

Blood Pressure Management for Stroke Prevention and in Acute Stroke

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Elevated blood pressure (BP) is the leading modifiable risk factor for stroke and the benefit of BP lowering therapy on the stroke risk reduction is well established. The optimal BP target for preventing stroke and other vascular events have been controversial, but the evidences from epidemiological studies and randomized controlled trials (RCTs) support intensive BP lowering for greater vascular protection, particularly for stroke prevention. For secondary stroke prevention, the evidence of intensive BP lowering benefit is limited since only a single RCT for patients with lacunar infarctions was conducted and most data were driven by exploratory analyses. In acute intracerebral hemorrhage, immediate BP lowering targeting systolic BP < 140 mm Hg is recommended by guidelines based on the results from RCTs. In contrast, in acute ischemic stroke, early BP lowering is not usually recommended because of no benefit on functional outcome and future vascular events and potential harm of stroke progression. This review aims to summarize the updated evidence for optimal BP management for primary and secondary stroke prevention and in patients with acute stroke.

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Introduction

Worldwide, more than one billion people have elevated blood pressure (BP),¹ and elevated BP is the leading modifiable risk factor for stroke.² The association of high BP and stroke risk is well demonstrated by large epidemiological studies, and the BP lowering benefit on the stroke risk reduction is clearly confirmed by well-designed randomized controlled trials (RCTs). Since the incidence and mortality of stroke as well as major cardiovascular events increase with increasing BP levels beyond 115/75 mm Hg,³⁻⁵ the optimal BP in general population is defined as < 120/80 mm Hg. However, for individuals with elevated BP, the target for BP lowering, intensive versus less intensive lowering, has long been debated. The uncertainty of target BP for secondary stroke prevention is even greater.

Among patients with acute stroke, BP is elevated in 70–75%

of the patients. Underlying hypertension and physiological or pathological responses to acute stroke likely contribute to the BP elevation. However, the optimal BP management during the acute stage still remains unclear, particularly in patients with acute ischemic stroke.

The last decades have seen accumulated evidences of BP management and stroke. This narrative review will present and discuss the findings from major epidemiological studies and RCTs, focusing on BP management for primary and secondary stroke prevention and patients with acute stroke.

BP Control for Primary Stroke Prevention

Epidemiological studies

Multiple epidemiological studies showed that high BP was as-

sociated with an increased risk of stroke mortality. A large collaborative meta-analysis of individual participant data from 61 prospective observational studies (958,074 individuals with 12.7 million person-years follow-up; 56,335 vascular deaths including 11,960 stroke deaths, 34,283 ischemic heart disease deaths, and 10,092 other vascular deaths) showed that, for BP \geq 115/75 mm Hg, the risk of stroke mortality in all age groups significantly increased with increasing BP levels, and the association of BP was greater with stroke mortality than with ischemic heart disease mortality. In individuals aged 40–69 years, every 20 mm Hg decrease in systolic BP (SBP) or 10 mm Hg decrease in diastolic BP (DBP) was associated with more than 2-fold decrease in the stroke mortality.³

High BP is associated with an increased risk of stroke incidence as well as stroke mortality. The Asia Pacific Cohort Studies Collaboration study including 58 cohort studies (more than 3 million person-year follow-up and 5,178 stroke incidental cases) showed that the risk of stroke incidence increased with increasing BP levels in a dose-dependent manner from the SBP level of 115 mm Hg. For every 10 mm Hg decrease in SBP, the expected risk reduction of stroke incidence was 54% (95% confidence interval [CI] 53–56%), 36% (34–38%) and 25% (22–28%) in individuals with age <60, 60–69, and \geq 70 years, respectively. For both men and women and for both ischemic and hemorrhagic strokes, the risk increased with increasing BP levels.⁴ For North American and European populations, an earlier meta-analysis already demonstrated the association of high BP and stroke incidence. Within the range of DBP 70–110 mm Hg, DBP reduction of 5 mm Hg, 7.5 mm Hg, and 10 mm Hg was associated with 34%, 46%, and 56% reduction of stroke risk.⁵

In the updated INTERSTROKE phase 2 study with a large standardized case-control set of 26,919 individuals from 32 countries worldwide showing that 10 modifiable risk factors collectively accounted for about 90% of population-attributable risk for all stroke, hypertension defined as self-reported hypertension or BP \geq 140/90 mm Hg had the largest population-attributable risk of 47.9% (99% CI 45.1–50.6). The population-attributable risk was 45.7% (42.4–49.0) for ischemic stroke and 56.4% (52.0–60.6) for intracerebral hemorrhage (ICH). The contribution of hypertension to regional stroke burden was greater in Asian region than in Europe, North America, and Australia.²

Population-based studies conducted in developed countries suggested that BP control contributes to the reduction of stroke incidence and mortality. In a United Kingdom study, between 1981 and 2004, first ever stroke fell by 29% (relative risk [RR] 0.71, 95% CI 0.61–0.83), ischemic stroke by 27% (0.73, 0.62–0.86), and primary ICH by 53% (0.47, 0.27–0.83), which was likely attributed to the improvement in risk factor control and

antiplatelet use. Mean BP decreased from 156.3/88.0 mm Hg to 147.6/82.0 mm Hg, and the proportion of taking antihypertensive agents increased from 19.8% to 47.3%.⁶

The Framingham Study of the United States (US) also showed that, over the periods of 1950–1977, 1978–1989, and 1990–2004, the age-adjusted incidence of first-ever stroke fell by 25% (RR 0.75, 95% CI 0.59–0.95) in men and 24% (0.76, 0.61–0.94) in women. During the study period, risk factor profiles except for diabetes significantly improved, which likely accounted for the decline in the stroke incidence. From 1950–1977 to 1990–2004, the proportion of individuals with BP $>$ 140/90 mm Hg decreased from 48% to 34% in men and from 56% to 30% in women, and the proportion of taking antihypertensive agents increased from 11% to 37% in men and from 19% to 27% in women.⁷ In the US, stroke mortality has also declined since the early 20th century, resulting in repositioning stroke from the third to the fourth leading cause of death. The National Health and Nutrition Examination Survey data indicated a reduction of SBP in US population (mean SBP, 131 mm Hg in 1960–1962 and 122 mm Hg in 2001–2008), which might explain the decline in the stroke mortality.⁸

Among Asian studies, the Hisayama study in Japan showed a substantial decline in stroke incidence. The age-adjusted incidence for ischemic stroke significantly declined by 37% for men and by 32% for women from the first cohort (enrolled in 1961) to the second cohort (enrolled in 1974), and 29% for men and 14% for women from the second cohort to the third cohort (enrolled in 1988). The age-adjusted incidence of ICH also declined in men and women, particularly with a huge reduction of 61% from the first cohort to the second cohort in men. During the period, the prevalence of severe hypertension defined as BP \geq 160/100 mm Hg significantly decreased from 19.1% to 11.2% in men and from 17.9% to 12.0% in women along with increasing use of antihypertensive agents from 2.1% to 14.3% in men and 2.2% to 15.3% in women.⁹

In 2014, the Eighth Joint National Committee (JNC8) published an updated guideline recommending a relaxed SBP goal of <150 mm Hg for individuals aged \geq 60,¹⁰ which elaborated substantial debates among experts and relevant academic societies. In a recent study of individuals aged \geq 60 of the Northern Manhattan Study cohort with a 13-year follow-up, individuals with SBP 140–149 mm Hg compared to those with SBP<140 mm Hg had an increased risk of stroke (hazard ratio [HR] 1.72, 95% CI 1.20–2.65), adding concern on the JNC8 recommendation.¹¹

RCTs

RCTs clearly confirmed the benefit of BP lowering expected

from epidemiological studies. The majority of individuals enrolled in RCTs were non-stroke population, and the evidences from most RCTs would be more relevant to primary stroke prevention than secondary stroke prevention. Accordingly, large meta-analyses to explore pooled estimates of BP lowering benefit have been conducted and updated.

Pooling 42 RCTs (23 RCTs for stroke endpoint), antihypertensive therapy versus placebo reduced the risk of stroke by 32% (95% CI 24–39). The benefit of stroke risk reduction was greater than those of coronary or major cardiovascular event risk reduction.¹² In another meta-analysis including 147 RCTs (72 RCTs for stroke endpoint), the RR with the standardized BP lowering of 10/5 mm Hg was 0.59 (95% CI 0.52–0.67) for stroke endpoint and 0.78 (0.73–0.83) for coronary heart disease endpoint.¹³

In a recent updated meta-analysis of 123 RCTs (53 RCTs for stroke endpoint), the RR with every 10 mm Hg reduction in SBP was 0.73 (95% CI, 0.68–0.77), which was smaller than observed in the earlier meta-analysis. However, this updated meta-analysis showed that the benefit of BP lowering for stroke prevention was consistent across diverse baseline SBP levels (*P* for trend=0.38), suggesting no J-curve relationship with BP level and stroke risk. In particular, 10 mm Hg reduction in SBP was associated with a significant stroke risk reduction in individuals with baseline SBP 130–139 mm Hg (RR 0.73, 95% CI 0.62–0.85), 140–149 mm Hg (0.78, 0.70–0.87), 150–159 mm Hg (0.65, 0.54–0.78), and ≥ 160 mm Hg (0.70, 0.64–0.78). The benefit of SBP 10 mm Hg reduction on stroke risk was comparable between individuals with established cardiovascular disease (0.74, 0.67–0.81) and those without established cardiovascular disease (0.75, 0.63–0.89).¹⁴

Class effect

Of the modern antihypertensive agents, chlorothiazide was introduced to clinical practice in late 1950s, and then beta-blockers (BBs) in early 1960s, calcium channel blockers (CCBs) and angiotensin converting-enzyme inhibitors in 1970s, and angiotensin receptor blockers (ARBs) in 1990s. Earlier RCTs demonstrated the benefit of diuretics and BBs over placebo for preventing cardiovascular disease. Since then, which antihypertensive agent or combination would be more protective for stroke prevention has been of interest.

Looking at individual large RCTs reporting stroke endpoint, earlier large RCTs showed that CCBs or angiotensin converting-enzyme inhibitors were not superior to diuretics or BBs.^{15–17} In Nordic Diltiazem (NORDIL) study, diltiazem compared to diuretics or BB had a lower risk of stroke (RR, 0.80; 95% CI, 0.65–0.99) only after adjusting for covariates.¹⁸ However, Losartan Intervention For Endpoint reduction (LIFE) showed that losartan

compared to atenolol had a lower risk of stroke (HR 0.75, 95% CI 0.63–0.89).¹⁹ Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that amlodipine-based BP lowering was better than atenolol-based BP lowering for stroke endpoint (HR 0.77, 0.66–0.89).²⁰ In Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), chlorthalidone had a lower risk of stroke compared to doxazosin (RR 0.84, 0.71–0.99) and lisinopril (0.87, 0.77–0.98), and amlodipine compared to lisinopril had a lower risk of stroke (odds ratio [OR] 0.82, 95% CI 0.71–0.94).^{21,22} However, in these trials designed to compare different antihypertensive classes, other antihypertensive agents were often required for BP control, which might confound the effects of the tested antihypertensive agents.

For patients with BP >160/100 mm Hg, combination of antihypertensive agents as an initial therapy is recommended, and many of hypertensive patients require 2 or more antihypertensive agents for achieving target BP level. Therefore, the optimal combination therapy is of great interest. In Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) that enrolled 11,506 patients with SBP ≥ 160 mm Hg or on antihypertensive agents and at high risk for cardiovascular disease, benazepril plus amlodipine compared to benazepril plus hydrochlorothiazide reduced the primary endpoint of the composite of major cardiovascular events (HR 0.80, 95% CI 0.72–0.90). Stroke endpoint occurred less frequently with benazepril plus amlodipine, but the difference was not significant (0.84, 0.65–1.08).²³ In another Japanese trial enrolling 3,501 patients, the stroke risk with benidipine plus thiazide was lower compared to benidipine plus BB (HR 0.43, 95% CI 0.22–0.85), but did not differ when compared to benidipine plus ARB (0.72, 0.34–1.45).²⁴

An earlier network meta-analysis published in 2003 showed that diuretics were better than angiotensin converting-enzyme inhibitors and similar to CCBs for stroke endpoint. Since other cardiovascular endpoints generally favored diuretics over other antihypertensive classes, this meta-analysis suggested diuretics as a first-line antihypertensive agent, taking into account the overall benefit and cost.¹² However, in a subsequent meta-analysis, compared to other antihypertensive classes, CCBs were more effective and BBs were less effective for stroke prevention even after adjusting BP reduction difference between comparative agents.¹³ In a recent meta-analysis published in 2016, compared to the other classes, CCBs and ARBs were superior, but angiotensin converting-enzyme inhibitors and BBs were inferior for stroke risk reduction. However, CCBs compared to the other antihypertensive classes were less favorable for heart failure outcome. Of note, these findings were derived from non-standardized analyses without accounting for BP lowering intensity

and other factors.¹⁴

Pleiotropic effect, BP variability, and central BP have been proposed to explain the different effect on stroke outcome between antihypertensive classes. However, it should be noted that, in all RCTs comparing different antihypertensive strategies, stroke endpoint was not a primary endpoint, but one of secondary endpoints. Thereby, the positive findings should be interpreted cautiously. Study-level meta-analyses without individual patient data have additional limitations of 1) confounding of achieved BP levels, which influences the study results, and 2) bias from indirect comparison. Therefore, the available evidence from individual RCTs and meta-analyses regarding the differential effects of antihypertensive classes on stroke risk is only suggestive, but not confirmative.

BP Control for Secondary Stroke Prevention

About 70% of stroke patients have hypertension.²⁵⁻²⁸ In contrast to primary stroke prevention, there is no large epidemiological study that evaluates whether high BP is associated with an increased risk of recurrent stroke. However, secondary stroke prevention RCTs and their meta-analyses confirmed that BP lowering reduced the risk of recurrent stroke as well as subsequent major cardiovascular events. In addition, post hoc analyses of RCTs testing interventions other than BP lowering showed that high BP during follow-up was associated with an increased risk of recurrent stroke.

RCTs testing BP lowering effect

The first formal RCT testing BP control to prevent subsequent clinical events in stroke patients was conducted in 1960s. The trial enrolled only 99 hypertensive patients with stroke presumed of ischemic origin and randomized to no BP lowering or BP lowering with methyl dopa, bethanidine, debrisoquinine, or thiazide diuretics combined with lifestyle modification of salt intake restriction and weight reduction. The target BP was SBP < 160 mm Hg and DBP 90–100 mm Hg. Despite of the small sample size, during the follow-up of 2 to 5 years, the BP lowering group compared to the non-BP lowering group had a lower mortality (26% vs. 46%; $P=0.05$), and the mortality reduction was greater in patients who achieved well-controlled BP levels. The BP control group versus the non-BP control group had a lower rate of recurrence of major stroke (20% vs. 44%).²⁹ However, three subsequent RCTs with small to moderate sample sizes (ranging between 452 and 1,473 patients) failed to demonstrate the benefit of BP lowering (deserpine plus methylothiazide in one RCT and atenolol in two RCTs) for preventing recur-

rent stroke or major cardiovascular events.³⁰⁻³²

The first large RCT was Post-stroke Antihypertensive Treatment Study (PATS), which randomized 5,665 Chinese patients with stroke or transient ischemic attack (TIA) (ischemic stroke/TIA 84% and hemorrhagic stroke 16%) to indapamide 2.5 mg or placebo.^{33,34} During a median 2-year follow-up, indapamide (BP lowering of 6.8/3.3 mm Hg compared to placebo) significantly reduced recurrent stroke by 30% (HR 0.70, 95% CI 0.57–0.86) and major cardiovascular events by 25% (0.75, 0.62–0.89).

A subsequent large RCT, Perindopril Protection Against Recurrent Stroke Study (PROGRESS), demonstrated the benefit of BP lowering for secondary stroke prevention.³⁵ PROGRESS randomized 6,105 patients with a history of TIA or stroke (ischemic stroke/TIA 84%, hemorrhagic stroke 11%, and undetermined stroke 5%) to perindopril-based BP lowering or to placebo. During the 4-year follow-up, the BP difference between the two groups was 9/4 mm Hg, and BP lowering reduced the primary end point of recurrent stroke by 28% (95% CI 17–38%) and major cardiovascular events by 26% (16–34%). The magnitude of benefit for preventing recurrent stroke was similar to that observed in PATS.

In a meta-analysis involving 15,527 patients from 7 RCTs published until 2002 (6 RCTs exclusively enrolling stroke/TIA patients and one RCT with prior stroke/TIA subgroup), BP lowering with antihypertensive agents reduced stroke (OR 0.76, 95% CI 0.63–0.92), nonfatal stroke (0.79, 0.65–0.95), myocardial infarction (0.79, 0.63–0.98), and overall vascular events (0.79, 0.66–0.95).³⁶

After then, Prevention Regimen For Effectively avoiding Second Strokes (PROFESS), the largest secondary stroke prevention RCT with a sample size of 20,332, compared telmisartan versus placebo on top of background antihypertensive treatment as needed. For 2.5 years, telmisartan did not significantly reduce recurrent stroke (HR 0.95, 95% CI 0.86–1.04) or the composite of recurrent stroke, myocardial infarction, new or worsening heart failure, or vascular death (0.94, 0.87–1.01). However, by the end of the trial, the placebo group compared to the telmisartan group more frequently took other antihypertensive agents, and the mean BP difference was only 3.8/2.0 mm Hg. In post hoc analyses, the clinical event rates did not differ in the first 6 months (1.07, 0.92–1.25), but lowered with telmisartan after 6 months (0.88, 0.78–0.99), suggesting that more prolonged treatment with telmisartan could have resulted in a significant benefit.³⁷

In an updated meta-analysis involving 38,421 patients from 10 RCTs published until 2009 (7 RCTs exclusively enrolling stroke/TIA patients and 3 RCTs with prior stroke/TIA subgroup), antihypertensive therapy reduced stroke (OR, 0.78, 95% CI

0.68–0.90).³⁴ In another meta-analysis of 11 placebo-controlled RCTs published until July 2016, antihypertensive therapy reduced recurrent stroke (RR 0.73, 95% CI 0.62–0.87), disabling or fatal stroke (0.71, 0.59–0.85) and vascular death (0.85, 0.75–0.96).³⁸

Post hoc analyses of RCTs testing intervention other than BP lowering

In a post hoc analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial which enrolled patients with recent stroke, patients with mean follow-up BP <140/90 mm Hg versus those with BP ≥140/90 mm Hg had lower risks of recurrent stroke (HR 0.76, 95% CI 0.59–0.98) and major cardiovascular events (0.76, 0.62–0.92). Of note, among patients with baseline SBP in the highest quartile (>153 mm Hg), patients with BP controlled ≥75% of the trial period compared to those with BP controlled <25% had a lower risk of stroke (0.46, 0.26–0.84), and major cardiovascular events (0.51, 0.32–0.82).³⁹

In a post hoc analysis of PROFESS, compared to patients with mean follow-up SBP 130–139 mm Hg, the SBP 140–149 mm Hg group had a higher risk of recurrent stroke (adjusted HR, 1.23, 95% CI 1.07–1.41) and major cardiovascular events (1.24, 1.11–1.39). The risk was further increased in the SBP ≥150 mm Hg group; 2.08 (1.83–2.37) for recurrent stroke and 1.94 (1.74–2.16) for major cardiovascular events.⁴⁰

Patients with symptomatic extracranial or intracranial stenosis might have impaired regional cerebral perfusion, and thereby some advocate maintaining high BP in these patients. However, data have suggested that high BP is associated with a higher risk of recurrent stroke, even in the territory of symptomatic stenosis.

For symptomatic extracranial carotid stenosis, a pooled analysis of individual patient data from the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) studies showed that high BP was associated with an increased risk of recurrent stroke in patients assigned to medical treatment. The presence of contralateral asymptomatic occlusion did not change the relationship between BP level and stroke risk. Only in patients with bilateral stenoses ≥70%, the relationship was reversed (higher stroke risk with lower BP). In patients with unilateral stenosis ≥70%, there was a positive relationship between BP level and stroke risk. The findings from this post hoc analysis support BP lowering in the majority of patients with symptomatic carotid stenosis except for bilateral severe stenosis.⁴¹

For symptomatic intracranial stenosis, uncontrolled BP is likely to increase the risk of subsequent vascular events. In a post hoc analysis of Warfarin–Aspirin Symptomatic Intracranial Dis-

ease (WASID) trial, compared to patients with mean SBP <140 mm Hg during the trial, those with mean SBP >140 mm Hg had an increased risk of recurrent stroke (adjusted HR, 1.63, 95% CI 1.11–2.40) and major cardiovascular events (1.79, 1.27–2.52). Based on the WASID data, the Stenting and Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) investigators targeted SBP <140 mm Hg.^{42,43} Data from the medical arm in SAMMPRIS showed that the risk of the composite of stroke, myocardial infarction, or vascular death at 3 years was higher with follow-up SBP >140 mm Hg vs. SBP ≤140 mm Hg (unadjusted OR 2.1, 95% CI 1.2–4.0),⁴⁴ but the risk of recurrent ischemic stroke did not increase in patients with mean follow-up SBP ≥144 mm Hg vs. SBP <144 mm Hg (unadjusted HR 0.6, 95% CI 0.3–1.2).⁴⁵ However, results from adjusted analyses are not available.

Intensive vs. Less Intensive BP Lowering for Stroke Prevention

Evidences from non-stroke population in majority

As previously described, large meta-analyses of epidemiological studies showed that the association of BP and the stroke incidence as well as stroke mortality is continuous down to 115/75 mm Hg, suggesting “the lower, the better.” The expected benefit was consistent across a wide range of subgroups.^{3–5}

In post hoc analyses of two large RCTs testing BP lowering therapy (International Verapamil–Trandolapril Study [INVEST] that enrolled patients with coronary heart disease; Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [ONTARGET] that enrolled patients with established cardiovascular disease or diabetes plus end-organ disease), there were J-curve relationships between follow-up BP level and major cardiovascular events or coronary event. However, the risk of stroke increased with increasing follow-up BP level, indicating no J-curve phenomenon for the BP and stroke risk relationship.^{46,47}

Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a pivotal large RCT that specifically compared intensive (SBP <120 mm Hg) versus conventional (SBP <140 mm Hg) BP lowering in patients with type 2 diabetes and at high risk for major cardiovascular events. Intensive BP lowering compared to conventional BP lowering did not reduce the primary endpoint of major cardiovascular events. However, among prespecified secondary endpoints, the stroke endpoint was significantly reduced with intensive BP lowering (HR 0.59, 95% CI 0.39–0.89).⁴⁸ In a subsequent meta-analysis of 13 RCTs involving 37,736 patients with type 2 diabetes or impaired fasting glucose, intensive SBP control (≤135 or 130 mm Hg) versus less in-

tensive SPB control was associated with a lower risk of stroke (OR 0.83, 95% CI 0.73–0.95) as well as all-cause death (0.90, 0.83–0.98), but with an increased risk of serious adverse events (1.20, 1.08–1.32). With more intensive SBP lowering of <130 mm Hg, the stroke risk was further reduced (0.53, 0.38–0.75), but the risk of serious adverse events also increased (1.40, 1.19–1.64).⁴⁹

For Asian data, the investigators of China Stroke Primary Prevention Trial (CSPPT), which tested the effect of folate on primary stroke prevention, conducted a post-hoc analysis exploring the relationship between the average follow-up SBP level and the risk of first stroke. The stroke risk was lowest in patients with the average SBP level of 120–130 mm Hg, and the risk increased in those with SBP <120 mm Hg (HR 4.37, 95% CI 2.10–9.07) as well as those with SBP 130–135 mm Hg (1.63, 1.01–2.63), 135–140 mm Hg (1.85, 1.17–2.93), and >140 mm Hg (3.83, 2.54–5.76), indicating a J-curve relationship. However, for DBP, patients with DBP <80 mm Hg had the lowest stroke risk, compared to those with DBP 80–90 mm Hg (2.14, 1.65–2.77) and DBP >90 mm Hg (5.55, 4.04–7.62). Similar findings were also observed for the endpoint of ischemic stroke.⁵⁰

In an earlier meta-analysis of 11 studies involving 42,572 patients, achieving SBP <130 mm Hg compared to SBP 130–139 mm Hg was associated with a lower risk of stroke (RR 0.80, 95% CI 0.70–0.92) and major cardiovascular events (0.91, 0.86–0.96). However, the benefit of achieving SBP <130 mm Hg was heterogeneous (P for heterogeneity=0.002) between subjects with established cardiovascular disease (0.88, 0.76–1.03) and those without established cardiovascular disease (0.49, 0.34–0.69). Reported hypotension was more common with intensive lowering (1.4% vs. 0.4%, RR 3.43, 95% CI 2.46–4.79).⁵¹ An updated meta-analysis of 19 trials ($n=44,989$) also demonstrated similar findings; intensive BP lowering (mean BP, 133/76 mm Hg) versus less intensive BP lowering (mean BP, 140/81 mm Hg) was associated with a lower risk of stroke (RR 0.78, 95% CI 0.68–0.90) and major cardiovascular events (0.86, 0.78–0.96). In this meta-analysis, the reduction of major vascular events with intensive BP lowering was consistent across a wide range of subgroups. Serious adverse events was not significantly increased with intensive BP lowering (1.2% vs. 0.9%, RR 1.35, 95% CI 0.93–1.97). Severe hypotension was more common with intensive lowering (2.68, 1.21–5.89), but the absolute increase was not substantial (0.3%/year vs. 0.1%/year).⁵²

The Systolic Blood Pressure Intervention Trial (SPRINT) was the first large trial that confirmed the benefit of intensive BP lowering over less intensive BP lowering. SPRINT compared SBP target <120 mm Hg vs. <140 mm Hg in individuals with SBP ≥130 mm Hg and at high risk of cardiovascular disease. Pa-

tients with diabetes, stroke, or congestive heart failure were excluded. It was early terminated because of a clear benefit of intensive BP lowering after a median follow-up of 3.26 years. The intensive BP lowering significantly reduced the primary endpoint of major cardiovascular events (HR 0.75, 0.64–0.89). The benefit on the primary endpoint was consistent across prespecified subgroups regarding age (<75 years vs. ≥75 years), sex, race, established cardiovascular disease, chronic kidney disease, and baseline SBP levels. In addition, intensive BP lowering significantly reduced all-cause death (0.73, 0.60–0.90) and cardiovascular death (0.57, 0.38–0.85). Serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure were more common in the intensive BP lowering group, but there was no difference in the overall serious adverse event rate.⁵³ Therefore, the target BP <140/90 mm Hg in individuals aged <60 and <150/90 mm Hg in those aged ≥60 recommended by the Eighth Joint National Committee Guidelines should be reconsidered.¹⁰ Unexpectedly, there was no significant stroke risk reduction with intensive BP lowering (0.89, 0.63–1.25).⁵³ However, if the ACCORD and SPRINT data combined, target SBP <120 mm Hg vs. <140 mm Hg was associated with a reduction in stroke risk (0.75, 0.58–0.97).⁵⁴ The magnitude of stroke risk benefit was largely in accord with the findings estimated by the earlier meta-analyses.^{51,52}

In contrast, for individuals at intermediate risk who did not have established cardiovascular disease, the Heart Outcomes Prevention Evaluation (HOPE)-3 trial showed that active BP lowering with candesartan plus hydrochlorothiazide did not reduce the risk of stroke (HR 0.80, 95% CI 0.59–1.08) as well as the primary endpoint of major cardiovascular events (0.93, 0.79–1.10). However, dizziness, lightheadedness, or symptomatic hypotension leading to permanent study medication discontinuation was more common with antihypertensive therapy (3.4% vs. 2.0%, $P<0.0001$). Compared to the ACCORD and SPRINT populations, the HOPE-3 population was at intermediate risk, reflected by the much lower rate of major cardiovascular events compared to those in the ACCORD and SPRINT trials. Of the prespecified subgroups based on follow-up mean SBP levels, only the participants in the highest tertile group (mean SBP >143.5 mm Hg) benefited from antihypertensive therapy for stroke endpoint (0.58, 0.37–0.90) and the primary endpoint (0.73, 0.56–0.94). Therefore, the findings suggest that, in individuals without high risk, antihypertensive therapy would be beneficial only for SBP >140 mm Hg. Of note, the effect of antihypertensive therapy on the primary endpoint differ significantly according to mean SBP levels (antihypertensive therapy effect; better in the highest tertile,

neutral in the intermediate tertile, and worse in the lowest tertile; P for trend=0.02), suggesting a J-curve phenomenon. In contrast, the effect of antihypertensive therapy on stroke endpoint showed no significant interaction with the mean SBP levels, supporting no J-curve relationship.⁵⁵

Evidences from stroke population

Several post hoc analyses of RCTs data have explored whether intensive BP lowering would further reduce the risk of recurrent stroke in stroke patients. In a post-hoc analysis of PROGRESS, there was no J-curve relationship between follow-up BP levels and the risk of recurrent stroke. When patients were categorized into 4 groups according to their follow-up SBP levels (<120, 120–139, 140–159, and \geq 160 mm Hg), the lowest SBP group had the lowest risk of recurrent stroke, and the risk monotonically and significantly increased with increasing follow-up SBP level (P for trend <0.0001). The relationship was also significant for both ischemic and hemorrhagic stroke risks, and it was stronger for the hemorrhagic stroke risk than the ischemic stroke risk. Lower SBP levels were associated with more frequent minor adverse events, but did not significantly increase serious adverse events. Therefore, this post hoc analysis supports intensive BP lowering for secondary stroke prevention.⁵⁶

In contrast, data from PROGRESS, a more recent and larger trial than PROGRESS, showed a J-curve relationship between follow-up BP levels and stroke risk as well as major cardiovascular events risk. The risk of recurrent stroke was lowest in patients with follow-up SBP 130–139 mm Hg (as reference), and significantly increased in those with very low-normal (<120 mm Hg, HR 1.29, 95% CI 1.07–1.56), high (140–149 mm Hg, 1.23, 1.07–1.41), or very high (\geq 150 mm Hg, 2.08, 1.83–2.37) SBP level. There was a similar relationship between the major cardiovascular events risk and the follow-up SBP level. Therefore, the PROGRESS post hoc analysis supports the conventional BP lowering, targeting SBP<140 mm Hg, rather than intensive BP lowering.⁴⁰

For symptomatic intracranial stenosis, a WASID post hoc analysis ($n=567$) showed that the recurrent risks of any ischemic stroke and ischemic stroke in the stenotic territory increased with increasing mean follow-up SBP (P for trend=0.0008, and 0.0002, respectively) and DBP (P for trend <0.0001, and 0.0005, respectively) levels. However, the increased risks were largely driven by the highest SBP group (SBP \geq 160 mm Hg) (any ischemic stroke, HR 4.6, 95% CI, 1.3–16.2; ischemic stroke in the stenotic territory, 3.9, 1.1–14.1), and these risks did not significantly increase in the mean SBP 120–139 mm Hg and 140–159 mm Hg groups compared to the

mean SBP<120 mm Hg group. For DBP levels, the risks of any ischemic stroke and ischemic stroke in the stenotic territory had significantly increased in the DBP 80–89 mm Hg ([any ischemic stroke, 2.2, 1.4–3.4]; stroke in the stenotic territory 2.2, 1.3–3.7) and DBP \geq 90 mm Hg ([any ischemic stroke, HR 4.6, 2.1–10.4]; stroke in the stenotic territory 5.1, 2.1–12.4) compared to the lowest DBP group (DBP<80 mm Hg). In subgroups according to stenosis severity, the relationship between the risk and follow-up BP levels was more apparent in patients with stenosis <70% than in those with stenosis \geq 70%. The study findings do not strongly support intensive BP lowering in symptomatic intracranial stenosis, but do not support maintaining high BP for cerebral perfusion in patients with symptomatic intracranial stenosis. In addition, there was no J-shape relationship between BP levels and any ischemic stroke or ischemic stroke in the stenotic territory.⁵⁷

In the Carotid Occlusion Surgery Study (COSS) trial that enrolled patients with symptomatic carotid artery occlusion and hemodynamic cerebral ischemia, the target BP level was \leq 130/85 mm Hg, a moderately intensive BP lowering target. Among 91 patients assigned to the medical treatment arm, patients achieving BP levels \leq 130/85 mm Hg compared to those with BP>130/85 mm Hg had a lower risk of recurrent ipsilateral ischemic stroke (HR 0.27, 95% CI 0.08–0.94). In addition, there was no J-curve relationship between the ipsilateral ischemic stroke risk and SBP levels (categorized as <120, 120–129, 130–139, 140–149, and >150 mm Hg).⁵⁸

However, the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERITAS) study which enrolled 72 patients with recent vertebrobasilar TIA or stroke and \geq 50% of vertebral or basilar arteries showed that the association with BP levels and stroke risk differed by flow status determined by quantitative magnetic resonance angiography. For 20 \pm 8 months follow-up, the annual rate of the vertebrobasilar artery territory ischemic stroke was highest in patients with low flow and mean follow-up BP<140/90 mm Hg (27.1%/year, 95% CI 10.2–72.2) followed by those with low flow and mean BP \geq 140/90 mm Hg (9.3%/year, 1.3–66.0), those with normal flow and mean BP<140/90 mm Hg (6.0%/year, 1.9–18.5), and those with normal flow and mean BP \geq 140/90 mm Hg follow-up (4.8%/year, 1.2–19.1), suggesting that strict BP control might increase the recurrent stroke risk in patients with reduced distal flow.⁵⁹

Secondary Prevention of Small Subcortical Strokes (SPS3) is the only one RCT that formally compared intensive (SBP<130 mm Hg) versus less intensive (SBP 130–149 mm Hg) BP control in stroke patients. The trial exclusively enrolled patients with ischemic stroke due to small vessel occlusion, who are expected

to benefit most from intensive BP control. The SPB difference at 1-year after randomization was 11 mm Hg (127 mm Hg vs. 138 mm Hg). During a 3.7-year follow up, there was no significant reduction with intensive lowering in the primary endpoint of all recurrent stroke (HR 0.81, 95% CI 0.64–1.03). However, intensive BP control significantly reduced the risk of ICH (0.37, 0.15–0.95), and did not increase the risk of treatment-related serious adverse events.⁶⁰ Based on the findings from SPS3, the current American Stroke Association guidelines recommend SBP<130 mm Hg in patients with stroke due to small vessel occlusion (Class IIb, Level of Evidence B).⁶¹

A recent systematic review explored whether the intensive BP lowering might further reduce the recurrent stroke and subsequent major cardiovascular events in stroke patients. Meta-regression analysis showed that the intensity of SBP reduction was linearly related to reduced risk of recurrent stroke ($P=0.049$), myocardial infarction ($P=0.024$), all-cause death ($P=0.001$), and cardiovascular death ($P<0.001$). When the achieved mean SBP levels were categorized into three groups, patients with mean SBP<130 mm Hg compared to those with SBP 130–140 mm Hg and those with SBP>140 mm Hg had a lower risk of recurrent stroke (8.3% vs. 9.2% vs. 11.7%; $P=0.048$) and cardiovascular death (0.8% vs. 3.3% vs. 5.5%; $P=0.049$), suggesting a target SBP<130 mm Hg in stroke patients.³⁸

BP Management in Acute Stroke

In a representative large data set in the US involving 563,704 patients with stroke admitted to ER, initial SBP was 140–184 mm Hg in 56%, and ≥ 185 mm Hg in 13%.⁶² In the majority of patients, BP spontaneously falls over the first 7 days after stroke onset. Because cerebral autoregulation is impaired in acute stroke, elevated BP might be beneficial by increasing perfusion in ischemic penumbra area. However, high BP might be harmful by aggravating hematoma expansion or edema in ICH and symptomatic hemorrhagic transformation or edema in large ischemic stroke. Several RCTs have been conducted to test BP lowering effect in acute stroke.

BP management in acute ischemic stroke

Data from the International Stroke Trial (IST) showed a U-shaped relationship between SBP measured immediately after randomization and 14-day clinical outcomes. SBP level around 150 mm Hg was associated with the lowest risks mortality and poor outcome of death or dependency. High BP was associated with early recurrent stroke and death presumed of cerebral edema, while low BP was associated with early coronary

death.⁶³

Acute Candesartan Cilixetil Therapy in Stroke Survivors (ACCESS) was a small phase II RCT comparing candesartan (initiated at 30 hours after onset) versus placebo for the first 7 days in patients with acute ischemic stroke. After 7 days, both groups received candesartan if BP control was required. The trial was early terminated after enrolling 342 patients because the candesartan group had a significant lower rate in the composite of vascular events and death at one year (OR 0.48, 95% CI 0.25–0.90). However, the mechanism of candesartan benefit was unclear because the SBP and DBP levels during the trial did not differ between the two groups and the event rates diverged after 2 weeks. In addition, candesartan did not improve the primary endpoint of 3-month disability as measured by Barthel Index.⁶⁴

The Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) compared active BP lowering (lisinopril or labetalol) versus placebo in 179 patients with acute stroke (57.6% ischemic stroke, 14.5% primary ICH, 27.9% undetermined) within 36 hours and SBP>160 mm Hg. SBP decline during the first 24 hours was greater with active BP lowering than placebo (21 mm Hg vs. 11 mm Hg, $P=0.004$). There were no differences in the primary endpoint of 14-day death or dependency (modified Rankin Scale [mRS] 4–6), early neurological deterioration, and serious adverse events. However, 3-month mortality showed a trend of favoring active BP lowering (9.7% vs. 20.3%, HR 0.40, 95% CI 0.2–1.0). However, CHHIPS was a small pilot trial at high risk of type I error.⁶⁵

Because of the uncertainty with the ACCESS results, Scandinavian Candesartan Acute Stroke Trial (SCAST), a large phase III trial, was conducted. SCAST, using a design similar to ACCESS, randomized 2,029 patients with acute stroke (ischemic stroke in 85%, hemorrhagic stroke in 14%, and TIA or non-stroke in 1%) and SBP ≥ 140 mm Hg within 30 h from onset. BP was lower on day 7 with candesartan (mean difference, 5/2 mm Hg), but was similar during the following 6-month between the two groups. The composite endpoint of major cardiovascular events for 6 months did not differ between the candesartan and placebo groups (HR 1.09, 95% CI 0.84–1.41). However, the mRS distribution at 6 months showed a worse trend with candesartan treatment (OR 1.17, 95% CI 1.00–1.38). Therefore, SCAST suggested a harmful effect with early BP lowering with candesartan.⁶⁶

The Valsartan Efficacy on modest blood pressure Reduction in acute ischemic stroke (VENTURE) trial, which enrolled 393 patients with acute ischemic stroke within 48 hours, also showed a harmful effect of early BP lowering. Valsartan treatment versus no antihypertensive treatment for the first 7 days

did not reduce functional disability and major cardiovascular events at 90 days, but had more early neurological deterioration within 7 days (OR 2.43, 95% CI 1.25–4.73). Particularly, in subgroups of patients with large artery atherosclerosis and those with any degree of symptomatic stenosis, early valsartan treatment significantly increased the risk of early neurological deterioration.⁶⁷ SCAST subgroup analysis showed similar findings. In patients with moderate to severe carotid artery stenosis, progressive stroke occurred more frequently in the candesartan group than in the placebo group (11.5% vs. 4.0%), and the risk increased with increasing severity of stenosis (P for trend=0.04).⁶⁸

Another large RCT also showed no benefit of early BP lowering in acute ischemic stroke. The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) trial enrolled 4,071 patients with acute ischemic stroke within 48 hours and SBP between 140–220 mm Hg. BP lowering intervention targeted SBP lowering by 10% to 25% within the first 24 hours after randomization and <140/90 mm Hg within 7 days, while the control group did not receive antihypertensive treatment during hospitalization. SBP difference was significant over the first 14 days; 9.1 mm Hg at 24 hours, 9.3 mm Hg at day 7, and 8.6 mm Hg at 14 days after randomization. The primary outcome of mRS score 3–6 at 14 days or discharge did not differ between the BP lowering and control arms (33.6% vs. 33.6%, OR 1.00, 95% CI 0.88–1.14). At 3 months, there were no differences in the mRS score 3–6 (25.2% vs. 25.3%, 1.00, 0.88–1.14), recurrent stroke (1.4% vs. 2.2%, 0.65, 0.40–1.04), vascular event (2.4% vs. 3.0%, 0.81, 0.55–1.19), and death or vascular events (4.6% vs. 4.7%, 0.98, 0.73–1.31).⁶⁹

In a meta-analysis of 13 RCTs with 12,703 patients comparing early BP lowering versus control within 3 days of ischemic stroke onset, BP lowering did not reduce the risk of death or dependency (mRS 3–6 or equivalent) at 3 months or at trial end (RR 1.04, 95% CI 0.96–1.13). In addition, the effect of early BP lowering was not significant for 3 or 6-month recurrent stroke (1.00, 0.54–1.84), subsequent vascular events (0.90, 0.65–1.25), all-cause mortality (0.99, 0.83–1.17), and mRS 2–6 outcome (1.01, 0.98–1.04). BP lowering was not associated with an increased risk of serious adverse event at 14 or 30 days (1.32, 0.80–2.18). However, limited data did not allow an adequate exploration of the stroke progression risk associated with early BP lowering.⁷⁰

BP management after reperfusion therapy

In patients treated with intravenous tissue plasminogen activator (IV-TPA), guidelines are recommending BP<180/105 mm Hg.⁷¹ However, this recommendation is based on expert consen-

sus, extrapolating the findings from thrombolysis trials in myocardial infarction, and is largely applicable to BP management in patients with IV-TPA treatment.^{72,73} Currently, the optimal BP management after reperfusion therapy remains unclear.

Data from In the Safe Implementation of Thrombolysis in Stroke (SITS) register showed that baseline high SBP was associated with symptomatic ICH and baseline DBP>90 mm Hg was associated with poor outcome.⁷⁴ For BP between 2–24 hours after IV-TPA, the symptomatic ICH risk increased with increment in the average SBP levels, whereas the average SBP level of 141–150 mm Hg was associated with the highest odds of achieving mRS 0–2 at 3 months.⁷⁵ Therefore, the SITS data suggest that SBP 141–150 mm Hg might be optimal after IV-TPA therapy. Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), which compares SBP 130–140 mm Hg vs. SBP<180 mm Hg in patients treated with IV-TPA, is ongoing and may help to resolve the uncertainty.⁷⁶

The optimal BP level after thrombolysis should be differed by recanalization status. In patients with successful recanalization, immediate BP lowering might reduce the risk of symptomatic ICH. In a single center study, the association of BP level in the first 24 hours after reperfusion therapy and functional outcome differed by recanalization status. In patients without recanalization, the relationship between BP level and outcome was U-shaped. In contrast, in patients with early recanalization, the relationship was linear and high BP was associated with worse outcome, possibly due to an increased risk of hemorrhagic transformation or symptomatic ICH.⁷⁷ However, the reperfusion status after IV-TPA treatment is not readily evaluable in clinical practice and even in clinical trial settings.

In contrast to IV-TPA therapy, endovascular recanalization therapy can immediately assess the recanalization status. Patients who achieved successful recanalization are at risk of reperfusion hemorrhage. Since high BP likely increases the risk of symptomatic ICH, aggressive BP control might be warranted. However, the current guidelines recommend a target BP<180/105 mm Hg in patients treated with IV-TPA, but do not provide a specific recommendation for target BP in those treated with endovascular therapy. Therefore, a relevant RCT is needed to define the optimal BP target after endovascular reperfusion therapy.

BP management in acute ICH

Current guidelines recommend lowering SBP<140 mm Hg within 6 hours of ICH onset,^{78,79} largely based on the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) 2 results. Among earlier pilot RCTs, INTERACT enrolling 404 patients with ICH within 6 hours showed that early inten-

sive BP lowering (target SBP 140 mm Hg) vs. SBP<180 mm Hg was safe and might reduce the risk of hematoma expansion.⁸⁰ The Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH) trial also showed that acute BP lowering down to SBP 110–140 mm Hg with intravenous nicardipine was safe and feasible.⁸¹

INTERACT2 was a phase III trial enrolling 2,839 patients with ICH within 6 hours. Intensive SBP lowering <140 mm Hg compared to SBP<180 mm Hg did not significantly reduce the primary endpoint of 90-day mRS 3–6 (52.0% vs. 55.6%, OR 0.87, 95% CI 0.75–1.01), but had a favorable shift on the 90-day mRS distribution (OR 0.87, 95% CI 0.77–1.00), which was a prespecified analysis. Between the two groups, the rate of all-cause death was comparable (0.99, 0.79–1.25), and the contribution of ICH to death was also comparable. Intensive BP lowering increased neither neurological deterioration within 24 hours (0.95, 0.77–1.17) nor non-fatal serious adverse events (3.4% vs. 3.8%, $P=0.92$).⁸²

ATACH-2 compared SBP target of 110–139 mm Hg vs. 140–179 mm Hg within 4.5 hours of ICH onset. Because of futility, the trial was early terminated after enrolling 1,000 patients. Between the SBP 110–139 mm Hg and 140–179 mm Hg groups, there was no difference in the primary endpoint of 90-day mRS 4–6 (38.7% vs. 37.7%, RR 1.04, 95% CI 0.85–1.27) and the rate of hematoma expansion >33% at 24 hours (18.9% vs. 24.4%; 0.78, 0.58–1.03). The intensive BP lowering group had more renal adverse events within 7 days (9.0% vs. 4.0%, $P=0.002$). The achieved SBP at 2–3 hours after randomization was around 120 mm Hg in the intensive arm and 140 mm Hg in the standard arm. Therefore, the ATACH-2 results suggest that a desirable SBP target would be 140 mm Hg and very aggressive SBP lowering down to 120 mm Hg seems unnecessary.⁸³

Summary

RCTs confirmed the epidemiologically expected benefits of BP lowering for the prevention of stroke and major cardiovascular events. Among several antihypertensive classes, which one is better for stroke prevention is still less clear, and adequate BP lowering is of great importance. Regarding intensive or less intensive BP lowering for primary stroke prevention, accumulated evidences favor intensive lowering. However, caution is needed to minimize the risk of adverse events. For secondary stroke prevention, the evidence supporting intensive BP lowering over less intensive BP lowering is limited and indirect, particularly patients with stroke due to large artery atherosclerosis. However, in patients with small vessel occlusion, SPB target <130 mm Hg is like-

ly more beneficial based on data from a single large RCT. Therefore more RCTs testing BP target for secondary stroke prevention are eagerly needed. In acute ICH, the evidence from RCTs supports the immediate BP lowering targeting SBP<140 mm Hg, which is now recommended by guidelines. However, in acute ischemic stroke, large RCTs did not demonstrate the benefit of early BP lowering, but suggested an increased risk early neurological deterioration. Therefore, otherwise indicated, it would be better to delay BP lowering in acute ischemic stroke.

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