2021 Taiwan Stroke Society Guidelines of blood pressure control for ischemic stroke prevention

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Abstract

Background: Since the publication of the 2015 Taiwan Stroke Society Blood Pressure for Treatment and Prevention of Stroke Guideline (2015 TSS BP Guideline), several new clinical studies have addressed whether a stricter blood pressure (BP) target would be effective for stroke prevention.

Methods: TSS guideline consensus group provides recommendations on BP targets for stroke prevention based on updated evidences.

Results: The present guideline covers five topics: (1) diagnosis of hypertension; (2) BP control and primary prevention of ischemic stroke; (3) BP control and secondary prevention of ischemic stroke; (4) BP control and secondary prevention of large artery atherosclerosis ischemic stroke; and (5) BP control and secondary prevention of small vessel occlusion ischemic stroke.

Conclusion: The BP target for most stroke patients with hypertension is <130/80 mm Hg.

Keywords: Atherosclerosis; Blood pressure; Ischemic stroke

1. INTRODUCTION

This guideline proposes recommendations for blood pressure (BP) control in patients with ischemic stroke on the basis of the latest clinical evidence. The members of the Taiwan Stroke Society (TSS) Guideline Consensus Group were invited to a discussion by the chairperson of the TSS. The topics and chapters of this guideline were mutually decided by all the members in the initial consensus meeting held in 2020. One or two members were assigned the task of reviewing the evidence relevant to each chapter for guideline development. Subsequently, a systemic search was performed for all relevant studies—randomized controlled trials, nonrandomized trials, meta-analyses, cohort studies, and retrospective studies. After reviewing all the available summarized evidence, the members of the Guideline Consensus Group determined the level of evidence and proposed recommendations in the subsequent consensus meetings. The included studies were confirmed to fulfill the eight standards of clinical practice guidelines proposed by the Institute of Medicine at the consensus meetings.

Recommendations for BP control proposed by the members mainly focus on the prevention of ischemic stroke and prognosis before stroke onset and after the acute phase, namely primary and secondary prevention. In addition, the guidelines individually provide recommendations for BP control for the two most common stroke causes: large-artery atherosclerosis and small-vessel occlusion; the optimal BP target may not be the same for these two causes. However, clinically, the risk of other cardiovascular diseases must be considered during the formulation of BP control policies. According to

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Conflicts of interest: Dr. Chi has been on the speaker's bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, and Sanofi. Dr. Chung has been on the speakers bureau for AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Viatris, and Sanofi. Dr. Li has been on the speakers bureau for Bayer, Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer. Dr. Wang has been on the speakers bureau for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Cordis, Daiichi-Sankyo, GSK, Medtronic, MSD, Novartis, Pfizer, Sanofi, and Takeda. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS), the empirical reference of this guideline is categorized into the classes of recommendation (CORs) I, IIa, IIb, and III on the basis of the strength of the recommendation and divided into the levels of evidence (LOEs) A, B-R, B-NR, C-LD, and C-EO on the basis of the quality of evidence.

The guideline contains five chapters:

1. Diagnosis and Definition of Hypertension.
2. BP Control and Primary Prevention of Stroke.
3. BP Control and Secondary Prevention of Stroke.
4. BP Control and Secondary Prevention of Ischemic Stroke Caused by Large-artery Atherosclerosis.
5. BP Control and Secondary Prevention of Ischemic Stroke Caused by Small-vessel Occlusion.

2. DIAGNOSIS AND DEFINITION OF HYPERTENSION

Hypertension is the most important risk factor for stroke. In recent years, guidelines for the treatment of hypertension worldwide have been continually updated (Table 1). With accumulating clinical evidence, diagnostic criteria of hypertension have changed from emphasizing the importance of diastolic BP in the 1980s to the importance of systolic BP in the 1990s, especially since the Joint National Committee 7 published guidelines for the treatment of hypertension in 2003. Controlling patients' BP below the treatment target for different comorbidities has become the major aim of hypertension treatment. After the publication of Systolic BP Intervention Trial study (SPRINT) in 2015, in which the substantial benefits of strict BP control were demonstrated, AHA revised the definition of hypertension as systolic and diastolic BP above 130 and/or 80 mmHg in 2017, respectively. In addition, the definition of hypertension is based on an office BP reading in all guidelines (Table 1). However, BP readings can be obtained through home and ambulatory BP monitoring and are essential in the management of hypertension. The use of out-of-office BP data in clinical practice has gradually become an important practice in clinical practice. The Taiwan Society of Cardiology (TSOC) has actively promoted the use of home BP in clinical diagnosis and treatment for a long time. BP values vary markedly from day to night and night to day (Table 2). This chapter briefly summarizes the definitions of hypertension provided in guidelines for the treatment of hypertension in the United States, Europe, and Taiwan, including the use of home or ambulatory BP data in addition to office BP data for making a diagnosis of hypertension and describes similarities and differences between these guidelines and related precautions.

2.1. Taiwan Society of Cardiology/Taiwan Hypertension Society Hypertension Guidelines: definition of hypertension based on office BP

The Taiwan Hypertension Guidelines issued by the TSOC and the Taiwan Hypertension Society (THS) in 2015 retain the definition presented in the 2010 Taiwan Hypertension Guidelines,[1,2] classifying office BP readings into normal (systolic BP: <120 mmHg and diastolic BP: <80 mmHg), prehypertension (systolic BP: 120-139 mmHg or diastolic BP: 80-89 mmHg), stage 1 hypertension (systolic BP: 140-159 mmHg or diastolic BP: 90-99 mmHg for general population; systolic BP ≥ 130 mmHg or diastolic BP ≥80 mmHg in patients with coronary heart disease, diabetes, and proteinuric chronic kidney disease as well as in patients who receive antithrombotics for stroke prevention), stage 2 hypertension (systolic BP: 160-179 mmHg or diastolic BP: 100-109 mmHg), and stage 3 hypertension (systolic BP: ≥180 mmHg or diastolic BP: ≥110 mmHg).

According to the 2017 updated version of the Taiwan Hypertension Guidelines, high BP readings are no longer used for diagnosing hypertension in the older population. In the 2015 version, the initial BP threshold for hypertension treatment in the older population was 150/90 mmHg. However, after the publication of the SPRINT study, the BP thresholds included in the AHA's 2017 Hypertension Guidelines (130/80 mmHg) and Taiwan Hypertension Treatment Guidelines (140/90 mmHg) for the older population were the same as those for the general population. In addition, according to the 2015 Taiwan Hypertension Guidelines, BP of ≥130/80 mmHg is recommended for the diagnosis of hypertension in patients with diabetes, coronary artery disease, and chronic kidney disease combined with proteinuria if an office BP reading is used. The diagnostic criterion for patients with stroke has been maintained at ≥140/90 mmHg.

2.2. TSOC/THS Hypertension Guidelines: definition of hypertension for home and ambulatory BP measurements

It has been demonstrated that as compared with office BP readings, home and 24-hour ambulatory BP measurements are better predictors of cardiovascular events and provide additional information regarding BP fluctuations.[3,4] The diagnostic criteria of hypertension based on home and ambulatory BP measurements are provided in the Taiwan Hypertension Treatment Guidelines (Table 3). The current recommendations of the TSOC and THS for home BP measurement are based on the 722 (please measure) principle: "7" refers to measuring BP for 7 consecutive days and "2" refers to measuring BP once after getting up in the morning and once before going to bed at night. Because stroke and myocardial infarction mostly occur from 5 AM to 10 AM, a BP measurement made in the morning would reflect the BP overnight. In addition, stroke can occur during nighttime; thus, BP should be measured before going to bed. The additional "2" refers to measuring BP twice each time, with an interval of one minute between the two times, and then calculating the average value.

The TSOC/THS updated the Taiwan Hypertension Treatment Guidelines in 2017[5] on the basis of the results of the randomized clinical trial SPRINT published in 2015[6] in patients at high risk for cardiovascular disease but who do not have a history of stroke or diabetes. The study reported that compared with standard BP control (systolic BP<140 mmHg), aggressive BP control (systolic BP < 120 mmHg) results in a lower risk of cardiovascular events, death due to cardiovascular disease, and all-cause mortality. Because some centers in the SPRINT study adopted unattended automated office BP (uAOBP) data, the 2017 Taiwan Hypertension Treatment Guideline introduces the four basic elements of uAOBP measurement as "electronic and automated device multiple readings averaged mean unattended and undisturbed spaces" (Table 4). However, uAOBP is majorly for research purposes in Taiwan at present because it needs unattended and undisturbed spaces, which are not available in most medical institutions. In addition, uAOBP needs averaging three times of measurements, the complex protocol also limits its promotion in clinical practices.

Recommendations for the diagnosis of hypertension:

1. The diagnosis of hypertension can be made by using BP values obtained from office, home, and ambulatory BP monitoring (COR: I, LOE: B-NR).
2. For the diagnosis of hypertension, BP data can be obtained by using uAOBP values (COR: IIa, LOE: B-NR).
3. For the diagnosis of hypertension using office BP measurements, systolic BP of ≥140 mmHg or diastolic BP of ≥90 mmHg is the recommended diagnostic criterion (COR: I, LOE: A).

Table 1

Comparison of office BP classifications of hypertension guidelines for adult BP (mmHg)

Guidelines	BP classification					
American JNC7 2003	Normal	Prehypertension		Stage 1 hypertension	Stage 2 hypertension SBP ≥160 or DBP ≥100	
	SBP<120 and DBP<80	SBP 120-139 or DBP 80-89		SBP 140-159 or DBP 90-99		
Taiwan TSOC/THS 2015	Normal	Prehypertension		Stage 1 hypertension[a]	Stage 2 hypertension	Stage 3 hypertension
	SBP<120 and DBP<80	SBP 120-139 or DBP 80-89		SBP 140-159 or DBP 90-99	SBP 160-179 or DBP 100-109	SBP ≥180 or DBP ≥110
American ACC/ AHA 2017	Normal	Elevated		Stage 1 hypertension	Stage 2 hypertension	
	SBP<120 and DBP<80	SBP 120-129 and DBP<80		SBP 130-139 or DBP 80-89	SBP ≥140 or DBP ≥90	
European ESC/ ESH 2018	Optimal	Normal	High normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension
	SBP<120 and DBP<80	SBP 120-129 or DBP 80-84	SBP 130-139 or DBP 85-89	SBP 140-159 or DBP 90-99	SBP 160-179 or DBP 100-109	SBP ≥ 180 or DBP ≥ 110

ACC = American College of Cardiology; AHA = American Heart Association; DBP= diastolic blood pressure; ESC = European Society of Cardiology; ESH = European Society of Hypertension; SBP= systolic blood pressure; THOC = Taiwan Society of Cardiology; THS = Taiwan Hypertension Society.

[a]SBP ≥ 130 or DBP ≥ 80 are considered hypertension in patients with coronary heart disease, diabetes, and proteinuric chronic kidney disease, as well as in patients who receive antithrombotics for stroke prevention.

Table 2

Correspondence table of office BP, home BP and ambulatory BP (mmHg) (ACC/AHA, 2017)

Office BP	Home BP	Ambulatory BP daytime	Ambulatory BP night	AmbulatoryBP 24 h
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ACC = American College of Cardiology; AHA = American Heart Association; BP = blood pressure.

Table 3

The definitions of hypertension (mmHg) for home and ambulatory BP measurements in the Taiwan Hypertension Treatment Guidelines 2017

Home BP	Ambulatory BP 24 hours	Ambulatory BP Daytime	Ambulatory BP Night
SBP ≥ 135 or DBP ≥ 85	SBP ≥ 130 or DBP ≥ 80	SBP ≥ 135 or DBP ≥ 85	SBP ≥ 120 or DBP ≥ 70

BP = blood pressure; DBP = diastolic BP; SBP = systolic BP.

Table 4

Four elements of automated office BP measurement (TSOC/THS, 2017)[a]

E	Automatic electronic equipment: need to use automatic electronic sphygmomanometer
M	Multiple measurements: measure BP at least three times, at one-min intervals
A	Average BP value: the sphygmomanometer needs to automatically calculate the average value
U	Unattended and undisturbed spaces: no medical personnel are present, in a separate room and undisturbed

A = averaged mean; BP = blood pressure; E = electronic and automated device; M = multiple readings; THS = Taiwan Hypertension Society; TSOC = Taiwan Society of Cardiology; U = unattended and undisturbed spaces.

[a]Taiwan Society of Cardiology and Taiwan Hypertension Society (translated)

4. For the diagnosis of hypertension using home BP measurements, systolic BP of ≥135 mmHg or diastolic BP of ≥85 mmHg is the recommended diagnostic criterion (COR: I, LOE: A).
5. For the diagnosis of hypertension using ambulatory BP measurements, systolic BP of ≥130 mmHg or diastolic BP of ≥80 mmHg can be considered as the diagnostic criterion (COR: IIb, LOE: B-NR).
6. When using office BP measurements for the diagnosis of hypertension in patients with diabetes, coronary heart disease, or chronic kidney disease combined with proteinuria, systolic BP of ≥130 mmHg or diastolic BP of ≥80 mmHg is a reasonable diagnostic criterion (COR: IIa, LOE: B).

3. BP CONTROL AND PRIMARY PREVENTION OF STROKE

3.1. General Concept

Although the definition of hypertension and the target value of control has been controversial in recent years,[5,7–9] scholars agree that hypertension causes more harm to the Asian population than the Western population.[10] With an increase in systolic BP, the risk of stroke in the Asian population increased twice as much as that in the Western population.[11] By contrast, this phenomenon was not observed in nonfatal coronary heart disease.[12] Satisfactory BP control plays a crucial role in the prevention of stroke in the Asian population.

A prospective community study conducted in China examined differences in the incidences of ischemic stroke and hemorrhagic stroke between different BP control trajectories. The study tracked 79 385 individuals who never had stroke or myocardial infarction, grouped them according to their BP trajectory changes from 2006 to 2010 and followed up on the occurrence of stroke from 2010 to 2014.[13] Compared with adults with normal and stable BP, those with stable prehypertension or those with stage 1 hypertension with gradually improving BP had increased long-term risk of stroke (patients with stable BP in the prehypertension stage: ischemic stroke, hazard ratio [HR], 2.05; 95% CI, 1.64-2.56; patients with grade 1 hypertension with gradually improving BP: ischemic stroke, HR, 3.36; 95% CI, 2.58-4.39).[13] The risk of hemorrhagic stroke was considerably higher with sustained hypertension than was the risk of ischemic stroke, and the gap was wider for a poorer degree of long-term BP control. In patients with stage 2 hypertension with stable BP, after adjusting for other confounding factors, the HR of hemorrhagic stroke increased to 12.4 times (95% CI, 5.95-26.0) and that of ischemic stroke increased to 5.07 times (95% CI, 3.77-6.82) compared with those in adults with normal BP.[13] These findings indicate that satisfactory BP control can more effectively reduce the risk of hemorrhagic stroke than that of ischemic stroke.

3.2. BP control goals for primary prevention of stroke

The goal of BP control is to consider the degree of the cardiovascular risk in different patients for the primary prevention of stroke. Lifestyle modifications can reduce the number and dose of antihypertensive drugs and are recommended for all patients; they include sodium restriction (2-4 g/d), alcohol limitation (<30 g/d for men and <20 g/d for women), weight reduction (target body mass index: 22.5-25.0 kg/m^2), cigarette smoking cessation, diet adaptation (8-10 servings/day of fruit and vegetables, 2-3 servings/day of low-fat dairy products, and decreased consumption of saturated fat and cholesterol), and exercise adoption (aerobic exercise of >40 min/day for at least 3-4 d/wk).[1]

The Heart Outcomes Prevention Evaluation (HOPE)-3 trial provides a good data reference for patients who have not had cardiovascular disease and who have moderate risk of cardiovascular disease.[14] A total of 12 705 patients were enrolled in the HOPE-3 trial. Men aged >55 years, women aged >65 years with at least one cardiovascular risk factor (high waist-to-hip ratio, low high-density lipoprotein level, smoking, abnormal blood sugar level, mild renal dysfunction, and family history of cardiovascular disease), and women aged >60 years with at least two cardiovascular risk factors were included in the trial. However, patients who had previous cardiovascular disease were excluded from this trial. The patients were divided into two groups. One group received candesartan and hydrochlorothiazide and maintained their systolic BP at <130 mmHg. The other group received placebo treatment, and their long-term systolic BP was between 130 and 140 mmHg. After an average of 5.6 years of follow-up, the drug treatment group receiving candesartan and hydrochlorothiazide did not exhibit lower risk of primary endpoints (including sudden cardiac death, nonfatal myocardial infarction, and nonfatal stroke) than the placebo group (HR, 0.93; 95% CI, 0.79-1.10). Moreover, the risk of nonfatal stroke was not lower in the treatment group than in the placebo group (HR, 0.80; 95% CI, 0.59-1.08).[14] Therefore, these findings did not support the benefits of lower BP control goals in the primary prevention of stroke in patients who have not previously had cardiovascular disease but who have moderate risk of cardiovascular disease.

In patients who had increased risk of cardiovascular disease but never had stroke, the results of SPRINT are worthy of reference.[13] A total of 9361 patients with increased risk of cardiovascular disease were enrolled in SPRINT. These patients may have had clinical or subclinical cardiovascular disease, had chronic kidney disease with a Framingham risk score of >15%, or were aged ≥75 years. The average Framingham risk score of these patients was 20.1 ± 10.9%. In particular, SPRINT excluded patients who had had stroke or diabetes. The patients were divided into two groups. The systolic BP of the trial and control groups was controlled below 120 mmHg (automated office BP monitoring) and 140 mmHg, respectively. After an average of 3.26 years of follow-up, the primary outcome rate of the trial group was significantly better than that of the control group (HR, 0.75; 95% CI, 0.64-0.89).[6] In addition, the trial reported that the clinical benefit resulted from a reduction in sudden cardiac death (HR, 0.57; 95% CI, 0.38-0.85) and heart failure (HR, 0.62; 95% CI, 0.45-0.84). Lowering the systolic BP to <120 mmHg did not further reduce the risk of stroke (HR, 0.89; 95% CI, 0.63-1.25).[6]

Patients with diabetes have high risk of cardiovascular disease. In terms of BP control, the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial and Action to Control Cardiovascular Risk in Diabetes BP (ACCORD-BP) trial are both crucial references. The ADVANCE trial enrolled 11 140 patients with diabetes including 3590 (32%) patients with history of major macrovascular diseases, among whom, 1022 (9%) had stroke. After an average of 4.3 years of follow-up, compared with the placebo group, the patients who received perindopril and indapamide on a fixed basis had a further 5.6 mmHg reduction in mean systolic BP (falling to ≈135 mmHg) and a reduction in the risk of combined macrovascular or microvascular events (HR, 0.91; 95% CI, 0.83-1.00).[15] The ACCORD-BP trial examined whether a lower BP target (<120 mmHg systolic) would lead to better outcomes.[16] The ACCORD-BP trial enrolled 4733 patients with type 2 diabetes. This study included patients who were aged >40 years and had history of cardiovascular disease (33.7% of the enrolled patients had history of cardiovascular disease) or those who were aged >55 years and had two or more comorbid cardiovascular disease risk factors. The patients were divided into two groups with systolic BP controlled below 120 and 140 mmHg, respectively, and the average follow-up was 4.7 years.[17] The ACCORD-BP trial found no significant difference between the two groups in the combined events of nonfatal myocardial infarction, nonfatal stroke, and sudden cardiac death (HR, 0.88; 95% CI, 0.73-1.06). Control of systolic BP below 120 mmHg was associated with a significant increase in severe side effects including drug-related hypotension, hyperkalemia, bradycardia, arrhythmia, and increased myohepatic acid values (3.3% vs 1.27%, $p < 0.001$).[17] The group whose systolic BP was controlled below 120 mmHg had lower risk of stroke (HR, 0.59; 95% CI, 0.39-0.89).[17] Among the patients enrolled in the ACCORD-BP trial, after excluding those with glycated hemoglobin below 6.0%, a total of 1284 patients with cardiovascular disease risk were selected in accordance with the same inclusion principle used in SPRINT (approximately 61% of the included patients had history of cardiovascular disease with an average Framingham risk score between 14.5 ± 9.2% and 14.8 ± 9.2%, which is higher than that of the original patients enrolled in the ACCORD-BP trial with history of cardiovascular disease) and grouped in accordance with systolic BP controlled below 120 mmHg and below 140 mmHg for analysis. The results of the study are consistent with those of SPRINT: the combined incidence of sudden cardiac death, nonfatal myocardial infarction, and nonfatal stroke was significantly lower in the strict BP control group than in the control group (HR, 0.69; 95% CI, 0.51-0.93); however, no significant difference was noted in the incidence of nonfatal stroke between the two groups (HR, 0.54; 95% CI, 0.27-1.10).[18] Currently, the American Diabetes Association still recommends that BP should be controlled below 140/90 mmHg.[19,20] However, for patients with diabetes, who have higher risk of cardiovascular disease, lowering BP to below 130/80 mmHg may be considered

within tolerable limits.[19,20] A meta-analysis examining the effects of the goal of BP control in patients with diabetes reported that a 10 mmHg decrease in systolic BP effectively reduced the risk of stroke (relative risk [RR]: 0.73; 95% CI, 0.64-0.83), and this benefit remained at a target systolic BP of <130 mmHg.[21] However, this meta-analysis also included patients with history of stroke. Therefore, additional studies are required to determine whether a more stringent BP standard than a threshold of 140/90 mmHg should be adopted for the primary prevention of ischemic stroke in patients with diabetes.

Currently, the Hypertension Guidelines of the TSOC and TSH for the primary prevention of cardiovascular disease still set the target BP to lower <140/90 mmHg (COR: I and LOE: B).[5] The BP control targets for primary prevention should be set in the context of overall cardiovascular event prevention and not separately for the primary prevention of ischemic stroke. In recent years, some meta-analyses including patients with different cardiovascular disease risks have indicated that strict BP control can further reduce the risk of cardiovascular events and stroke.[21–23] Therefore, in terms of the BP target for the primary prevention of ischemic stroke, treatment guidelines published by the AHA in 2017 may be referred to if considering a patient's cardiovascular risk. The guidelines recommend that patients with 10-year risk of atherosclerotic cardiovascular disease of <10% (http://tools.acc.org/ASCVD-Risk-Estimator/) should begin BP-lowering medication when the average BP is >140/90 mmHg (COR: I and LOE: LD). By contrast, for patients with 10-year risk of atherosclerotic cardiovascular disease of >10%, BP-lowering medication should be initiated when the average BP is >130/80 mmHg (COR: I and LOE: systolic BP A, diastolic BP C-EO).[7]

The goal of BP control in the primary prevention of ischemic stroke must consider the effect of race and other factors in addition to patients' cardiovascular risk. Hypertension poses a higher risk of stroke, particularly that of hemorrhagic stroke, in patients from Asian countries than in those from Europe, the United States, and Australia.[10,11] In addition, Asian patients receiving anticoagulants for atrial fibrillation or antithrombotic drugs for the prevention of stroke due to other reasons exhibited higher risk of cerebral hemorrhage.[24–26] Guidelines recently published in Japan regarding the treatment of hypertension indicate that for patients aged <75 years, the target BP value is <130/80 mmHg.[8,27] Studies have considered setting the BP control target to <130/80 mmHg for patients receiving antithrombotic drugs to prevent stroke due to atrial fibrillation or other reasons.[28,29] The guidelines for the treatment of hypertension issued by the TSOC and THS in 2015 and 2017 suggest that patients receiving antithrombotic drugs to prevent stroke should reduce their BP to below 130/80 mmHg (COR: I and LOE: B).[1,5] In view of differences in the disease pattern and physique of patients from Eastern and Western countries, more Asian studies with the main goal of stroke prevention are required as reference for treatment in the future.

3.3. BP control goals for the primary prevention of stroke in older patients with hypertension

Whether BP control goals in older patients are comparable to those in younger patients is always an important issue. Recent meta-analyses have indicated that the clinical benefit of strict BP control (systolic BP < 140 mmHg) is not affected by advanced patient age.[22,30] However, the studies included in these meta-analyses were not limited to patients who had never had stroke. The Hypertension in the Very Elderly Trial (HYVET) examined whether patients aged >80 years with systolic BP controlled below 150 mmHg had lower stroke risk. The study found that patients whose BP was controlled below 150 mmHg had significantly decreased risk of death due to stroke (HR, 0.61; 95% CI, 0.38-0.99).[31] In the Systolic Hypertension in the Elderly Program (SHEP) study focusing on the older population, although the age of patients included in the study was lower than that of patients included in the HYVET (>60 years), the RR of ischemic stroke in patients whose BP was controlled below 150 mmHg was significantly decreased (RR: 0.63; 95% CI, 0.48-0.82).[32] A comprehensive study focusing on Asian populations reported that systolic BP controlled below 140 mmHg in individuals aged >65 years reduced the risk of major cardiovascular events by 29% and the risk of cardiac death by 33%.[33] In SPRINT, for patients aged >75 years, BP controlled below 140 mmHg could still reduce the stroke risk (HR, 0.67; 95% CI, 0.46-0.97).[34] However, regarding clinical evidence for older Asian patients, the results of the Japanese Trial to Assess Optimal Systolic BP in Elderly Hypertensive Patients study must be considered. The study enrolled 4418 Japanese patients with hypertension who were aged ≥65 years and had baseline systolic BP of ≥160 mmHg and followed them for a long period. The study reported that only in the subgroup aged <75 years did systolic BP controlled below 140 mmHg significantly reduce the number of cerebrovascular events.[35] For the primary prevention of ischemic stroke in Taiwan's older population (aged ≥75 years) with hypertension, BP should still be controlled below 140/90 mmHg in accordance with BP treatment guidelines issued by the TSOC and TSH in 2017. For older patients whose basal BP exceeds 160 mmHg before control, caution should be exercised.

3.4. BP medication recommendations for the primary prevention of stroke

The previous guidelines placed more emphasis on control of the BP goal than the types of drugs used.[36] Although many meta-analyses have compared the effects of different BP-lowering drugs on the primary prevention of stroke,[37,38] empirical evidence supporting a marked predominance of one class of BP-lowering drugs over another is insufficient.[36,39,40] Therefore, this guideline maintains the same recommendations as the "Guidelines for Prevention and Treatment of Stroke Risk Factors: Hypertension 2015" of the Taiwan Stroke Society (https://www.stroke.org.tw/GoWeb2/include/pdf/04%20guideline_%E8%85%A6%E4%B8%AD%E9%A2%A8%E5%8D%B1%E9%9A%AA%E5%9B%A0%E5%AD%90%E9%98%B2%E6%B2%BB%E6%8C%87%E5%BC%95%E9%AB%98%E8%A1%80%E5%A3%93.pdf) for the selection of BP-lowering drugs.

Recommendations for BP control for the primary prevention of stroke (BP values recommended are measurements derived from office BP):

1. For the primary prevention of stroke, it is recommended to lower the target BP below 140/90 mmHg (COR: I, LOE: A).
2. For the primary prevention of stroke in patients with hypertension aged >75 years, it is reasonable to control the target BP below 140/90 mmHg (COR: IIa, LOE: B-R).
3. When the primary prevention of stroke is implemented in conjunction with the prevention of other cardiovascular diseases, it is recommended that the goal of BP control take into account the patient's overall cardiovascular risks (COR: I, LOE: A).
4. The control of a BP goal is more important than the types of drugs used. Evidence supporting the predominance of one class of BP-lowering drugs over another is not yet available (COR: I, LOE: A).

4. BP CONTROL AND SECONDARY PREVENTION OF STROKE

Patients who have experienced ischemic stroke have higher risk of stroke recurrence. The recurrence rate in the first year after stroke is 3% to 22% (the rate in Taiwan in 2011 was 7.8%).[41–44]

Moreover, the severity and probability of disability and death after the second stroke are higher than those after the first stroke.[45] Therefore, effective prevention of the recurrence of ischemic stroke (secondary prevention) is of clinical importance. Among many adjustable cardiovascular risk factors, hypertension exhibits the strongest correlation with ischemic stroke. At least 50% of patients with ischemic stroke have history of hypertension (62.5% of patients with ischemic stroke had history of hypertension in Taiwan),[10,44] making hypertension one of the most crucial treatable risk factors for stroke (odds ratio [OR]: 2.98; 95% CI, 2.72-3.28).[10] Therefore, the control of hypertension can be an effective treatment strategy for the secondary prevention of stroke. This treatment guideline was rewritten and updated on the basis of the third section of the 2015 version of the hypertension treatment guideline for BP control and the secondary prevention of stroke.

4.1. Randomized clinical trials regarding BP control for secondary prevention of stroke

Compared with studies on the primary prevention of BP and stroke, only a few experimental studies have specifically focused on BP and secondary prevention of stroke. The important studies are summarized here and in Table 5 in the order of publication year:

1. The earliest randomized trial on BP control to prevent stroke recurrence was begun in the 1960s.[46] The study included only 99 patients with hypertension who had experienced ischemic stroke. These patients were divided into two groups: the control group (no medication) and treatment group (using methyldopa, bethanidine, debrisoquinine, or thiazide diuretic combined with improvements in lifestyle, including weight loss and restriction of salt intake). The target BP was systolic BP < 160 mmHg and diastolic BP < 90 to 100 mmHg. After 2 to 5 years of follow-up, compared with the control group, the treatment group had a lower rate of mortality (26% vs 46%, $p = 0.05$) and a lower recurrence rate of severe cerebral stroke (20% vs 44%).
2. Poststroke Antihypertensive Treatment Study (PATS): This is the first large-scale randomized clinical trial[47] that determined whether controlling BP can reduce the incidence of fatal and nonfatal stroke in patients with history of stroke and transient ischemic attack. This trial included 5665 Chinese at time points ≥1 to 120 months (median: 30 months) after stroke (64.4% of patients experienced ischemic stroke). The drug treatment group used a single BP-lowering drug (depot diuretic indapamide: 2.5 mg/d), the control group was administered placebo, and the follow-up period was 24 months. Furthermore, 83.9% of participants had history of hypertension, and the average BP at the time of enrollment was 154/93 mmHg. Compared with the control group, the treatment group exhibited a reduction of >6.8/3.3 mmHg in their BP after 2 years, and the incidence of all types (ischemic and hemorrhagic) of stroke was 30% lower (relative risk reduction [RRR]: 30%; 95% CI, 43%-14%, $p < 0.001$).
3. Perindopril Protection Against Recurrent Stroke Study (PROGRESS): This was the first large-scale prospective international multicenter clinical trial investigating the effects of BP control on the secondary prevention of stroke.[48] The study included 6105 patients with an average age of 64 years and stroke (71% of patients had ischemic stroke) within the past 5 years (2-22 months, median: 8 months). The patients were randomly divided into the treatment group and control (placebo) group: the treatment group was administered either an angiotensin-converting enzyme inhibitor (ACEI; perindopril, 4 mg/d) or ACEI (perindopril, 4 mg/d) combined with a diuretic (indapamide, 2.5 mg/d). The average BP at the time of enrollment was 147/86 mmHg, and 48% of the patients had history of hypertension (in PROGRESS, hypertension was defined as ≥160/90 mmHg). After an average of 3.9 years of follow-up, the study reported the following findings:

   a. Compared with the control group, the treatment group had a 9/4 mmHg lower BP on average, and the incidence of fatal and nonfatal strokes (RRR) was significantly reduced by 28% (95% CI, 17%-38%, $p < 0.0001$); the risk of all cardiovascular events was significantly reduced by 26% (95% CI, 16%-34%).
   b. The probability of ischemic stroke (RRR) and hemorrhagic stroke was 24% (95% CI, 10%-35%; 8% vs 10%) and 50% (95% CI, 26%-67%; 1% vs 2%) lower in the treatment group than in the control group, indicating that controlling high BP is effective in preventing hemorrhagic stroke.
   c. The benefits of preventing stroke recurrence are related to the degree of BP reduction. Compared with the BP of the control group, the BP of patients receiving both perindopril and indapamide was 12/5 mmHg lower on average, indicating a significantly lower risk of stroke (RRR, 43%; 95% CI, 30%-45%). However, in patients who used perindopril alone to lower their BP, compared with that of the control group, their BP was only 5/3 mmHg lower, and no significant difference was observed in the rate of stroke recurrence between the two groups (RRR, 5%; 95% CI, –19% to 23%).
   d. In both patients with and without hypertension, the treatment significantly reduced the risk of recurrence of all types of stroke compared with the control. However, the risk of stroke recurrence (all types of stroke) was more greatly reduced for patients with hypertension in the treatment group than those without hypertension (RRR: 32% vs 27%), although this difference was not significant (p for homogeneity =.7). In PROGRESS, hypertension was defined as ≥160/90 mmHg.
   e. In the posthoc analysis,[49] the risk of stroke recurrence differed among patients who had different basal BPs at the time of enrollment. The RRRs of all types of stroke recurrence were 39% (95% CI, 21%-53%), 31% (95% CI, 11%-46%), and 14% (95% CI, –13% to 35%) in patients with systolic BP of ≥160, 140 to 159, and 120 to 139 mmHg, respectively (p for trend = 0.05). Moreover, 68%, 58%, and 53% of the patients in the three basal BP groups received combined perindopril and indapamide, respectively.
   f. The benefits to these different basal BP groups differed between ischemic stroke and hemorrhagic stroke. Combined perindopril and indapamide were more effective in preventing ischemic stroke when the basal BP was high; the RRR (the combined drug group compared with the control group) was 43% (95% CI, 19%-60%), 30% (95% CI, –2% to 52%), and 28% (95% CI, –16% to 55%) in patients with systolic BP of ≥160, 140 to 159, and 120 to 139 mmHg, respectively. Combined perindopril and indapamide could significantly prevent hemorrhagic stroke in the various basal BP groups. The RRR was 70% (95% CI, 19%-89%), 88% (95% CI, 50%-97%), and 69% (95% CI, 15%-89%) in patients with a systolic BP of ≥160, 140 to 159, and 120 to 139 mmHg, respectively.[49]

   The findings of the PATS and PROGRESS indicate that controlling hypertension is significantly effective in the secondary prevention of ischemic stroke. Due to ethical considerations, most future trials would not use only placebo without other drugs in the control group to control hypertension.

4. Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention: Principal Results of a Prospective Randomized Controlled Study (MOSES):

Table 5

Randomized clinical trial for BP control for secondary prevention of stroke

Name of the trial, year (n)	Age/gender	Trial group	Types of strokes when enrolled	How long after stroke	Proportion of hypertension/basal BP before enrollment	Control the average value of BP or control the difference in BP value between groups	Average follow-up time	Effectiveness of stroke recurrence prevention
PATS, 1995 (5665)	60.2 ± 8.3 y 28% female	Indapamide 2.5 mg qd vs placebo	64.4% IS, 10.5% TIA, 14.4% ICH	≥1-120 mo (median, 30 mo)	83.9% 154/93 mmHg	Dropped by 12.6/8.9 vs 6.7/5.8 mmHg ΔBP:6.8/3.3 mmHg	2 y	All types of stroke RRR, 30% (95% CI, 43%-14%, $p < 0.001$)
PROGRESS, 2001 (6105)	64 ± 10 y 30% female	Perindopril 4 mg ±indapamide 2.5 mg qd vs placebo	71% IS, 22% TIA, 11% ICH	Median (range), 8 (2-22)mo	48%[a] 147/86 mmHg	ΔBP, 9/4 mmHg (single drug 4.9/2.8 combined drug 12.3/5 mmHg)	3.9 y	All types of stroke RRR, 28% (95% CI, 17%-38%, $p < 0.001$) Ischemic strokeRRR, 24% (95% CI, 10%-35%)
MOSES, 2005 (1405)	67.9 ± 10 y 45.8% female	Eprosartan 600 mg qd vs nitrendipine 10 mg qd	61% IS, 27% TIA, 5% ICH	Mean, 11.6 mo (3% within one week)	100% 151/84 vs 152/87 mmHg	138/81 vs 136/80 mmHg 76% vs 78% reached <140/90 mmHg	2.5 y	All types of stroke incidence density ratio 0.75 (95% CI, 0.58-0.97, $p = 0.03$)
PRoFESS, 2008 (20 332)	66.1 ± 8.6 y 36% female	Telmisartan 80 mg qd vs placebo (other hypertensive medicines allowed in both groups)	100% noncardiogenic IS (52% SVO, 28% LAA)	Median, 15 d 40% ≤ 10 d, 69% ≤1 mo	74%, 144/84 mmHg	ΔBP, 3.8/2 mmHg	2.5 y	All types of stroke 8.7% vs9.2%, HR, 0.95 (95% CI, 0.86-1.04, $p = 0.23$)
RESPECT, 2019 (1280)	67.2 ± 8.8 y 30.6% female	<120/80 mmHg vs<140/90 mmHg (if DM, CKD, CAD <130/80 mmHg)	85% IS, 15% ICH	>1 mo–3 y Median, 4.6 mo	100% 145/84 mmHg	127/77 vs 133/78 mmHg ΔBP:6.5/3.3 mmHg	3.9 y	All types of stroke HR, 0.73 (95% CI, 0.49-1.11), intracerebral hemorrhage HR, 0.09 (95% CI, 0.01-0.70), ischemic stroke HR, 0.91 (95% CI, 0.59-1.42)

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; ICH = intracranial hemorrhage; IS = ischemic stroke; LAA = large-artery atherosclerosis; MOSES = Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention: Principal Results of a Prospective Randomized Controlled Study; PATS = Poststroke Antihypertensive Treatment Study; PRoFESS = revention Regimen for Effectively Avoiding Second Strokes; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RESPECT = Recurrent Stroke Prevention Clinical Outcome Study; RRR = relative risk reduction; SVO = small-vessel occlusion; TIA = transient ischemic attack.

[a]PROGRESS defined hypertension as ≥160/90 mmHg.

This was the first clinical trial to compare the effects of different BP medications on the secondary prevention of stroke.[50] In this study, 1352 patients with hypertension with history of stroke (61% with ischemic stroke) in the preceding 2 years (average, 11.6 months) were analyzed, and they were divided into the eprosartan group (angiotensin II receptor blocker; 600 mg/d) and nitrendipine group (calcium channel blocker [CCB], 10 mg/d). After 2.5 years of follow-up, the BP of the two groups was similar (137.5/80.8 mmHg vs 136.0/80.2 mmHg). However, the risk of stroke was 25% lower (incidence density ratio, 0.75; 95% CI, 0.58-0.97, p = 0.03) and the risk of the composite cardiovascular event (cardiovascular death, myocardial infarction, and stroke) was 21% lower (incidence density ratio, 0.79; 95% CI, 0.66-0.96, p = 0.014) in the eprosartan group than in the nitrendipine group.

5. Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS): To date, the PRoFESS trial is the largest secondary stroke prevention clinical trial.[51] A total of 20 332 patients with recent noncardiogenic ischemic stroke (within 3 months of the stroke event; median: 15 days, 40% within 10 days) were randomized into this study; the mean BP of the patients was 144/84 mmHg at the time of enrollment. The patients were divided into the telmisartan (80 mg/d) and control groups. All other types of BP-lowering drugs (except for angiotensin receptor blockers) were allowed as additional treatment medications in both groups. After an average of 2.5 years of follow-up, no significant differences in the risks of recurrent stroke (8.7% vs 9.2%, HR, 0.95; 95% CI, 0.86-1.04, p = 0.23) and major cardiovascular events (13.5% vs 14.4%, HR, 0.94; 95% CI, 0.87-1.01) were observed between the telmisartan and control groups. The expected result was not obtained for the telmisartan group possibly because their BP was only 3.8/2 mmHg lower than that of the control group; this reduction is the same as that observed in patients receiving perindopril monotherapy alone in the PROGRESS trial (5/3 mmHg lower than the control group).
6. Recurrent Stroke Prevention Clinical Outcome Study (RESPECT): RESPECT, published in 2019, was a secondary stroke prevention clinical trial conducted in the Japanese population.[52] A total of 140 Japanese hospitals participated, and the study examined whether aggressive BP control is more beneficial for stroke prevention. A total of 1280 patients with stroke (85% with ischemic stroke) within the preceding 3 years (>1 month, median: 4.6 months) were included; the average BP of the patients was 145/84 mmHg at the time of enrollment. A total of 633 patients were randomized to the aggressive control group (expected BP control <120/80 mmHg) and 630 were randomized to the standard treatment group (expected BP control <140/90 mmHg and <130/80 mmHg for those with diabetes, chronic kidney disease, or myocardial infarction). After an average of 3.9 years of follow-up, the difference in average BP between the two groups was 6.5/3.3 mmHg. No significant difference in the prevention of stroke recurrence was observed between the two groups (HR, 0.73; 95% CI, 0.49-1.11, p = 0.15). In terms of the subtype of stroke, aggressively controlling BP could reduce the incidence of cerebral hemorrhage (HR, 0.09; 95% CI, 0.01-0.70, p = 0.02) but not that of ischemic stroke (HR, 0.91; 95% CI, 0.59-1.42, p = 0.69).

4.2. Systemic reviews and meta-analyses of BP control for secondary prevention of stroke

This update includes only results published after 2015.

1. A systematic review published in 2017 including 14 RCTs on the secondary prevention of stroke reported that in patients

with history of stroke,[53] antihypertensive medications could effectively reduce the risks of recurrent stroke (risk ratio, 0.73; 95% CI, 0.62-0.87), disabling or fatal stroke (risk ratio, 0.71; 95% CI, 0.59-0.85), and death due to cardiovascular disease (risk ratio, 0.85; 95% CI, 0.75-0.96). In addition, decrease in systolic BP and stroke recurrence exhibited a linear correlation (regression slope: 0.02; 95% CI, 0.02-0.04, p = 0.049). Similarly, a decrease in diastolic BP was linearly correlated with stroke recurrence (regression slope, 0.08; 95% CI, 0.01-0.15, p = 0.026).

2. An article published in a Cochrane review in 2018 included 11 RCTs on secondary stroke prevention. A total of 38 742 patients were recruited with an average of at least 48 hours from the onset of stroke to enrollment; the average follow-up among the RCTs ranged from 12 to 47 months.[54] Of the 11 RCTs, 8 investigated the effects of antihypertensive medication vs placebo and 3 examined differences between aggressive BP-lowering and standard BP control. The review found that hypertension medication reduced the risk of recurrent stroke (pooled risk ratio, 0.81; 95% CI, 0.70-0.93) and major vascular events (pooled risk ratio, 0.90; 95% CI, 0.78-1.04).
3. In 2019, a meta-analysis including the Secondary Prevention of Small Subcortical Stroke (SPS3), Prevention After Stroke-BP, Prevention of Decline in Cognition After Stroke, and RESPECT trials reported that active control of BP (systolic BP of <125 or <130 mmHg) could effectively reduce the recurrence of all types of stroke (relative risk, 0.78; 95% CI, 0.64-0.96, p = 0.02). However, active control of BP was only effective for hemorrhagic stroke (relative risk, 0.25; 95% CI, 0.07-0.90) but not ischemic stroke (relative risk, 0.88; 95% CI, 0.71-1.08).[52]

4.3. Target population

The 2014 AHA/ASA Stroke Guidelines recommend that except for a few patients, all patients with history of stroke or transient cerebral ischemia should receive BP control.[55] This recommendation is based on the results of multiple RCTs. However, patients should be educated regarding the symptoms of low BP including weakness and dizziness.

4.4. When to start treatment

Relevant clinical trials discussing when to start BP treatment after 24 hours of the acute phase are not available. In most of the large trials on BP control for the secondary prevention of stroke, patients were enrolled during the chronic phase of stroke (>3 months after stroke onset; median values, PATS: 30 months, PROGRESS: 8 months, and MOSES: 11.6 months)[47,48,50]; only PRoFESS enrolled more recent patients with stroke (median 15 days, 40% of patients with stroke onset within 10 days after stroke).[51] The treatment effect did not differ between patients with stroke onset within 10 days vs those beyond 10 days. In a PRoFESS subgroup analysis,[56] the number of eligible patients with mild functional impairment (modified Rankin Scale < 3) and stable neurological deficits within 72 hours of stroke was 647 in the telmisartan group and 713 in the control group. This finding indicated that although telmisartan did not exert a more favorable preventive effect on recurrent stroke (3-month recurrence rate for all types of stroke, OR, 1.40; 95% CI, 0.68-2.89), it was at least safe (severe side effects within 3 months, OR, 1.43; 95% CI, 0.93-2.22).

The current consensus of experts is that for inpatients who are stable (the neurological deficit is not continually worsened by insufficient cerebral perfusion) and patients with stroke in outpatient clinics after at least 24 hours in the acute phase of ischemic stroke, BP control drugs should be used immediately.

4.5. BP treatment goals for patients with stroke

The new versions of the AHA/ASA and Japanese Society of Hypertension (JSH 2019) guidelines recommend a target value of <130/80 mmHg.[7,57] The recommendations of the European Society of Cardiology and European Society of Hypertension (ESC/ESH) are slightly different from those of the AHA/ASA. Their recommended target value for patients who experienced stroke is ≈130 mmHg over 70 to 79 mmHg.[58] The recommended target value stipulated by the TSOC and TSH in 2017 is <140/90 mmHg.[5] By contrast, the European Stroke Society recommends that BP-lowering drugs should be used for the secondary prevention of all types of stroke. Even if BP is within the normal range, an average BP drop of 10/5 mmHg is recommended.[59] The guidelines in the United Kingdom recommend maintaining BP below 130/80 mmHg.[60]

A large proportion of these recommendations are based on the different interpretations of the results of clinical trials.

A subanalysis of the PROGRESS trial indicated that patients whose average BP was controlled as low as 112/72 mmHg, regardless of ischemic or hemorrhagic stroke, had the lowest risk of stroke recurrence. In addition, no so-called J-curve phenomenon was observed. These findings support the importance of active BP control in the secondary prevention of stroke.[49]

In the PRoFESS trial, compared with patients with systolic BP controlled at 130 to 140 mmHg, patients with systolic BP controlled at <120 mmHg had higher risk of recurrence of all types of stroke (adjusted HR, 1.29; 95% CI, 1.07-1.56).[61] In addition, compared with patients with systolic BP of 130 to 140 mmHg, patients with average systolic BP of 120 to 130 mmHg did not experience an additional benefit of reduction in stroke recurrence (adjusted HR, 1.10; 95% CI, 0.95-1.28); however, this level of control slightly increased the risk of secondary outcomes (composite events of stroke, myocardial infarction, or death from vascular causes; adjusted HR, 1.16; 95% CI, 1.03-1.31).

The SPS3 trial divided patients with small-vessel occlusion ischemic stroke (symptomatic lacunar infarction) into two groups: systolic BP of <130 mmHg and 130 to 149 mmHg.[62] After an average of 3.7 years of follow-up, no significant differences in the risk of stroke recurrence (HR, 0.81; 95% CI, 0.64-1.03) and that of disabling or fatal stroke (HR, 0.81; 95% CI, 0.53-1.23) were observed between the two groups. The only significant difference was noted in the prevention of hemorrhagic stroke (HR, 0.37; 95% CI, 0.15-0.95).

A meta-analysis including the large-scale SPS3 and RESPECT trials found that aggressively controlling BP (systolic BP <125 or <130 mmHg) effectively reduced the recurrence of all types of stroke (relative risk, 0.78; 95% CI, 0.64-0.96, p = 0.02). Upon analysis by stroke type, the reduction was only observed for hemorrhagic stroke (relative risk, 0.25; 95% CI, 0.07-0.90) and not for ischemic stroke (relative risk, 0.88; 95% CI, 0.71-1.08).[52] However, in SPS3, all patients with small-vessel occlusion ischemic stroke were included.

4.6. Most suitable antihypertensive drug for patients with stroke

No study has yet reported the type of BP medication that is most suitable as the initial medication for patients with ischemic stroke, and the consensus is that the degree of BP control exerts a greater effect on stroke recurrence than the type of medication. However, some treatment guidelines, such as National Institute for Health and Care Excellence and 2015 TSOC/TSH,[1,63] recommend that compared with other drugs, beta-blockers cannot reduce the risk of stroke. A meta-analysis of 15 studies including 39 329 patients reported that compared with placebo, only ACEIs and diuretics could effectively reduce stroke recurrence (OR: 0.54; 95% CI, 0.33-0.90).[64] Another systematic review

reported that compared with placebo, only ACEIs, diuretics, and CCBs could effectively reduce the risk of stroke in patients with cardiovascular disease.[65]

Recommendations for BP control for secondary prevention of stroke (BP values recommended are measurements derived from office BP data):

1. For patients who have history of hypertension and have been treated with BP-lowering medication, after the acute phase of ischemic stroke, it is recommended to resume BP control to prevent recurrent stroke and other vascular events (COR: I, LOE: A).
2. For patients who have never received BP treatment, after the acute phase of ischemic stroke, it is recommended to start treatment with a target BP <140/90 mmHg (COR: I, LOE: B-R).
3. After the acute phase of ischemic stroke, it is reasonable to treat for the BP at target <130/80 mmHg to prevent all types of stroke (ischemic and hemorrhagic stroke; COR: IIa, LOE: B-R).
4. The control of BP goals is more important than the types of drugs used. The choice of antihypertensive drugs and the recommended BP targets for control should be individualized in accordance with the pharmacological characteristics and mechanisms of drugs, patient characteristics, and the cause of stroke (COR: I, LOE: B-NR).

5. BP CONTROL AND SECONDARY PREVENTION OF LARGE-ARTERY ATHEROSCLEROSIS ISCHEMIC STROKE

Large-vessel atherosclerosis can cause vascular stenosis. In addition to compromising cerebral blood flow, unstable atherosclerotic plaques may induce platelet activation and thrombus formation, thus resulting in arterial embolism. Approximately 20% to 30% of ischemic strokes are caused by the aforementioned two mechanisms of large-artery atherosclerosis.[66] Hypertension is a known risk factor for atherosclerosis. Clinical trials have shown that lowering BP improves the severity of coronary atherosclerosis[67] and reduces carotid intima-media thickness.[68] Therefore, lowering BP may exert a preventive effect on large-vessel atherosclerosis ischemic stroke. For the prevention of this type of stroke, the target value of BP control and BP drugs to be used are crucial clinical issues.

Compared with the primary prevention of stroke, only a few clinical trials investigating the secondary prevention of stroke have specifically examined the effects of lowering BP on stroke prevention (PATS, PROGRESS, MOSES, PRoFESS, and RESP ECT),[48,50,52,69,70] Moreover, patients with ischemic stroke of all causes (large-artery atherosclerosis, small-vessel occlusion, and cardioembolism) were enrolled in those trials. At present, the available evidence is still insufficient to make recommendations for BP control for strokes with specific causes. Both the 2017 guidelines of the TSOC and THS and the 2014 guidelines of the AHA/ASA recommend a BP target for secondary stroke prevention of <140/90 mmHg (regardless of the cause of stroke).[5,55] However, in the ESC/ ESH 2018 guidelines and ACC 2017 guidelines, the recommended target is <130/80 mmHg (regardless of the cause of stroke).[7,58] The RESPECT trial conducted in 2019 showed that aggressively controlling BP to <120/80 mmHg more effectively reduced the risk of cerebral hemorrhage than controlling BP to <140/90 mmHg; however, the effect of this control on the prevention of ischemic stroke (including the subanalysis of large-artery atherosclerosis and other causes) was not significantly different. Therefore, evidence indicating the necessity of different BP targets in different stroke causes is inadequate. However, on the basis of the aforementioned findings, setting the BP target to <130/80 mmHg raises no safety concerns. This article summarizes the relevant evidence to recommend a BP control target in patients with ischemic stroke caused by large-vessel atherosclerosis.

Ischemic stroke caused by large-artery atherosclerosis is associated with significant intracranial or extracranial artery stenosis. Whether a decrease in BP in patients with ischemic stroke and severe arterial atherosclerotic stenosis would decrease cerebral perfusion and thus increase the risk of stroke remains unclear. However, no clinical trials have explored BP control goals specific for the secondary prevention of stroke caused by intracranial and extracranial large-artery atherosclerosis. The research results described in this chapter are all based on the clinical trials of surgery or endovascular treatment for ischemic stroke caused by large-artery atherosclerosis. Only selected patients who received medical treatment but did not receive surgery or endovascular treatment (control group) were evaluated to determine the relationship between BP and the recurrence rate of ischemic stroke after large-artery atherosclerosis ischemic stroke.

5.1. Extracranial artery stenosis

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) enrolled patients with symptomatic extracranial carotid artery stenosis. NASCET enrolled patients within 120 days after onset, whereas ECST did so within 6 months after onset. The patients were randomized to medical treatment ± carotid endarterectomy. A total of 5903 patients were included. The BP target was selected according to clinicians' judgment. NASCET and ECST followed up the patients for an average of 60 and 73 months, respectively.[71,72] Higher BP increased the risk of stroke (for every 10 mmHg increase in diastolic BP, HR, 1.37 [95% CI, 0.97-1.96, p =.09] in ECST and HR, 1.51 [95% CI, 1.06-2.02, p = 0.01] in NASCET). However, in patients with bilateral extracranial carotid artery stenosis ≥7 0% (n = 150), those with higher BP had lower risk of stroke (systolic BP: ≥146 mmHg compared with <146 mmHg, HR, 0.41; 95% CI, 0.19-0.90, p =.02).[73] The Carotid Occlusion Surgery Study (COSS) trial enrolled patients with symptomatic extracranial carotid artery occlusion and randomized them into medical treatment (within 120 days of onset) ± extracranial to intracranial arterial bypass grafting surgery (n = 195; BP target: ≤130/85 mmHg).[74] The median follow-up period was 723 days. Even when the cerebral blood flow was reduced, positron emission tomography revealed that the oxygen extraction rate of the diseased side was increased to more than 1.13 times that of the healthy side due to complete occlusion of the ipsilateral internal carotid artery. Patients with BP of >130/85 mmHg had higher risk of stroke than did those with BP of ≤130/85 mmHg (HR, 3.74; 95% CI, 1.07-13.15, p = 0.027).[75]

5.2. Intracranial artery stenosis

The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial enrolled patients with symptomatic intracranial arterial stenosis of >50% within 90 days of onset and randomized them into aspirin vs warfarin groups (n = 569).[76] The BP target was selected according to clinicians' judgment, and the mean follow-up period was 1.8 years. The Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial enrolled patients with symptomatic intracranial arterial stenosis of >70% within 30 days of onset and randomized them into medication ± percutaneous transluminal angioplasty and stenting groups (n = 451).[77] The systolic BP control target was <140 mmHg for patients without diabetes and <130 mmHg for patients with diabetes. The patients were followed up for 15 months. Higher BP was associated with increased risk of stroke, and the risk of stroke did not increase in patients with lower BP (WASID: diastolic BP of ≥90 mmHg vs ≤79 mmHg, HR, 5.1; 95% CI, 2.1-12.4,

p = 0.0003; SAMMPRIS: BP met the target vs missed the target, OR, 2.1; 95% CI, 1.2-4.0; p < 0.05).[78,79] In the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) observational study, patients with symptomatic vertebral arterial or basilar arterial stenosis of >50% within 60 days after onset (n = 72) were included.[80] The BP target was <140/90 mmHg for patients without diabetes and <130/80 mmHg for patients with diabetes. The median follow-up period was 23 months. Patients had insufficient flow in vertebral-basilar posterior circulation arteries (n = 18, quantified using NOVA software for magnetic resonance angiography; insufficient was defined as 20% lower than the lower limit of the reference value). In total, 16 of the 18 patients (89%) had arterial stenosis of >70%. The risk of stroke in patients with BP of <140/90 mmHg was higher than that in those with BP of ≥140/90 mmHg (HR, 4.5; 95% CI, 1.3-16.0, P = 0.02). In 2018, a clinical trial enrolled 111 patients with symptomatic intracranial arterial stenosis of >50% within 7 to 42 days of onset and excluded patients who planned to undergo endovascular intervention or surgery within 7 months. The patients were randomized into groups with a systolic BP control target of <120 vs <140 mmHg. The patients with a systolic BP target of <120 mmHg had a greater increase in white-matter hyperintensities after 24 weeks than did those with a systolic BP target of <140 mmHg (the proportion of having new white-matter hyperintensities was 16.9% vs 9.6%, respectively; noninferiority test p = 0.26). Thus, systolic BP of <120 mmHg was not found to be inferior to that of <140 mmHg.[81]

The aforementioned results indicate that BP control is necessary in patients with symptomatic intracranial and extracranial arterial atherosclerotic stenosis; however, more attention should be paid to the possible adverse effects of hypotension and hypoperfusion when lowering BP. In patients with high-grade stenosis of bilateral internal carotid arteries and patients with insufficient flow in posterior circulation arteries, excessive lowering of BP may increase the risk of stroke.

Among the aforementioned clinical trials on the secondary prevention of stroke, only MOSES compared the efficacy of the angiotensin II receptor antagonist eprosartan and the CCB nitrendipine (the addition of other antihypertensive drugs was allowed to achieve the target of <140/90 mmHg). Other trials did not compare the effects of different types of antihypertensive drugs. The MOSES trial reported that the recurrence rate of stroke was lower with eprosartan than with nitrendipine. However, MOSES did not classify the causes of stroke. Therefore, no evidence has yet indicated the antihypertensive drug that is most effective for stroke prevention in patients with large-artery atherosclerosis.

Recommendations for BP control for secondary prevention of ischemic stroke caused by large-artery atherosclerosis (BP values recommended are measurements derived from office BP data):

1. After the acute phase of ischemic stroke caused by large-artery atherosclerosis, it is recommended to start treatment with a target BP <140/90 mmHg (COR: I, LOE: B-R).
2. In patients with intracranial or extracranial artery stenosis, especially those with bilateral internal carotid arterial stenosis >70% or basilar arterial stenosis >70%, more attention should be paid to the adverse effects of hypotension and hypoperfusion when lowering BP (COR: IIb, LOE: B-NR).

6. BP CONTROL AND SECONDARY PREVENTION OF SMALL-VESSEL OCCLUSION ISCHEMIC STROKE

Cerebral small-vessel disease is an important cause of acute stroke. Epidemiological data show that cerebral infarction caused by small-vessel diseases in the brain accounts for approximately a quarter or more of all ischemic stroke cases.[82] The proportion of cerebral small-vessel disease is higher in Asians than in European and American Caucasians.[66,83] In a study including >30 000 people registered in the Taiwan stroke database in 2010, ischemic stroke and cerebral small-vessel disease accounted for ≈74% and 37.7% of ischemic stroke patterns, respectively.[66] Cerebral small-vessel diseases are also a crucial cause of intracerebral hemorrhage (ICH).[84] A study on the National Taiwan University Hospital's Stroke Registration Database published in 2014 reported that cerebral small-vessel disease, including hypertensive angiopathy and cerebral amyloid angiopathy, accounted for 54.9% and 12.2% of all ICH cases, respectively.[85] In addition, cerebral small-vessel diseases are the most common cause of neurovascular degenerative diseases such as vascular dementia and vascular Parkinsonism. Therefore, effectively preventing cerebral small-vessel diseases is of clinical importance.[86]

Cerebral small-vessel diseases have many causes that can be divided into six categories.[82,87,88] The first category is arteriosclerosis related to vascular risk factors such as hypertension, diabetes, cigarette smoking, aging, and dyslipidemia. The blood vessels affected are mainly deep subcortical arterioles due to chronic hypertension. The second category is cerebral amyloid angiopathy caused by amyloid deposition in the blood vessel wall; the affected blood vessels are mainly superficial arterioles. The third category is hereditary small-vessel diseases, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy caused by *NOTCH3* gene mutations.[89,90] The fourth category is immune-related vasculitis, the fifth category is venous collagenosis, and the sixth category is other unknown causes.

The clinical manifestations of cerebral small-vessel diseases are diverse and not restricted to stroke syndrome.[86,91] In addition to history taking and neurological examinations by clinicians, brain imaging examinations, especially magnetic resonance imaging (MRI), are the most crucial first-line diagnostic tools.[92] In addition to lacunar infarction and ICH, abnormalities that may be observed on MRI scans of patients with cerebral small-vessel diseases include lacunae, cerebral microbleeds (CMBs), white-matter hyperintensities, and obvious perivascular space.[82,91,93] The degree of nerve damage caused by cerebral small-vessel diseases varies, and clinical manifestations may range from asymptomatic to disability due to stroke or dementia. Early diagnosis of cerebral small-vessel diseases and effective prevention of the deterioration of these diseases are crucial.

Hypertension is the main cause of cerebral small-vessel diseases, and fluctuations in BP may affect overall perfusion in the brain with corresponding ischemic changes or cause small-vessel rupture with hemorrhage. Therefore, appropriately controlling BP in patients with cerebral small-vessel disease is a clinically crucial topic for discussion. Observational studies have reported that the value and variation of BP were related to the severity of small-vessel disease, future cardiovascular events, or deterioration of small-vessel imaging features.[94–97] Clinical trials on BP in patients with cerebral small-vessel disease can be divided into two categories: those including patients with stroke but not limited to patients with small-vessel disease[48,51] and those including patients with cerebral small-vessel disease with the endpoint being a change in clinical or imaging features associated with cerebral small-vessel disease (including the SPS3 and PRESERVE trials).[62,92] The following is a brief description of these trials' content.

The PROGRESS trial published in 2001 included 6105 patients with past ischemic or hemorrhagic stroke or transient cerebral ischemia.[48] The trial group was administered 4 mg of perindopril (angiotensin-converting enzyme inhibitor) per day and 2.5 mg of indapamide, a diuretic, as appropriate, whereas

the control group was administered placebo. The average follow-up period of the trial was 4 years. At the beginning of the trial, the average BP of the two groups was 147 ± 19/86 ± 11 mmHg. The average drop in BP was 9/4 mmHg in the trial group compared with the control group after drug administration. At the end of the trial, 307 (10%) and 420 (14%) patients had had a stroke event in the trial group and control group, respectively. The adjusted RRR of the trial drug was 28% (95% CI, 17%-38%). In addition, one of the follow-up studies of PROGRESS was published in 2005.[98] This study analyzed 192 patients who underwent brain MRI at the time of enrollment in the trial and at the endpoint. Among these patients, 12.5% developed new or worsening white-matter hyperintensities during the average follow-up period of 3 years. Further analysis showed that compared with the control group, the trial group had nonsignificantly lower risk of new white-matter hyperintensities, and the total volume of new white-matter hyperintensities was significantly smaller (0.4 mm^3 vs 2.0 mm^3, p = 0.012). Such results indirectly reflect that use of antihypertensive drugs may delay the progression of cerebral small-vessel diseases.

The PRoFESS trial was published in 2008.[51] The trial included patients with ischemic stroke within 3 months of the stroke onset. The trial group was administered telmisartan (80 mg per day), and the control group was administered placebo. All other types of BP-lowering drugs (except angiotensin receptor blockers) could be used as additional BP treatment drugs in the two groups. A total of 20 332 patients were enrolled in the trial. On average, they participated in the trial 15 days after stroke. At the time of enrollment, 52.1% and 52.0% of patients had small-vessel occlusion ischemic stroke in the two groups, respectively. The follow-up period was 2.5 years. Furthermore, 880 (8.7%) and 934 (9.2%) patients had stroke events in the treatment and control groups, respectively. The HR of using telmisartan was 0.95 (95% CI, 0.86-1.04, p = 0.23). The PRoFESS trial also involved a follow-up image analysis study to evaluate whether the use of telmisartan slows the development of white-matter hyperintensities. The results were published in 2012.[99] A total of 771 patients underwent brain MRI at the time of enrollment in the trial and at the endpoint. However, no significant difference in changes in white-matter hyperintensities during the follow-up period was observed between the two groups.

Compared with the PROGRESS trial, the PRoFESS trial had simpler criteria for including patients. The PRoFESS trial included all recent cases of ischemic stroke and had a larger sample; more than half of the cases had small-vessel occlusion ischemic stroke. The results of PRoFESS indicated no significant difference in stroke recurrence between the treatment and control groups. In addition to using the trial drug telmisartan, the PRoFESS trial allowed the use of other types of BP-lowering drugs (except angiotensin receptor blockers). Therefore, in the treatment group, the BP value was only 3.8/2 mmHg lower than that in the control group, which may be one of the reasons why the trial obtained nonsignificant results.

The SPS3 trial was published in 2013.[62] This is the only clinical trial focusing on the secondary prevention of small-vessel occlusion ischemic stroke. This study enrolled recent (within 6 months) cases of small-vessel occlusion ischemic stroke diagnosed through brain MRI and excluded cases of psychogenic or ipsilateral carotid arterial stenosis and disabling stroke (modified Rankin Scale ≥ 4). In addition, cases with history of nontraumatic ICH or cerebral cortical ischemic stroke were excluded. Patients were divided into two groups with systolic BP controlled at or below 130 to 149 mmHg. A total of 3020 people were enrolled in the trial and followed for an average of 3.7 years. One year after the enrollment, the mean systolic BP in the two groups was 138 (95% CI, 137-139) and 127 mmHg (95% CI, 126-128), respectively. The results showed that aggressively controlling BP did not significantly reduce the incidence of all stroke events (HR, 0.81; 95% CI, 0.64-1.03, p = 0.08) or that of comprehensive cardiovascular events (HR, 0.84; 95% CI, 0.68-1.04, p = 0.32) or improve the prognosis of disability or death due to stroke (HR, 0.81; 95% CI, 0.53-1.23, p = 0.32). However, aggressively controlling BP significantly reduced the risk of ICH (HR, 0.37; 95% CI, 0.15-0.95, p =.03). The proportion of adverse events that may be related to more aggressive BP treatment—including postural fainting, falls, stroke caused by hypotension, dizziness when standing, blurred vision, and unstable balance—did not significantly differ between the two groups. Because it can significantly reduce the risk of cerebral hemorrhage and does not increase the likelihood of other related events or adverse reactions, aggressive control of systolic BP to <130 mmHg may be considered a control target for treatment in cases of small-vessel occlusion ischemic stroke.

A subanalysis of SPS3 evaluated whether more aggressive BP control affected the cognitive function of patients who recently experienced small-vessel occlusion ischemic stroke during the follow-up period. The results were published in 2014.[100] A total of 2916 cases were enrolled. Cognitive screening tests were conducted before and after the trial. The patients were followed for an average of 3 years. The results did not reveal significant differences between the treatment groups. Another SPS3 subanalysis examining CMBs and prognosis was published in 2017.[101] The results showed that 30% of the 1278 patients who received MRI had CMBs. During the trial with follow-up for an average of 3.3 years, the risk of stroke recurrence in patients with CMBs increased by two times (HR, 2.1; 95% CI, 1.4-3.1). In addition, aggressive BP control could significantly reduce the incidence of recurrent stroke in both patients with ≥1 CMBs and those with ≥3 CMBs (≥1 CMBs, HR, 0.5; 95% CI, 0.3-0.9; ≥3 CMBs, HR, 0.2; 95% CI, 0.1-0.8). However, such a correlation was not obvious in patients without CMBs. Another SPS3 subanalysis study explored whether more aggressive BP control deteriorated renal function (defined as a decrease in estimated glomerular filtration rate by more than 30%).[102] Among the 2610 patients enrolled in the analysis, more patients in the aggressive treatment group than the control group had worsening renal function in the first year (24% vs 19%, OR, 1.4; 95% CI, 1.1-1.6). However, this difference was not significant after the second year of the trial. Further analysis showed that the deterioration of renal function in the aggressive treatment group was not related to the occurrence of clinical events defined by the trial. These results indicated that after small-vessel occlusion ischemic stroke, attention should be paid to changes in renal function while aggressively controlling BP.

In the PRESERVE trial published in 2018, brain perfusion images were employed to explore whether aggressive control of BP in patients with cerebral small-vessel disease affects cerebral blood flow.[92] The trial included 70 patients with high BP who were diagnosed as having cerebral small-vessel disease through MRI (symptomatic lacunar infarct + confluent white-matter hyperintensities) and divided them into two groups: standard BP treatment group (systolic BP: 130-140 mmHg) and aggressive BP treatment group (systolic BP: <125 mmHg). The two groups were subjected to magnetic resonance scanning arterial spin labeling at the beginning of the trial and 3 months later. At the beginning of the trial, the systolic BP of the standard and aggressive BP treatment groups was 150 ± 10 and 153 ± 12 mmHg, respectively. During the trial, the systolic BP decreased by 8 ± 12 and 27 ± 17 mmHg, respectively; however, the difference in cerebral blood perfusion was not significant before or after the BP control regardless of whether a comparison was made between the two groups or within a group. Although the number of cases in this trial was small, the results showed that aggressive BP control in patients with cerebral small-vessel diseases does not lead to lower cerebral blood flow or cause cerebral ischemia.

Table 6

Recommended BP control targets (mmHg) for ischemic stroke prevention in different conditions

	Target (mmHg)	
Primary prevention	<140/90	(COR: I, LOE: A)
Secondary prevention-general	<140/90	(COR: I, LOE: B-R)
	<130/80 is reasonable	(COR: IIa, LOE: B-R)
Secondary prevention-LAA	<140/90	(COR: I, LOE: B-R)
Secondary prevention-SVO	<140/90	(COR: I, LOE: B-R)
	SBP < 130 is reasonable	(COR: IIa, LOE: B-R)

BP = blood pressure; COR = class of recommendation; LAA = large-artery atherosclerosis; LOE = level of evidence; SBP = systolic blood pressure; SVO = small-vessel occlusion.

In conclusion, with the development of imaging and laboratory diagnostic tools in recent years, the crucial role of cerebral small-vessel diseases in various cerebrovascular and neurodegenerative diseases has become increasingly clear. Although the cause and mechanism of cerebral small-vessel diseases are complicated, BP remains the most critical risk factor. Several unresolved questions include whether BP medicines and BP targets should be different for cerebral small-vessel lesions of different causes; whether different BP drugs have individual effects on cerebral small-vessel disease prevention; whether different prevention strategies should be adopted for small-vessel–related strokes of different types (hemorrhage or ischemia); and whether the reasons underlying the cerebral small-vessel diseases in Eastern vs Western populations and treatment responses are different. Answers should be sought in future studies. To date, for cases of small-vessel occlusion ischemic stroke, BP should be aggressively controlled, especially to prevent cerebral hemorrhage; however, it is necessary to pay attention to the risk of renal function decline, which can occur in the first year.

Recommendations for BP control for secondary prevention of small-vessel occlusion ischemic stroke (BP values recommended are measurements derived from office BP data):

1. After the acute phase of small-vessel occlusion ischemic stroke, it is recommended to start treatment with a target BP <140/90 mmHg (COR: I, LOE: B-R).
2. After the acute phase of small-vessel occlusion ischemic stroke, it is reasonable to control the systolic BP <130 mmHg, and changes in renal function after active BP control should be monitored (COR: IIa, LOE: B-R).

The recommended BP control targets for ischemic stroke prevention in different conditions are summarized in Table 6.

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