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Guidelines

2015 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension

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Abstract

It has been almost 5 years since the publication of the 2010 hypertension guidelines of the Taiwan Society of Cardiology (TSOC). There is new evidence regarding the management of hypertension, including randomized controlled trials, non-randomized trials, post-hoc analyses, subgroup analyses, retrospective studies, cohort studies, and registries. More recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) published joint hypertension guidelines in 2013. The panel members who were appointed to the Eighth Joint National Committee (JNC) also published the 2014 JNC report. Blood pressure (BP) targets have been changed; in particular, such targets

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have been loosened in high risk patients. The Executive Board members of TSOC and the Taiwan Hypertension Society (THS) aimed to review updated information about the management of hypertension to publish an updated hypertension guideline in Taiwan.

We recognized that hypertension is the most important risk factor for global disease burden. Management of hypertension is especially important in Asia where the prevalence rate grows faster than other parts of the world. In most countries in East Asia, stroke surpassed coronary heart disease (CHD) in causing premature death. A diagnostic algorithm was proposed, emphasizing the importance of home BP monitoring and ambulatory BP monitoring for better detection of night time hypertension, early morning hypertension, white-coat hypertension, and masked hypertension. We disagreed with the ESH/ESH joint hypertension guidelines suggestion to loosen BP targets to <140/90 mmHg for all patients. We strongly disagree with the suggestion by the 2014 JNC report to raise the BP target to <150/90 mmHg for patients between 60-80 years of age. For patients with diabetes, CHD, chronic kidney disease who have proteinuria, and those who are receiving antithrombotic therapy for stroke prevention, we propose BP targets of <130/80 mmHg in our guidelines. BP targets are <140/90 mmHg for all other patient groups, except for patients ≥80 years of age in whom a BP target of <150/90 mmHg would be optimal.

For the management of hypertension, we proposed a treatment algorithm, starting with life style modification (LSM) including **S-ABCDE** (**S**odium restriction, **A**lcohol limitation, **B**ody weight reduction, **C**igarette smoke cessation, **D**iet adaptation, and **E**xercise adoption). We emphasized a low-salt strategy instead of a no-salt strategy, and that excessively aggressive sodium restriction to <2.0 gram/day may be harmful. When drug therapy is considered, a strategy called "**PROCEED**" was suggested (**P**revious experience, **R**isk factors, **O**rgan damage, **C**ontraindications or unfavorable conditions, **E**xpert's or doctor's judgment, **E**xpenses or cost, and **D**elivery and compliance issue). To predict drug effects in lowering BP, we proposed the "**Rule of 10**" and "**Rule of 5**". With a standard dose of any one of the 5 major classes of anti-hypertensive agents, one can anticipate approximately a 10-mmHg decrease in systolic BP (SBP) (Rule of 10) and a 5-mmHg decrease in diastolic BP (DBP) (Rule of 5). When doses of the same drug are doubled, there is only a 2-mmHg incremental decrease in SBP and a 1-mmHg incremental decrease in DBP. Preferably, when 2 drugs with different mechanisms are to be taken together, the decrease in BP is the sum of the decrease of the individual agents (approximately 20 mmHg in SBP and 10 mmHg in DBP). Early combination therapy, especially single-pill combination (SPC), is recommended.

When patient's initial treatment cannot get BP to targeted goals, we have proposed an adjustment algorithm, "**AT GOALs**" (**A**dherence, **T**iming of administration, **G**reater doses, **O**ther classes of drugs, **A**lternative combination or SPC, and **L**SM + **L**aboratory tests). Treatment of hypertension in special conditions, including treatment of resistant hypertension, hypertension in women, and perioperative management of hypertension, were also mentioned.

The TSOC/THS hypertension guidelines provide the most updated information available in the management of hypertension. The guidelines are not mandatory, and members of the task force fully realize that treatment of hypertension should be individualized to address each patient's circumstances. Ultimately, the decision of the physician decision remains of the utmost importance in hypertension management.

Keywords: Asia; guidelines; hypertension; Taiwan

Contents

1. Introduction

High blood pressure (BP) is the most important risk factor for global disease burden.[1, 2] Among the 25 leading risk factors for global DALYs (Disability-Adjusted Life-Years), high BP was ranked number 4 in 1990, but moved up to number 1 in 2010.[3] The number of deaths attributable to high BP rose from 7.2 million in 1990 to 9.4 million in 2010.[2] Appromimately 54% of stroke and 47% of coronary heart disease (CHD) worldwide were attributable to high BP.[4] Hypertension is also a very common disease, in fact, the life time risk of having hypertension is about 90%.[5] Additionally, it has been noted that the prevalence rate of hypertension is rapidly growing. There was 972 million patients with hypertension (26.4%) in 2000 and that number will reach 1.56 billion (29.2%) in 2025, an alarmingly 60% increase in just 25 years.[6]

Despite being a major risk factor for cardiovascular morbidity and mortality, the control rate of hypertension is generally low. Except for in the United States, the control rate for hypertension in most countries is generally below 50%.[7] For instance, the control rate in 2009 was 32.0% in England, and 24.8% in Japan.[7] In a survey in 2002 in Taiwan, the control rate was only 21% in men, and 29% in women.[8]

The Taiwan Society of Cardiology (TSOC) has previously published its 2010 guidelines for the management of hypertension.[9] More recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) have published their joint hypertension guidelines in 2013.[10] The panel members who were appointed to the Eighth Joint National Committee (JNC) also published the 2014 JNC report.[11] Based on some new data from clinical trials, post-hoc analyses, and meta-analyses, the Executive Board Members of TSOC and the Taiwan Hypertension Society (THS) decided to publish an updated hypertension guidelines in Taiwan.

1.1. How were the guidelines created?

The Executive Board of TSOC appointed a chairperson to nominate a task force of 15 members, based on their expertise, from both TSOC and THS. Each member was assigned a specific writing task. Systemic review was performed by searching for all available evidences, including randomized controlled trials (RCTs), non-randomized trials, post-hoc analyses, subgroup analyses, retrospective studies, cohort studies, and registries. Eight face-to-face advisory board meetings have been held in 2013 (Table 1). In these meetings, members of the task force gave presentations, and were joined by other advisory board members (38 experts in total) for detailed discussions. All the presentations were recorded and could be viewed on line (http://tw.i519.org/tsoc). Thereafter, the text was finalized over a period of 6 months.

The task force uses evidence-based methodologies similar to those developed by the American College of Cardiology (ACC) and the American Heart Association (AHA).[12] The Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits, as well as evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may be harmful (Table 2). The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The task force reviewed and ranked evidence supporting each recommendation, with the weight of evidence ranked as LOE A, B, or C, according to specific definitions that are included in Table 3.

Table 1
Advisory board meetings for 2015 TSOC/THS hypertension guidelines.

Time	Location
May 11, 2013, AM	Taichung
May 11, 2013, PM	Taipei
May 25, 2013, AM	Taipei
May 25, 2013, PM	Taichung
July 27, 2013, AM	Kaohsiung
July 27, 2013, PM	Taichung
November 10, 2013, AM	Tainan
November 24, 2013, PM	Taipei

THS = Taiwan Hypertension Society; TSOC = Taiwan Society of Cardiology.

1.2. Comparison of hypertension guidelines

Similarities and differences between the 2013 ESH/ESC hypertension guidelines,[10] the 2014 JNC report,[11] and the present TSOC/TSH hypertension guidelines were shown in Table 4. The most important differences are the BP targets. The rationale of BP targets in the present TSOC/THS hypertension guidelines were discussed in other parts of this paper (Section 6.2 to Section 6.9). To make the guidelines simple, we did not cover treatment of associated risk factors-such as high cholesterol or elevated blood sugar. In general, each of these 3 hypertension guidelines fulfilled the standards for guideline formation, suggested by the Institute of Medicine (IOM).[13] The present TSOC/THS hypertension guidelines emphasized the importance of stroke when considering the cardiovascular endpoints, making it more Asian-oriented.

2. Epidemiology

2.1. Hypertension in Asia

The age-adjusted prevalence rate of hypertension is around 20–30% in Asian countries,[8, 14] similar to that in developed countries in the Western world.[6] However, the expected increase in prevalence is higher in Asians than in the rest of the world.[6] Between the years 2000 to 2025, there will be a 65.4% increase in prevalence of hypertension in Asia compared with a 51.2% increase in the rest of the world. This change is even more severe in females, with a 81.6% increase in Asia compared to a 54.4% increase in the rest of the world.[6]

In east Asian countries (China, Japan, and Korea), the death rate attributable to stroke is higher than that due to CHD.[15, 16] While hypertension is the most important risk factor for stroke,[17] the impact of hypertension on stroke and CHD in

Table 2
Classes of recommendations.

Classes of recommendation	Definition	Strength
Class I	Evidence and/or general agreement that a given treatment of procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

Asians is higher than that in Caucasians.[18, 19] With a similar increase in systolic BP (SBP) of 15 mmHg, the hazard ratio for CHD and stroke is higher for Asians than that for Caucasians.[18] In a clinical trial in 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 to a 20% reduction in Caucasians, with a similar decrease in BP.[20] This information suggested that controlling hypertension is the most important strategy to decrease cardiovascular events in Asian countries, especially stroke.

2.2. Hypertension in Taiwan

In a previous survey in Taiwan, the nationwide prevalence rates of hypertension (defined by SBP $\geq$ 140 mmHg or diastolic BP [DBP] $\geq$ 90 mmHg) were 25% in men and 18% in women, and that rate increased to 47% among individuals of age $\geq$60 years.[8] The prevalence of hypertension in Taiwan is increasing due to a surge in the prevalence rates of prehypertension, obesity and metabolic syndrome.[21] Prehypertension is an important risk factor for the development of hypertension in Taiwan, with an odds ratio of 1.71, compared to normotensives.[21] It is estimated that 59% of patients with prehypertension would develop hypertension after 8 years.[21] Interestingly, in patients less than 60 years of age, the prevalence rate of hypertension is higher in men than in women.[8] After that threshold age, women are more likely to have hypertension than men. These findings were similar to those from the US.[22]

In the report of the Nutrition and Health Survey in Taiwan (NAHSIT) (1993–1996), the control rate of hypertension (by JNC VI definition)[23] in patients $\geq$19 years of age was only 2% in men and 5% in women.[24] In the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) in 2002,[8] the control rate in patients $\geq$19 years of age was improved to 21.0% in men and 28.5% in women. It is reasonable to believe that the implementation of the National Health Insurance system since 1995 has contributed to the improvement of hypertension control. More recently, the control rate of hypertension has been further improved to 58.8% in a report from Southern Taiwan,[25] by way of implementation of the 2010 hypertension guidelines of TSOC and frequent phone contacts by study nurses. However, the control rate of hypertension varies in different areas in Taiwan; it reached as high as approximately 50% for women in the northern area, but was less than 10% for men in eastern parts of Taiwan, reflecting the disparity in medical resources.[9]

The impact of controlling hypertension in Taiwan has been demonstrated in the decrease in cardiovascular mortality. The mortality rate attributed to stroke decreased from 64.8/100,000 in 1994 to 53.5/100,000 in 2002, and in heart disease, from 56.9/100,000 in 1994 to 50.9/100,000 in 2002.[8] Stroke had been the second leading cause of death in Taiwan for more than 30 years until 2007, when CHD surpassed stroke to become the second leading cause of death.

Table 3
Level of evidence.

Level of evidence A	Data derived from multiple ($\geq$2) randomized clinical trials
Level of evidence B	Data derived from a single randomized clinical trial, meta-analyses, or large non-randomized studies
Level of evidence C	Subgroup analyses, post-hoc analyses, retrospective studies, cohort studies, registries, small studies, or expert opinion

3. Definition and classification of hypertension

Both stroke and CHD mortality are positively correlated with both office SBP (down to 115 mmHg) and office DBP (down to 75 mmHg).[26] It would be difficult to draw a line to differentiate hypertensives from normotensives. But for descriptive purposes and therapeutic guidance, cut-off BP values are universally used. Hypertension is defined as values $\geq$140 mmHg in SBP, and/or $\geq$90 mmHg in DBP, using office BP measurement, based on the evidence from randomized controlled trials (RCTs) suggesting that treatment-induced BP reductions are beneficial to patients with these BP values (Table 5). We further stratified stages of hypertension by a 20-mmHg increase in SBP and a 10-mmHg increase in DBP, because doubling of CHD death has been observed by the same increments in BPs in an epidemiological study[26] (Table 5). For patients with diabetes, CHD, or proteinuric chronic kidney disease (CKD) (special patient groups), a SBP $\geq$ 130 mmHg and/or a DBP $\geq$ 80 mmHg were considered high BPs (Sections 6.4, 6.5, 6.7). The staging of hypertension was defined by the highest level of BPs, whether systolic or diastolic.

Table 4
Comparison of the 2013 ESH/ESC hypertension guidelines, the 2014 JNC Report, and the 2015 TSOC/THS hypertension guidelines.

	2013 ESH/ESC	2014 JNC Report	2015 TSOC/THS
Diagnosis flow chart	−	−	+
Treatment flow chart	−	+	+
Adjustment flow chart	−	+	+
Life style modification	+	−	+
Blood pressure targets	+	+	+
	Universally <140/90	<140/90 (<150/90 for age>60)	<140/90 (or <130/80 for special patient groups[a])
Treatment in special conditions	+	−	+
Treatment of associated risk factors	+	−	−
Standards of IOM			
Transparency	?	?	+[b]
Conflict of interests	Full disclosure	Full disclosure	Full disclosure
Group compositions	N = 55	N = 51	N = 53
Advisory board member			
Systemic review	+[c]	+[d]	+[e]
Strength of recommendation	+	+	+
Articulation	+	?	+
External review	+	+	+
Updating	+	+	+
Appropriateness for Asians	?	?	+

ESC = European Society of Cardiology; ESH = European Society of Hypertension; IOM = Institute of Medicine; JNC = Joint National Committee; THS = Taiwan Hypertension Society; TSOC = Taiwan Society of Cardiology.
[a] Patients with diabetes, or coronary heart disease, or proteinuric chronic kidney disease.
[b] All presentations can be viewed on website (http://tw.i519.org/tsoc).
[c] Randomized controlled trials, meta-analyses, and cohort studies.
[d] Only randomized controlled trials.
[e] Randomized controlled trials, meta-analyses, non-randomized trials, subgroup analyses, post-hoc analyses, retrospective studies, cohort studies, registration studies, small studies, especially focused on available data for Asians.

4. Diagnosis

4.1. Blood pressure measurement

The diagnosis of hypertension depends of office BP measurement, complemented by home BP monitoring (HBPM), and ambulatory BP monitoring (ABPM).

4.1.1. Office blood pressure measurement

The measurement of BP is likely the single clinical procedure of greatest importance that is actually performed in the sloppiest manner. The measurement of BP should follow the noted recommendations.[27] Table 6 summarized correct methods for office BP measurement. Patient BP should be measured in both arms during the initial visit, and then the arm with a higher BP should be used in the following visits. When orthostatic hypotension is suspected, especially in elderly patients or diabetic patients, BP should be measured at 1 minute and 3 minute intervals after assumption of standing position. Orthostatic hypotension is a strong predictor of CV events and total mortality.[28, 29]

Table 5
Definition and classification of hypertension by office blood pressure measurement.

Staging	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	160-179	or	100-109
Stage 3 hypertension	≥180	or	≥110
Isolated systolic hypertension	≥140	and	<90

Systolic BP ≥130 mmHg or diastolic BP≥80 mmHg are considered high blood pressures in special patient groups (coronary heart disease, diabetes, and proteinuric chronic kidney disease), and also in patients who receive antithrombotics for stroke prevention. (Modified from Chiang et al.[9] with permission.)

The "gold standard" device for office BP measurement has been the mercury sphygmomanometer, but these are being removed from clinical practice because of environmental concerns about mercury contamination.[27] Therefore, auscultatory or oscillometric semiautomatic sphygmomanometers are typically used in most practices. Validated devices are recommended, and several lists of validated devices are available online (http://www.bhsoc.org; or http://www.hypertension.ca).

Although the data from the Framingham Heart Study showed that DBP is a stronger predictor for CHD than SBP in patients less than 50 years of age,[27] it is generally believed that SBP is a more important predictor for overall cardiovascular risk in elderly patients (65 years or older).[30-32] Because about 75% of people with high BP are over the age of 50, the burden of disease is mainly due to elevation of SBP.[33] It has also been shown that anti-hypertensive drugs improved patient outcomes mainly through lowing SBP.[34, 35] However, SBP is more difficult to control compared with DBP.[35]

4.1.2. Ambulatory blood pressure monitoring (ABPM)

ABPM has become a useful tool in the diagnosis and management of hypertension.[36] ABPM is superior to office BP

Table 6
Correct methods for office blood pressure measurement.

Before measurement	
Timing	
1 hour	Avoiding coffee, food, smoking, decongestants
30 minutes	Avoiding exercise
5 minutes	Sitting calmly
Preparation	Emptying bladder and bowel, and removing all clothing that covers the location of cuff placement
Environment	Calm and warm place
During measurement	
Body position	Seated, back supported, legs uncrossed, feet flat on floor, and relaxed
Arm	Supported, using the arm with higher value
Cuff	at heart level, using appropriate sized one
Measurement	Taking two measurement, spaced 1-2 minutes apart, and additional measurement if needed
	Measuring heart rate by pulse palpation (at least 30 seconds) after the second measurement
	For patients with atrial fibrillation, measuring blood pressure manually, using direct auscultation over the brachial artery
	When suspecting orthostatic hypotension, measuring blood pressure 1 and 3 minutes after assumption of standing position
After measurement	
Blood pressure readings	Averaging, but not rounding them
	Recording

measurement in the prediction of future cardiovascular events.[37, 38] In 2001, the Centers for Medicare and Medicaid Services in the United States approved ABPM for reimbursement for the identification of individuals with white-coat hypertension; in 2011 the National Institute for Health and Care Excellence (NICE) in the United Kingdom recommended that ABPM be offered as a cost-effective technique for all people suspected of having hypertension.[36] Unfortunately, the National Health Insurance Administration in Taiwan has not included ABPM in its reimbursement lists.

The ABPM devices are typically programmed to take readings every 15 to 30 minutes throughout the day and night. At the end of the recording period, the readings are downloaded into a computer. Standard protocols are used to evaluate the accuracy of the devices. Approved devices are usually accurate to within 5 mm Hg of readings taken with a mercury sphygmomanometer.[39] Methodological details can be referred to the practice guidelines of ESH,[36] and would not be mentioned here. Cut-off values for the definition of hypertension for ABPM were shown in Table 7. Additionally, advantages and weaknesses of ABPM were shown below:

4.1.2.1. Advantages of ABPM[36]

- Is a much stronger predictor of cardiovascular events than office BP
- Provides larger number of BP readings
- Identifies white-coat hypertension, and masked hypertension
- Discloses nocturnal hypertension, and dipping patterns

Table 7
Definition of hypertension by HBPM and ABPM.

Category	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
HBPM	≥135	or	≥85
ABPM	≥130	or	≥80
Daytime	≥135	or	≥85
Nighttime	≥120	or	≥70

ABPM = ambulatory blood pressure monitoring; HBPM = home blood pressure monitoring. (Modified from Chiang et al.[9] with permission.)

- Provides averaged daytime, night-time, and 24-hour values
- Assesses BP variability over 24 hours
- Evaluates the 24-hour efficacy of antihypertensive drugs

4.1.2.2. Weaknesses of ABPM[36]

- Cost (reimbursement issue)
- Limited availability in private practice
- Discomfort in patients
- Repeated measurement not likely in short term.

The averaged night-time BP has become a stronger predictor than averaged daytime BP.[40-42] The sleep-time BP mean has also been reported to be the most significant prognostic predictor of cardiovascular morbidity and mortality.[43] A patient's BP normally decreases during the night, defined as a "dipping" pattern.[44] It is generally agreed that a night-time BP fall of >10% of daytime values (night-day ratio <0.9) is the cut-off value for normal dipping.[39] Approximately 70% of individuals dip ≥10% at night, while 30% have non-dipping patterns.[44] A different degree of dipping has been proposed, but the reproducibility of dipping pattern is limited.[10]

Early morning hypertension defined as elevation of averaged BP over the 2 hours after awaking has been reported to be associated with higher risk of stroke.[45] Both HBPM and ABPM were interchangeable methods for the assessment of early morning hypertension.[46] Circumstantial evidence for the validity of early morning hypertension as an index of disease risk is provided by a peak in myocardial infarction and stroke compared with other periods of the day.[47] A morning BP surge, on the other hand, is an increase in BP occurring from the night-time to the early morning.[47] Morning BP surge can be measured reliably by ABPM. Similar to early morning hypertension, it has been reported to be a risk factor for cardiovascular events,[48] especially hemorrhagic stroke.[49] In a recent analysis of 5,645 individuals recruited from eight different countries, the morning BP surge was associated with a 30–45% increase in the risk of cardiovascular events.[50]

4.1.3. Home blood pressure monitoring (HBPM)

High BP detected by HBPM is more closely related to hypertension-related TOD and predicts the risk of cardiovascular events better than office BP measurement.[51, 52] Some studies and meta-analyses have suggested that HBPM is as good as ABPM and superior to office measurements in regard

to their association with preclinical organ damage.[53-55] Home BP should be measured by validated semi-automated oscillometric (electric) devices, and under similar requirements as office BP measurement (Table 6).

A minimum of 12 measurements and up to 25 measurements over a few days might be desirable.[56] Two morning readings and 2 evening readings for 7 days immediately before each visit, excluding the readings from the first day, would be measured and stored in devices for HBPM.[57] Thus, there would be 12 readings either in the morning or in the evening, with a total of 24 readings. These readings can be averaged for each visit. Physicians may use separated averages of morning or evening BP to adjust the timing of administration of antihypertensive drugs. Cut-off values for the definition of hypertension for HBPM were shown in Table 7. Advantages and weakness of HBPM were shown below:

4.1.3.1. Advantages of HBPM[36, 57]

- Is a stronger predictor of cardiovascular events than office BP
- Provides a larger number of BP readings
- Can be repeated more frequently than ABPM
- Identifies white-coat hypertension, and masked hypertension
- Evaluates the efficacy of antihypertensive drugs at different times of the day and night, except sleep
- High acceptance by patients
- Relatively low cost

4.1.3.2. Weaknesses of HBPM[36, 57]

- Necessity for patient training (simple for automated devices)
- Possible use of un-validated devices
- Lack of night time recordings.

The investigators of the TASMIN-SR (The Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups) recently studied the impact of BP self-monitoring at home with self-titration of antihypertensive medication, compared with usual care, on SBP among high-risk patients with existing cardiovascular disease, diabetes mellitus, or CKD.[58] The mean baseline BP was 143.1/80.5 mmHg and 143.6/79.5 mmHg in the intervention and the control groups, respectively. The mean BP decreased to 128.2/73.8 mmHg and 137.8/76.3 mmHg in the intervention and the control groups, respectively, after 12 months.[58] There was a difference of 9.2 mmHg ($p < 0.05$) in SBP and 3.4 mmHg in DBP between groups. The authors concluded that self-management of BP in patients with or at high risk of cardiovascular disease resulted in lower SBP at 12 months.[58]

4.2. White-coat hypertension

White-coat hypertension is defined in subjects who have elevated office BP (≥140/90 mmHg), but with ABPM < 130/80 mmHg,[36] or HBPM < 135/85 mmHg.[57] The term should be reserved for un-treated patients. In patients who have received treatment, the term "white-coat effect" is preferred.[44] The prevalence of white-coat hypertension was estimated to be around 10−15%.[59, 60] However, in patients with elevated office BP, white-coat hypertension was common, particularly in the untreated group (42.9%).[60] The long-term prognosis of untreated patients with white-coat hypertension is controversial. In a meta-analysis using IDACO (International Database on Ambulatory Blood Pressure Monitoring in relation to Cardiovascular Outcomes) Population data, the adjusted hazard ratio of subjects with white-coat hypertension was similar to subjects with normal BP (1.17, $p = 0.29$).[61] On the contrary, data from IDHOCO population (International Database of Home Blood Pressure in Relation to Cardiovascular Outcome) show that among untreated subjects cardiovascular risk was higher in those with white-coat hypertension compared with normotensive subjects (adjusted hazard ratio of 1.42, $p = 0.02$).[60] In a recent study from Taiwan using ABPM to define white-coat hypertension, 15-year cardiovascular mortality was higher in subjects with white-coat hypertension.[62] It is suggested that ABPM and HBPM are complementary for the diagnosis of white-coat hypertension.[60] This view was supported by a recent analysis of the PAMELA general population study.[63] Among subjects with white-coat hypertension, those with low home and ambulatory BP had lower cardiovascular mortality than those with only one of them being low.[63]

It is debatable that subjects with white-coat hypertension need treatment. The majority of evidence supports increased TOD in cross-sectional studies of subjects with white-coat hypertension, including left ventricular hypertrophy and increased carotid intima-media thickness.[64, 65] Furthermore, a higher prevalence of metabolic derangement has been reported,[62, 66] including increased new-onset diabetes.[67] In a Taiwanese study, subjects with white-coat hypertension were characterized by higher arterial stiffness and lower estimated glomerular filtration rate.[62] We suggest that patients with white-coat hypertension should be treated with life style modification (LSM), and regularly followed up by ABPM or HBPM to detect any evidence of progression to sustained hypertension.

For treated patients who have "white-coat effect", the cardiovascular events were lower than in those with resistant hypertension, but similar to patients with well-controlled hypertension.[68, 69] Notably, 20 to 25% of patients with white-coat effect would develop true resistant hypertension within 3 to 6-months of follow-up.[70] Therefore, continued HBPM or ABPM are advised.

4.3. Masked hypertension

Masked hypertension is defined in untreated subjects who have normal office BP (<140/90 mmHg), but with elevated ABPM (≥130/80 mmHg),[36] or elevated HBPM (≥135/85 mmHg).[57] Masked uncontrolled hypertension is defined in treated patients utilizing similar criteria.[36, 57] The prevalence of masked hypertension was estimated to be around 10-

15%,[59, 60, 71] higher in patients with prehypertension than in patients with normal BP.[71] In the Masked Hypertension Study in the untreated subjects, it was shown that the prevalence of masked hypertension increased to 34% in subjects with prehypertension, and reached 52% in subjects with higher prehypertensive BP (SBP 130–139 mmHg or DBP 80–89 mmHg), whereas the prevalence of masked hypertension was only 3.9% in participants with normal office BP (SBP <120 mmHg and DBP < 80 mmHg).[71] Other studies have similarly shown that office BP in the upper prehypertensive range predicts masked hypertension.[72] Masked hypertension was not uncommon in patients with diabetes,[73] CKD,[74] and obstructive sleep apnea syndrome.[75] On the other hand, the prevalence of masked uncontrolled hypertension was high (up to 41.4%),[60] and highlights the need for ABPM or HBPM in all treated patients.[60] Meta-analyses of prospective studies demonstrated that subjects with masked hypertension had twofold higher cardiovascular event rates than normotensives, similar to the event rates in patients with sustained hypertension.[59, 76, 77]

Anti-hypertensive management may be considered in patients with masked hypertension, but there are currently no RCTs that have evaluated this strategy, and the best method to identify subjects with masked hypertension has not yet been established.[44] A diagnostic algorithm using ABPM (or HBPM) for follow-up has been proposed to evaluate subjects with masked hypertension, if their office BP is in the prehypertensive range.[78] If office BP is <120/80 mmHg, there will be no need to arrange ABPM, as the prevalence of masked hypertension is quite low in this group.

4.4. Diagnosis algorithm

A diagnosis algorithm was proposed in Fig. 1. For patients presenting with office BP ≥ 140/90 mmHg (or ≥130/80 mmHg in special patient groups, i.e. diabetes, CHD, and proteinuric CKD), physical examination (Section 5.2) and routine laboratory tests (Section 5.3) (Table 8) should be performed, and a medical history obtained (Section 5.1). After 2 weeks to 1 month, office BP can be rechecked. If office BP is still <140/90 mmHg (or <130/80 mmHg in special patient groups), continued outpatient clinic follow-up is suggested (unless in patients who have office BP in the prehypertension range [120-139/80-89 mmHg, or 120-129/70-79 mmHg in special patient groups] in whom ABPM or HBPM can be performed in 3-6 months to confirm the diagnosis of masked hypertension). For patients who have repeated office BP ≥140/90 mmHg (or ≥130/80 mmHg in special patient groups), physicians should look for evidence of TOD (including left ventricular hypertrophy by electrocardiogram, microalbuminuria, or asymptomatic atherosclerosis [carotid intima-media thickening or aortic plaque], ankle-brachial index<0.9, or increased pulse wave velocity). In case of positive TOD, physicians should proceed to the Treatment Algorithm (Fig. 2). If there is no evidence of TOD, HBPM or ABPM should be performed to rule out the possibility of white-coat hypertension. If HBPM is ≥135/85 mmHg or ABPM ≥130/80 mmHg, physicians should proceed to the Treatment Algorithm (Fig. 2). For patients with normal HBPM and normal ABPM, continued follow-up is suggested. Physicians can arrange ABPM or ask patients to

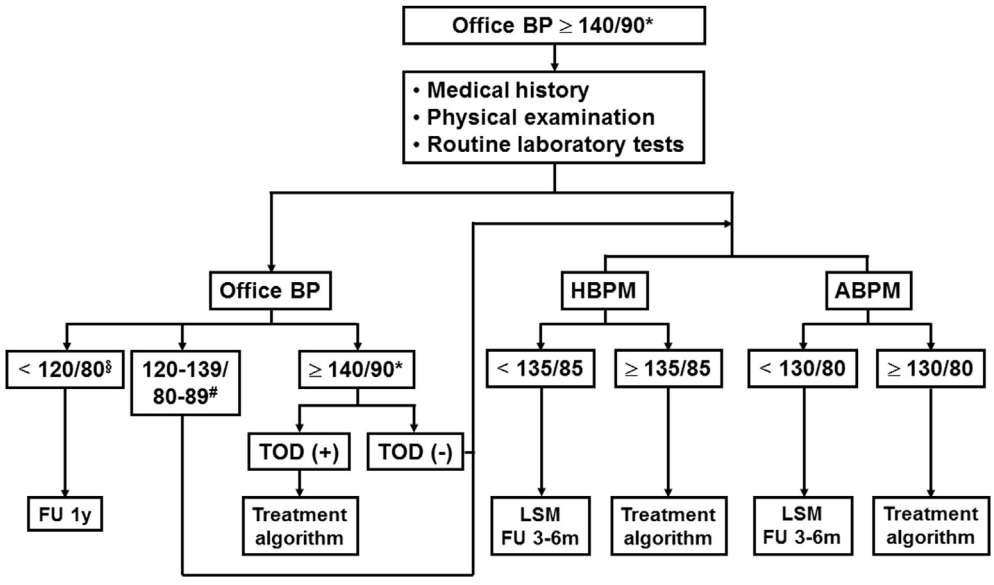

Fig. 1. Diagnosis algorithm. This algorithm does not apply to very elderly patients (age ≥80 years) because their treatment threshold and targets are 150/90 mmHg. For special patient groups (coronary heart disease, diabetes, or proteinuric chronic kidney disease), lower BPs are applied (* ≥130/80 mmHg; # 120–129/70–79 mmHg; § <120/70 mmHg). ABPM = ambulatory blood pressure monitoring; BP = blood pressure; FU = follow-up; HBPM = home blood pressure monitoring; LSM = life style modification; m = month; TOD = target organ damage (including left ventricular hypertrophy by electrocardiogram, microalbuminuria, or asymptomatic atherosclerosis [carotid intima-media thickening or aortic plaque], ankle-brachial index<0.9, or increased pulse wave velocity); y = year. (Modified from Chiang et al.[9] with permission.)

Table 8
Laboratory tests.

Routine tests
Hemoglobin and hematocrit
Serum creatinine with estimated creatinine clearance (Cockroft-Gault formula) or glomerular filtration rate (Modification of Diet in Renal Disease formula)
Serum sodium, potassium and calcium
Fasting glucose
Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides
Serum uric acid
Urinalysis
Electrocardiogram
Chest X-ray
Recommended tests
Oral glucose tolerance test or HbA1C (if fasting plasma glucose ≥100 mg/dL)
High sensitivity C reactive protein
Quantitative microalbuminuria/proteinuria
Fundoscopy
Echocardiography
Carotid ultrasound
Home and ambulatory blood pressure monitoring
Ankle-brachial index
Pulse wave velocity
Extended evaluation (domain of the specialist)
Further search for cerebral, cardiac, renal and vascular damage. Mandatory in complicated hypertension
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

(Modified from Chiang et al.[9] with permission.)

provide HBPM data at the second visit (2 weeks to 1 month after the first visit), and manage patients accordingly. Although the cut-off values of 135/85 mmHg for HBPM and 130/80 mmHg for ABPM are well established, the cut-off values of HPBM and ABPM for special patient groups (diabetes, CHD, proteinuric CKD) are unknown. We may consider that the cut-off values for HBPM and ABPM should be lower than office BP thresholds (130/80 mmHg) in special patient groups.

5. Evaluation

5.1. Medical history

A complete medical history should be taken during the first visit for patients with high BP. The information of interest to clinicians is related to treatment threshold, BP targets, and choice of management strategy. Medical history includes:

- Previous cardiovascular events and diseases: CHD, stroke or transient ischemic attack, diabetes, heart failure, CKD, peripheral artery disease, and sleep apnea.
- Personal history: dietary habit, salt intake, alcohol intake, smoking history, and exercise habit.
- Previous drug history: anti-hypertensive drugs, non-steroid anti-inflammatory drugs (NSAIDs), cyclooxigenase-2 (COX-2) inhibitors, steroids, oral contraceptives, migraine medications, cold remedies (containing pseudoephedrine), systemic or intra-vitreal use of anti-vascular endothelial growth factor (anti-VEGF), etc.

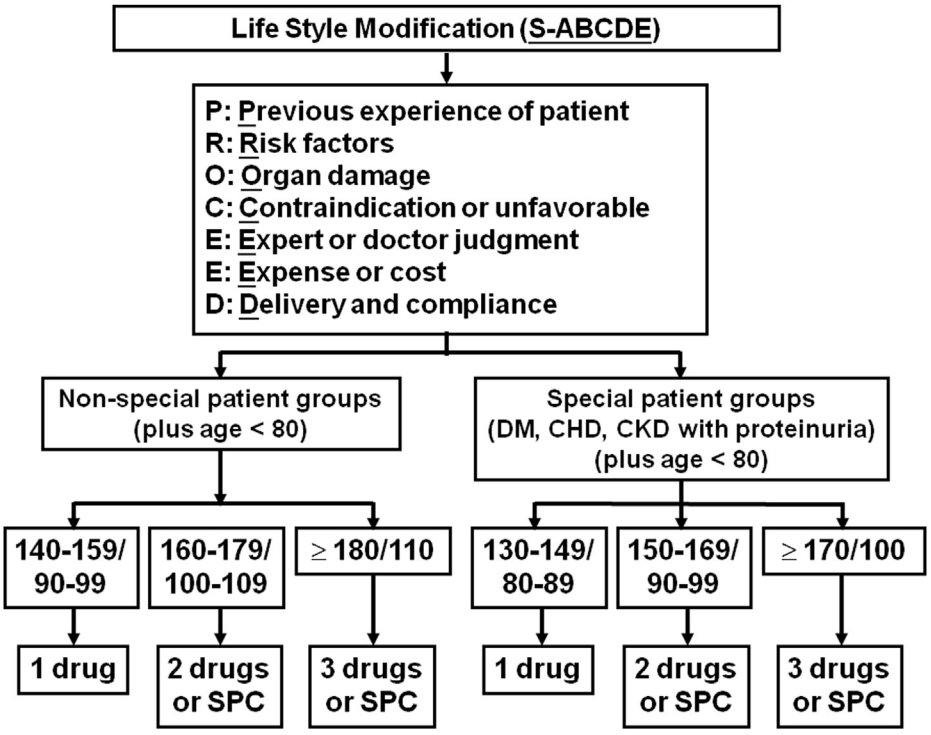

Fig. 2. Treatment algorithm. This algorithm is not applicable in very elderly patients (age ≥80 years). CHD = coronary heart disease; CKD = chronic kidney disease; DM = diabetes mellitus; SPC = single-pill combination. (Modified from Chiang et al.[9] with permission.)

5.2. Physical examination

Physical examination plays an essential role in the assessment of hypertensive patients. The purposes of physical examinations include establishing the diagnosis and determining the severity of hypertension, searching for signs of secondary hypertension and TOD, and refining global cardiovascular risk.[9] Initially, BP should be measured correctly (Section 4.1.1) (Table 6). Physical examination should include the followings: 1) calculation of body mass index (BMI); 2) inspection of Cushingoid appearance including moon face, buffalo hump, truncal obesity, and wide purple striae; 3) evaluation of optic fundi for hypertensive retinopathy; 4) palpation of the thyroid gland for hyperthyroidism; 5) auscultation of carotid, abdominal and femoral bruits for renovascular disease and peripheral artery disease; 6) auscultation over the back for a loud murmur suggesting coarctation of aorta; 7) comprehensive examination of the heart and lungs for left ventricular hypertrophy, and ventricular gallop of congestive heart failure; 8) examination of the abdomen for enlarged kidneys, masses, and pulsation of abnormal aorta; 9) palpation of the lower extremities for edema and pulses; and 10) a complete neurological assessment.[9] The aforementioned evaluation should be undertaken in every patient in the first visit.

5.3. Laboratory tests

Laboratory tests aim to search for additional risk factors, provide evidence of secondary hypertension, and look for TOD (Table 8). A more detailed diagnostic work-up should be performed in younger patients, patients with very high BP, and patients with TOD. Routine tests should be considered in every patient at the first visit. Recommended studies are optional (Table 8). Measurement of urinary albumin excretion or albumin/creatinine ratio is strongly recommended in Taiwan, a country with the highest prevalence of ESRD in the world.[79] High-sensitivity C reactive protein (hs-CRP) predicts the incidence of cardiovascular events and optimizes the use of statins in hypertensive patients who have a high cardiovascular risk.[80]

5.4. Central blood pressure

All the traditional ways of measuring BP, including office BP measurement, HBPM, and ABPM, use recordings from the brachial arteries, and may be different from the central BP measured in the ascending aorta or carotid arteries, due to the well-recognized BP amplification from the central aorta to the peripheral arteries.[81] Recent data suggested that central BP may be more relevant than peripheral BP in predicting TOD and cardiovascular outcomes.[82] although central and peripheral BP may respond differently to antihypertensive medication in RCTs,[83] end-organ changes after antihypertensive medication are more strongly related to changes in central BP than peripheral BP.[84] The individual discrepancies between central BP and peripheral BP may be substantial and highly variable, and may be magnified during hemodynamic changes or after pharmacological interventions.[83] Thus, BP measurements in the peripheral arteries cannot serve as a direct substitute for their central counterpart.[85] More importantly, an office measurement of central BP is not inferior to ambulatory BP in the prediction of future outcomes.[86]

Currently, central BP can be obtained non-invasively with either tonometry-based[87] or cuff-based techniques.[88] Using an outcome-driven approach to examine the discriminatory ability of central BP for long-term cardiovascular outcomes,[89] an operational threshold for central BP has been derived and validated in two independent Taiwanese cohorts.[90, 91] A central BP cut-off value of 130/90 mm Hg has a greater discriminatory power for long-term events, and can be considered to be implemented for the management of hypertension in routine daily practice.[92] Central BP may have higher sensitivity and negative predictive value than peripheral BP in the diagnosis of hypertension.[93]

Recommendation

- Measurement of central BP with a cut-off value of 130/90 mmHg is recommended when a diagnosis of hypertension is clinically suspected but cannot be established by current conventional BP criteria. (COR IIb, LOE B)

5.5. Blood pressure variability

BP is not static but has significant fluctuations. The phenomenon of BP variability (BPV) is well-recognized as short-term fluctuation occurring within a 24-hour period, including beat-to beat, minute-to-minute, hour-to-hour, and day-to-night variations. Long-term variations including day-to-day as well as more prolong interval such as week-to-week, month-to-month, and even seasonal changes are noted.[94] BPV is thought to be the result of complex interactions between intrinsic cardiovascular physiologic regulation and extrinsic environmental and behavior factors, but are not yet completely elucidated. Although previous studies have shown increased BPV was associated with adverse cardiovascular consequences, the clinical utility of BPV is not yet well established.[10]

Most of the evidence suggesting an association between BPV and cardiovascular events are based on observational studies and post-hoc analyses of clinical trials.[95] Prospective studies have provided evidence that increased short-term BPV with 24 hours independently predicted progression of subclinical organ damage, structural cardiac and vascular changes, cardiovascular events, and cardiovascular mortality.[96-98] ABPM is used for assessment of BPV within 24 hours. It is possible to perform the calculation of standard deviation (SD) of average systolic, diastolic, and mean arterial pressure values over the 24-hour period, or during the daytime and night-time sub-periods.[99] The SD can be weighted by the 24-hour mean value, and has been proposed as a method to exclude day-to-night BP changes from the quantification of overall 24-hour SD.[94] Since BPV is largely dependent on

mean BP, the average SD of BP can also be divided by the corresponding mean BP and multiplied by 100 to express a normalized measure of BPV as a coefficient of variation.[94] ABPM also provides information on diurnal BP changes. The prognostic relevance of nocturnal BP and reduced night-time BP dipping has been assessed in several studies. A community study in Taiwan has shown that night-time BP drop was associated with TOD.[100]

Evidence also suggests that increased mid-term (such as day-to-day) BPV is associated with increased cardiovascular events. The Ohasama study provided the evidence that increased day-to-day variability in SBP assessed by HBPM is associated with an increased risk of cardiovascular mortality.[101] HBPM is an appropriate method for the assessment of mid-term and long-term BPV.[94] HBPM allows day-to-day BP measurement in fairly standardized conditions, and the use of HBPM is recommended in current international guidelines.[10] Increased long-term BPV such as visit-to-visit variability is associated with TOD and cerebral damage in previous studies.[102, 103] Longitudinal studies and post-hoc analyses of clinical trials in hypertension have shown that increased intra-individual visit-to-visit variability is predictive of fatal and non-fatal cardiovascular and cerebrovascular events, and all-cause mortality.[104-106]

Currently, no large randomized placebo-controlled trials are available to study the effect of antihypertensive drugs. A post-hoc analysis of data from ASCOT and MRC-elderly showed that long-term intra-individual visit-to-visit variability might be affected differently by various classes of antihypertensive drugs, and that these differences might reflect various effects of different drugs on BP.[104] The most important finding of the analysis was calcium-channel blocker-based regimen was associated with lower intra-individual BPV and a lower incidence of stroke than a beta-blocker-based regimen. However, before BPV is recommended as a routine measure or as a target for antihypertensive treatment, further prospective outcome studies should be conducted.

5.6. Screening for secondary hypertension

The causes of secondary hypertension are listed in Table 9. A secondary form of hypertension should be suspected in patients with younger or older onset of hypertension, marked BP elevation, sudden onset or worsening of hypertension, poor BP response to drug therapy, and significant TOD at initial presentation. Screening for secondary hypertension includes history taking, physical examination, and laboratory tests.

Renal parenchymal disease is the leading cause of secondary hypertension. Bilateral upper abdominal masses upon physical examination could be detected in patients with polycystic kidney disease. Renal ultrasound provides the necessary anatomical data including kidney size and shape, cortical thickness, urinary tract obstruction and renal masses. Serum creatinine concentration and urinalysis are screening tests for renal parenchymal disease.

Renovascular hypertension is the second most common cause of secondary hypertension. Renal artery stenosis due to atherosclerosis or fibromuscular dysplasia is the leading cause in the elderly and younger population, respectively. It should be considered in those with renal artery bruit, unexplained hypokalemia, hypertension onset before age 30 years or worsening after age 55 years, resistance to antihypertensive therapy, sustained rise in creatinine after initiation of angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), presence of hypertensive retinopathy, or flash pulmonary edema.[107] Renal ultrasound can be used as a screening tool to determine the longitudinal diameter of both kidneys, and a difference of >1.5 cm in length between two kidneys suggested a diagnosis of renal artery stenosis.[108] Color Doppler ultrasonography is helpful for detection of renal artery stenosis. Three-dimensional, gadolinium-enhanced magnetic resonance renal angiography or spiral computed tomography renal angiography is the diagnostic choice for renovascular hypertension. Digital subtraction angiography is the gold standard for detection.

Pheochromocytoma should be considered in patients with paroxysmal BP elevation. The typical symptoms of this disease include headache, perspiration, palpitations, and pallor. The diagnosis is confirmed by an increase in plasma or urinary catecholamines or their metabolites.

Serum potassium level is a routine screening test. It has been suggested that patients with unprovoked hypokalemia or truly resistant hypertension should be evaluated for primary aldosteronism.[109] The disease can be confirmed by the fludrocortisone suppression test of aldosterone and renin, under standardized conditions.[110] A cut-off of aldosterone to 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.[111]

About 80% of patients with Cushing's syndrome have hypertension. The syndrome is usually suggested by the typical

Table 9
Causes of secondary hypertension.

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

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body habitus such as moon face, buffalo hump and central obesity. 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.

It is important to consider sleep apnea in obese hypertensive patients. Signs and symptoms include daytime somnolence, impaired concentration, unrefreshing and restless sleep, choking episodes during sleep, witnessed apneas, nocturia, irritability and personality changes, decreased libido, and increased motor vehicle accidents. Furthermore, hypertensive patients with "non-dippers" on ABPM should be investigated for obstructive sleep apnea. 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. A mid-systolic murmur can be heard over the anterior part of the chest and back. The femoral pulse is weak or delayed relative to the radial pulse. Hypertension is found in the upper extremities concomitantly with low or unmeasurable BP in the legs.

Finally, medication history should be reviewed carefully. Substances or drugs that can raise BP include pills used to treat common colds such as licorice in antitussive syrup, oral contraceptives, steroids, NASIDs, cocaine, amphetamines, erythropoietin, cyclosporin, tacrolimus, and anti-VEGF.

6. Blood pressure thresholds and targets

In the most robust meta-analysis of individual data from 1 million adults in 61 prospective studies (11 million person-years), both stroke and CHD mortality increased continuously from a nadir of 115 mmHg in SBP and a nadir of 75 mmHg in DBP.[26] Similarly, in the Asia Pacific Cohort Study Collaboration study consisting of data from 425,325 participants (3 million patient-years), the risk of stroke and CHD started to increase from 115 mmHg in SBP and from 75 mmHg in DBP.[112] More recently, in a study of a cohort of 1.25 million patients from United Kingdom, the lowest risk for cardiovascular disease was in people with SBP of 90-114 mmHg and DBP of 60-74 mmHg.[32] In contrast, in a recent publication from the Atherosclerosis Risk in Communities Study (ARIC) it was found that there was no difference in incident cardiovascular event-free survival among those in the standard SBP group (120-139 mmHg) vs the low SBP group (<120 mmHg).[113] It would be difficult to define thresholds for starting treatment, and it would be even more difficult to set targets for BP control.

Recently, 2013 ESH/ESC hypertension guidelines defined a universal target of <140/90 mmHg for all patients, except the very elderly (target of <150/90 mmHg for age ≥80 years).[10] The 2014 JNC report took similar steps, and further raised the target to <150/90 mmHg for patients aged ≥60 years,[11] though 5 members of the committee of 2014 JNC report published a minority view refusing to compromise with a target of 150/90 mmHg for aged ≥60 years.[114] It has been estimated that the proportion of older patients (≥60 years) with treatment-eligible hypertension would decrease from 68.9% under JNC7[115] to 61.2% under the 2014 JNC report.[116] This translates to a decrease in treatment-eligible patients of 5.8 million in the US in whom treatment is no longer needed.[116] The proportions of patients reaching BP goals would, however, artificially increase from 40.0% under JNC7[115] to 65.8% under the 2014 JNC report.[116]

Because only a few RCTs were available to compare different BP targets, disparity in BP targets among different hypertension guidelines is not uncommon. Two ongoing trials are much anticipated. The Systolic Blood Pressure Intervention Trial (SPRINT) is an RCT that compares two targets (<140 mmHg and <120 mmHg) in patients aged ≥50 years with evidence of cardiovascular disease, CKD, 10-year Framingham cardiovascular disease risk score ≥15%, or age ≥75 years.[117] The SPRINT trial has completed the enrollment (n = 9361) and the results will be available in the Fall of 2017. The Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertension (ESH-CHL-SHOT) is an RCT (NCT01563731) that compares three SBP targets (<145 mmHg, <135 mmHg, and <125 mmHg) in patients aged ≥65 years with prior stroke or transient ischemic attack. The ESH-CHL-SHOT trial will enroll 7500 patients and has been started in the Fall of 2012.

6.1. J-curve revisit

The J-curve (or U-curve) phenomenon was first mentioned in 1979.[118] A study conducted in 169 patients with severe hypertension disclosed a relative 5-fold risk of myocardial infarction in those who had achieved a DBP <90 mmHg compared with a DBP in the range of 100–109 mmHg.[118] Coronary blood flow, which occurs predominantly in the diastole, may cease at a myocardial perfusion pressure <40 mmHg.[119] More recently, there have been some data on the J-curve phenomenon for SBP.[120] It is generally believed that the "J-curve" phenomenon is true, and there must be a lowest value of BP (nadir), which represents a point at which BP is too low to maintain perfusion of vital organs, particularly the heart. The precise question remains-where is the nadir?

In general, data from large-scaled epidemiological studies did not support the concept of the J-curve phenomenon. In 1 million subjects with or without risk factors, but free from cardiovascular diseases, both CHD and stroke mortality appeared to begin at around 115/75 mmHg, without any J-curve phenomenon.[26] In a cohort of 1.25 million subjects, initially free from cardiovascular disease, the lowest risk for cardiovascular disease was in people with SBP of 90-114 mmHg and DBP of 60-74 mmHg, without any evidence of J-curve phenomenon.[32] In the Multiple Risk Factor Intervention Trial (MRFIT) which enrolled 332,554 subjects without end organ damage, the lowest risk of ESRD was found in subjects with a BP of <120/80 mmHg, without any J-curve phenomenon.[121] In the UK prospective diabetes study (UKPDS) 36, the lowest risk of all-diabetes related macro- and micro-vascular endpoints were in those patents with SBP less than 120 mm Hg, without any J-curve phenomenon.[122] In the

Asia Pacific Cohort Studies enrolling 425,325 subjects, the lowest risk of CHD and stroke was found in patients with a BP <120/80 mmHg, without a J-curve phenomenon.[112]

Among RCTs, it is also uncommon to find any J-curve phenomenon if cardiovascular endpoints were evaluated prospectively, though the BP levels obtained in RCTs were generally higher than what we have mentioned in the epidemiological studies. In the three most important RCTs in isolated systolic hypertension (SHEP, Syst-Eur, Syst-China), stroke risk was significantly decreased in the treatment group compared to the placebo group.[123-125] No J-curve phenomenon was observed. In fact, the DBP in the treatment group in the SHEP trial was only 68 mmHg, and the risk of myocardial infarction was still significantly decreased by 33%.[123]

Most of the data suggesting a J-curve phenomenon came from post-hoc analyses of RCTs.[120, 126-129] One should be aware that these RCTs were not designed to compare the effects of different BP targets, and they were mostly comparing different drugs. As pointed out by a recent review,[130] the main limitations of post-hoc analyses are 1) lack of randomization, and 2) very small number of patients in the group of patient with low or very low achieved BP.

1). Lack of randomization: There are very few RCTs comparing different BP targets. Most of the RCTs were compared the effects of different drug or different drug combinations. In post-hoc analyses, investigators tried to study the outcomes based on different ranges of achieved BP in trials. Therefore, patients were not randomized into different BP categories, and the baseline risk factors or co-morbidities were not evenly distributed in different BP groups. Both measurable and un-measured confounding factors were imbalanced, a major weakness in these kind of analyses. For instance, in a key post-hoc analysis of the INVEST trial, the achieved systolic and diastolic BPs were categorized into 7 groups respectively (SBP: ≤ 110, >110-≤120, >120-≤130, >130-≤140, >140-≤150, >150-≤160, >160 mmHg; DBP: ≤ 60, >60-≤70, >70-≤80, >80-≤90, >90-≤100, >100-≤110, >110 mmHg).[126] Patients with an achieved SBP ≤110 mmHg, when compared to patients with an achieved SBP of >130-≤140, had higher baseline cardiovascular diseases or co-morbidities including: myocardial infarction (47.9% vs 30.1%), coronary artery bypass graft (32.9% vs 27.9%), stroke or transient ischemic attack (8.5% vs 7.1%), left ventricular hypertrophy (28.6% vs 19.8%), heart failure (15.0% vs 4.4%), and cancer (6.8% vs 3.2%). Similar trends were observed when comparing patients with a DBP of ≤60 mmHg vs >80-≤90 mmHg. These observations have repetitively been shown in other post-hoc analyses.[120, 127-129] In fact, when all these confounders were fully adjusted in the post-hoc analyses of the INVEST trial, the J-curve phenomenon disappeared.[126] The worse outcome in patients with lower BP is attributable not to a lower BP, but to the effect of concomitant diseases ("reverse causality"). The "reverse causality" has also been observed in another meta-analysis of 7 randomized trial of 40,233 patients using individual-patient data.[131] A J-shaped relationship was observed between DBP and mortality in both treated and untreated hypertensive subjects. There was also a J curve for non-cardiovascular mortality in the treated group (but not in the untreated subjects). It was concluded that the increased risk for events observed in patients with low BP was not related to antihypertensive treatment and was not specific to BP-related events. Poor health conditions leading to low BP and an increased risk for death probably explain the J-curve phenomenon.[131]

2). Low patient number: The patient number in the lowest BP group was generally small. In the INVSET host-hoc analysis, there were only 234 of 22,576 patients, who had SBP of ≤110 mmHg and only 176 patients had a DBP of ≤60 mmHg.[126] It would be difficult to draw conclusions from these data due to skewed distribution attributable to patient numbers.

6.2. Overall BP thresholds and targets

Table 10 shows the overall BP targets for various clinical conditions. These values are also BP thresholds. Treatment should be considered when BP readings, confirmed in the office or by ABPM or HBPM, are higher than these values (Please also see Fig. 1). The thresholds and targets for patients with diabetes, CHD, and proteinuric CKD (special patient groups) are 130/80 mmHg, lower than other patient groups, and lower than those suggested in the 2013 ESH/ESC hypertension guidelines[10] and in the 2014 JNC report.[11] The rationale for defining these thresholds and targets are described in the following sections.

6.3. Primary prevention

In patients aged less than 80 years of age, earlier hypertension studies such as the Medical Research Council (MRC) trial (age 35-64 years)[132] and the Felodipine Event Reduction (FEVER) trial (age 50-79 years)[133] showed that a final SBP <140 mmHg in the treatment group conferred a decreased incidence of cardiovascular events in comparison to that in the control group (138 mmHg versus 149 mmHg in the MRC

Table 10
Blood pressure targets.

Categories	Targets (mmHg)	COR	LOE
Primary prevention	<140/90	IIa	B
Secondary prevention			
Diabetes	<130/80	I	B
CHD	<130/80	I	B
Stroke	<140/90	I	A
CKD	<140/90	I	A
CKD with proteinuria	<130/80	IIb	C
Very elderly (age ≥80 years)	<150/90	IIa	B
Patients receiving antithrombotics for stroke prevention	<130/80	I	B

CHD = coronary heart disease; CKD = chronic kidney disease; COR = class of recommendation; LOE = level of evidence.

trial, and 137 mmHg versus 142 mmHg in the FEVER trial, respectively). Recently, the *Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica* (Cardio-Sis) trial (age ≥ 55 years) has shown that patients with tight BP control (SBP = 131.9 mmHg) had a better secondary cardiovascular outcome than those with usual BP control (SBP = 135.6 mmHg).[134] Subgroup analysis of FEVER trials disclosed that a SBP <140 mmHg resulted in a 39% reduction in stroke in patients without previous cardiovascular disease and diabetes ($p = 0.0016$), and a 44% reduction of stroke in patients aged >65 years ($p = 0.0001$).[135] Additional important information came from a recent publication from the Atherosclerosis Risk in Communities Study (ARIC).[113] In patients with hypertension but without CV disease at baseline, those with a treated BP in the range of 120-139 mmHg had the lowest CV events compared to those with a treated BP >140 mmHg, or a treated BP <120 mmHg.[113]

In the Hypertension Optimal Treatment (HOT) trial, patients were randomized into 3 groups, aiming to achieve DBPs ≤80, ≤85, or ≤90 mmHg.[136] The lowest risk of CV events was observed at a DBP of 82.6 mmHg, while a decrease of DBP below this level had no effect on the reduction of risk of cardiovascular complications. The study did not demonstrate any increase in cardiovascular events in the group of patients with a DBP <70 mmHg.[136]

Recommendation

- For patients <80 years of age and without diabetes, CHD, and proteinuric CKD, BP targets are <140/90 mmHg. (COR IIa, LOE B)

6.4. Patients with diabetes

In a prospective observation study in the UK (UKPDS 36), 4,801 patients were followed up for 10 years.[122] The incidence of clinical complications was significantly associated with SBP. Each 10 mm Hg decrease in mean SBP was associated with 12% reductions in the risk of any complication related to diabetes ($p < 0.0001$), 15% reduction in deaths related to diabetes ($p < 0.0001$), 11% reduction in myocardial infarction ($p < 0.0001$), and 13% reduction in micro-vascular complications ($p < 0.0001$). No threshold of risk was observed for any end point. The risk of all diabetes-related macro- and microvascular endpoints were lowest in those patients with a SBP less than 120 mm Hg, without any J-curve phenomenon.[122]

Several RCTs have been done to compare aggressive BP lowering vs standard BP lowering in patients with type 2 diabetes. In the SANDS trial, an aggressive SBP lowering strategy (<115 mmHg) was compared with a standard strategy (<130 mmHg), and the final values of SBP were 117 vs 129 mmHg.[137] There was a significant regression of carotid intimal medial thickness and greater decrease in left ventricular mass in the aggressive treatment group. However, clinical events did not differ significantly between groups.[137]

There were only 2 RCTs to prospectively evaluate CV outcomes with more aggressive vs conventional BP lowering in type 2 diabetes. In the UKPDS 38 trial, a tight control strategy aiming at a BP of <150/85 mm Hg was compared with less tight control strategy aiming at a BP of <180/105 mm Hg in 1148 hypertensive patients with type 2 diabetes (mean age 56, mean BP at entry 160/94 mm Hg).[138] After a median follow-up of 8.4 years, mean BP was significantly reduced in the group assigned to tight BP control (144/82 mm Hg) compared with the group assigned to less tight control (154/87 mm Hg) ($p < 0.0001$). There was significant reduction in almost all of the macro- and microvascular events: −24% in diabetes-related end points ($p = 0.0046$), −32% in deaths related to diabetes ($p = 0.019$), −44% in strokes ($p = 0.013$), and −37% in microvascular end points ($p = 0.0092$).[138] There was also a non-significant reduction in all-cause mortality. In the ACCORD trial, patients with type 2 diabetes were randomly assigned to intensive therapy, targeting a SBP <120 mmHg, or standard therapy, targeting a SBP<140 mmHg.[139] At 1 year, the mean SBP was 119.3 mmHg in the intensive-therapy group and 133.5 mmHg in the standard-therapy group. After a mean follow-up of 4.7 years, the annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; $p = 0.20$).[139] Non-fatal myocardial infarction was decreased by 13% in the intensive-therapy group ($p = 0.25$). Though there was no significant difference in total mortality, the annual rate of stroke, a pre-specified secondary outcome, was decreased by 41% ($p = 0.01$).[139] The serious adverse events was, however, more common in the intensive-therapy group (3.3% vs 1.3%, $p < 0.001$).[139] It should be known that the ACCORD trial was comparing BP targets of <120 mmHg vs <140 mmHg, not <130 mmHg vs 140 mmHg. While a SBP target <120 mmHg was not supported by the ACCORD trial, one cannot deny the intensive BP target of <120 mmHg was beneficial in reducing stroke risk, which is the most important cardiovascular event in East Asia. It should also be noted that there was no increase in the risk of myocardial infarction. In fact, non-fatal myocardial infarction was decreased by 13%, though not statistically significant.[139]

The HOT trial is the most important RCT to test optimal DBP in hypertensive patients. A total of 18,790 hypertensive patients from 26 countries, with a DBP between 100 mm Hg and 115 mm Hg (mean 105 mm Hg), were randomly assigned to 3 target DBP groups: <90, <85, and <80 mmHg.[136] The lowest incidence of major cardiovascular events occurred at a mean achieved DBP of 82.6 mmHg. Further reduction below this level was safe. In a subgroup analysis of patients with diabetes, there was a 51% reduction in major cardiovascular events, including myocardial infarction, stroke, and CV deaths, in target group <80 mm Hg compared with the group <90 mmHg ($p = 0.005$).[136] The percentages of previous cardiovascular diseases and risk factor were well balanced between the 3 groups. There was also a trend favoring a target of <80 mmHg in reducing total mortality (relative risk = 1.77 for a target of <90 mmHg, $p = 0.068$).[136]

Concerns about the risk of lowering BP in diabetic patients or in patients with high CV risk mainly came from post-hoc analyses of several RCTs, including INVEST, LIFE, ONTARGET, etc.[120, 127, 140] The INVEST trial was designed to compare mortality and morbidity outcomes in patients with hypertension and CHD treated with calcium antagonist strategy or a non-calcium antagonist strategy.[141] The result showed that the verapamil-trandolapril-based strategy was as clinically effective as the atenolol-hydrochlorothiazide-based strategy.[141] Seven years after the original publication, investigators of the INVEST trial reported a post-hoc analysis of the results of diabetic patients in the original INVEST trial.[120] Patients were categorized as having tight control if they could maintain their SBP< 130 mm Hg; usual control if it ranged from 130-139 mmHg; and uncontrolled if it was ≥140 mm Hg. Patients in the uncontrolled group had a significantly higher cardiovascular event rate than the usual-control group (adjusted hazard ratio 1.46; $p < 0.001$). However, little difference existed between those with tight control and those with usual control ($p = 0.24$). The all-cause mortality rate did not show significant difference either ($p = 0.06$), except when extended follow-up was included (HR = 1.15; $p = 0.04$). One should realize that this is an observational subgroup analysis. The baseline CV diseases and risk factors were un-balanced, and more common in the tight control group compared to the usual-control group (e.g. left ventricular hypertrophy 26% vs 22%; heart failure 8.8% vs 6.8%, smoking 48% vs 45%, and renal impairment 3.5% vs 2.4%; all $p < 0.05$). These measurable and other un-measurable confounders might explain why "lower-is-worse".[130] In fact, the rates of fatal- and non-fatal myocardial infarction, and fatal- and non-fatal stroke were still numerically lower in the tight control group.[120] Similar controversial observations were reported in the post-hoc analyses in the LIFE and the ONTARGET trials.[127, 140] Disproving a target of <130 mmHg can only be achieved by an RCT randomizing patients into different target SBP, including <130 mmHg, to balance the baseline co-morbidities and CV risk factors.

Several meta-analyses did support lower SBP targets for patients with diabetes.[142-144] It has been consistently shown in these meta-analyses that with a more intensive lowering of SBP to <130 mmHg, there was a significant decrease in stroke and nephropathy, and a non-significant decrease in myocardial infarction.[143, 144] The recent report from the Cochrane Database of Systematic Reviews did not support BP targets lower than the standard targets in people with elevated BP and diabetes.[145] Using tight SBP control to <130 mmHg was a major contributor in reducing microalbuminuria in a Taiwanese trial[146] and in reducing ESRD and death in a Hong Kong trial.[147] In a recent report from National Survey of Diabetes Health Promotion Institutes in Taiwan, using SBP<130 mmHg as a BP target,[148] the mortality rate in diabetics in Taiwan decreased in the recent decade.[149]

The BP target for diabetes is probably the most controversial issue in the management of hypertension. The 2013 ESH/ESC hypertension guidelines,[10] the 2014 JNC report,[11] and the hypertension guidelines of the American Society of Hypertension/International Society of Hypertension[150] all suggested a loosening of the target BP to <140/90 mmHg for diabetes. Standards of Medical Care in Diabetes-2014, proposed by the American Diabetes Association, suggested SBP targets of <140/80 mmHg, but a SBP target <130 mmHg may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.[151] Based on meta-analyses and the status of diabetes control in Taiwan, we set BP targets of <130/80 mmHg in this guideline, similar to recent hypertension guidelines from the Japanese Society of Hypertension,[152] the Global Guideline for Type 2 Diabetes from International Diabetes Federation Guideline Development Group,[153] and the 2014 Canadian Hypertension Guidelines.[154]

Recommendation

- For patients with diabetes, BP targets are <130/80 mmHg. (COR I, LOE B)

6.5. Patients with coronary heart disease

A large body of evidence suggests that the coexistence of hypertension and CHD has a substantial negative impact on a patient's clinical profile and prognosis. The report of the INTERHEART study involving 52 countries showed that compared with diabetes, hypertension resulted in a higher risk of acute myocardial infarction.[155] Hypertension accelerates the development and progression of atherosclerosis. Sustained elevation of BP can destabilize vascular lesions and precipitate acute coronary events. High BP per se can cause myocardial ischemia in the absence of CHD. Lowering both systolic and diastolic BP reduces ischemia and prevents adverse cardiovascular events in patients with CHD, partly by reducing myocardial oxygen demand. The overall aims of treating hypertension in patients with CHD are to lower BP, reduce ischemia, and prevent cardiovascular events and death.

There has been no trial prospectively evaluating and comparing different BP targets in patients with CHD. Three large RCTs (HOPE, EUROPA, and PEACE) have been done to evaluate the effects of ACE inhibitors versus placebo in CHD.[156-158] Re-analysis of these trials provided some clues for determining BP targets in CHD patients. Baseline BP of all these 3 trials were in the range of prehypertension (139/79, 137/82, and 133/78 mmHg for HOPE, EUROPA, and PEACE, respectively).[156-158] The final BP values were 136/76, 132/80, and 129/74 mmHg, respectively. Primary endpoints decreased by 22% in the HOPE trial ($p < 0.001$), 20% in the EUROPA trial ($p = 0.0003$), and 4% in the PEACE trial ($p > 0.05$). No J-curve phenomenon was observed. A combined analysis of these 3 trials indicated that ACE inhibitors significantly reduced all-cause mortality, non-fatal MI, and all stroke in patients with CHD, and no J-curve was found.[159] In the CAMELOT trial testing amlodipine and enalapril versus placebo in patients with CHD, BP was decreased from a baseline of 129/78 mmHg to 124/75 mmHg (all in the prehypertension range).[160] Primary endpoints was decreased by 31% ($p = 0.003$) in the amlodipine group.[160] In a sub-study of CAMELOT using intra-vascular ultrasound, patients with final BP ≥140/90 mmHg had a significant increase in atheroma

volume. Those who had a final BP in the range of 120-139/80-89 mmHg had no major change in atheroma volume. Interestingly, those with a final BP in the normal BP range (<120/80 mmHg) had a significant decrease in atheroma volume.[161] Finally, in the COURAGE trial which randomized patients with stable CHD, optimal medical therapy alone was compared to optimal medical therapy plus percutaneous coronary intervention (PCI) in normotensive patients (mean baseline BP 130/74 mmHg).[162] The optimal medical therapy regimen included long-acting beta blockers, calcium channel blockers (CCBs), and ACE inhibitor or ARB. The final BP was 122/70 mmHg. Interestingly, the addition of PCI to optimal medical therapy as an initial management strategy did not reduce the risk of death or myocardial infarction.[162] This study confirmed that, in the era of bare metal stent, optimal medical therapy including aggressive BP-lowering is as effective as PCI in the treatment of patients with stable CHD.

Three important meta-analyses supported aggressive BP lowering in patients with CHD. One meta-analysis of 15 RCTs, enrolling 66,504 participants with 276,328 patient-years of follow-up, has shown that in subjects with CHD a target SBP goal <130 mm Hg was associated with a significant decrease in heart failure (−27%) and stroke (−18%), together with a modest decrease in myocardial infarction and angina, when compared with a goal <140 mmHg.[163] Another meta-analysis of 25 trials consisted of 64,162 patients with history of cardiovascular diseases and a pre-treatment BP <140/90 mmHg.[164] Antihypertensive medications resulted in a 23% reduction in stroke, 20% reduction in myocardial infarction, 29% reduction in heart failure, 15% reduction in composite cardiovascular endpoints, 17% reduction in cardiovascular mortality, and a 13% reduction in total mortality (all $p < 0.05$). The most important meta-analysis supporting aggressive BP lowering consisted of 464,000 subjects from 147 trials.[165] It shows that for a given BP reduction by using BP-lowering drugs the risk of CHD and stroke decreased by a constant proportion irrespective of pretreatment BP and the presence or absence of existing cardiovascular diseases.[165] In patients with a pretreatment DBP of 70-74 mmHg or SBP of 110-119 mmHg, anti-hypertensive drugs decreased the risk of stroke and CHD, without any evidence of J-curve phenomenon.[165] A meta-analysis from the BP Lowering Treatment Trialists' Collaboration (BPLTTC) also supported a similar concept.[166] In the recent re-analysis using data from the INVEST trial, switching the BP target to a higher 150 mmHg, suggested by the recent 2014 JNC report,[11] was associated with worse outcomes in patients with CHD.[167]

Recommendation

- For patients with a history of CHD, BP targets are <130/80 mmHg. (COR I, LOE B)

6.6. Patients with a history of stroke

The decision to treat hypertension in patients with a history of stroke depends on the disease type and stage. The appropriate treatment of hypertension in acute stroke remains controversial. During the initial 24 hours in the acute stage of ischemic stroke, antihypertensive drugs should not be used unless BP is >220/120 mmHg.[168] In the CATIS trial, patients with acute ischemic stroke within 2 days, controlling BP with a target of <140/90 mmHg at 7 days did not reduce the likelihood of death and major disability at 14 days or hospital discharge.[169] But in patients with recent lacunar stroke, a tight control of BP to <130 mmHg reduced intracerebral hemorrhage compared to a target of 130−149 mmHg, though there was no differences in the rate of all stroke.[170] In patients who are eligible for acute reperfusion therapy, a BP level >185/110 mmHg should be lowered to <180/105 mmHg before reperfusion therapy.[171]

In patients with hemorrhagic stroke, cumulating evidence indicated that early BP lowering could reduce hematoma expansion. Therefore, in patients with acute hemorrhagic stroke, a SBP >180 mmHg can be decreased to <140 mmHg.[172] Most patients can receive antihypertensive treatment when BP is >140/90 mmHg after several days in the convalescent state.

For long-term hypertension control in patients with a history of stroke, BP control to the target level is the first consideration. There were 3 trials that enrolled patients who had experienced previous stroke.[156, 173, 174] Aggressive BP lowering reduced stroke and CV events, but the achieved BP was higher than 130 mmHg. The target BP level is <140/90 mmHg for patients with stable cerebrovascular disease.[173-175]

Recommendations

- For patients with a history of stroke, BP targets are <140/90 mmHg. (COR I, LOE A)
- During the initial 24 hours in the acute stage of ischemic stroke, antihypertensive drugs should not be used unless BP is >220/120 mmHg. (COR I, LOE C)
- In patients who are eligible for acute reperfusion therapy, a BP level >185/110 mmHg should be lowered to <180/105 mmHg before reperfusion therapy. (COR I, LOE B)
- In patients with acute hemorrhagic stroke, an SBP >180 mmHg can be decreased to <140 mmHg. (COR IIa, LOE B)
- After several days in the convalescent state of hemorrhagic stroke, most patients can receive antihypertensive treatment when BP is >140/90 mmHg. (COR I, LOE C)

6.7. Patients with chronic kidney disease

6.7.1. Threshold and target for patients with CKD in stages 2 - 4

Although CKD is the most common cause of secondary hypertension, hypertension can impair kidney function as well. If combined with proteinuria,[176] hypertension may result in a more rapid deterioration of kidney function in patients with CKD.[177] Patients with lower eGFR and higher albuminuria have an increased risks of all-cause mortality, CV mortality, and ESRD, though the risk seems to be higher in women than in men.[178] The stages of CKD have been defined and widely adopted.[179]

Most of the previous guidelines have recommended a BP target of <130/80 mmHg for patients with CKD, with or without diabetes.[9, 115, 180] However, there has been scant evidence to date that supported this target. In 3 trials enrolling patients with non-diabetic CKD, patients who were randomized to a target SBP of 125−130 mmHg did not have a reduced risk of ESRD or all-cause death, compared with patients who were randomized to a target BP of <140 mmHg.[181-183] Meta-analyses did not support a target of <130/80 mmHg, either.[184, 185] A recent analysis from a nationwide cohort of US veterans with prevalent CKD, using stricter SBP control to <120 mmHg, and compared to a target of 120−139 mmHg, was associated with higher all-cause mortality.[186] For patients with proteinuria, post-hoc analysis from MDRD indicated that the benefit of a lower BP target (<130/80 mm Hg) was limited to renal outcomes.[187] The results regarding proteinuria were not repeated in the primary analyses in either the AASK or REIN-2 trials.[182, 183]

Regarding the relation between BP control and diabetic nephropathy, three large trials showed that ARBs prevented the development of clinical proteinuria or delayed the progression of nephropathy in type 2 diabetes.[188-190] But the renoprotective effect was independent of the blood pressure lowering effect, and the achieved SBP was >130 mmHg. In diabetic patients with normal eGFR,[139] more intensive lowering of BP (119/67 vs. 134/73 mmHg) was associated with significant impairment of renal function.

Recommendations

- For patients with CKD stages 2 − 4 without albuminuria, BP targets are <140/90 mmHg. (COR I, LOE A)
- In patients with CKD stages 2 − 4, but with albuminuria, BP targets are <130/80 mmHg. (COR IIb, LOE C)

6.7.2. Threshold and target for patients with ESRD (stage 5 CKD)

In patients with ESRD, who have undergone multiple surgical procedures for vascular access in both arms, BP should be measured in the thighs or legs. Among patients receiving maintenance hemodialysis, observational studies have demonstrated a U-shaped relationship between BP and mortality.[191, 192] One study suggested that the increased mortality associated with low SBP was more pronounced among older patients and patients with diabetes.[193] There have been no RCTs to examine the BP targets for patients receiving dialysis. In general, BP goals should be individualized, based upon patients' cardiac and neurologic status, comorbidities, age, and other clinical conditions. The National Kidney Foundation K/DOQI guidelines suggested that pre-dialysis and post-dialysis BPs should be <140/90 and <130/80 mmHg, respectively.[194, 195]

Recommendations

- For patients with CKD stage 5, BP targets are <150/90 mmHg. (COR I, LOE C)
- For patients receiving maintenance dialysis, BP targets are <140/90 mmHg before dialysis, and <130/80 mmHg after dialysis, respectively. (COR IIb, LOE C)

6.8. Elderly patients

For patients over 60 years of age, 3 RCTs (SHEP, Syst-Eur, and Syst-China) randomized patients with isolated systolic hypertension (ISH) (baseline SBP >160 mmHg and DBP<90 or 95 mmHg).[123-125] Patients received chlorthalidone (SHEP) or nitrendipine (Syst-Eur and Syst-China) and achieved lower BP than those patients who took a placebo (143/68 vs 155/72 mmHg in the SHEP trial; 151/79 vs 162/85 mmHg in the Syst-Eur trial; and 151/81 vs 159/84 mmHg in the Syst-China trial).[123-125] These 3 trials consistently demonstrated a significantly lower risk of stroke and other cardiovascular events in treated patients compared to placebo.[123-125] However, 2 recent Japanese trials produced different findings.[196, 197] The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) trial randomized patients 65-85 years of age.[196] The achieved BP in the strict treatment group was lower than the mild treatment group (135.9/74.8 vs 145.6/78.1 mmHg), but there was no difference in cardiovascular outcomes. The Valsartan in Elderly Isolated Systolic Hypertension (VALISH) trial randomized patients from 70 to 84 years of age.[197] In that trial, strict BP control to 136.6/74.8 mmHg did not decrease CV events compared to moderate control group (142.0/76.5 mmHg). However, the patients enrolled in these 2 trials had very low event rate (1.1−1.2%/year in JATOS, 0.82−0.85%/year in VALISH), and might not represent real world conditions.[196, 197] Therefore, the 2009 Japanese HT guidelines adopted a target of <140/90 mmHg in the elderly,[198] instead of <150/90 mmHg which was suggested by these 2 trials.[196, 197] Furthermore, a subgroup analysis of the elderly patients in the FEVER trial in China showed a reduction of CV events by lowering SBP below 140 mmHg, compared to 145 mmHg.[135]

For patients aged ≥80 years of age, a subgroup meta-analysis of RCTs showed a significant reduction (−34%) in stroke, with an achieved SBP <150 mmHg.[199] Rates of major cardiovascular events and heart failure were also significantly decreased, by 22% and 39%, respectively.[199] However, there was no treatment benefit for cardiovascular death, and a non-significant increase of 6% (−5 to 18%) in all-cause mortality.[199] Recently, the Hypertension in the Very Elderly Trial (HYVET) randomized elderly patients ≥80 years of age and a baseline BP of 173.0/90.8 mmHg. The investigators aimed to achieve a target BP of 150/80 mmHg, using diuretic versus placebo, while ACE inhibitors could be added when required.[200] The final achieved BP was 144/78 mmHg in the treatment group, significantly lower than that in the control group (161/84 mmHg). The trial was prematurely stopped due to a significant decrease in total mortality in the treatment group (−21%, $p = 0.02$).[200] There were also a 30% reduction in the rate of fatal or nonfatal stroke ($p = 0.06$), a 39% reduction in the rate of death from stroke ($p = 0.05$), a 23% reduction in the rate of death from cardiovascular causes ($p = 0.06$), and a 64% reduction in the rate of heart failure ($p < 0.001$).[200] Fewer serious adverse events were reported in the active-treatment group.[200]

Recommendations

- For patients with an age ≥80 years, irrespectively of other clinical conditions, BP targets are <150/90 mmHg. (COR IIa, LOE B)
- For patients with an age <80 years and without diabetes, CHD, and proteinuric CKD, BP targets are <140/90 mmHg. (COR IIa, LOE B)

6.9. Patients receiving antithrombotic therapy for stroke prevention

Hypertension is closely related to the risk of hemorrhagic stroke.[201] In patients with both hypertension and atrial fibrillation, controlling BP is important if oral anticoagulants are to be used. Asians are especially vulnerable to oral vitamin-K antagonists for the treatment of atrial fibrillation.[202] While anti-coagulation was less intensively controlled and higher percentages of patients in Asians had international normalized ratio (INR) in the range of <2.0 when compared to that in Westerns, higher bleeding risk, especially higher intra-cranial hemorrhage, was observed in Asians in all recent RCTs.[203] In a prospective, multicenter, observational cohort study (BAT Study) of 4009 Japanese patients taking oral antithrombotic agents for cardiovascular or cerebrovascular diseases, the optimal cutoff BP level to predict impending risk of intracranial hemorrhage was ≥130/81 mmHg.[204] Lower SBP reduced intra-cranial hemorrhage in the PROGRESS trial, in which the lowest risk of intracranial bleeding was observed in participants with the lowest follow-up SBP (median, 113 mm Hg).[205] In most of the RCTs comparing non-vitamin K dependent oral anticoagulants (NOACs) versus warfarin, the baseline BP was well controlled (131/77 mmHg in the RE-LY trial, 131/80 mmHg in the ROCKET AF trial, and 130 mmHg in the ARISTOTLE trial).[206-208] So, predictors for intra-cranial hemorrhage did not include SBP, except in the ARISTOTLE trial in which the hazard ratio was 1.17 for every 10 mmHg increase in DBP ($p < 0.05$).[207]

Recommendation

- For patients receiving antithrombotic therapy for stroke prevention, BP targets are <130/80 mmHg. (COR I, LOE B)

7. Treatment

Treatment of hypertension should include non-pharmacological management and drug therapy. LSM is the essential component of non-pharmacological management. LSM is the initial treatment for the first 3 months in patients with uncomplicated stage 1 hypertension, or those with diabetes, CHD, or proteinuric CKD (special patient group) whose BP is between 130-149/80-89 mmHg. If BP is still above target, drug therapy should be initiated. For patients with stage 2 hypertension or above, including special patient group whose BP is above 150/90 mmHg, LSM should be combined with drug therapy. In general, LSM should be regarded as a complement to drug therapy rather than an alternative.[150]

7.1. Life style modification

LSM is an essential part in the prevention and management of hypertension.[209] It is generally believed that the BP-lowering effect of LSM is equivalent to drug monotherapy.[210] If applied appropriately, LSM can delay drug therapy in patients with stage 1 hypertension, allowing reduction in the number and doses of anti-hypertension drugs. The major limitation of LSM lies in the poor consistency and adherence.[211] LSM can be summarized as **S-ABCDE**: **S**odium restriction, **A**lcohol limitation, **B**ody weight reduction, **C**igarette smoke cessation, **D**iet adaptation, and **E**xercise adoption (Table 11).

Table 11
Life style modification for managing hypertension (**S-ABCDE**).

Changes	Recommendation	Expected benefits in SBP reduction	COR	LOE
Sodium restriction	2.0–4.0 gm/day	2.5 mmHg/1 gm sodium reduction	I	B
Alcohol limitation	Men: <30 gm/day ethanol Women: <20 gm/day ethanol	2–4 mmHg	I	B
Body weight reduction	BMI: 22.5–25.0	1 mmHg/per 1 kg reduction	I	B
Cigarette smoking cessation	Complete abstinence	No independent effect	I	C
Diet adaptation	**DASH** diet: rich in fruits and vegetables (8–10 servings/day), rich in low-fat dairy products (2–3 servings/day), and reduced in saturated fat and cholesterol	10–12 mmHg	I	A
Exercise adoption	Aerobic, at least 40 minutes/day, and at least 3-4 days/week	3–7 mmHg	I	A

BMI = body mass index; COR = class of recommendation; DASH = Dietary Approaches to Stop Hypertension; LOE = level of evidence; SBP = systolic blood pressure. (Modified from Chiang et al.[9] with permission.)

7.1.1. Sodium restriction

The role of sodium in cardiovascular diseases has recently become very controversial. For BP control, it is generally agreed that higher sodium intake increases BP. In the recent PURE study of 102,216 adults from 18 countries, the 24-hour sodium and potassium excretion were measured, using a single fasting morning urine specimen.[212] It was shown that for each 1-gram (gm) increment in estimated sodium excretion, SBP increased by 2.11 mmHg, and DBP by 0.78 mmHg.[212] The slope of association was steeper for persons with hypertension (2.49 mmHg per gm) than for those without hypertension (1.30 mmHg per gm, $p < 0.001$ for interaction) and was steeper with increased age (2.97 mmHg per gm at >55 years of age, 2.43 mmHg per gm at 45 to 55 years of age, and 1.96 mmHg per gm at <45 years of age; $p < 0.001$ for interaction). Potassium excretion was inversely associated with SBP, with a steeper slope of association for persons with hypertension than for those without it ($p < 0.001$) and a steeper slope with increased age ($p < 0.001$).[212] The PURE study is the most robust one to confirm that increased intake of sodium is related to an increase in BP. Sodium restriction is especially effective in patients with resistant hypertension[213] and in patients with metabolic syndrome in Asia.[214]

Intensive lowering of sodium intake has been proposed by major scientific societies. In the recent 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk,[215] it was proposed that reducing sodium intake that achieved a mean 24-hour urinary sodium excretion of approximately 2.4 gms/day, relative to approximately 3.3 gms/day, lowers BP by 2/1 mm Hg, and reducing sodium intake that achieved a mean 24-hour urinary sodium excretion of approximately 1.5 gms/day lowers BP by 7/3 mm Hg.[215] This statement was supported by a recent report from the NUTRICODE investigators.[216] The NUTRICODE investigators collected data from surveys on sodium intake as determined by urinary excretion and diet in persons from 66 countries, and quantified the global consumption of sodium. The effects of sodium on BP were calculated from data in a new meta-analysis of 107 randomized interventions.[216] The effects of BP on cardiovascular mortality were calculated from a meta-analysis of cohorts.[216] It was found that in 2010 the estimated mean level of global sodium consumption was 3.95 gms per day. Globally, 1.65 million deaths from cardiovascular causes per annum were attributed to sodium intake above the reference level 2.0 gms of sodium per day.[216]

A contradictory report came from a recent publication from another contemporary report from PURE investigators.[217] The PURE investigators obtained morning fasting urine samples from 101,945 persons in 17 countries, and found the mean estimated sodium excretion was 4.93 gms per day. As compared with an estimated sodium excretion of 4.00 to 5.99 gms per day (reference range), a higher estimated sodium excretion (≥7.00 gms per day) was associated with an increased risk of the composite outcome (death and major CV events) (odds ratio, 1.15; $p < 0.05$).[217] Interestingly, as compared with the reference range, an estimated sodium excretion that was below 3.00 gms per day was also associated with an increased risk of the composite outcome (odds ratio, 1.27; $p < 0.05$).[217] Thus, there is a J-shape association between sodium intake and cardiovascular disease or death, and an estimated sodium intake between 3 gms per day and 6 gms per day was associated with a lower risk of death and cardiovascular events than either a higher or lower estimated level of intake.[217] This J-shape association has been reported in other studies,[218] and a recent meta-analysis.[219] In fact, in a prospective cohort study in Taiwan a significant J-shape relationship between urinary sodium excretion and the risk of hypertension has also been observed, and the nadir of the J-shape was around 100 mmol (2.4 gms)/day.[220]

The most important long term intervention trial for effects of dietary sodium reduction on cardiovascular disease outcomes came from TOHP I and TOHP II trials.[221] In these trials, the risk of cardiovascular event was 30% lower among those in the intervention group.[221] The final level of achieved daily sodium excretion (or intake) was 2.3 gms/day for TOHP I and 3.2 gms/day for TOHP II.[221] Thus, the optimal target for sodium restriction is still controversial, but an optimal level will be around 2.0-4.0 gms/day. Too aggressive sodium restriction to <2.0 gms/day should be avoided. Supplemental calcium, potassium, or magnesium have been proposed to lower BP, but data are not entirely consistent.[222]

Recommendations

- For controlling hypertension, the optimal daily sodium consumption is 2.0-4.0 gms/day. (COR I, LOE B)
- Too aggressive sodium restriction to <2 gms/day may be harmful. (COR III, LOE B)

7.1.2. Alcohol limitation

Excessive drinking is associated with high BP.[223] In the PATHS trial investigating the effects of an alcohol treatment program on BP, there was a 1.2/0.7 mmHg greater reduction for every 1.3 drink/day difference.[224] In a meta-analysis of 15 RCTs with a total of 2,234 participants, alcohol reduction was associated with a significant reduction of 3.31 mmHg in SBP and 2.04 mmHg in DBP.[225] It is generally agreed that alcohol intake should be limited to <30 gms/d in men and <20 gms/d in women.[222]

Recommendation

- For controlling hypertension, the daily intake of alcohol should be limited to <30 gms/d in men and <20 gms/d in women. (COR I, LOE B)

7.1.3. Body weight reduction

Obesity is related to increased cardiovascular mortality. A meta-analysis of 25 RCTs with 4,874 participants was performed to estimate the effect of weight reduction on BP.[226] A net weight reduction of −5.1 kilogram (kg) reduced SBP by 4.44 mmHg and DBP by 3.57 mmHg.[226] SBP was reduced by 1.05 mmHg, and DBP by 0.92 mmHg per kg of weight loss.[226] The relationship of BMI with overall mortality shows a U-shape phenomenon. In the Prospective Studies Collaboration of 57 prospective studies with 894,576 participants, mostly in

western Europe and North America, mortality was lowest in the range of 22.5-25.0 kg/m^2.[227] Similarly, in a prospective cohort study of 224,064 Chinese men followed up for 15 years, the association between BMI and all-cause mortality was U-shaped with the lowest mortality at 22.5-25.0 kg/m^2.[228] Interestingly, an intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes.[229]

Recommendation

- For controlling hypertension, the ideal BMI is 22.5-25.0/m^2. (COR I, LOE B)

7.1.4. Cigarette smoke cessation

Stopping smoking did not reduce BP,[230] though smoking may cause an acute increase in heart rate and BP. Smoking is the most important preventable risk factor in myocardial infarction, and smoking cessation is one of the most important causes of reduced stroke death in Taiwan in the recent decade.[231] Therefore, cessation in cigarette smoking should be an integral part of the whole LSM in the management of hypertension.

Recommendation

- For the purpose of reducing overall cardiovascular risk, cessation of cigarette smoking is an integral part of LSM. (COR I, LOE C)

7.1.5. Diet adaptation

The DASH (Dietary Approaches to Stop Hypertension) diet is high in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts; it is low in sweets, sugar-sweetened beverages, and red meats.[232] The DASH diet reduced SBP and DBP by 11.4 and 5.5 mmHg, respectively, in hypertensive persons.[232] The combination of DASH and low sodium diet could reduce the SBP by 11.5 mmHg compared with the combination of control and high sodium diet.[233] The combination of DASH diet and a weight management program was even more effective than the usual diet controls, in which BP was reduced by 16.1/9.9 mmHg.[234] Better adherence to the DASH diet was significantly associated with lower CHD and stroke.[235, 236]

Recommendation

- For controlling hypertension and reducing overall cardiovascular risk, the DASH diet should be an integral part of LSM. (COR I, LOE A)

7.1.6. Exercise adoption

In two meta-analyses, aerobic exercise was associated with a significant reduction in mean SBP (−3.8 and −6.9 mmHg, respectively) and DBP (−2.6 and −4.9 mmHg, respectively).[237, 238] Typical interventions shown to be effective in lowering BP include aerobic physical activity of, on average, at least 12 weeks duration, 3 to 4 sessions per week, lasting on average 40 minutes/session, and involving moderate-to-vigorous intensity physical activity.[215]

Recommendation

- For controlling hypertension, regular aerobic exercise should be an integral part of LSM. (COR I, LOE A)

7.2. Principles of drug therapy

Drug therapy should be initiated in patients with stage 1 hypertension if their BP is still above targets, after 3-month LSM. For patients in the special patient group (diabetes, CHD, or proteinuric CKD), drug therapy should be initiated if BP is still >130/80 mmHg after 3-month LSM. For patients with stage 2 hypertension or above, including special patient group whose BP is above 150/90 mmHg, drug therapy should be started, concomitant with LSM as initial management.

The main benefits of antihypertensive agents are derived from lowering of BP *per se*, and are generally independent of classes of drugs.[239, 240] Substantial data has come from the largest meta-analysis of 147 trials consisting of 958,000 people.[165] With the exception of the extra protective effect of beta-blockers given shortly after a myocardial infarction and the additional effect of CCBs in preventing stroke, all classes of BP lowering drugs have similar effects in reducing CHD events and stroke for a given reduction in BP. Pleiotropic effects were not observed.[165] For every 10 mmHg difference in SBP or every 5 mmHg difference in DBP compared with placebo, a 22% reduction in CHD and a 41% reduction in stroke were observed.[165] In a recent meta-analysis of 18 trials of 23,215 Asian patients, a 10 mmHg reduction in SBP was associated with a 39.5% reduction in composite CV endpoints, and a 30% reduction in stroke, regardless of drug class.[241]

Some RCTs included patients with specific diseases or conditions, so it has been proposed that one drug or certain combinations of drugs might be superior to other drugs or other combinations in reducing stroke,[242] end-stage renal disease,[190] or cardiovascular events.[243 244] Some recommendations for different clinical conditions were shown in Table 12. Because more than 70% of patients require more than 1 drug to reach targets, it seems more important to choose appropriate combination of drugs, instead of chasing a single drug in our daily practice.

Based on data from a meta-analysis of 354 randomized, double-blind, placebo-control trials comprising 40,000 drug-treated patients and 16,000 placebo-treated patients,[245] we have proposed a “Rule of 10” (Fig. 3) and a “Rule of 5” (Fig. 4) to predict the reduction in SBP and DBP, respectively, from mono-therapy or combination therapy.[9] These rules can be used to predict how many drugs are needed to achieve BP targets. With a standard dose of any one of the 5 major classes of anti-hypertensive agents, one can anticipate approximately a 10-mmHg decrease in SBP (Rule of 10) (Fig. 3, Panel A) and a 5-mmHg decrease in DBP (Rule of 5) (Fig. 4, Panel A) (all after placebo-subtraction), when the baseline pre-treatment BP is 154/97 mmHg.[245] The efficacy of BP lowering depends on the pre-treatment BP. For every 10 mmHg above 154 mmHg in baseline SBP or above 97 in the DBP mmHg, a further decrease of 1.0 mmHg in SBP and 1.1 mmHg in DBP can be observed. For example, one can anticipate a 11-mmHg

Table 12
Recommended drugs.

Clinical conditions	Drugs
Target organ damage	
Left ventricular hypertrophy	ARB
Microalbuminuria	ACEI, ARB
Asymptomatic atherosclerosis	CCB
Clinical events	
History of myocardial infarction	BB, ACEI, ARB
Coronary Heart Disease	BB, ACEI, ARB, CCB (long-acting)
Heart failure	Thiazide diuretic, loop diuretic, BB, ACEI, ARB, MRA
Stroke	ACEI, ARB, Thiazide diuretic, CCB,
Chronic kidney disease	ACEI, ARB, loop diuretic
Peripheral artery disease	CCB
Diabetes mellitus	ACEI, ARB, DRI
Associated conditions	
Isolated systolic hypertension	Thiazide diuretic, CCB, ARB
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; MRA = mineralocorticoid receptor antagonist. (Modified from Chiang et al.[9] with permission.)

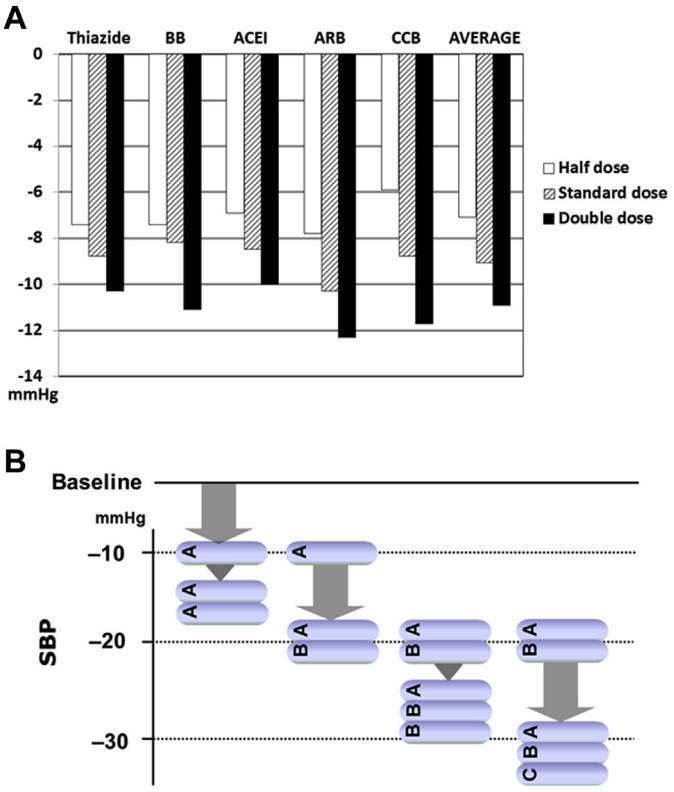

Fig. 3. Rule of 10. **Panel A**. Comparison of effects of incremental doses of 5 classes of anti-hypertension drugs on reducing systolic blood pressure (SBP) at a baseline SBP of 154 mmHg. On average, there is a 10-mmHg decrease in SBP by a standard dose of any kind of the 5 classes of drugs (Rule of 10). Doubling the dose of any drug brings out only a 2-mmHg incremental decrease in SBP. **Panel B**. Combination of drugs from different classes is more effective in reducing SBP than increasing doses of the same drug. The combination of 2 drugs from different classes decreases SBP by 20 mmHg (10 + 10 = 20); whereas doubling doses decreased SBP further by 2 mmHg only (10 + 2 = 12). To decrease SBP by 30 mmHg, 3 drugs of different classes are generally needed. Data were modified from article by Laws et al.[245]

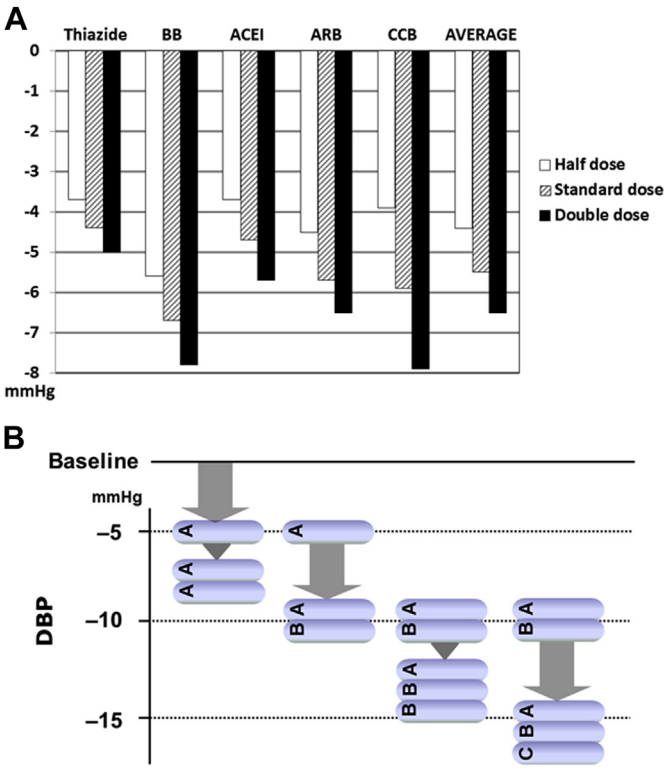

Fig. 4. Rule of 5. **Panel A**. Comparison of the effects of incremental doses of 5 classes of anti-hypertension drugs on reducing diastolic blood pressure (DBP) at a baseline DBP of 97 mmHg. On average, there is a 5-mmHg decrease in DBP by a standard dose of any kind of the 5 classes of drugs (Rule of 5). Doubling the dose of any drug brings out only a 1-mmHg incremental decrease in DBP. **Panel B**. Combination of drugs from different classes is more effective in reducing DBP than increasing doses of the same drug. The combination of 2 drugs from different classes decreases DBP by 10 mmHg (5 + 5 = 10); whereas doubling doses decreased DBP further by 1 mmHg only (5 + 1 = 6). To decrease DBP by 15 mmHg, 3 drugs of different classes are generally needed. Data were modified from article by Laws et al.[245]

decrease in SBP and a 6-mmHg decrease in DBP if the pretreatment BP is 164/107 mmHg. When the doses of the same drug were doubled, there was only a 2-mmHg incremental decrease in SBP (Fig. 3, Panel A and B) and a 1-mmHg incremental decrease in DBP (Fig. 4, Panel A and B).[245] Preferably, when 2 drugs in standard doses but with different mechanisms are taken together, the decrease in BP is the sum of the decrease of the individual agents (approximately 20 mmHg in SBP and 10 mmHg in DBP) (Fig. 3 and 4, Panels B).[245, 246] Similarly, if a 30-mmHg decrease in SBP or a 15-mmHg decrease in DBP is to be obtained, a 3-drug combination may be needed (Figs. 3 and 4, Panels B).[245]

When drug therapy is considered after a 3-month trial of LSM or in patients with stage 2 hypertension or above, a strategy called "**PROCEED**" is suggested.[9] First, Previous unfavorable experience of the individual patient with a given class of antihypertensive drug should be carefully explored, because adverse events are the most important cause of nonadherence. Adverse events are inevitable, or even unpredictable, because they may have a psychological basis and are frequently reported during placebo treatment. Great effort should be advocated to limit drug-related side effects. Drug-

related side effects are usually dose-dependent for diuretics, beta-blockers, and CCBs, whereas there is little or no dose-dependent increase in side effects with ACE inhibitors and ARB.[245] 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 target. Third, Organ damage, even sub-clinical, or previously associated cardiovascular conditions may favor certain classes of drugs or certain combinations (Table 12). Fourth, Contraindications or unfavorable conditions should be examined (Table 13). Fifth, an Expert's or doctor's judgment is of paramount importance in managing patients. Any guideline can only serve as reference in treating individual patient. Sixth, Expenses or cost may be taken in account. However, the cost issue should never predominate over efficacy, tolerability, and protection of the patient. Finally, Delivery and compliance issue is the key to successful treatment of hypertension. WHO has estimated that 50–70% of patients did not take their antihypertensive drugs as prescribed and has identified poor adherence as the most important cause of uncontrolled hypertension. Physicians should include patients as an essential part of the whole treatment program in hypertension and communicate with individual patients.

The optimal time for taking anti-hypertensive drugs has been a matter of debate for decades. Morning administration of antihypertensive drugs was routinely performed in the past. However, it has been recently more common to switch to a bedtime administration. In the MAPEC trial, 3344 subjects were prospectively randomized to ingest all their prescribed hypertension medications upon awakening or ≥1 of them at bedtime, for a follow-up of 5.6 years.[43] The nighttime BP was more effectively decreased by bedtime administration of drugs. More importantly, asleep BP was the most significant predictor of event-free survival. In fact, the same investigators have demonstrated earlier that patients who took ≥1 antihypertensive drug at bedtime showed a significant reduction in the 24-hour mean of SBP and DBP.[247] The reduction was more prominent during nighttime. The diurnal/nocturnal BP ratio was significantly increased and the prevalence of non-dipping was reduced.[247] This finding was supported by 2 studies using ARB at bedtime.[248, 249] The nocturnal BP is significantly better controlled by bedtime administration as compared with morning administration, without any loss in efficacy during diurnal active hours.[250] Studies on surrogate endpoints, such as urinary albumin excretion, also demonstrated that switching the time that hypertensive drugs are taken (from morning to evening) was beneficial in patients with CKD.[251, 252] In fact, the American Diabetes Association has proposed the administration of one or more antihypertensive medications at bedtime.[151] Since nighttime BP has been shown to be a more important predictor of cardiovascular risk than diurnal mean values, the bedtime administration of anti-hypertensive drugs may be a correct way to decrease future cardiovascular events. Several classes of medications, such as ACE inhibitors,[156, 250] ARB,[249] or CCB,[124] have been proven to be safe and effective for bed-time administration. There has been no evidence supporting the use of diuretics or beta-blockers at bedtime.

Another important issue is how soon we should control BP to targets. Important information came from the VALUE trial.[253] The valsartan-based group had similar CV outcomes as the amlodipine-based group at the end of the trial. There were 3.8 mmHg differences in SBP at 3 months, and they were higher in the valsartan-group. Except for heart failure admission, the primary endpoints, stroke, and all-cause death were significantly higher in the valsartan group than in the amlodipine group in the first 3 months.[253] The BP differences became insignificant after 3 months, and all the differences in these CV endpoints did not show any difference thereafter. The immediate responders, defined as those who could achieve a 10-mmHg decrease in the first month of treatment, had lower CV events than non-immediate responders.[254] Similar findings were reported from the SCOPE trial.[255] Patients in the placebo group received placebo for the first 3 months, and eventually had a higher incidence of non-fatal stroke compared with patients in the treatment group who received candesartan immediately after randomization.[255] We therefore suggest it appropriate to control BP to targets at 3 months, and preferably within 1 month, for high-risk patients.

Table 13
Contraindications or unfavorable conditions.

	Contraindications	Unfavorable conditions
Thiazide diuretics		Gout, hypokalemia, hyponatremia, metabolic syndrome, pregnancy
BB	Bronchial asthma, sick sinus syndrome, 2nd and 3rd degree AV block	Peripheral artery disease, Metabolic syndrome
CCB (non-DHP)	Sick sinus syndrome, 2nd and 3rd 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
MRA	Hyperkalemia	
Alpha-blocker		Systolic heart failure

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CCB = calcium channel blocker; DHP = dihydropyridine; DRI = direct renin inhibitor; MRA = mineralocorticoid receptor antagonist. (Modified from Chiang et al.[9] with permission.)

7.3. Monotherapy

There are 5 major classes of anti-hypertension drugs: diuretics, beta-blockers, CCBs, ACE inhibitors, and ARBs. As previously mentioned, every kind of antihypertension drugs can be used as the first line medications, per physician's discretion. The NICE clinical guideline on hypertension from UK (http://pathways.nice.org.uk/pathways/hypertension) has recently abandoned the first-line use of diuretics and beta-blockers. The 2014 JNC report dismissed beta-blockers as first-line therapy.[11]

Nevertheless, the 2013 ESH/ESC hypertension guidelines keep all 5 major classes of drugs in their recommendations.[10] There are contraindications and unfavorable conditions when using these different classes of drugs (Table 13).

7.3.1. Diuretics

7.3.1.1. Thiazides and thiazide-like diuretics. Thiazide diuretics and thiazide-like diuretics (e.g. indapamide, chlorthalidone, etc) remain essential in the treatment of hypertension. The ALLHAT trial has confirmed the equivalent effect of chlorthalidone in reducing CHD as compared to CCB and ACE inhibitor.[256] In fact, chlorthalidone is the best drug in reducing heart failure in the ALLHAT trial.[256] The efficacy of thiazide diuretic in reducing heart failure has also been confirmed in a large meta-analysis of 147 RCTs.[165] When BP cannot be controlled with ACE inhibitors or ARBs, low-dose thiazide diuretics are usually very effective as add-on drugs. Hypertension cannot be called "resistant" if a diuretic was not included in the medications.[257] In a recent analysis from the ACCOMPLISH trial, thiazide-based treatment provided less cardiovascular protection in normal weight than in obese patients, but amlodipine-based therapy was equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension.[258] Since averaged BMI in Asians are lower than in Caucasians, thiazide diuretics might be less effective in Asians as well. But double-blind RCT to compare diuretics versus CCB in terms of cardiovascular outcomes has not been performed in Asia.

A major concern regarding the use of thiazide diuretics is the plethora of metabolic side effects.[259] Thiazides reduced potassium, increased uric acid, and increased total cholesterol and triglycerides.[260] Hypokalemia was not uncommon in patients receiving thiazide diuretics. In the ALLHAT trial, the relative risks of hypokalemia were 10.61 compared with the lisinopril group and 4.50 compared with the amlodipine group. The prevalence of hypokalemia (<3.5 mmol/l) was reported as varying between approximately 7.2% and 8.5% at doses of 12.5-25 mg of chlorthalidone,[261, 262] and up to 56% with 50 mg hydrochlorothiazide.[263] Thiazide-induced hypokalemia was more than twice as high in men as in women, and was doses and age-related.[264] The combination of triamterene would not attenuate this side effect.[264]

The annual incidence of thiazide-induced hyponatremia (≤130 mmol/L) is about 14%.[265] Thiazide exposure was associated with an almost 5 times higher risk of hyponatremia (≤135 mmol/L) than no exposure.[266] The risk did not differ between male and female. Interestingly, the risk of hyponatremia due to thiazide exposure decreased with older age, and higher BMI.[266] The highest risk of hyponatremia with thiazide exposure was seen within the highest eGFR quartile.[266] Low-dose thiazide is preferred in the treatment of hypertension to avoid these electrolyte abnormalities.

In a recent meta-analysis, thiazide diuretic users had the highest potential to develop new-onset diabetes.[267] 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 have significantly less CHD events in chlorthalidone group compared with the amlodipine group in the 4 to 8-year follow-up period of ALLHAT, in spite of an increase in diabetes rate.[268] The argument is that 4 to 8-year follow-up may be too short to observe the negative impact of new-onset diabetes. In a long-term cohort study of treated hypertension patients for a follow-up of up to 16 years, the occurrence of new diabetes portends a risk for subsequent cardiovascular disease that is not dissimilar from that of previously known diabetes.[269] In a 28-year follow-up of treated hypertension patients, new-onset diabetes carries a significantly higher cardiovascular risk.[270] The mean observation time from onset of diabetes to the first stroke was 9.1 years, and it was 9.3 years to the first myocardial infarction.[270] Another important concern about diuretics is the adverse events. In a meta-analysis of 354 trials, the dose-dependence increase in the adverse effect of diuretic is the most severe compared to other drugs.[245] A dose more than 25 mg/d of hydrochlorothiazide is considered to be a high dose and is associated with a significant increase in side effects including metabolic derangement. According to recent data from Canada, the long-term persistence rate was lowest for users of diuretics, compared with users of other antihypertensive drugs.[271]

Are all thiazide diuretics equally effective in lowering BP? In a study comparing hydrochlorothiazide 50 mg/d with chlorthalidone 25 mg/d, the latter provided a greater decrease in ambulatory SBP, with the greatest difference occurring at nighttime.[272] From a retrospective observational cohort study from the Multiple Risk Factor Intervention Trial (MRFIT) data set, chlorthalidone displayed significantly lower SBP, lower total cholesterol, lower LDL-C, lower potassium, and higher uric acid over time compared with hydrochlorothiazide.[273] The data for head-to-head comparison of indapamide versus other thiazide diuretics could not be found.

For effects on cardiovascular outcomes, there is no RCT for head-to-head comparison of different thiazides. RCTs testing of thiazides versus comparators had neutral or worsening effects, as shown in the ASCOT (benzofluthiazide)and the ACCOMPLISH (hydrochlorothiazide) trial.[243, 244] Indapamide has outperformed placebo in some RCTs, such as the PROGRESS trial,[174] the ADVANCE trial,[274] and the HYVET trial.[200] Chlorthalidone was quite successful in RCTs, such as the SHEP trial and the ALLHAT trial.[123, 256] Based on data from meta-analysis of MRFIT, chlorthalidone users had significantly fewer cardiovascular events compared with hydrochlorothiazide users ($p = 0.0016$).[273] In another meta-analysis, chlorthalidone outperformed hydrochlorothiazide in reducing cardiovascular events, after correction of difference in BP.[275] These data suggested that chlorthalidone may be the preferred thiazide-type diuretic for hypertension in patients at high risk of cardiovascular events.[273] Until a head-to-head RCT is available, it is too early to reach a final conclusion.

7.3.1.2. Mineralocorticoid receptor antagonists. Aldosterone and its receptor have been shown to play important roles in the

pathogenesis of hypertension and hypertension-related cardiovascular outcomes.[276] Many reports have demonstrated that circulating aldosterone levels are positively associated with both incident[277] and resistant hypertension[278] (see definition below), as well as obstructive sleep apnea- and obesity-related hypertension.[279, 280] In addition, the prevalence of primary aldosteronism in hypertensive patients was reported to increase along with hypertension stages.[281] Hypertensive patients in the real world practice are less commonly to be treated with aldosterone antagonists, given that almost 15-20% of stage II-III patients have aldosterone hypersecretion.[281] Importantly, patients with higher aldosterone levels but with similar levels of BP still had significantly higher rates of myocardial infarction, stroke and atrial fibrillation.[282]

According to currently available evidence, aldosterone antagonists are beneficial for hypertensive patients with one of the following two conditions: 1) primary aldosteronism; 2) resistant hypertension. Solid evidence has also shown that aldosterone antagonists significantly reduce mortality in patients with severe systolic heart failure,[283] or with prior myocardial infarction,[284] and even in patients with mild systolic heart failure.[285] However, the enrolled patients in these clinical trials were basically normotensive and there has been no data revealing outcomes for hypertensive subgroup, making it difficult to see whether aldosterone antagonists would add additional benefits to hypertensive patients with systolic heart failure when standard heart failure treatment has been provided. On the other hand, the effects of spironolactone on heart failure with preserved ejection fraction patients, who are characterized by a high prevalence rate (>90%) of hypertension, have recently been evaluated in a small-scale study (total 422 patients).[286] There was significant improvement in left ventricular diastolic function, left ventricular remodeling, and N-terminal-proBNP levels, but no benefit on clinical symptoms and outcomes.[286] In a similar but larger scale randomized clinical trial in patients with heart failure and a preserved ejection fraction (TOPCAT), treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome including death from cardiovascular causes.[287]

Treatment-resistant hypertension (TRH) is defined in a recent review as high BP (≥140/90 mmHg), resistant to a treatment regimen that includes proper lifestyle modification plus a diuretic and two other antihypertensive agents of different classes at their optimal doses.[288] Among patients with resistant hypertension, the prevalence of primary aldosteronism is around 17 to 23%.[278, 281] Other possible reasons accounting for high aldosterone levels in patients with resistant hypertension are a rebound after volume reduction by diuretics[289] or an escape from early reduction associated with RAS blockade.[290] Overwhelming evidence has confirmed that aldosterone antagonists, even at low doses, were effective in resistant hypertension.[291–296] Adding spironolactone 25 mg/day is more effective in BP reduction than adding ramipril 5 mg/day to a background irbesartan treatment in resistant hypertension.[296] In patients with resistant hypertension, who had received the combination of irbesartan, hydrochlorothiazide, and amlodipine, adding 25 mg spironolactone was more effective than adding 5 mg ramipril in reducing daytime ABPM (−19/11 vs −8/7 mmHg, $p = 0.0003$) and left ventricular mass index.[297] In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) substudy, spironolactone was an effective add-on drug after treatment with two or more antihypertensive combination.[291] ASPIRANT (Addition of Spironolactone in Patients with Resistant Arterial Hypertension Trial) is currently the only double-blind RCT to evaluate the effect of aldosterone antagonist in resistant hypertension.[295] With a high percentage of background RAS blockade coverage (76.5% and 46.5% with ACE inhibitors and ARB, respectively), the addition of spironolactone decreased SBP by 9.8 mmHg on ABPM and also significantly improved microalbuminuria.[295] A similar BP reduction in ABPM was observed in another RCT involving patients with resistant hypertension and diabetes mellitus when spironolactone was added to a triple-drug regimen containing either ACE inhibitors or ARBs.[298] Eplerenone, a more selective mineralocorticoid receptor antagonist without the antiandrogenic effects, was associated with a 10-mmHg reduction in SBP in ABPM, when used as a fourth-line agent at the dose of 50 mg twice daily.[299] The antihypertensive associations of both spironolactone and eplerenone were observed even in the presence of normal serum aldosterone levels.[295, 299]

Although aldosterone antagonists are effective add-on drugs for resistant hypertension, caution has to be taken when adding them to background RAS inhibitors. The occurrence of hyperkalemia and the possibility of rapid reduction of eGFR should be carefully monitored. The addition of aldosterone antagonists is generally contraindicated if serum potassium levels >5.0 meq/l, and should be used with caution if eGFR is less than 30 ml/min/1.73 m^2.[288]

7.3.1.3. Loop diuretics. Loop diuretics are less effective than thiazide diuretics in lowering BP, so that their major use is in edematous patients with congestive heart failure, and in patients with more severe CKD (eGFR < 30 ml/min/1.73 m^2).[300] Loop diuretics should not be used as first-line therapy in hypertension since they have generated no outcome data. They can be combined with thiazide-type diuretics.[300]

7.3.1.4. Other potassium-sparing diuretics. Other potassium-sparing diuretics, such as amiloride and triamterene, block the epithelial sodium channel. They are widely prescribed for hypertension as a second line drug in patients taking other diuretics (e.g. thiazide diuretics). However, there has been no trial evaluating the BP lowering efficacy of these drugs as monotherapy in patients with primary hypertension. Even in trials evaluating the efficacy of low doses of amiloride and triamterene as a second drug, BP was not reduced.[300] Therefore, these agents should not be routinely used.

7.3.2. Beta-blockers

Whether beta-blockers should be placed as one of the first-line drugs for hypertension is probably the most controversial among major hypertension guidelines.[10, 11] (http://pathways.nice.org.uk/pathways/hypertension) The ESH/ESC 2013

hypertension guideline maintained its position to categorize beta-blocker as a first-line drug.[10] However, the 2014 JNC report rejected it as a first-line drug.[11] The 2014 NICE hypertension guides put beta-blockers as step-4 drugs. (http://pathways.nice.org.uk/pathways/hypertension) According to the largest meta-analysis of 147 trials consisting of 958,000 people,[165] all major classes of anti-hypertensive drugs, including beta-blockers, reduced CHD and stroke when compared to placebo. Beta-blockers had a special benefit in preventing recurrent CHD events in people with a history of CHD: a risk reduction of 29% compared with 15% in trials of other drugs, though the extra effect was limited to a few years after myocardial infarction.[165] But in patients without CHD, beta-blockers increased stroke by 18%, while CCB decreased stroke by 9% (all $P < 0.05$). It has been demonstrated In the meta-analysis of BPLTTC that beta-blockers had a similar effect in reducing CV events compared to other drug classes, and no sign of increasing stroke rate was found.[239] It has recently been shown that there might be some differences in the effects of atenolol versus non-atenolol beta-blockers.[301] In the meta-analysis including 145,811 patients, it was shown that among the elderly (≥60 years) atenolol was associated with an increased risk of stroke (relative risk 1.17, $p < 0.05$) compared with other anti-hypertensive drugs.[301] The risk of stroke for non-atenolol beta-blockers, when compared with other drugs, did not reach statistical difference. In the young (age <60 years), atenolol was associated with reduced risk of stroke compared with other drugs (relative risk 0.78, $p < 0.05$), whereas non-atenolol beta-blockers were associated with a lower risk of composite cardiac events (relative risk 0.86, $p < 0.05$) compared with placebo, with no significant differences in events compared with other drugs.[301] It seems that all the beta-blockers, including atenolol and non-atenolol drugs, performed equally well in the young (<60 years) compared to other drugs.[301] Only in the elderly (≥60 years), atenolol was inferior to other drugs in reducing stroke.[301] In this guideline, we suggest that beta-blockers, except atenolol, can be used as the first-line therapy, especially in patients with CHD, history of myocardial infarction, and in patients with higher heart rate (≥80 beats/min).

Bronchial asthma is an absolute contraindication for the use of both beta-1 selective or non-selective beta-blockers, but chronic obstructive pulmonary disease (COPD) is not a contraindication. In an observational cohort study, treatment with beta-blockers reduced the risk of exacerbation and improved survival in patients with COPD.[302] In a retrospective cohort study, beta-1 selective, but not non-selective, beta-blockers were suggested to be safe in patients hospitalized with acute exacerbation of COPD with underlying CHD, heart failure, or hypertension.[303] But in a retrospective analysis of the OPTIMIZE-HF registry,[304] both beta-1 selective and non-selective beta-blockers were associated with lower death rate in patients with and without COPD.[304] There was no evidence that beta-blocker selectivity was associated with a difference in outcomes between patients with and without COPD.[305]

The major side effects with beta-blockers are reduced sexual function, fatigue, reduced exercise capacity, and body weight increase. One important side effect is new-onset diabetes,[267, 306] especially in combination with diuretics.

7.3.2.1. Atenolol. In the LIFE trial and the ASCOT trial,[242, 243] atenolol was the main component of one of the treatment arms. Compared with ARB, atenolol group had higher cardiovascular events, especially stroke.[242] Atenolol, in combination of thiazide diuretics, has an increased total mortality and cardiovascular events, compared with the combination of CCB and ACE inhibitors in the ASCOT trial.[243] A possible reason for the increase in cardiovascular events, especially stroke, is that atenolol was less effective in decreasing central aortic pressure and pulse pressure.[83, 307] Another possible reason is that atenolol has a short half-life of about 6-9 hours,[308] but most RCTs for atenolol took a QD dosing regimen. In a meta-analysis comparing beta-blockers (mainly atenolol) with other anti-hypertensive drugs, beta-blockers increased the risk of cardiovascular events and death for hypertensive patients.[309] It is suggested that atenolol should not be used as a first-line beta-blocker in the treatment of hypertension, especially for patients aged ≥60 years.

7.3.2.2. Non-atenolol beta-blockers. Other beta-blockers, such as metoprolol and bisoprolol, have not been extensively tested in RCTs. The effect of bisoprolol versus atenolol on central aortic pressure is more controversial.[310, 311] Newer vasodilating beta-blockers, such as carvedilol or nebivolol, reduced central pulse pressure and aortic stiffness better than atenolol or metoprolol.[312-314] Both nebivolol and carvedilol have a favorable effect on blood glucose compared to metoprolol,[315, 316] and have been favorably tested in RCTs for heart failure.[317-319] There has been no RCT to test their long-term cardiovascular effects in patients with hypertension.

7.3.3. Calcium channel blockers (CCBs)

CCBs have potent BP-lowering effects, and have been the most widely used anti-hypertensive drugs, especially in Asia. Several recent large clinical trials have confirmed their efficacy not only in lowering BP but also in reducing cardiovascular morbidity and mortality in hypertensive patients with a normal or high cardiovascular risk profile. CCBs can be broadly classified into 2 groups: dihydropyridine (DHP) and non-dihydropyridine (non-DHP) groups. Most of the recent RCTs tested DHP CCBs, whereas RCTs for non-DHP CCBs occur much less frequent.

7.3.3.1. Dihydropyridine calcium channel blockers (DHP CCBs). Short-acting DHP CCBs cause reflex tachycardia and are generally not recommended as first-line anti-hypertensive drugs. The effect of nitrendipine versus placebo in reducing stroke in isolated systolic hypertension has been confirmed in the Syst-Eur and Syst-China trials.[124, 125] Other DHP CCBs have also been studied in RCTs, including the INSIGHT trial,[320] the HOT trial,[136] and the FEVER trial.[133] In the ALLHAT trial,[256] the CAMELOT trial,[160] the VALUE trial,[253] or the ASCOT trial,[243] an amlodipine-based therapy was at least as effective, when not slightly superior, in lowering BP

and sometimes more effective in preventing TOD than BP lowering strategies based on the use of diuretics, beta-blockers and blockers of the renin-angiotensin system.[160, 243, 253, 256] In the ACCOMPLISH trial, the combination of ACE inhibitor and amlodipine was superior to the combination of ACE inhibitor and a thiazide diuretic in reducing composite CV endpoints.[244] According a meta-analysis of 147 trials, DHP CCB is the most effective drug class to decrease stroke.[165] The efficacy of CCBs may be due to their potent BP-lowering effect, and the ability to decrease BP variability.[104] However, DHP CCBs might be less effective in reducing heart failure, as reported in the ALLHAT trial,[256] the VALUE trial,[253] and the ACCOMPLISH trial.[244] In the meta-analysis of 147 trials, CCB was less effective in reducing heart failure compared to other anti-hypertensive drugs.[165]

In Asians more specifically, the effects of DHB CCBs have been tested in the Syst-China trial and the FEVER trial.[125, 133] In the felodipine group in the FEVER trial, the primary endpoint (fatal and non-fatal stroke) was reduced by 27% ($p = 0.001$).[133] Among secondary endpoints, all cardiovascular events were reduced by 27% ($p < 0.001$), and all-cause death by 31% ($p = 0.006$) in the felodipine group.[133] A meta-analysis of 12 trials reported that DHP CCB was more effective than other anti-hypertensive drugs in reducing both day-time and night-time SBP in east Asians.[321]

The main side effect of DHP CCBs is peripheral edema, which is most prominent at high doses. This side effect can be attenuated by combining these agents with ACE inhibitors, ARBs, or direct renin inhibitors (DRI).[322] More importantly, there is no contraindication for the use of DHP CCBs (Table 13).

7.3.3.2. Non-dihydropyridine calcium channel blockers. Non-DHP CCBs, include verapamil and diltiazem, are less potent than DHP groups, but generally non-inferior to comparators in several RCT.[141, 323, 324] Diltiazem could decrease albuminuria in a small scale RCT.[325] Non-DHP CCB are more negatively chronotropic and inotropic than the DHP groups, and have more contraindications as shown in Table 13. Both verapamil and diltiazem are metabolized by CYP3A4, and have more drug-drug interaction than DHP group.[326] In general, non-DHP CCBs should not be used as first-line drugs in the treatment of hypertension.

7.3.4. Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors have been extensively studies in many RCTs for the treatment of hypertension.[174, 256] Even in high risk patients with pre-hypertension (120-139/80-89 mmHg), several RCTs have confirmed their efficacy and safety compared to placebo or other anti-hypertensive drugs.[156, 157, 327] ACE inhibitors are preferentially indicated in patients with heart failure,[328-332] diabetes,[274, 333-335] and CKD.[182, 183 336, 337]

The major side effects of ACE inhibitors include cough and angioedema. The incidence of ACE inhibitor-induced cough is reported to be 5-35%.[338] It is generally believed that cough due to ACE inhibitors are more common in Asians.[339, 340] Although ACE inhibitor-induced cough seems to be a class effect, some reports claimed that certain ACE inhibitors might have less cough than others.[341, 342] The major dangerous side effect of ACEI inhibitors is angioedema.[343] Fortunately, its incidence is <1%,[344] and is especially rare in Chinese.[345]

7.3.5. Angiotensin receptor blockers (ARBs)

ARBs have been proven by multiple RCTs to be effective in reducing BP and cardiovascular events.[188-190, 242, 327, 337, 346-348] Because they are well-tolerated and have effects and benefits similar to ACE inhibitors,[327] they are now generally preferred over ACE inhibitors. But ARBs should not be combined with ACE inhibitors, because both its side effects and acute renal impairment were higher than in monotherapy with ACE inhibitor or ARB.[327]

The tolerability of ARBs is the highest, and the discontinuation rate is the lowest among all 5 classes of anti-hypertensive drugs.[242, 327] Cough and angioedema were very rarely reported in patients receiving ARBs.[327]

7.3.6. Direct renin inhibitor (DRI)

The only available DRI, aliskiren, has been shown to be effective in lowering BP,[349] and has favorable effects on TOD, such as proteinuria or left ventricular hypertrophy,[350, 351] or on biomarkers for heart failure.[352] In a large RCT,[353] aliskiren was added on top of pre-existing ACE inhibitor or ARB in patients with high risk diabetes. The trial was prematurely terminated due to a non-significant increase in primary endpoints, and an increase in adverse events, such as hyperkalemia and hypotension.[353] The RCT testing the effect of aliskiren, on top of ACE inhibitors or ARBS, in heart failure had a neutral effect, but had increased adverse events, such as hyperkalemia, hypotension and renal impairment.[354] Nevertheless, aliskiren can be safely combined with hydrochlorothiazide or amlodipine in the elderly (age ≥65 years) with stage 1 hypertension, as shown in the APOLLO trial.[355] The contraindications for aliskiren are similar to ACE inhibitors or ARBs (Table 13).

7.3.7. Other anti-hypertensive agents

Alpha-blockers are less widely used as a first-line drug for hypertension, especially after the ALLHAT trial showing increased heart failure by the use of doxazosin compared with the use of chlorthalidone.[356] However, there has been some disagreement about the design of the ALLHAT trial. Doxazosin can be used in the treatment of resistant hypertension when combined with other drugs.[243] Alpha-blockers are effective in the treatment of benign prostate hypertrophy, and are a valuable part of hypertension treatment regimens in elderly men.

Centrally acting drugs, such as clonidine and alpha-methydopa, have bothersome side effects and have not been proven in RCTs. They are not recommended as first-line therapy. The use of alpha-methyldopa in pregnancy was discussed in Section 8.2.

Direct vasodilators, such as hydralazine and minoxidil, cause fluid retention and tachycardia. No RCTs for the treatment of hypertension have been done for hydralazine, nor for

minoxidil.[357 358] Adverse effects of hydralazine include reflex tachycardia, hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome.[357] However, hydralazine in combination with isosorbide dinitrate, is effective in African-Americans who have symptomatic heart failure.[359] Because of the severity of adverse effects with minoxidil, its usage is limited to persons with severe hypertension unresponsive to other treatment.[358] Vasodilators should not be used as first-line anti-hypertensive drugs.

Among all the drugs in the investigational stages, LCZ696 merits additional mention here. LCZ696 is a dual-acting angiotensin receptor-neprilysin inhibitor (ARNI).[360] In a proof-of-concept trial, LCZ696 was compared with valsartan.[361] LCZ696 provides complementary and fully additive reduction of BP, and no cases of angioedema were reported.[361] Though LCZ 696 has not been approved for the treatment of hypertension, it has been successfully tested in patients with systolic heart failure. In the PARADIGM trial, 8442 patients with class II-IV heart failure and an ejection fraction <40% were enrolled.[362] LCZ696 was demonstrated to be superior to enalapril in reducing the risks of death and hospitalization for heart failure (−20%, $p < 0.0001$).[362]

7.4. Combination therapy

Patients with hypertension may have different pathophysiological derangement.[363] Therefore, combining drugs with different anti-hypertensive mechanisms may be more effective than titrating doses of a single agent. Indeed, multiple classes of drugs might be needed in clinical practice to control BP to targets. In the ALLHAT trial, an average of 2 drugs were required for SBP control in two thirds of participants, but only 67% of patients reached SBP targets by the end of the trial.[364] In the ASCOT trial, only 27% patients were on monotherapy and 73% on 2 or more drug after 3.5 years of follow-up.[243]

According to the "Rule of 10" (Fig. 3) and "Rule of 5" (Fig. 4), a standard dose of every drug can decrease SBP by approximate 10 mmHg, and DBP by 5 mmHg.[9, 245] Preferably, when 2 drugs with different mechanisms are taken together, the decrease in BP is the sum of the decrease of the individual agents (approximately 20 mmHg in SBP and 10 mmHg in DBP).[9, 245, 246] Therefore, in order to treat to a target of 140/90 mmHg in patients with a pre-treatment BP of 160/90 mmHg or above, two drugs are usually needed.

In order to control BP sooner to targets, early combination is suggested by this guideline. In a population-based, nested case-control study of 209,650 patients, those who were treated with initial combination therapy and were maintained on combination therapy along the entire period, had a 26% lower CV risk compared with patients who maintained monotherapy throughout the treatment course.[365]

Based on data from a meta-analysis of 354 randomized, double-blind, placebo-control trials comprising 40,000 drug-treated patients and 16,000 placebo-treated patients,[245] the BP lowering effects of different classes of drugs were additive.[245] Side effects attributable to thiazides, beta blockers, and CCBs were strongly dose-related; side effects caused by ACE inhibitors (mainly cough) were not dose-related.[245] ARBs caused no excess of side effects. The prevalence of side effects with two drugs in combination was less than additive. Adverse metabolic effects were negligible at half of the standard doses.[245] The conclusion is that a combination of low doses of drugs increases efficacy and reduces adverse effects.[245] A similar finding was reported recently that initiating treatment with a combination of two drugs is associated with a reduced risk of treatment discontinuation.[366]

7.4.1. Choice of combination

Three large-scale RCTs have tested the superiority of one combination versus the other.[242-244] In the LIFE trial, the combination of losartan (ARB) plus hydrochlorothiazide (diuretic) was compared with the combination of atenolol (beta-blocker) plus hydrochlorothiazide (diuretic), showing that ARB+diuretic combination was better than beta-blocker+diuretic combination in reducing CV endpoints, mainly stroke.[242] The difference of achieved SBP was only 1.3 mmHg, lower in the ARB+diuretic group. In the ASCOT trial, the combination of amlodipine+perindopril (CCB+ACE inhibitor) was better than the combination of atenolol+benzofluthiazide (beta-blocker+diuretic) in reducing total mortality and other CV endpoints with a SBP difference of 2.7 mmHg, lower in the CCB+ACE inhibitor group.[243] Besides, the risk of new-onset diabetes from the combination of beta-blocker+diuretic was higher than other combinations.[367] Therefore, the combination of beta-blocker+diuretic is inferior to the combination of ARB+diuretic or CCB+ACE inhibitor combinations.

The strongest evidence supporting the combination of ACE inhibitor+CCB came from the ACCOMPLISH trial.[244] In this double-blinded RCT, the single-pill combination (SPC) of benazepril+amlodipine (ACE inhibitor+CCB) was compared with the SPC of benazepril+hydrochlorothiazide (ACE inhibitor+diuretic). This trial was prematurely terminated due to overwhelming benefits in reducing CV endpoints favoring the combination of ACE inhibitor+CCB, though the SBP was only 0.9 mmHg lower in the ACE inhibitor+CCB group.[244] The benefits of ACE inhibitor+CCB combination could not be explained by the difference in ABPM, because the mean SBP was 125.3 mmHg for ACE inhibitor+CCB group, and 123.7 mmHg for ACE inhibitor+diuretic group.[368] The renal outcomes also favored the ACE inhibitor+CCB combination.[369] In a subgroup analysis in diabetic patients, the ACE inhibitor+CCB combination were similarly superior to the ACE inhibitor+diuretic combination.[368] Almost all CV endpoints and renal endpoints, except heart failure admission, were lower in the ACE inhibitor+CCB group.[368] In a post-hoc analysis in high-risk patients with stage 2 hypertension in the ACCOMPLISH trial, the combination of benazepril+amlodipine has also been shown to be better than the combination of benazepril+diuretic therapy.[370] One finding in the ACCOMPLISH trial that might be related to the Asian patients is that the combination of ACE inhibitor+diuretic gave less cardiovascular protection in normal weight than in obese patients, but ACE inhibitor+amlodipine combination

was equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension, such as in Asian patients.[258] But we do need an RCT involving an Asian population to prove this.

When compared to the ALLHAT trial in which diuretic-based therapy was not inferior to ACE inhibitor-based or CCB-based therapy,[256] it appears that CCB is better than diuretic as a component in combination therapy. However, chlorthalidone was used in the ALLHAT trial whereas hydrochlorothiazide was used in the ACCOMPLISH trial.[244, 256]

Recommended 2-drug combinations include:

✓ ARB+CCB (A+C)
✓ ACE inhibitor+CCB (A+C)
✓ ARB+thiazide diuretic (A+D)
✓ ACE inhibitor+thiazide diuretic (A+D)
✓ CCB+beta-blocker (B+C)

There have been no RCTs to test the efficacy of any 3-drug combination in reducing CV endpoints. Based on the pathophysiological mechanism of hypertension, we recommended ACE inhibitor (or ARB)+CCB+Thiazide diuretic (A+C+D) combination. A post-hoc analysis of the ADVANCE trial shows that the combination of perindopril and indapamide with CCBs (A+C+D) provided further protection in reducing mortality in patients with type 2 diabetes.[371] In patients with heart failure or CHD, or with a high resting heart rate, beta-blockers may precede thiazide diuretics. Alpha-blocker has been used as the third drug in the ASCOT trial,[243] but its priority is usually lower than diuretics.

Some unfavorable combinations were listed below. Combination of a beta-blocker and a thiazide diuretic should be used with great caution because of higher diabetogenic potential.[267] The combination of 2 drugs of renin-angiotensin system inhibitors is generally prohibited. The risk of hyperkalemia and renal impairment have been shown both in RCTs and in a population-based cohort study.[327, 353, 372, 373]

Unfavorable or prohibited 2-drug combinations include:

Beta-blocker + diuretic (except in heart failure)
ACE inhibitor + ARB
(ACE inhibitor or ARB) + DRI

7.4.2. Single-pill combination

Combining anti-hypertensive drugs of different classes in a single tablet (single pill combination, SPC), previously called fixed-dose combination, has become more common in daily practice. In general, SPCs of antihypertensive agents reduce pill burden, and are associated with a significant improvement in compliance, compared with free-drug combinations.[374, 375] Use of SPC could help patients to continue treatment and result in lower BP than in free combination.[376] Interesting findings came from a recent report from the NHIRD in Taiwan that SPC is not effective in patients adequately adhering to their free-combined antihypertensive regimens.[377] But it is generally accepted that initial therapy with SPCs provided better hypertension control in the first year than free combinations or monotherapy.[378] In the STITCH trial (Simplified Treatment Intervention to Control Hypertension) done in Canada, initial use of SBP was associated with a significant decrease of 5.4 mmHg in SBP compared to the free combination group.[379] SPC also increased the chance of reaching the target by 20%.[379] The use of SPC was also associated with a trend of less adverse events than free combination.[374] SPC of anti-hypertensive drugs, statin, and aspirin was tested in the UMPIRE trial.[380] Use of SPC resulted in significantly improved medication adherence.[380]

The most successful experience came from the recent report from the Kaiser Permanente Northern California (KPNC) hypertension program. From 2001 to 2009, the control rate of hypertension increased from 43.6% to 80.4%. One of the key factors was the widespread use of SPC.[381] Therefore, in this guideline, the use of SPC is encouraged. In patients with BP ≥160/100 mmHg, or in special patient group whose BP is >150/90 mmHg, SPC can be used as the first-line therapy (Fig. 2).

7.5. Treatment algorithm

A treatment algorithm was shown in Fig. 2. The initial treatment should always include LSM (Please see Section 7.1). When drug therapy is considered, a strategy called "**PROCEED**" can be considered (Section 7.2). As mentioned before, special patient groups include patients with diabetes, CHD, and CKD with proteinuria. The suggestions about drug therapy in this algorithm are not applicable to very elderly patients (age ≥80 years).

For patients who do not belong to special patient groups, LSM is the initial treatment for the first 3 months in patients with a stage 1 hypertension (BP = 140–159/90–99 mmHg). If BP is still >140/90 mmHg after 3 months, pharmacological therapy with 1 drug should be initiated. For patients with stage 2 HT (BP = 160–179/100–109 mmHg) or stage 3 HT (BP≥180/110 mmHg), drug therapy should be combined with LSM as the initial step. Two-drug combination, or SPC of 2 drugs, can be considered in patients with stage 2 HT. We recommend a 3-drug combination for patients with stage 3 hypertension, except in fragile patients, or patients with postural hypotension, or patients ≥80 years of age. SPC of 3 drugs may be considered in patients with stage 3 HT, if an initial combination of 2 drugs has failed.

For patients who belong to special patient groups, LSM is still the initial treatment for the first 3 months in patients with baseline BP of 130–149/80–89 mmHg. If BP is still >130/80 mmHg after 3 months, pharmacological therapy with 1 drug should be initiated. For patients with baseline BP ≥150/90 mmHg, drug therapy should be combined with LSM as the initial step. A two-drug combination, or SPC of 2 drugs, can be considered in patients with BP of 150–169/90–99 mmHg. We recommend a 3-drug combination for patients with BP ≥170/100 mmHg, except in fragile patients, or patients with postural hypotension, or patients ≥80 years of age. SPC of 3 drugs may be considered in patients with BP ≥170/100 mmHg, if an initial combination of 2 drugs has failed.

For very elderly patients ≥80 years of age, a more conservative strategy is taken. Because BP targets are <150/90 mmHg, we suggest that drug therapy be initiated when baseline BP is ≥150/90 mmHg. A two-drug combination can be used when baseline BP is ≥170/100 mmHg. A three-drug combination is not suggested as the initial therapy, unless a 2-drug combination is not effective. Titration of medications should be more careful in elderly patients who have experienced a previous fall.[382] On the other hand, the control of BP in the very elderly patients (≥80 years) should not be delayed. In the one-year open-labeled extension trial of the HYVET study, participants on active BP lowering treatment continued taking active drug; those on placebo were given active BP lowering treatment.[383] By 6 months, the difference in BP between the two groups was only 1.2/0.7 mmHg. However, total mortality and cardiovascular mortality were still lower in the previously treated group (HR 0.48, $p = 0.02$; HR 0.19, $p = 0.03$; respectively).[383] This finding suggested that early and long-term treatment of hypertension in very elderly patients is beneficial.

7.6. Adjustment algorithm

The effect of antihypertensive drugs reached to 50% and 80% of their maximal effects in 1 week and 2 weeks, respectively.[384] Therefore, a period of 2 to 4 weeks of treatment is allowed before adjustment of management. If BPs are not at goals after 4 weeks of treatment, adjustment of management is suggested. An Adjustment algorithm called "AT GOALs" is shown in Fig. 5: **A**dherence, **T**iming of administration, **G**reater doses, **O**ther classes of drugs, **A**lternative combination or SPC, and **L**SM (+**L**aboratory tests).

The first thing is to re-confirm patient adherence, because non-adherence is very common in daily practice.[385] Timing of drug administration can be adjusted according to the diurnal BP profile of individual patients, provided by ABPM or HBPM. If early morning hypertension is observed, switching of medication from morning dosing to bedtime dosing may be useful. Increasing or maximizing doses should be considered thereafter. The next step is to add or switch to other classes of drugs, or to use different combination of drugs, including SPC. LSM needs to be intensified, too. Medications should be modified by findings from laboratory tests. For instance, if there is a deterioration of renal function in patients using A+D combination, A+C should replace A+D. In patients suffered from hypokalemia by the use of thiazide diuretics, mineralocorticoid receptor antagonist is a reasonable alternative.

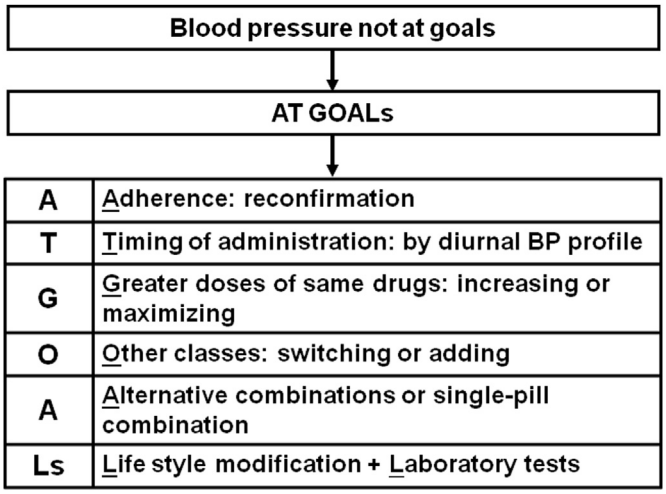

Fig. 5. Adjustment algorithm. BP = blood pressure.

7.7. Non-pharmacological therapy

7.7.1. Renal nerve denervation

The sympathetic nervous system seems to play an important role in resistant hypertension.[386] More recently, denervation of the renal arteries by radiofrequency energy has emerged as a potentially effective procedure to treat resistant hypertension.[387, 388] Initial un-blinded trials have shown significant reductions in office BP.[389, 390] There is an overwhelming enthusiasm for performing this procedure in patients with resistant hypertension.[391, 392]

In the SYMPLICITY HTN-3 trial, a single-blind RCT with a sham-controlled group, a total of 535 patients were randomized.[393] The baseline office BPs were 179.7/96.5 mmHg in the denervation group, and 180.2/98.9 mmHg in the sham group, under a mean of 5 anti-hypertensive drugs of different classes. The primary efficacy endpoints (change in office SBP at 6 months) were −14.13 mmHg in the denervation group as compared with −11.74 mmHg in the sham-group ($p = 0.26$).[393] The secondary efficacy endpoints (change in mean SBP in ABPM) were −6.75 mmHg vs −4.79 mmHg ($p = 0.98$).[394] No significant differences in the safety endpoints were observed. The SYMPLICITY HTN-3 trial brings the renal-denervation train to a grinding halt.[395] It has been suggested in a recent publication that adjustment of drug treatment had superior BP lowering effects compared with renal denervation in patients with true treatment-resistant hypertension.[396]

7.7.2. Other non-pharmacological therapy

Devices that stimulate the carotid baroreflex have been developed to treat patients with hypertension.[360] Activation of central baroreflex pathways by continuous electrical stimulation of the nerves of carotid sinus baroreceptors reduced sympathetic outflow from the central nervous system and reduced BP.[397] Results from a double-blind, randomized, placebo-controlled pivotal trial of 265 subjects with resistant hypertension did not meet the endpoints for acute responders or procedural safety.[398] Thus, all the non-pharmacological therapies, including deep brain stimulation, brainstem neurovascular decompression, etc. are still in the investigation stage, and have not yet reached clinical practice.[360]

8. Treatment strategies in special conditions

8.1. Treatment resistant hypertension

TRH was defined by the American Heart Association as BP above goals on ≥3 medications or controlled to goal on ≥ 4

BP medications prescribed at optimal doses, including a diuretic.[399] The prevalence of TRH has been reported to range from 5 to 30% of the overall hypertensive population.[10, 399] However, the true percentage might be lower than what has been previously shown.[257, 400, 401] The prevalence of TRH was 12.7% in the REACH registry,[402] but was only 1.9% from a recent report from the combined Kaiser Northern California and Kaiser Colorado databases.[403] TRH is associated with a high cardiovascular risks. In the sub-analyses of the REACH registry,[402] the INVEST trial,[404] and the Kaiser database,[403] patients with TRH had higher risk of composite cardiovascular events than patients with controlled hypertension (hazard ratios 1.11, 1.27, and 1.47, respectively, all $p < 0.05$).[402-404]

Before making a diagnosis of TRH, care must be taken to exclude the white-coat effect and non-adherence.[288] The prevalence of white-coat effect may be as high as 30% among patients with elevated office BP despite treatment with at least 3 drugs.[405] Non-adherence is another important cause of pseudo-resistant hypertension.[288] Medication non-adherence is very common in daily practice,[385] and might be as high as 8 to 40%, detected by use of questionnaires or pharmacy refill data.[406, 407] If therapeutic drug monitoring using serum samples was applied, the prevalence of non-adherence would be 50-60%.[408] Other causes of TRH are shown in Table 14.

LSM should be intensified in patients with TRH. Sodium restriction is the most important modification among all the strategies in LSM. Intensive sodium lowering might decrease BP by 23/9 mmHg in ABPM in patients with TRH.[213] Physical inactivity is also very common in patients with TRH, and could be identified in more than 40% of patients.[409] A recent RCT in patients with resistant hypertension, consisting of walking on a treadmill 3 times weekly for 8-12 weeks, has demonstrated a 6/3 mmHg reduction in ABPM compared with sedentary control group.[410]

Drug therapy for TRH should begin with optimization of diuretic use.[406] While hydrochlorothiazide 12.5 mg/d to 25 mg/d is the most commonly prescribed antihypertensive drug worldwide, and the most common component in the SPC, 50 mg/d hydrochlorothiazide was more effective in reducing ABPM than doses of 12.5 mg/d or 25 mg/d.[411] Metabolic effects of high dose thiazide are a concern. Chlorthalidone is at least twice as potent as hydrochlorothiazide,[412] and should be considered as the initial therapy for patients with TRH.[288] In fact, chlorthalidone is the only diuretic recommended by the 2008 AHA position statement.[399] However, chlorthalidone is not available in Taiwan. NICE hypertension guideline recommended indapamide instead of hydrochlorothiazide for TRH. (http://pathways.nice.org.uk/pathways/hypertension)

Given the prevalence of sub-clinical or clinical apparent mineralocorticoid excess of up to 20% in patients with TRH,[278] the 2008 AHA position statement proposed the use of aldosterone antagonists as part of a multi-drug regimen.[399] In the ASCOT trial, adding spironolactone as the fourth-line drug decreased office BP by 21.9/9.5 mmHg in approximately 1400 patients.[291] The ASPIRANT (Addition of Spironolactone in Patients with Resistant Arterial Hypertension Trial) is the only double-blind RCT to evaluate the effect of aldosterone antagonist in resistant hypertension.[295] With a high percentage of RAS blockade coverage (76.5% and 46.5% with ACE inhibitors and ARB, respectively), the addition of spironolactone was still able to decrease SBP further by 9.8 mmHg on ABPM and also significantly improved microalbuminuria.[295] Because the potential risk of hyperkalemia with mineralocorticoid receptor antagonists, they may counteract the risk of hypokalemia by thiazide diuretics. Thus, spironolactone or eplerenone can be initiated and combined with thiazide diuretics before maximizing the doses of thiazide diuretics.

Alpha-blockers can be considered as the fourth-line drug, but the priority of use of alpha-blocker should be after the use of mineralocorticoid receptor antagonists. Beta-blockers can be used as the fourth-line drug if the resting heart rate is high. Non-pharmacological therapy, such as baroreceptor stimulation or renal denervation, are to date, either unsuccessful or unproven in the management of TRH.[395, 398]

8.2. Hypertension in women

Both SBP and DBP are generally lower in pre-menopausal women (<50 years) than in men at the same age.[6, 8] On the other hand, SBP increases more rapidly with age in women than in men.[8] After the age of 60, women have higher BPs and higher prevalence of hypertension than men.[8] According to the TwSHHH conducted in 2002, women with indigenous ancestry had a 2-fold higher prevalence of hypertension compared to women with mainland ancestry.[413] The continuous relationship between BP and cardiovascular events is similar between men and women. In a meta-analysis of 31 RCTs including 103,268 men and 87,349 women, the efficacy of antihypertensive drugs with regard to BP reduction and cardiovascular protection is comparable for men and women.[414] However, there is still no large-scale (>1000 patients) RCT specifically enrolling female hypertensive patients to assess the efficacy of antihypertensive treatment. There is no evidence that regimens based on ACE inhibitors, ARBs, CCBs, or diuretics/beta-blockers are more effective in one sex than the other.[414]

Table 14
Causes of treatment resistant hypertension.

Improper blood pressure measurement technique
Failure to modify lifestyle including
Heavy sodium intake
Weight gain
Heavy alcohol intake
Intake of drugs that raise blood pressure
Cocaine, sympathomimetics, glucocorticoids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporine, anti-VEGF, 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

VEGF = vascular endothelial growth factor.
(Modified from Chiang et al.[9] with permission.)

Recommendation

- The efficacy of antihypertensive treatment with regard to BP reduction and cardiovascular protection is comparable for men and women. (COR I, LOE B)

8.2.1. 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 unknown. The progestogen-only pill is a contraceptive option for women having hypertension. Use of oral contraceptives is associated with a 2- to 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 over 35 years of age and in those who smoke. However, a case-control study showed that use of oral contraceptives was not associated with cardiovascular death in Taiwanese women.[415] Observational data showed that progestogen-only pills did not increase the risk of myocardial infarction.[416] In summary, women ≥35 years of age should be assessed for cardiovascular risk factors, including hypertension, before taking oral contraceptives. In women who smoke and were ≥35 years of age, oral contraceptives should be prescribed with caution. In women with uncontrolled hypertension, oral contraceptives are not recommended.

Recommendation

- Oral contraceptives should not be used in women with uncontrolled hypertension. (COR III, LOE C)

8.2.2. Effect of hormone replacement therapy

Postmenopausal women taking hormone replacement therapy may experience a mild increase in SBP over time. A recent Cochrane systematic review shows that hormone replacement therapy is associated with a significantly increased risk of coronary events, stroke, and venous thromboembolic disease.[417] However, in a retrospective analysis of Taiwan NHIRD, postmenopausal women treated with hormone replacement therapy (estrogen with or without progesterone) for an average of 8 months did not have increased risks of CHD and stroke with a median follow-up of 110 months.[418] A 44% increase in the risk of breast cancer was observed in women treated with estrogen plus progesterone.[418] It is generally recommended that hormone replacement therapy, as well as selective estrogen receptor modulators, should not be used for primary or secondary prevention of cardiovascular diseases in postmenopausal women.[419]

Recommendation

- Hormone replacement therapy, as well as selective estrogen receptor modulators, should not be used for primary or secondary prevention of cardiovascular diseases in postmenopausal women. (COR III, LOE C)

8.2.3. Hypertension in pregnancy

In the second trimester, BP normally falls by about 15 mmHg from the pre-pregnancy level. In the third trimester, BP returns to, or even exceeds, the pre-pregnancy level. The hypertensive disorders of pregnancy complicate 5 to 10% of pregnancies. Hypertension during pregnancy is generally classified into 4 categories: (1) chronic hypertension, (2) chronic hypertension with superimposed preeclampsia, (3) preeclampsia-eclampsia, and (4) gestational hypertension.[420] The preferred definition of hypertension in pregnancy is when SBP ≥140 mmHg or DBP ≥90 mmHg. Chronic (or "pre-existing") hypertension is defined as BP ≥140/90 mmHg either before pregnancy or develops before 20 weeks of gestation. Gestational hypertension generally develops after 20 weeks of gestation and, in most cases, resolves within 6 weeks postpartum. According to the severity of BP elevation, gestational hypertension is divided into mild (140/90−149/99 mmHg), moderate (150/100−159/109 mmHg), and severe (≥160/110 mmHg).[421] Traditionally, preeclampsia is defined as gestational hypertension associated with significant proteinuria (>300 mg/24 h, protein/creatinine ratio >0.3 [each measured as mg/dl] or dipstick ≥1+). It is now recognized that the placenta is the root cause of preeclampsia. Preeclampsia is a multisystem disease, not merely hypertension and renal dysfunction. The diagnosis of preeclampsia is therefore not dependent on proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension together with thrombocytopenia (platelet count <100,000/l), impaired liver function (elevated transaminases >2-fold upper normal limits), renal insufficiency (serum creatinine >1.1 mg/dl or doubling of serum creatinine), pulmonary edema, or cerebral or visual disturbances.[420]

For women with gestational hypertension with or without preeclampsia, a normal diet without salt restriction is recommended. Physicians should consider early initiation of antihypertensive treatment to keep BP lower than 150/100 mmHg but do not lower DBP below 80 mmHg, because decreased BP in women taking antihypertensive agents is associated with decreased birth weight. In non-severe hypertension in pregnancy (<160/110 mmHg), oral methyldopa, labetalol, and nifedipine are preferred drugs. Atenolol has been reported to be associated with fetal growth retardation. ACE inhibitors, ARBs, direct renin inhibitors, mineralocorticoid receptor antagonists, and chlorothiazide (not other thiazides-like diuretics) should not be used in pregnancy because of their teratogenicity.[420, 421] Diuretic therapy is inappropriate in women with preeclampsia, which may precipitate volume depletion.

A BP ≥160/110 mmHg during pregnancy should be considered an emergency requiring hospitalization. Intravenous labetalol with sequential doses of 20, 40, 80, 80, and 80 mg every 20 minutes, or oral nifedipine (10 mg every 20 minutes up to 5 doses) can be used as first-line treatment.[422, 423] Intravenous hydralazine should not be used due to a higher incidence of perinatal adverse events. Intravenous nitroglycerin is the drug of choice in preeclampsia with pulmonary edema. Intravenous sodium nitroprusside 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 the treatment of seizure.

The following antihypertensive drugs do not have adverse effects on babies receiving breast milk: labetalol, nifedipine, enalapril, captopril, atenolol, and metoprolol.[421] Daily low-dose aspirin (60–80 mg) is advised for a period of time from 12 weeks until the birth of the baby. Low dose aspirin prevents preeclampsia in women with a history of early-onset (<28 weeks) preeclampsia or preeclampsia in more than one prior pregnancy.[424] Based on the retrospective analyses of Taiwan NHIRD, women who have had gestational hypertensive disorders (including preeclampsia) have increased short-term (<1 year) and long-term (up to 9 years) risks of stroke, cardiovascular events, ESRD, and diabetes.[425-428] It is generally believed that preeclampsia does not cause all of these adverse events, but rather preeclampsia and these adverse events share common risk factors. For women with preeclampsia and preterm delivery (<37 weeks of gestation) or recurrent preeclampsia, yearly assessment of BP, lipid profile, fasting blood glucose, and BMI is suggested.

Recommendations

- ACE inhibitors, ARBs, DRI, mineralocorticoid receptor antagonists, and chlorothiazide are teratogenic. They should be avoided or immediately withdrawn in case of pregnancy. (COR III, LOE C)
- For women with gestational hypertension, a normal diet without salt restriction is recommended. (COR IIa, LOE C)
- For women with hypertension during pregnancy, early initiation of antihypertensive treatment to keep BP lower than 150/100 mmHg and DBP≥80 mmHg is suggested. Oral methyldopa, labetalol, and nifedipine are preferred drugs. (COR IIb, LOE C)
- A BP ≥160/110 mmHg during pregnancy should be considered an emergency requiring hospitalization. Intravenous labetalol or oral nifedipine can be used as the first-line treatment. (COR IIa, LOE B)
- In women with a history of early-onset (<28 weeks) preeclampsia or preeclampsia in more than one prior pregnancy, low-dose aspirin (60–80 mg/d) for a period of time from 12 weeks until the birth of the baby is suggested to prevent preeclampsia. (COR IIb, LOE B)

8.3. Perioperative management of hypertension

Untreated hypertension or pre-operative hypertension with other cardiovascular risk factors increase perioperative morbidity and mortality.[429] Although it is arguable whether postponing operation is necessary, delay in surgery in patients with stage 1 or 2 hypertension is not necessary.[430, 431] In patients who have stage 3 hypertension without high cardiovascular risk, an RCT has shown similar clinical outcome between the postponing operation group and the control group.[432] Therefore, routine postponing of operation would not be necessary in such situations. In these cases, anti-hypertensive drugs should be continued in perioperative periods. However, in patients with stage 3 hypertension and high cardiovascular risk, the potential benefits of delaying surgery to optimize BP control should be weighed against the risk.[430, 431]

Use of diuretics should be avoided on the day of surgery because of potential aggravation of surgery-dependent fluid depletion.[10] There are inconsistent results regarding perioperative use of RAS inhibitors. Increased risks with the use of RAS inhibitors were observed in one RCT[433] and 3 observational studies,[434-436] whereas reduced risks were found in 2 observational studies.[437, 438] Owing to potential surgery-related volume depletion, use of RAS inhibitors in the perioperative periods should be individualized, based on the fluid status of patients. Sympathetic overactivity might occur after withdrawal of some anti-hypertensive drugs, especially clonidine, beta-blockers, and methyldopa.[439-441] Furthermore, 2 observational studies showed that perioperative withdrawal of beta blockers predicted morbidity and mortality in patients undergoing vascular surgery.[442, 443] Therefore, sudden cessation of these drugs in perioperative periods should be avoided.

Routine use of beta-blockers in perioperative periods of non-vascular surgery is still controversial.[444-447] In the DECREASE IV trial of 1066 patients with intermediate cardiac risk, use of bisoprolol was associated with a significant reduction of 30-day primary endpoints (cardiac death and myocardial infarction).[444] In the POISE trial of 8351 patients at risk of atherosclerotic disease, the 30-day primary endpoints (a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest) were decreased by metoprolol succinate.[446] But total mortality and stroke was increased.[446] Although recent observational studies showed prognostic benefits of perioperative beta-blockaders in patients with higher Revised Cardiac Risk Index,[448, 449] the most updated meta-analyses of RCTs have different conclusions.[450, 451] In a systemic review for the 2014 ACC/AHA Guidelines on perioperative cardiovascular evaluation and management, there were 17 studies included, of which 16 were RCTs.[451] It has been shown that perioperative beta-blockers started within 1 day or less before noncardiac surgery prevented nonfatal myocardial infarction, but increased the risks of stroke, death, hypotension, and bradycardia. Without the controversial DECREASE studies, there are insufficient data on beta-blockers started 2 or more days prior to surgery. Multicenter RCTs are needed to address this knowledge gap.[451]

Clevidipine is a rapid-acting L-type DHP CCB with a ultrashort half-life, without reflex tachycardia or tachyphylaxis.[452-454] The ECLIPSE trial which enrolled 1512 participants undergoing cardiac surgery showed superior BP reduction with intravenous clevidipine as compared to other anti-hypertensive drugs, such as sodium nitroprusside, nitroglycerin or nicardipine, across all baseline BP subgroups.[452] Therefore, clevidipine is preferred in the management of hypertensive crisis during cardiac surgery.

Recommendations

- Delay in surgery in patients with stage 1 or 2 hypertension is not necessary. (COR IIb, LOE C)

Table 15
Comparison of 2010 hypertension guidelines of TSOC and 2015 hypertension guidelines of TSOC/THS.

	2010 TSOC	2015 TSOC/THS
Classification of recommendation	−	+
Level of evidence	−	+
Standards of IOM	−	+
Table for correct BP measurement	−	+
BP variability	−	+
Diagnostic algorithm	−	+
Treatment algorithm	+	+
Adjustment algorithm	−	+
Blood pressure targets		
<130/80 mmHg	Diabetes, CHD and CHD equivalents, CKD, stroke	Diabetes, CHD, proteinuric CKD, antithrombotic therapy
<140/90 mmHg	Primary prevention,	Primary prevention, CKD, stroke
<150/90 mmHg	Very elderly (≥80y)	Very elderly (≥80y)
Life style modification		
S-ABCDE	+	+
S	Salt restriction <6.0 gm/day	Sodium restriction 2.0−4.0 gm/day
Body weight reduction (BMI)	18.5−24.9 kg/m^2	22.5−25.0 kg/m^2
Exercise adoption (aerobic)	30 minutes/day, at least 5 days/week	40 minutes/day, at least 3−4 days/week
List of recommended drugs	+	+
List of recommended combinations	+	−
Figure for "Rule of 10"	−	+
Figure for "Rule of 5"	−	+
Non-pharmacological therapy	−	+
Renal nerve denervation	−	+
Perioperative management	−	+

BP = blood pressure; CHD = coronary heart disease; CKD = chronic kidney disease; IOM = Institute of Medicine; THS = Taiwan Hypertension Society; TSOC = Taiwan Society of Cardiology.

- Delay in surgery in patients with stage 3 hypertension, who do not have high cardiovascular risk, is not necessary. (COR IIa, LOE B)
- In patients with stage 3 hypertension and high cardiovascular risk, the potential benefits of delaying surgery to optimize BP control should be weighed against the risk. (COR IIb, LOE C).
- Use of diuretics should be avoided on the day of surgery because of potential aggravation of surgery-dependent fluid depletion. (COR IIa, LOE C)
- Use of RAS inhibitors in the perioperative periods should be individualized, based on fluid status of patients. (COR IIa, LOE B)
- Sudden cessation of beta-blockers, clonidine, and methyldopa in perioperative periods should be avoided. (COR III, LOE C)
- Intravenous clevidipine is preferred in the management of hypertensive crisis during cardiac surgery. (COR IIb, LOE B)

9. Comparison of 2010 Hypertension Guidelines of TSOC and 2015 Hypertension Guidelines of TSOC/THS

Table 15 shows the similarities and differences of the 2010 hypertension guidelines of TSOC and the 2015 hypertension guidelines of TSOC/THS. Apparently, the updated 2015 version is more comprehensive. More information and algorithms were provided.

In conclusion the 2015 TSOC/THS hypertension guidelines provide the most updated information about the management of hypertension in Taiwan. We emphasized a more aggressive BP management in certain high risk patients. Useful diagnosis, treatment, and adjustment algorithms were highlighted. Recommendations and suggestions regarding S-ABCDE, PROCEED, Rule of 10, Rule of 5, and AT GOALs make it unique among contemporary hypertension guidelines. We hope the guidelines can be useful to Taiwanese physicians in helping their patients in daily practice. We also respect that the physician's decision remains most important in the management of hypertension.

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Appendix A.

Chern-En Chiang has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Servier, Tanabe, Takeda, and TTY.

Tzung-Dau Wang has been on the speakers bureau for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Cordis, Daiichi-Sankyo, GSK, Medtronic, MSD, Novartis, Pfizer, Sanofi, and Takeda.

Kwo-Chang Ueng has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi-aventis, Servier, Tanabe, Takeda, and TTY.

Tsung-Hsien Lin: Nothing to disclose.

Hung-I Yeh: has been on the speakers bureau for AstraZeneca, Daiichi-Sankyo, GSK, MSD, Pfizer, Tanabe, and Takeda.

Chung-Yin Chen: Nothing to disclose.

Yih-Jer Wu: Nothing to disclose.

Wei-Chuan Tsai: Nothing to disclose.

Ting-Hsing Chao: Nothing to disclose.

Chen-Huan Chen has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Sanofi. Chen-Huan Chen reports non-financial support from Novartis company, personal fees from Novartis company. Microlife Co., Ltd., and National Yang-Ming University have signed a contract for transfer of the noninvasive central blood pressure technique.

Pao-Hsien Chu has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Servier, Tanabe, and Takeda.

Chia-Lun Chao: Nothing to disclose.

Ping-Yen Liu: Nothing to disclose.

Shih-Hsien Sung: Nothing to disclose.

Hao-Min Cheng: Nothing to disclose.

Kang-Ling Wang received honorarium from AstraZeneca and Bayer.

Yi-Heng Li has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, and Sanofi.

Fu-Tien Chiang: Nothing to disclose.

Jyh-Hong Chen has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, sanofi, and Takeda.

Wen-Jone Chen has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Takeda, Tanabe, MSD, Novartis, Pfizer, and sanofi.

San-Jou Yeh: Nothing to disclose.

Shing-Jong Lin: Nothing to disclose.

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