–24.0 Kg/m<sup>2</sup>) is recommended.<sup>2</sup>

### **Cessation of smoking**

Although the effects of smoking on BP are controversial, and the effects of smoking cessation on BP lowering are not definite, smoking cessation is the most effective lifestyle change for preventing cardiovascular events.<sup>3</sup>

### **Diet adaptation**

A diet rich in fruit and vegetables is better than tablets or other supplements.<sup>88,89</sup> The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes on fruit, vegetables, and low-fat dairy products; and includes whole grains, poultry, fish, and nuts; and is reduced in fats, red meat, sweets, and sugary drinks.<sup>90</sup> The DASH diet can reduce systolic and diastolic BP by 11.4 mmHg and 5.5 mmHg, respectively, in hypertensive persons.<sup>87</sup> The DASH diet is also effective in patients with isolated systolic hypertension.<sup>91</sup> The combination of DASH and low sodium diets can reduce systolic BP by 11.5 mmHg compared with the combination of control and high sodium diets.<sup>90,92</sup> However, because of their relatively high potassium, phosphorus, and protein content, these diets are not recommended in patients with stage 3 or 4 chronic kidney disease, that is, an estimated glomerular filtration rate < 60 mL/min/1.73 m<sup>2</sup>.<sup>93</sup>

### **Exercise adoption**

Some studies have suggested that moderate activity lowers systolic BP by 4–8 mmHg, and is more effective than more strenuous forms of exercise.<sup>88</sup> In two recent meta-analyses, aerobic exercise was

associated with a significant reduction in mean systolic BP (−3.8 mmHg and −6.9 mmHg, respectively) and diastolic BP (−2.6 mmHg and −4.9 mmHg, respectively).<sup>94,95</sup> Additional benefits of regular exercise include weight loss, enhanced sense of wellbeing, improved functional health status, and reduced risk of cardiovascular diseases.<sup>88</sup> Regular aerobic exercise such as brisk walking, swimming, or cycling, for at least 30 minutes a day, and at least 5 days a week, is recommended.<sup>2,88</sup>

## Pharmacological Therapy

### General concepts

The pathogenesis of hypertension involves multiple mechanisms.<sup>96</sup> Antihypertensive drugs that have a single mechanism of action would not be able to control all the patients with hypertension. Indeed, only about 30% of patients with hypertension can be controlled by a single drug, and about 40% of patients need two drugs. The remaining 30% of patients require three or more drugs. Indeed, only 27% of patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) were on monotherapy and 73% of patients received two or more drugs.<sup>97</sup> Multiple pharmacy is commonly required in patients with diabetes, chronic kidney disease, and in elderly patients.<sup>98</sup>

The main benefits of antihypertensive agents are derived from lowering of BP *per se*, and are generally independent of the drugs used.<sup>99</sup> Although there are some clinical trials that have supported the superiority of one drug or combination over another in reducing stroke,<sup>100</sup> end-stage renal disease,<sup>101</sup> or cardiovascular events,<sup>97</sup> controlling BP to target is more important than choosing the drug class.<sup>75</sup> There are some conditions for which preferred drugs might be considered (Table 6). Nevertheless, in >70% of patients, a single agent is not enough; therefore, it seems futile to emphasize the identification of the first preferred drug.<sup>3</sup>

To estimate the extent of BP reduction or to predict how many drugs are needed to achieve BP goals, the “rule of 10” and “rule of 5” can be

used to predict the reduction in systolic and diastolic BP, respectively.<sup>102</sup> In a meta-analysis of 354 randomized, double-blind, placebo-control trials that comprised 40,000 drug-treated and 16,000 placebo-treated patients, a standard dose of either one of the five major classes of antihypertensive agents produced approximately a 10-mmHg decrease in systolic BP (rule of 10) and a 5-mmHg decrease in diastolic BP (rule of 5) (all after placebo subtraction), when the baseline pretreatment systolic BP was 154/97 mmHg.<sup>102</sup> For 10 mmHg higher baseline systolic or diastolic BP, a further decrease of 1.0 mmHg in systolic and 1.1 mmHg in diastolic BP was observed. When the doses were doubled, there was only a 2-mmHg incremental decrease in systolic BP and a 1-mmHg incremental decrease in diastolic BP.<sup>102</sup> Alternatively, when two drugs in standard doses but with different mechanisms of action were taken together (except for combination of ACEI and ARB), the decrease in BP was the sum of the decrease of the individual agents (approximately 20 mmHg in systolic and 10 mmHg in diastolic BP).<sup>102,103</sup> Therefore, JNC 7 has strongly recommended that most patients with BP  $\geq$  160/100 mmHg require at least two antihypertensive drugs to achieve target BP.<sup>2</sup> Similarly, if a 30-mmHg decrease in systolic BP or a 15-mmHg decrease in diastolic BP is to be obtained, a three-drug combination might be needed.

The optimal time for taking antihypertensive drugs has been a matter of debate for several decades. There has been no standard suggestion in JNC 7,<sup>2</sup> nor in the 2007 European Society of Cardiology/European Society of Hypertension guidelines.<sup>3</sup> Based on study protocols of many previous clinical trials, antihypertensive drugs have mainly been administered in the morning. Therefore, morning administration of antihypertensive drugs has become routine. However, this daily practice has been recently challenged. In a 700-patient study, patients who took  $\geq$  1 antihypertensive drugs at bedtime showed a significant reduction in the 24-hour mean systolic and diastolic BP.<sup>104</sup> The reduction was more prominent during nighttime. The diurnal/nocturnal BP

**Table 6.** Recommended drugs

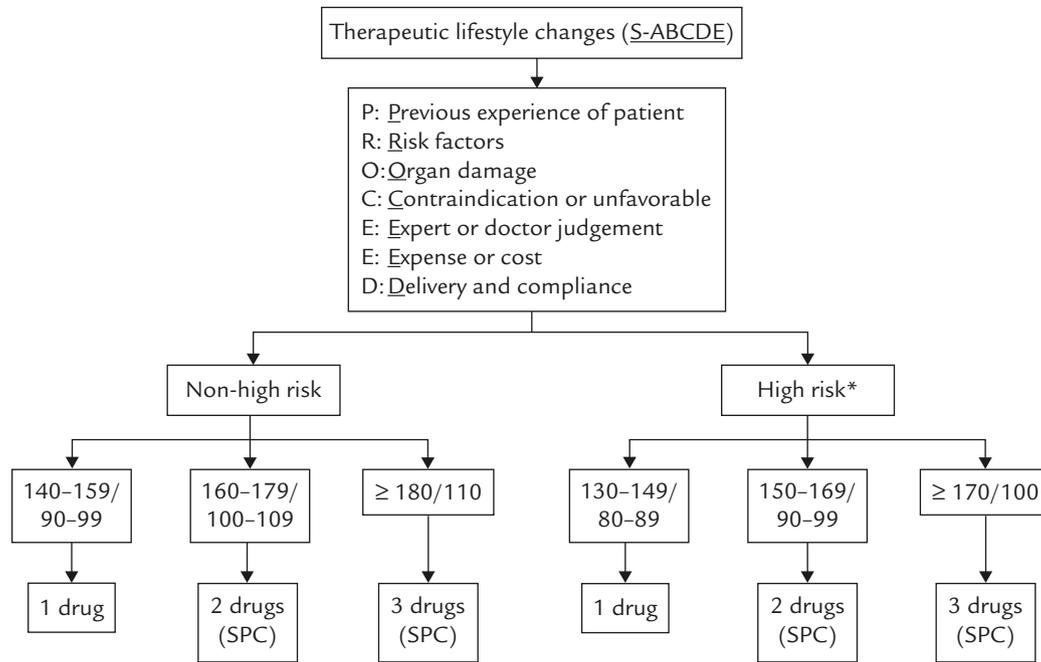
Clinical conditions	Drugs	Evidence
Target organ damage		
Left ventricular hypertrophy	ARB	LIFE <sup>160</sup>
Microalbuminuria	ACEI, ARB	Micro-HOPE, <sup>163</sup> IRMA-2, <sup>164</sup> MARVAL, <sup>190</sup>
Asymptomatic atherosclerosis	CCB	ELSA, <sup>191</sup> CAMELOT <sup>112</sup>
Clinical events		
History of myocardial infarction	BB, ACEI, ARB	Norwegian Timolol study, <sup>192</sup> Law's meta-analysis, <sup>99</sup> HOPE, <sup>110</sup> EUROPA, <sup>111</sup> ONTARGET <sup>140</sup>
Coronary Heart Disease	BB, ACEI, ARB, CCB (long-acting)	Law's meta-analysis, <sup>99</sup> HOPE, <sup>110</sup> EUROPA, <sup>111</sup> ONTARGET, <sup>140</sup> JIKEI Heart, <sup>193</sup> CAMELOT <sup>112</sup>
Heart failure	Thiazide diuretic, loop diuretic, BB, ACEI, ARB, aldosterone antagonist	AHA/ACC Heart Failure Guideline, <sup>194</sup> MERIT-HF, <sup>136</sup> CIBIS II, <sup>137</sup> COPERNICUS, <sup>138</sup> SOLVD, <sup>195</sup> SAVE, <sup>196</sup> AIRE, <sup>197</sup> TRACE, <sup>198</sup> Val-HeFT, <sup>199</sup> VALIANT, <sup>200</sup> CHARM, <sup>201</sup> RALES, <sup>146</sup> EPHEBUS <sup>146,202</sup>
Stroke	ACEI, ARB, Thiazide diuretic, CCB,	PROGRESS, <sup>139</sup> HOPE, <sup>203</sup> MOSES, <sup>170</sup> LIFE, <sup>100</sup> ONTARGET, <sup>140</sup> ALLHAT, <sup>169</sup> BPLTTC meta-analysis, <sup>168</sup> Verdecchia's meta- analysis, <sup>204</sup> FEVER, <sup>205</sup>
Chronic kidney disease	ACEI, ARB, loop diuretic	K/DOQI guideline, <sup>61</sup> AASK, <sup>174</sup> REIN, <sup>173,206</sup> RENAAL, <sup>101</sup> IDNT, <sup>165</sup>
Peripheral artery disease	CCB	
Diabetes mellitus	ACEI, ARB, DRI	ADA recommendation, <sup>161</sup> ABCD trial, <sup>162</sup> Micro-HOPE, <sup>163</sup> ADVANCE, <sup>112</sup> IRMA-2, <sup>164</sup> IDNT, <sup>165</sup> RENAAL, <sup>100</sup> ONTARGET, <sup>140</sup> AVOID <sup>142</sup>
Associated conditions		
Isolated systolic hypertension	Thiazide diuretic, CCB, ARB	SHEP, <sup>207</sup> HYVET, <sup>120</sup> Syst-Eur, <sup>119</sup> Syst-China, <sup>208</sup> LIFE <sup>100</sup>
Metabolic syndrome	ACEI, ARB	
Benign prostate hypertrophy	$\alpha$ -Blocker	

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB= $\beta$ -blocker; CCB=calcium channel blocker; DRI=direct renin inhibitor.

ratio was significantly increased and the prevalence of non-dipping was reduced. These findings have been supported by two independent studies, in that bedtime administration of valsartan and telmisartan improved the sleep-time-related BP decline more toward a dipper pattern, without a loss in 24-hour efficacy.<sup>105,106</sup> In a recent study in 115 untreated hypertensive patients, nocturnal BP regulation was significantly better achieved by bedtime administration as compared with morning administration of an ACEI, without any loss in efficacy during diurnal active hours.<sup>107</sup> Nighttime

BP has been shown to be a more important marker of cardiovascular risk than diurnal mean values, thus bedtime administration of antihypertensive drugs might be a correct way for the improvement of future cardiovascular events.

Clinical trials that have used surrogate endpoints, such as urinary albumin excretion, have also demonstrated that bedtime administration of ARB<sup>108</sup> or shifting one antihypertensive drug from morning to evening is beneficial in patients with chronic kidney disease.<sup>109</sup> However, a decrease in urinary albumin excretion is not necessarily



**Figure.** The algorithm of hypertension treatment. Therapeutic lifestyle changes (S-ABCDE, see Table 5 for details) are the cornerstone of hypertension treatment. Based on these, physicians may PROCEED (Previous experience of patient; Risk factors; Organ damage; Contraindication or unfavorable conditions; Expert or doctor judgment; Expense or cost; Delivery and compliance) to decide the treatment policy. \*High-risk patients include patients with diabetes, chronic kidney disease, stroke, established coronary heart disease, and its equivalents. SPC= single-pill combination (or fixed-dose combination).

associated with reduced cardiovascular outcomes. Prospective, randomized, controlled clinical trials to demonstrate the long-term effects of nocturnal administration of antihypertensive agents in reducing hard cardiovascular endpoints are definitely needed.

### Blood pressure target

The target office BP depends on patients' risk level. For patients with low (<10%) or moderate (10–20%) 10-year Framingham risk, a target of <140/90 mmHg is reasonable. For patients with high Framingham risk ( $\geq 20\%$ ), such as patients with diabetes, chronic kidney disease, stroke, established CHD, and CHD equivalents (carotid artery disease, peripheral arterial disease, and abdominal aneurysm), a target of <130/80 mmHg is recommended.<sup>5,110–113</sup> For patients with diabetes, more aggressive systolic BP control to <120 mmHg was not supported by the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD-BP) trial.<sup>114</sup>

The target BP for HBPM and ABPM should be lower than those for office BP, and at least lower than their BP thresholds. However, there is no well-defined BP goal for high risk patients.

### Algorithm

The algorithm for treating hypertension depends on BP values and the risk level of patients, as shown in the Figure. When a patient needs treatment, with background lifestyle changes, physicians should "PROCEED" (Previous experience of patient; Risk factors; Organ damage; Contraindication or unfavorable conditions; Expert or doctor judgment; Expense or cost; Delivery and compliance) to decide the optimal treatment for the patient: First, previous unfavorable experience of the individual patient to a given class of antihypertensive drug should be carefully sought out because adverse events are the most important cause of non-adherence.<sup>115</sup> Adverse events are not entirely avoidable, and sometimes unpredictable, because they might have a psychological basis and

**Table 7.** Contraindications or unfavorable conditions

	Contraindications	Unfavorable conditions
Thiazide diuretics		Gout, hypokalemia, metabolic syndrome, pregnancy
$\beta$ -Blocker	Bronchial asthma, 2 <sup>nd</sup> and 3 <sup>rd</sup> degree AV block	Peripheral artery disease, metabolic syndrome
CCB (non-DHP)	2 <sup>nd</sup> and 3 <sup>rd</sup> degree AV block	Systolic heart failure
ACEI	Bilateral renal artery stenosis, pregnancy, angioedema	Hyperkalemia
ARB	Bilateral renal artery stenosis, pregnancy	Hyperkalemia
DRI	Bilateral renal artery stenosis, pregnancy	Hyperkalemia
Aldosterone antagonist	Hyperkalemia	
$\alpha$ -Blocker		Systolic heart failure

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; DHP=dihydropyridine; DRI=direct renin inhibitor.

are frequently reported during placebo treatment.<sup>3</sup> Great efforts should be devoted to limit drug-related side effects. Drug-related side effects are usually dose-dependent for diuretics,  $\beta$ -blockers, and calcium channel blockers (CCBs), whereas there is little or no dose-dependent increase in side effects with ACEIs or ARBs.<sup>102</sup> Second, risk factors for an individual patient should be identified. For example, diuretics and  $\beta$ -blockers should not be considered as first-line therapy in patients with metabolic syndrome or glucose intolerance, unless strongly indicated or used as an add-on therapy to reach the target. Third, organ damage, even subclinical, or previous associated cardiovascular conditions might favor certain classes of drugs or certain combinations (Table 6). Fourth, contraindications or unfavorable conditions should be examined (Table 7). Fifth, an expert's or doctor's judgment is of paramount importance in managing patients. Any guidelines can only serve as a reference in treating individual patients. Sixth, although expenses or cost might be taken in account, cost issues should never predominate over efficacy, tolerability, and protection of the patient. Finally, delivery and compliance are key in the successful treatment of hypertension. Physicians should motivate patients and have good communication with individual patients. Simplified treatment with long-acting drugs or by using single-pill combination formulas might be required to obtain higher adherence rates.

Patients are considered to be at high risk if they have diabetes, chronic kidney disease, stroke, established CHD, and CHD equivalents (carotid artery disease, peripheral arterial disease, and abdominal aneurysm). For non-high risk patients, two drugs are recommended for patients with systolic BP ranging from 160 to 179 mmHg or diastolic BP from 100 to 109 mmHg; whereas three drugs are needed for patients with systolic BP  $\geq$  180 mmHg or diastolic BP  $\geq$  110 mmHg. Single-pill combination (fixed-dose combination) is recommended. For sensitive patients who need three or more drugs, splitting drugs into morning and evening doses seems appropriate to avoid a too rapid decrease in BP. For high risk patients, a tighter BP control is reasonable (Figure).

Whether there is a "J-curve" phenomenon in BP control is still controversial. The J-curve describes the shape of the relationship between BP and the risk of cardiovascular events. The J shape reflects increased risk at high levels of BP, with risk falling in parallel with BP reduction until a nadir is reached, below which further BP reduction begins to increase risk.<sup>116</sup> There must be a point at which BP becomes too low to sustain adequate perfusion to vital organs and life. The J-curve has been described mostly in the coronary events because the coronary circulation is unique in that most of coronary blood flow to the left ventricle occurs in diastole. During systole, the contracting left ventricular myocardium compresses

intramyocardial vessels and obstructs its blood flow.<sup>117</sup> Many observational cohort studies and *post hoc* analyses of clinical trials have suggested that a J-curve exists for diastolic BP for patients with CHD, but disagree that there is a J-curve phenomenon with BP-lowering therapy for renal disease or stroke prevention.<sup>117,118</sup> It should be noted that patients with low in-trial diastolic BP in the above-mentioned studies had low diastolic BP at baseline. Furthermore, low baseline diastolic BP automatically identifies a cohort of patients at high cardiovascular risk. These patients are more likely to have higher cardiovascular events not because lowering the diastolic BP has caused the events but rather because low baseline diastolic BP predicts their events.<sup>116</sup> It should also be remembered that patients with low diastolic BP will most likely be those with high systolic BP and pulse pressure (isolated systolic hypertension; ISH). Whether patients with ISH should have their BP lowered even if their diastolic BP is already low cannot be answered by *post hoc* analysis. Many randomized clinical trials of patients with ISH have overwhelmingly demonstrated the robust benefits of BP lowering, and the fall in systolic BP greatly exceeds the fall in diastolic BP.<sup>119,120</sup> What is strongly needed are extensive individual patient data analyses of those with low baseline diastolic BP who have been randomized to active BP-lowering treatment or placebo, to determine whether the high baseline risk of these patients is modified by treatment.<sup>116</sup> At present, these concerns should not deter physicians from pursuing a more aggressive control of hypertension because BP is currently below recommended target levels in only one-third of patients.<sup>117</sup>

### **Monotherapy**

There are five major classes of drugs for hypertension treatment: thiazide diuretics,  $\beta$ -blockers, CCBs, ACEIs, and ARBs. All these agents are suitable for the initiation and maintenance of anti-hypertensive treatment either as monotherapy or in combinations. The issues regarding  $\beta$ -blockers are discussed below.

### **Diuretics**

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) confirmed the equivalent effect of thiazide-like diuretics in reducing CHD as compared with CCBs and ACEIs.<sup>121</sup> Later, JNC 7 emphasized the importance of therapy with thiazide diuretics, and suggested that they should be considered as first-line therapy and a preferred component in combinations.<sup>2</sup> A major concern is the diabetogenic potential of diuretics.<sup>122</sup> In a recent meta-analysis, thiazide diuretic users had the highest potential to develop new-onset diabetes.<sup>123</sup> The long-term impact of diuretic-induced diabetes on future cardiovascular events is controversial. In a *post hoc* analysis of ALLHAT, patients with impaired fasting glucose actually had significantly less CHD events in the chlorthalidone group compared with amlodipine group in the 4–8-year follow-up period of ALLHAT, in spite of an increase in diabetes rate.<sup>124</sup> The argument is that 4–8 years follow-up might be too short to observe the negative impact of new-onset diabetes. In a long-term cohort study of treated hypertension patients for up to 16 years, occurrence of new diabetes predicted a risk for subsequent cardiovascular disease that was not dissimilar from that of previously known diabetes.<sup>125</sup> In a 28-year follow-up of treated hypertension patients, new-onset diabetes carried a significantly higher cardiovascular risk, and the mean observation time from onset of diabetes to the first stroke was 9.1 years and 9.3 years to the first myocardial infarction.<sup>126</sup> In contrast, the use of diuretics is sometimes indispensable in controlling BP. Hypertension cannot be called resistant if diuretics have not been included in the medication.<sup>127</sup> Indeed, thiazide diuretics were needed in >80% of patients in both arms (ARB and placebo) to achieve BP control in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study.<sup>101</sup> Accordingly, thiazide diuretics are usually required for patients with established diabetes to control BP, and are suggested by current guidelines as add-on therapy to ACEIs or ARBs.<sup>125</sup> Another important concern about diuretics is their side effects. In a 4-year

follow-up study that compared ARBs with other antihypertensive agents, patients taking diuretics had the lowest adherence rate.<sup>129</sup> In a meta-analysis of 354 trials, the dose-dependent increase in adverse effects of diuretics was the most severe among all the drugs tested.<sup>102</sup> A hydrochlorothiazide dose > 25 mg per day is considered high, and is associated with a significant increase in side effects including metabolic derangement.

Are all thiazide diuretics the same? In a recent study that has compared 50 mg per day hydrochlorothiazide with 25 mg per day chlorthalidone, the latter provided a greater decrease in ambulatory systolic BP, with the greatest difference occurring at nighttime.<sup>130</sup> Unfortunately, this no outcomes study compared different diuretics. Chlorthalidone is not commonly used in the single-pill combinations, and has to be given in separate doses.

#### *β-Blockers*

The use of β-blockers as first-line therapy has been challenged recently. Several meta-analyses have demonstrated an increased risk of stroke in users of β-blockers compared with other classes of drugs, and have negated the use of β-blockers as first-line therapy for hypertension.<sup>131–134</sup> In the Conduit Artery Function Evaluation (CAFE) study, a substudy of the ASCOT, it has been shown that, despite similar brachial systolic BP between treatment groups, there were substantial reductions in central aortic pressure with amlodipine ± perindopril-based therapy compared with atenolol ± thiazide-based therapy, and that central pulse pressure was significantly associated with a *post hoc*-defined composite outcome of total cardiovascular events/procedures.<sup>60</sup> β-Blockers also increase body weight, have negative effects on lipid profiles, and increase the incidence of new-onset diabetes.<sup>135</sup> They should be avoided, if possible, in patients with impaired fasting sugar, impaired glucose tolerance, abdominal obesity, and metabolic syndrome. However, most of the evidence for these observations has come from trials in which atenolol was the β-blocker being used. It might be inappropriate to apply to vasodilating β-blockers, such as carvedilol and nebivolol.

Nevertheless, β-blockers are still indicated for patients with heart failure,<sup>136–138</sup> a history of ischemic heart disease or myocardial infarction,<sup>99</sup> or a hyper-adrenergic state.

#### *Renin-angiotensin-system (RAS) inhibitors*

ACEIs have been convincingly shown to reduce rates of death, myocardial infarction, stroke, and revascularization among patients with previous cardiovascular disease and high-risk diabetes,<sup>110,111,139</sup> and are preferred drugs in these conditions. In the ONTARGET (The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Target) study, although not a strict hypertension study (about 69% patients did have hypertension), ARBs were equivalent to ACEIs in reducing myocardial infarction, stroke, cardiovascular death, and hospitalization for heart failure, that is, they were interchangeable.<sup>140</sup> The ARB myocardial infarction paradox has also been dispelled by the findings of the ONTARGET study. All the secondary endpoints, including revascularization, new-onset diabetes, incidence of heart failure, new-onset atrial fibrillation, and renal impairment, were similar.<sup>140</sup> The only difference was the compliance in the two groups: the ARB group showed significantly less discontinuation. ARBs have been shown to have a placebo-like tolerability in a meta-analysis.<sup>102</sup>

Direct renin inhibitors, such as aliskiren, are a new class of drugs that inhibit the renin-angiotensin-aldosterone system. Aliskiren has a dose-related BP-lowering effect that is better than that of placebo. This effect is similar to that for ACEIs and ARBs.<sup>141</sup> Clinical data for aliskiren are accumulating and suggest it has renoprotective effects that are independent of its BP-lowering effect in patients with hypertension, type 2 diabetes, and nephropathy, who are receiving the recommended renoprotective dose of ARB.<sup>142</sup> Aliskiren has also been shown to reduce left ventricular hypertrophy and decrease N-terminal pro-brain natriuretic peptide in patients with heart failure. The effect of aliskiren in reducing hard cardiovascular outcomes is under extensive investigation.<sup>143</sup>

*Other antihypertensive agents*

$\alpha$ -Blockers suffered from a major setback in ALLHAT, in which patients who took doxazosin had an increased incidence of heart failure compared with those receiving chlorthalidone.<sup>144</sup> This might have been due to an intrinsic defect in the design of ALLHAT.<sup>3</sup> Doxazosin use has been revived by the recent finding among the 10,069 participants in the ASCOT-BPLA.<sup>145</sup> Doxazosin GITS (gastrointestinal therapeutic system) was used as a third-line antihypertensive agent in patients whose BP remained above 140/90 mmHg (130/80 mmHg in those with diabetes). Mean BP fell by 11.7/6.9 mmHg after the addition of doxazosin, and 29.7% of participants achieved target BP. Importantly, there was no apparent excess of heart failure among doxazosin users. Doxazosin seems a safe and effective third-line antihypertensive agent.

Spironolactone reduces morbidity and mortality in patients with severe heart failure.<sup>146</sup> The best evidence for spironolactone as add-on antihypertensive therapy has come from the sub-analysis of ASCOT-BPLA.<sup>147</sup> In 1411 patients who received spironolactone mainly as a fourth-line antihypertensive agent for uncontrolled BP, mean BP fell by 21.9/9.5 mmHg with a median dose of 25 mg per day and a discontinuation rate of 6%. Thus spironolactone might be considered in patients with hypertension that is uncontrolled by three drugs. The risk of hyperkalemia should be evaluated in patients with impaired renal function.

**Combination therapy**

Combination of different drugs is frequently needed in patients with stage 2 or 3 hypertension or in high-risk patients when lower targets are pursued. The two or three different drugs with independent mechanisms could be used in low or standard doses to achieve more BP lowering than up-titration of the monotherapy alone, which removes the frustration of searching for effective monotherapy. A decrease of 20/10 mmHg in systolic/diastolic BP could be expected with a two-drug combination.<sup>102</sup> In general, the amount of BP decrease by a two-drug combination is at least the sum of the decrease by individual drugs if their

mechanisms were independent, with the exception of combination of ACEIs and ARBs.<sup>102</sup> Combination of drugs from different classes is approximately five times more effective in lowering BP than increasing the dose of the single drug.<sup>103</sup> When a decrease of 30 mmHg in systolic BP or a decrease of 15 mmHg in diastolic BP are to be achieved, a three-drug combination might be needed (Figure).

Combination therapy has other advantages. The target BP could be achieved more promptly by starting with combination therapy. The concept of "sooner is better" is important for high-risk patients, as shown in the VALUE (Valsartan Antihypertensive Long-term use Evaluation) trial in which greater BP reduction in the first 6 months in the amlodipine arm was associated with a lower cardiovascular event rate than in the valsartan arm.<sup>148</sup> Similarly, the combination of different drugs in low or standard doses is more likely to be free of side effects compared with higher doses of monotherapy. Furthermore, it might have a favorable tolerance profile because the complementary mechanisms of action of the components minimize their individual side effects. This has been demonstrated by treatment with combination of CCBs and ARBs (or ACEIs), in which CCB-induced edema was significantly ameliorated by the addition of ARBs (or ACEIs).<sup>149,150</sup> Many hypertension treatment guidelines have also emphasized the importance of combination therapy for better control of hypertension.<sup>3</sup>

For pathophysiological consideration, the A (ACEI or ARB) + C (CCB) or D (thiazide diuretic) formula is a reasonable first-step combination. This is in line with the algorithm as proposed by the British Hypertension Society.<sup>151</sup>  $\beta$ -Blockers can be used in special conditions as mentioned above or be combined with a CCB in patients with CHD. The frequently used two-drug combinations include the following: ACEI + CCB, ARB + CCB, ACEI + thiazide diuretic, ARB + thiazide diuretic, or CCB +  $\beta$ -blocker.

The recommended three-drug combination is A + C + D, except in patients with heart failure or CHD, for whom  $\beta$ -blockers are indicated. The recommended two- and three-drug combinations

**Table 8.** Recommended combinations

Clinical conditions	Single drug	2-drug combinations	3-drug combinations*
<b>Target organ damage</b>			
Left ventricular hypertrophy	ARB	ARB + D	ARB + CCB + D
Microalbuminuria	ACEI, ARB	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
Asymptomatic atherosclerosis	CCB	ACEI + CCB, ARB + CCB	ACEI + CCB + D, ARB + CCB + D
<b>Clinical events</b>			
History of myocardial infarction	BB, ACEI, ARB	ACEI + BB, ARB + BB	ACEI + BB + D, ARB + BB + D
Coronary heart disease	BB, ACEI, ARB, CCB (long-acting)	BB + CCB, ACEI + CCB, ARB + CCB, ACEI + BB, ARB + BB	ACEI + CB + CCB, ARB + BB + CCB
Heart failure	BB, ACEI, ARB, D <sup>†</sup>	ACEI + BB, ARB + BB, ACEI + D <sup>†</sup> , ARB + D <sup>†</sup> , BB + D <sup>†</sup>	ACEI + BB + D <sup>†</sup> , ARB + BB + D <sup>†</sup>
Stroke	ACEI, ARB, D, CCB	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
Chronic kidney disease	ACEI, ARB, loop diuretic	ACEI + loop diuretic, ARB + loop diuretic	ACEI + loop diuretic + CCB, ARB + loop diuretic + CCB
Peripheral artery disease	CCB	ACEI + CCB, ARB + CCB	ACEI + CCB + D, ARB + CCB + D
Diabetes mellitus	ACEI, ARB, DRI	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
<b>Associated conditions</b>			
Isolated systolic hypertension	D, CCB, ARB	ARB + CCB, ARB + D, CCB + D	ARB + CCB + D
Metabolic syndrome	ACEI, ARB	ACEI + CCB, ARB + CCB	ACEI + CCB + $\alpha$ -Blocker, ARB + CCB + $\alpha$ -Blocker

\*Expert consensus; <sup>†</sup>thiazide diuretic, or loop diuretic, or aldosterone receptor blocker (preferred); ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB= $\beta$ -blocker; CCB=calcium channel blocker; D=thiazide diuretic.

are listed in Table 8. It should be noted that randomized controlled trials that have compared different three-drug combinations are lacking, and therefore, the recommended three-drug combinations in Table 8 are mostly based on the expert's opinion. Combination of a  $\beta$ -blocker and a thiazide diuretic should be used with great caution because of higher diabetogenic potential. Combination of ACEIs and ARBs is also undesirable. In the ONTARGET study, the combination of ACEIs with ARBs not only had no additional benefits compared with each individual component, but also increased the incidence of renal impairment and other side effects.<sup>140,152</sup> Recently, the Canadian Hypertension Education Program urged physicians and patients to stop using these two drugs in combination.<sup>153</sup>

Patient compliance plays a pivotal role in treatment success in hypertension.<sup>154</sup> Poor adherence

can be regarded as a silent risk factor for hypertensive patients. Combinations of two drugs in a single tablet (single-pill combination) are now widely available. Although the fixed dose of the individual components limits the flexibility of upward and downward titration, single-pill combinations reduce the tablet number and improve compliance. It has been shown that the non-compliance rate for patients taking a single-pill combination is 26% lower compared with free combination regimens.<sup>155</sup> They can be used for first-line therapy, provided that initial use of two drugs rather than monotherapy is indicated, and for more rapid achievement of BP goals.<sup>156</sup> In a recent study that compared initial low-dose, single-pill combination therapy to guideline-based free combination, achieved systolic BP was 5.2 mmHg lower in the first group, and the proportion of patients who achieved the target was also significantly higher in the

first group.<sup>157</sup> Single-pill combinations are always cheaper than the total cost of the individual components and should be widely used in the future.

In the recently published ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) study, two single-pill combinations were compared.<sup>158</sup> Unexpectedly, the ACEI and CCB combination group had better cardiovascular and renal outcomes than the ACEI and diuretic combination group. The safety profile was similar, which suggests that A+C combination is better than A+D combination. However, it has been questioned recently that the diuretic used in the ACCOMPLISH study is hydrochlorothiazide instead of chlorthalidone. The result might be different if the latter were used in the combination.<sup>159</sup> The superiority of A+C should be confirmed by more data.

## Hypertension in Special Conditions

### *Treatment of hypertension in patients with diabetes*

The cardiovascular risk in diabetic patients without prior myocardial infarction equals that of non-diabetic patients with previous myocardial infarction.<sup>160</sup> Aggressive BP control can reduce the diabetic complications. The majority of diabetic patients require two or more drugs to reach a lower target BP in their hypertension control. Clinical evidence suggests that RAS blockers, including ACEIs or ARBs, should be the first-line therapy and one of the drugs in combination treatment in diabetic hypertension.<sup>161,162</sup> Beyond their BP-lowering effect, ACEIs and ARBs slow down the progression of microalbuminuria or proteinuria in diabetic nephropathy.<sup>102,113,140,163–166</sup> The direct renin inhibitor aliskiren might further reduce albuminuria in hypertensive diabetic patients.<sup>142</sup> Long-acting dihydropyridine CCBs have a neutral effect on lipid and glucose metabolism. They are appropriate drugs to use in combination with ACEIs or ARBs. Combination of long-acting dihydropyridine CCBs with ACEIs or ARBs is effective

in the treatment of diabetic hypertension. Thiazide diuretics are less expensive but affect electrolyte and metabolic balance. Thiazide diuretics also increase RAS activity. Thus diuretics in combination with ACEIs or ARBs are a good treatment regimen in diabetic hypertension.  $\beta$ -Blockers could be added in diabetic patients with concomitant coronary artery disease, myocardial infarction or congestive heart failure. However,  $\beta$ -blockers must be used cautiously because they can worsen insulin resistance and mask hypoglycemia symptoms in diabetic patients.  $\alpha$ -Blockers improve insulin resistance and can be used in diabetic patients associated with benign prostate hypertrophy. Orthostatic hypotension is the major side effect of  $\alpha$ -blockers, especially in diabetic patients. Combination therapy to achieve target BP is the most important factor in controlling diabetic hypertension.

### *Treatment of hypertension in patients with cerebrovascular disease*

The decision to treat hypertension in stroke patients depends on the disease stage. The appropriate treatment of hypertension in acute stroke remains controversial. Basically, the BP in acute stage of ischemic stroke should not be lowered. Antihypertensive drugs should be withheld unless there is severe hypertension ( $> 220/120$  mmHg), aortic dissection, acute pulmonary edema, or acute myocardial infarction.<sup>167</sup> In stroke patients who require thrombolytic therapy with tissue plasminogen activator, BP should be controlled to prevent cerebral hemorrhage. Most stroke patients can receive antihypertensive treatment for several days after the acute event when their condition has stabilized. For long-term hypertension control in stroke patients, control of BP to the target level is the first consideration, and all available antihypertensive drugs can be used.<sup>168</sup> Clinical data regarding the benefits of specific antihypertensive regimens for primary and secondary stroke prevention are limited. In primary prevention, thiazide diuretics and ARBs were found to be more effective in reducing stroke in the ALLHAT and LIFE (The Losartan Intervention For Endpoint reduction) trials.<sup>100,169</sup> In secondary prevention, the

PROGRESS (The Perindopril protection against recurrent stroke study) trial results favored the use of ACEI and diuretic combination treatment.<sup>139</sup> In the MOSES (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention) trial, ARBs have also been shown to reduce the risk of recurrent stroke in hypertension.<sup>170</sup> However, conflicting data also exist. In the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial, ARBs could not lower the recurrent stroke rate in patients who had a recent history of ischemic stroke.<sup>171</sup> Overall, the major benefits of hypertension treatment in stroke patients rely on effective BP reduction. Therefore, the choice of specific antihypertensive drugs in stroke patients should be individualized and based on specific patient characteristics, including associated diabetes mellitus, chronic kidney disease and cardiac disease. Currently, using combination treatment to achieve target BP is more important than emphasizing specific drugs for hypertension control in stroke patients.

#### *Treatment of hypertension in patients with chronic kidney disease*

Strict BP control slows down the progression of chronic kidney disease.<sup>172</sup> Proteinuria and microalbuminuria are important in chronic kidney disease and increase risk of disease progression and cardiovascular events. In addition to BP control, ACEIs and ARBs help to reduce proteinuria and microalbuminuria more effectively than other antihypertensive drugs.<sup>61,166</sup> ACEIs or ARBs should be the preferred drug and one of the drugs for combination treatment in hypertension treatment of chronic kidney disease patients.<sup>173,174</sup> However, serum creatinine and potassium levels should be carefully monitored within 1–2 weeks after the initiation of ACEIs and ARBs. If there is acute exacerbation of renal function and severe hyperkalemia, the drugs should be stopped. Some studies have shown that ACEI and ARB combination treatment can be more effective than either drug alone in reducing BP and proteinuria in chronic kidney disease.<sup>166</sup> However, recent data from the

ONTARGET trial have demonstrated that ACEI and ARB combination therapy might worsen major renal outcomes, including dialysis and doubling of serum creatinine.<sup>152</sup> Therefore, ACEI and ARB combination treatment is generally not recommended, and more data are required to prove its effectiveness and safety. Thiazide and loop diuretics are used for hypertension control because fluid retention is a common problem in chronic kidney disease patients. However, these drugs become less effective and require higher doses when there is severe reduction of glomerular filtration rate. Non-dihydropyridine CCBs are also known to have a proteinuria-lowering effect in chronic kidney disease. They should not be used in patients with congestive heart failure or conduction block. Long-acting dihydropyridine CCBs are also used for hypertension control in chronic kidney disease. CCBs are commonly used in combination with ACEIs or ARBs for better BP control in chronic kidney disease patients.  $\beta$ -Blockers can be used in chronic kidney disease patients, especially in those with concomitant coronary artery disease, myocardial infarction or congestive heart failure. Overall, the use of combination treatment to achieve target BP is the most important factor in hypertension control in patients with chronic kidney disease.

#### *Hypertension in elderly people*

##### *Characteristics of hypertension in elderly people*

The prevalence of hypertension increases with age. According to the 2002 National Health Survey in Taiwan, 47% of those in their 60s and 62% of those aged > 70 years had hypertension. Systolic BP increases, whereas diastolic BP decreases after the age of 60 years, which causes an increase in pulse pressure.<sup>10</sup> The rise in pulse pressure is the result of a decrease in the extensibility of the aortic wall, which is associated with the progression of atherosclerosis.

Autoregulation of the blood flow of target organs is impaired in elderly people. The lower limit of BP usually shifts to the hypertensive side. Therefore, a rapid and marked decrease in BP might cause ischemic symptoms in such organs. Hence, BP must be reduced with caution in elderly people.

Elderly people are more susceptible to disturbances of electrolyte homeostasis, particularly hyponatremia and hypokalemia, insulin resistance, and glucose intolerance. All these characteristics should be taken into consideration in the choice of antihypertensive agents.

#### *Diagnosis of hypertension in elderly people*

Meta-analyses that have integrated the results of many cohort studies at an individual level have shown a positive correlation between risks of cardiovascular morbidity and mortality and BP levels in all age groups, including those in their 80s.<sup>4,175,176</sup> Although the correlation slope becomes flatter in old age, the absolute cardiovascular risk increases with age. Therefore, the diagnostic criteria of hypertension for elderly people should be the same as those for adults in general ( $\geq 140/90$  mmHg). As the frequency of orthostatic hypotension increases, the measurement of BP in the standing position (within 3 minutes of standing) is also recommended. Blood pressure should be measured simultaneously by the palpation method to avoid overlooking pseudohypertension.

Attention should be paid to secondary hypertension, particularly to renovascular hypertension due to atherosclerosis, and primary aldosteronism. Secondary hypertension is indicated in patients who show a significant increase in BP within a short period of time, an exacerbation of high BP and refractory hypertension. As a result of the high frequency of polypharmacy in elderly people, attention to drug-induced hypertension is also warranted.

As elderly people often show asymptomatic multiple organ damage, efforts to detect latent complications are necessary. For example, reducing BP might increase the risk of stroke in patients with  $\geq 75\%$  stenosis of bilateral carotid arteries, thus particular attention is required in such patients.

#### *Treatment of hypertension in elderly people*

Elderly people generally have high salt sensitivity; therefore, salt intake restriction is effective. The target salt intake should be  $< 6$  g per day.

According to a meta-analysis of nine major clinical trials on the treatment of hypertension in elderly people, antihypertensive drug treatment significantly reduced all-cause death by 12%, stroke by 35%, and ischemic heart disease by 15%.<sup>177</sup> In the HYVET (Hypertension in the Very Elderly Trial) study, in which the participants were aged  $\geq 80$  years with stage 2 hypertension, the target control level was  $< 150/80$  mmHg, and a decision as to whether the dose should be increased was made every 3 months. The mean BP achieved in the treated group after 2 years was 144/78 mmHg.<sup>120</sup> A significant 30% decrease in death from stroke, 21% decrease in death from any cause, 64% decrease in heart failure, and a 34% decrease in cardiovascular events were observed.<sup>120</sup>

It is therefore suggested that sufficient antihypertensive treatment should be administered with a target of  $< 140/90$  mmHg for elderly hypertensive patients. In patients who have been treated before the age of 65 years and have controlled BP at  $< 130/80$  mmHg, there is no need to attenuate treatment after the age of 65 years. However, there are epidemiological studies that have reported that the threshold of BP for an increase in mortality increased with age and was 160 mmHg for men and approximately 170 mmHg for women  $\geq 65$  years of age.<sup>178,179</sup> Hence, for patients  $\geq 80$  years of age, BP should be reduced gradually and cautiously. Antihypertensive drug treatment should be started generally at half the regular dose, and the dose should be increased at an interval of 4 weeks to 3 months (according to the HYVET study),<sup>120</sup> by evaluating the presence or absence of signs of brain ischemia, such as dizziness and orthostatic dizziness, symptoms of angina pectoris, and electrocardiography changes that indicate myocardial ischemia. The optimal antihypertensive drug should be selected for each elderly patient based on the principles mentioned in the section of Pharmacological Therapy.

Poor adherence to antihypertensive medication associated with dementia must also be considered in elderly patients. The possibility of forgetting to take drugs because of impairment of cognitive function should be evaluated even in patients who

are capable of communication during the medical examination. Compliance management by the family or caregiver might be necessary.

### ***Treatment of hypertension in women and during pregnancy***

#### *Hypertension in women*

In Taiwan, as in western societies, premenopausal women generally have lower systolic and diastolic BP levels than men of the same age.<sup>10</sup> However, systolic BP increases more steeply with age in women than in men. After the age of 60 years, women have higher BP and greater prevalence of hypertension.<sup>10</sup>

The continuous relationship between BP and cardiovascular events is similar between men and women. The therapeutic effect of antihypertensive therapy versus placebo is also similar between men and women.<sup>179</sup> There is still no sex-based meta-analysis to compare different antihypertensive regimens, although most *post hoc* analyses have shown similar risk reductions by the various regimens in either gender group.

It is mandatory to avoid potential teratogenic antihypertensive drugs in women of child-bearing age. Among all antihypertensive agents, ACEIs and ARBs are well-known for their teratogenicity. They should be avoided in fertile women or immediately withdrawn in case of pregnancy.

#### *Effect of oral contraceptives*

Oral contraceptives result in a mild increase (~5%) in BP in most women. The increase in BP usually disappears within 6 months of withdrawal. Estrogens are generally believed to be the culprit responsible for the BP-raising effect, but the mechanisms are still not certain. The progestogen-only pill is a contraceptive option for women with hypertension, either induced by the use of combined oral contraceptives or other causes. Use of oral contraceptives is associated with a 2–6-fold increase in venous thromboembolic disease and a mild increase in stroke and myocardial infarction in western societies. The risk of cardiovascular complications is observed primarily in women aged > 35 years and in those who smoke. There is still

no relevant report regarding the thrombogenic risk of oral contraceptives in women in Taiwan.

#### *Effect of hormone replacement therapy*

Postmenopausal women who are taking hormone replacement therapy might experience a mild increase in systolic BP over time. A recent Cochrane systematic review has shown that hormone replacement therapy is associated with a significantly increased risk of coronary events, stroke and venous thromboembolic disease.<sup>181</sup> Therefore, hormone replacement therapy is not recommended for cardioprotection in postmenopausal women.

#### *Hypertension in pregnancy*

Blood pressure normally falls about 15 mmHg, compared with the pre-pregnancy level, in the second trimester. In the third trimester, BP returns to, or even exceeds, the pre-pregnancy level. The preferred definition of hypertension in pregnancy is based on absolute BP levels: systolic BP  $\geq$  140 mmHg or diastolic BP  $\geq$  90 mmHg. Gestational hypertension generally develops after 20 weeks of gestation and, in most cases, resolves within 6 weeks post partum. Pre-existing hypertension is defined as BP  $\geq$  140/90 mmHg, either before pregnancy or that develops before 20 weeks of gestation. Gestational hypertension associated with significant proteinuria (> 300 mg/L or > 500 mg/24 hr or dipstick  $\geq$  2+) is known as pre-eclampsia. Gestational hypertension is characterized by poor organ perfusion (reduced plasma volume) and might produce hematological, renal, and hepatic derangements that could adversely affect both maternal and neonatal outcomes. The hypertensive disorders of pregnancy complicate 5–10% of pregnancies.

For women with gestational hypertension, a normal diet without salt restriction is recommended. Calcium supplementation, fish oil and low-dose aspirin are not effective in reducing the incidence of gestational hypertension. In non-severe hypertension in pregnancy (< 170/110 mmHg), oral methyldopa, labetalol and CCBs are the preferred drugs. Atenolol has been reported to be associated with fetal growth retardation.

ACEIs and ARBs should never be used in pregnancy because of their teratogenicity. Diuretic therapy is not appropriate in women with pre-eclampsia, in which plasma volume is reduced.

Blood pressure  $\geq 170/110$  mmHg during pregnancy should be considered an emergency that requires hospitalization. Intravenous labetalol, oral methyldopa or oral nifedipine could be used to control BP. Intravenous hydralazine should not be used because of its association with a higher rate of perinatal adverse events. Intravenous nitroglycerin is the drug of choice in pre-eclampsia with pulmonary edema. Intravenous sodium nitropruside is useful in hypertensive crisis, but prolonged administration should be avoided because of the risk of fetal cyanide poisoning. Intravenous magnesium sulfate is effective in the prevention of eclampsia and treatment of seizure.<sup>182</sup>

For most antihypertensive agents, concentration in breast milk is very low, except for propranolol and nifedipine whose concentrations are similar to those in maternal plasma. Low-dose aspirin is reported to be effective in prevention of preeclampsia in women with a history of early-onset (<28 weeks) pre-eclampsia.

### **Hypertensive emergencies**

Hypertensive emergencies are defined as severe forms of high BP (mostly diastolic BP >130 mmHg) associated with acute damage of

target organs (Table 9). Patients with hypertensive emergency must be hospitalized. Intravenous antihypertensive treatment should be given immediately in an intensive care unit or a similar environment, with invasive monitoring of BP (Table 10). With any of these agents, intravenous furosemide is often needed to lower BP further and prevent retention of salt and water. General targets of BP control are a reduction in mean BP of 10% during the first hour and a further 15% during the next 2–4 hours (to avoid cerebral hypoperfusion), and then to 160/100 mmHg over 24 hours. The exception to this management strategy is aortic dissection, for which the target is systolic BP <120 mmHg and heart rate <70 beats/min after 20 minutes. Excessive or rapid reductions in BP in acute ischemic stroke should be avoided.<sup>183</sup>

Severe hypertension without acute damage of target organs is referred to as hypertensive urgency. Most hypertensive emergencies can be controlled by oral antihypertensive agents, with a goal of reduction in BP to 160/100 mmHg over 24–48 hours. Oral administration of short-acting CCBs, ACEIs, labetalol or loop diuretics is permitted.<sup>184</sup> The prior preference for liquid nifedipine by mouth or sublingually should be avoided because of occasional ischemic complications that result from too rapid reduction in BP. Captopril should be started at a low dose (6.25–12.50 mg) because it might cause an excessive decrease in BP in a dehydrated state, in which the RAS is markedly activated.

When the rise in BP causes retinal hemorrhage, exudate, or papilledema, the term malignant hypertension (diastolic BP usually >140 mmHg) is used. The most dangerous condition associated with malignant hypertension is hypertensive encephalopathy, which is manifested as reversible alterations in neurological function, including headache, disturbed mental status and visual impairment. Other associated organ derangements include renal function deterioration, hemolysis, and disseminated intravascular coagulation. The management of malignant hypertension is the same as that for hypertensive emergencies (malignant hypertension is in fact one particular form of hypertensive emergency). Severe or poorly

**Table 9.** Acute target organ damages in hypertensive emergencies

Hypertensive encephalopathy
Hypertension with subarachnoid hemorrhage
Hypertension with acute cerebrovascular events
Hypertension with acute coronary syndrome
Hypertension with aortic dissection
Hypertension with left-sided heart failure symptoms
Hypertension with acute glomerulonephritis
Renal crisis in collagen vascular diseases
Severe hypertension after kidney transplantation
Pheochromocytoma crisis
Use of recreational drugs such as amphetamines, LSD, or cocaine
Perioperative hypertension
Severe pre-eclampsia or eclampsia

**Table 10.** Parenteral drugs for treatment of hypertensive emergency

Drug	Dose	Onset of action	Adverse effects
<b>Diuretics</b>			
Furosemide	20-40 mg i.v. injection in 1-2 min, repeated and higher doses with renal insufficiency	5-15 min	Volume depletion, hypokalemia
<b>Vasodilators</b>			
Sodium nitroprusside	0.25-10 µg/kg/min as i.v. infusion	Within 30 sec	Nausea, vomiting, tachycardia, thiocyanate and cyanide intoxication
Nitroglycerin	5-100 µg/min as i.v. infusion	2-5 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use
Nicardipine	0.5-6 µg/kg/min as i.v. infusion	5-10 min	Headache, flushing, tachycardia, local phlebitis
Hydralazine	10-20 mg i.v. injection	10-20 min	Headache, flushing, tachycardia, worsening of angina
<b>Sympatholytics</b>			
Labetalol	20-80 mg i.v. injection every 10 min; 2 mg/min as i.v. infusion	5-10 min	Nausea, vomiting, bronchospasm, heart block, orthostatic hypotension
Phentolamine	1-10 mg i.v. injection, then 0.5-2 mg/min as i.v. infusion	1-2 min	Headache, flushing, tachycardia

controlled hypertension is usually the harbinger of hypertensive emergencies, although the presence of a secondary cause of hypertension has probably been underestimated and should not be overlooked.<sup>185</sup>

### **Resistant hypertension**

Resistant hypertension is a common medical disorder. Resistant hypertension is defined as failure to achieve target BP despite adherence to treatment of full or adequate doses of at least three antihypertensive medications, including a diuretic.<sup>124</sup> The exact prevalence of resistant hypertension is unknown. According to ALLHAT, approximately 15% of the study patients could be classified as having resistant hypertension.<sup>169</sup> Patients with resistant hypertension have greater target organ damage and a higher long-term cardiovascular risk compared with patients with controlled hypertension.

The factors for failure to control BP include patient factors, such as lack of understanding of the financial burden, and provider factors such as

**Table 11.** Causes of resistant hypertension\*

Improper blood pressure measurement technique
White-coat phenomenon
Failure to modify lifestyle including
Weight gain
Heavy alcohol intake
Intake of drugs that raise blood pressure
Cocaine, sympathomimetics, glucocorticoids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporine, etc.
Obstructive sleep apnea
Unsuspected secondary hypertension
Irreversible or scarcely reverse organ damage
Volume overload due to:
Inadequate diuretic therapy
Progressive renal insufficiency
High sodium intake
Hyperaldosteronism
Improper blood pressure measurement technique

\*Adapted from Mancia et al [3].

prescribing inappropriate combinations of drugs or inadequate dosages, despite poorly controlled BP.<sup>186</sup> The most common reason for resistant hypertension is the failure of providers to prescribe optimum therapy, and that titration of diuretics and increasing the number of antihypertensive drugs are the most likely interventions to achieve the target BP.<sup>187</sup> The causes of resistant hypertension are listed in Table 11.

A complete medical and drug history should be obtained for substances that exacerbate hypertension, as well as interfere with and diminish the effectiveness of antihypertensive medications. Evaluation is routinely warranted to look for evidence of end-organ damage related to hypertension and for other cardiovascular factors. Evaluation should be tailored based on the patient's history and physical examination.<sup>188</sup>

Patients with resistant hypertension should routinely be encouraged to reduce sodium intake, lose weight, engage in moderate exercise and reduce alcohol intake.<sup>189</sup> A generally useful strategy to optimize BP is to combine agents from various classes, each of which has one or more of the following effects: reduction in volume overload (diuretics and aldosterone antagonists), reduction in sympathetic overactivity ( $\beta$ -blockers), decrease in vascular resistance (ACEIs or ARBs), or promotion of smooth-muscle relaxation (dihydropyridine CCBs). A high prevalence of aldosterone excess has been found in patients with resistant hypertension. Low dose of spironolactone can be an excellent antihypertensive drug for management of resistant hypertension.<sup>147</sup>

## Conclusions

Hypertension remains the leading cause of cardiovascular morbidity and mortality. These guidelines are not meant to replace other treatment policies or rules, but to improve the control rate and provide the most updated information for the physician. The Guidelines Committee of Taiwan Society of Cardiology fully realizes that treatment of hypertension should be personalized and the

physician's decision remains most important in hypertension treatment.

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