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REVIEW ARTICLE

Special Issue: Current evidence and perspectives for hypertension management in Asia

Blood pressure management for secondary stroke prevention

Kazuo Kitagawa[1]

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Abstract

Hypertension is the most important vascular risk factor for stroke; therefore, optimal blood pressure (BP) management is essential for the prevention of recurrent stroke; lowering BP was shown to reduce the risk of recurrent stroke by 25–30%. A recent meta-analysis showed that intensive BP lowering to levels <130/80 mmHg significantly reduced the risk of recurrent stroke compared to standard management with BP levels <140/90 mmHg. The benefit of intensive BP management is evident with regard to a reduced risk of intracranial hemorrhage. Therefore, clinical practice guidelines have established a target BP of <130/80 mmHg. However, the target BP needs to be individualized. A stepped-care approach for cautious BP lowering (usually to levels <140/90 mmHg) is preferred for patients with severe diseases of the major cerebral vessels, who have a high risk of recurrent ischemic stroke. In contrast, more aggressive BP lowering (to levels <120/80 mmHg) tends to benefit patients at high risk of intracranial hemorrhage. The selection of BP management strategies should be guided by the risk of recurrent ischemic and hemorrhagic strokes.

Keywords Stroke · Blood pressure lowering · Intensive blood pressure control · Ischemic stroke · Hemorrhagic stroke

Introduction

Hypertension is the most important modifiable vascular factor that is strongly associated with the risk of stroke, and the treatment of hypertension using antihypertensive drugs serves as a primary preventive strategy that significantly reduces the rate of stroke onset [1, 2]. BP control is also beneficial for secondary stroke prevention [3]. Currently, the optimal BP level for secondary stroke prevention remains debatable. In this study, I review stroke subtypes and the role of specific risk factors relevant to each subtype, the evidence of the benefits of BP lowering for secondary stroke prevention, the effects of intensive BP lowering on total, ischemic, and hemorrhagic stroke recurrence, and finally, the target BP for secondary stroke prevention.

✉ Kazuo Kitagawa
kitagawa.kazuo@twmu.ac.jp

[1] Department of Neurology, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan

Stroke subtypes and risk factors in Japan

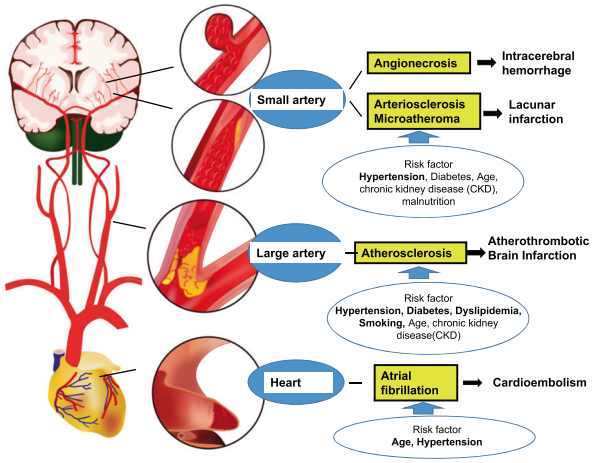
Stroke subtypes

Stroke is the fourth leading cause of mortality in Japan, with approximately 110,000 stroke-related deaths every year. Furthermore, together with dementia, stroke is the leading cause of disability in elderly individuals in Japan. Therefore, primary and secondary stroke prevention is essential to maintain independent activities of daily living and longevity. The medical management of vascular risk factors and antithrombotic strategies against ischemic stroke are important for secondary stroke prevention. Among the known medical risk factors, hypertension shows the strongest association with stroke. Notably, hypertension is the pathomechanism that underlies nearly all stroke subtypes, and other vascular risk factors, such as diabetes and dyslipidemia, show different patterns for involvement in stroke onset [1].

Stroke includes cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) (Fig. 1). Cerebral infarction includes the following subtypes: atherothrombotic brain infarction (ATBI), which is nearly identical to large artery atherosclerosis (LAA); lacunar infarction (LI), which is nearly identical to small vessel disease (SVD); and cardioembolism (CE) (Fig. 2). Among

Graphical Abstract

Hypertension shows a direct and indirect association with all stroke subtypes; the strongest association is observed between hypertension and SVD (which predisposes to LI and ICH), a modest association is observed with LAA, and an indirect association with NVAF and the development and enlargement of cerebral aneurysms. Direct and indirect association between hypertension and etiology of all stroke subtypes would underline the closest association between stroke and hypertension among vascular risk factors and explain the importance of blood pressure management for secondary stroke prevention.



Point of view

- Clinical relevance
  The present article summarizes the close association between hypertension and etiologies underlying each stroke subtype. For secondary stroke prevention, intensive BP treatment should be recommended in patients at high risk of intracerebral hemorrhage because it markedly reduced the risk of hemorrhagic stroke in patients with a history of ischemic stroke.
- Future directions
  The importance of not only mean BP levels but also BP variability needs to be examined in patients under intensive BP treatment. The kinds of conditions that require caution for aggressive BP lowering in terms of falls and kidney dysfunction need to be clarified.
- Considerations for the Asian Population

Asian people with a history of ischemic stroke have a higher risk of intracerebral hemorrhage under antithrombotic treatment than Caucasian people. Therefore, the benefit of intensive BP treatment on the prevention of intracerebral hemorrhage is much greater in Asian people than in Caucasian people. Compared with other medical vascular risk factors, BP management would be more important in Asian people than in Caucasian people for secondary stroke prevention.

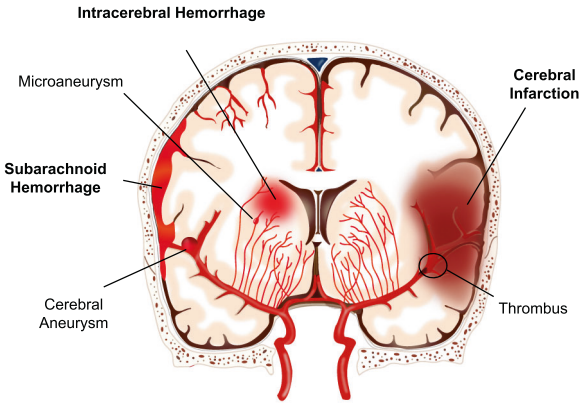


Fig. 1 Stroke subtypes. Cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage are primarily attributable to thrombus formation, microaneurysm secondary to angionecrosis, and cerebral aneurysm, respectively, as indicated by the arrows

the 169,991 patients registered in the 2021 Japan Stroke databank, 74.0% ($N = 125,722$) had cerebral infarction, 19.5% ($N = 33,178$) had ICH, and 6.5% ($N = 11,091$) had SAH (Fig. 3A) [4]. Among the patients with cerebral infarction, 31.5% ($N = 39,592$) had ATBI, 28.2% ($N = 35,395$) had LI, and 28.8% ($N = 36,179$) had CE (Fig. 3B). Among the patients with ICH, 59.2% showed involvement of the putamen and thalamus, 8.5% had brain stem hemorrhage, and 8.6% had cerebellar hemorrhage; hemorrhage primarily involved the perforating artery in approximately 75.0% of cases. The following were the primary etiopathogenetic contributors to each stroke subtype: SVD, including arteriosclerosis and angionecrosis, which

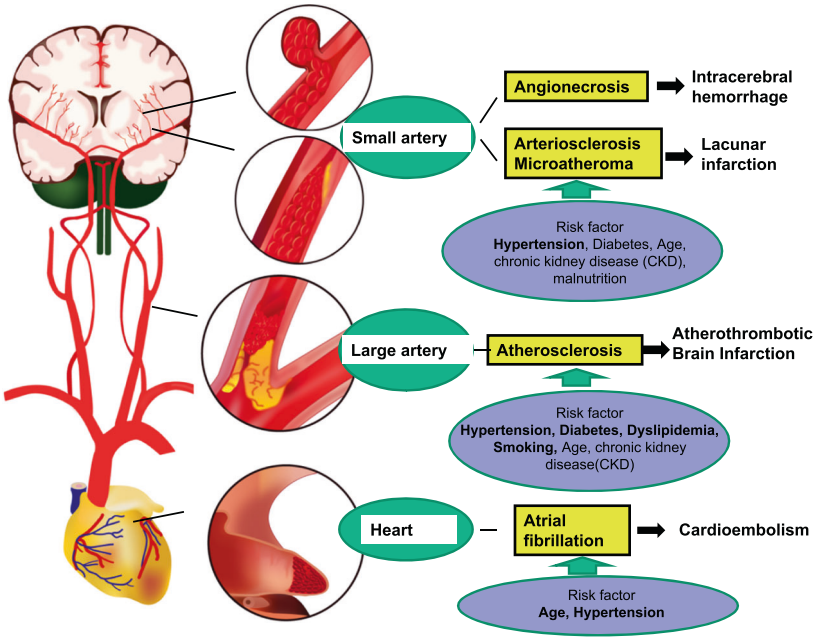


Fig. 2 Etiologies and risk factors associated with the three major subtypes of ischemic stroke and intracerebral hemorrhage

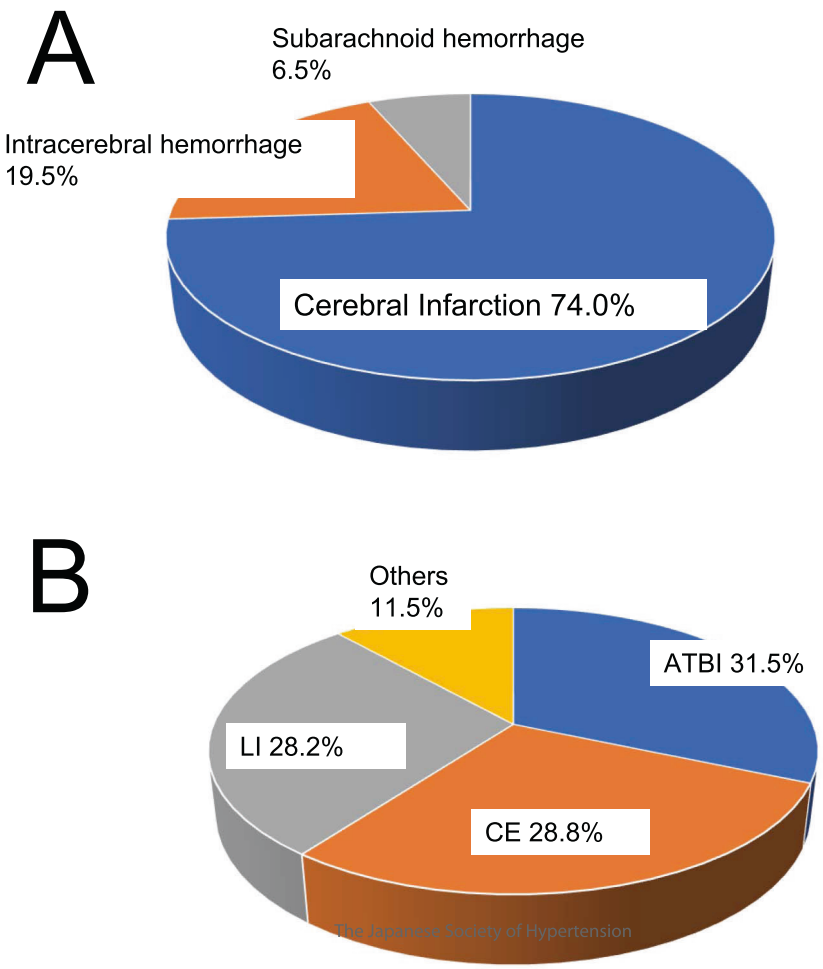


Fig. 3 Japan Stroke Databank 2021. **A** Percentages of different stroke subtypes **B** Percentages of ischemic stroke subtypes ATBI: atherothrombotic brain infarction, CE: cardioembolism, LI: lacunar infarction

underlies LI and hypertensive ICH; LAA, which underlies ATBI, and nonvalvular atrial fibrillation (NVAF), which underlies CE in most cases (Fig. 2); and cerebral aneurysms, which underlie SAH (Fig. 1).

Medical risk factors associated with each stroke subtype

Conventional and newer risk factors potentially increase stroke risk. Hypertension, diabetes mellitus, dyslipidemia, smoking, and alcohol consumption are well-known conventional risk factors for stroke [1] (Fig. 2). Hypertension shows a direct and indirect association with all stroke subtypes; the strongest association is observed between hypertension and SVD (which predisposes patients to LI and ICH), a modest association is observed with LAA, and an indirect association is observed with NVAF and the development [5] and enlargement of cerebral aneurysms [6]. In contrast, diabetes shows a strong association with LAA [7], a modest association with SVD and NVAF, and a weak association with ICH. The association between dyslipidemia and cerebral infarction differs from that between dyslipidemia and ICH. High levels of low-density lipoprotein (LDL) cholesterol increase the risk of cerebral infarction, particularly ATBI; however, epidemiological studies have reported that low levels of LDL cholesterol increase the risk of ICH [1]. The close association between hypertension and all stroke subtypes indicates that optimal BP control is the most effective strategy for the management of medical risk factors for the secondary prevention of all stroke subtypes.

Evidence of blood pressure lowering for secondary stroke prevention

The poststroke BP-lowering regimen used during the chronic stage in the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) reduced the rates of stroke recurrence among patients with and without hypertension [8]. However, the addition of telmisartan (an angiotensin receptor blocker) did not reduce the risk of recurrent stroke in patients with a history of ischemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study [9]. The disparity in the results of these studies may be attributable to differences in the levels of BP reduction; differences in the systolic BP (SBP) and diastolic BP (DBP) between the PROGRESS and PRoFESS trials were 9.0/5.0 mmHg and 3.8/2.0 mmHg, respectively. A meta-analysis of randomized controlled trials (RCTs) that investigated the use of antihypertensive treatment for secondary stroke prevention showed that active treatment with antihypertensive drugs significantly reduced the risk of recurrent stroke by 27.0% and that of cardiovascular-related death by 15.0%, compared with the placebo group [3]. Per the Cochrane library database [10], active treatment was shown to significantly reduce the risk of recurrent stroke by 18.0%. Therefore, evidence-based studies have conclusively established the effectiveness of BP lowering for secondary stroke prevention in patients with a history of stroke. A post hoc analysis of the PROGRESS trial [11] showed that antihypertensive treatment significantly reduced the risk of ischemic stroke by 24.0% and that of ICH by 50.0% in all patients; recurrent stroke was significantly reduced by 26.0% in patients with ischemic stroke as the index stroke and by 49.0% in those with hemorrhagic stroke as the index stroke.

A review of the Cochrane library database [10] showed that antihypertensive treatment significantly reduced the risk of recurrent stroke in patients with a baseline SBP > 140 mmHg; however, antihypertensive treatment produced only a marginal effect in those with an SBP < 140 mmHg.

Intensive vs. standard blood pressure control strategies

BP lowering is strongly recommended for secondary prevention with chronic management after stroke; however, the optimal BP level and significance of intensive BP lowering remain unclear. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial [12] and the Recurrent Stroke Prevention Clinical Outcome (RESPECT) study [13] were the only large-scale RCTs that investigated the effects of intensive BP lowering in stroke survivors. The SPS3 trial enrolled patients with LI within 180 days (median 62 days) of the stroke and showed that compared with standard BP lowering to a target level of 130–149 mmHg, intensive BP lowering to a target BP of <130 mmHg (mean 127 mmHg) resulted in a nonsignificant reduction in all strokes (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.64 to 1.03) and a significant reduction in ICH (HR 0.37, 95% CI 0.15 to 0.95). The RESPECT study included patients with a history of stroke within 3 years preceding study enrollment. A total of 1280 patients were randomly assigned to a standard treatment group ($N = 640$, target BP < 140/90 mmHg) or an intensive treatment group ($N = 640$, target BP < 120/80 mmHg) (ratio 1:1). However, 17 patients did not receive the intervention; therefore, the data from 1263 patients from the standard treatment ($N = 630$) and intensive treatment ($N = 633$) groups were analyzed. The primary outcome of this study was stroke recurrence. Among the 1263 patients investigated in this study, 99.5% completed a mean follow-up of 3.9 years. The mean baseline BP was 145.4/83.6 mmHg; the mean BP was 133.2/77.7 mmHg (95% CI 132.5 to 133.8/77.1 to 78.4) in the standard group and 126.7/77.4 mmHg (125.9 to 127.2/73.8 to 75.0) in the intensive group

throughout the study period. We observed 91 recurrent strokes. Compared with the standard group, a nonsignificant reduction in recurrent stroke rates was observed in the intensive group (HR 0.73, 95% CI 0.49 to 1.11, $p = .145$). The rates of syncope, falls, and fractures were similar; however, those of worsening kidney function were higher in the intensive group. This result is consistent with that reported by the Systolic Blood Pressure Intervention Trial [14]. When this finding was pooled for the SPS3 trial and other small RCTs in a meta-analysis, the risk ratio favored intensive BP control (relative risk 0.78, 95% CI 0.64 to 0.96, $p = 0.016$; absolute risk difference −1.5%, 95% CI −0.26 to −0.4%; 67 needed to treat, 95% CI 39 to 250) (Table 1) [13]. The target SBP values in the intensive BP control group differed between the aforementioned studies as follows: <130 mmHg, <130 mmHg, <125 mmHg, and <120 mmHg in the SPS3 trial, Prevention After Stroke–Blood Pressure trial, Prevention of Decline in Cognition after Stroke Trial, and RESPECT trial, respectively; however, the achieved SBP values were similar at 127 mmHg, 126 mmHg, 130 mmHg, and 124 mmHg, respectively (Table 1). Therefore, compared with standard BP control, intensive control with a target SBP < 130 mmHg was shown to be more effective for secondary stroke prevention. A meta-analysis of the SPS3 and RESPECT trials showed that compared with standard BP control, intensive BP control significantly reduced the risk of hemorrhagic stroke by 75.0%, although the risk of ischemic stroke was similar between the intensive and standard BP control groups. In a post hoc analysis of the 1074 patients with cerebral infarction as the index stroke in the RESPECT study, intensive BP treatment did not change the risk of ischemic stroke but it markedly reduced the risk of hemorrhagic stroke (Fig. 4) [15].

Optimal blood pressure level for secondary stroke prevention

A meta-analysis of RCTs showed that intensive control with a BP level <130 mmHg was effective for secondary stroke prevention. However, the optimal BP level for secondary stroke prevention remains debatable; the target BP level for the prevention of ischemic stroke may differ from that for hemorrhagic stroke. I will now review the published literature that discusses the association between achieved BP

Table 1 Summary of randomized controlled trials that compared intensive vs. standard blood pressure control for secondary stroke prevention

Trial	Year	Intensive treatment group		N of events/patients		Relative risk (95%CI)
		Target SBP (mm Hg)	Achieved SBP (mm Hg)	Intensive	Control	
SPS3	2013	<130	127	118/1501	147/1519	0.81 (0.64–1.02)
PAST-BP	2016	<130	126	0/266	3/263	0.14 (0.01–2.72)
PODCAST	2017	<125	130	1/41	3/42	0.34 (0.04–3.15)
RESPECT	2019	<120	124	39/633	52/630	0.75 (0.50–1.11)
Overall				158/2441	205/2454	0.78 (0.64–0.96)

CI confidence interval, *PAST-BP* Prevention After Stroke-Blood Pressure, *PODCAST* Prevention of Decline in Cognition after Stroke Trial, *RESPECT* Recurrent Stroke Prevention Clinical Outcome, *SBP* systolic blood pressure, *SPS3* The Secondary Prevention of Small Subcortical Strokes

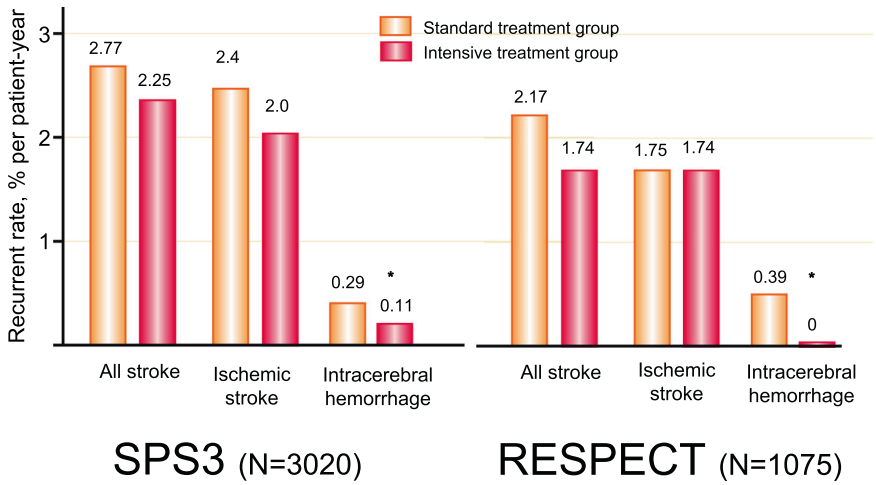


Fig. 4 Annual recurrence rates of all strokes, ischemic stroke and intracerebral hemorrhage in the SPS3 trial ($N = 3020$) and ischemic stroke patients enrolled in the RESPECT study ($N = 1075$)

and recurrent stroke in a post hoc analysis of RCTs and observational studies. In 1993, Irie et al. [16] reported the J-curve phenomenon when describing the association between poststroke DBP and stroke recurrence. In patients with ATBI, the lowest risk of recurrent stroke was observed in those with a DBP in the range of 85–89 mmHg. A post hoc analysis of the PROGRESS trial (index stroke: 71.0% ischemic stroke; 11.0% ICH; 22.0% transient ischemic attacks) [17] showed that achieving BP levels lowered to 115/75 mmHg was associated with a lower incidence of stroke recurrence (565 and 106 for ischemic and hemorrhagic strokes, respectively), without evidence of a J-curve in the range of the achieved BP, although the association between hemorrhagic stroke and achieved BP was stronger than that observed between achieved BP and ischemic stroke. However, the PRoFESS trial (index stroke: 100% ischemic stroke) [18] showed that the risk of recurrent stroke (87.3% and 7.1% for ischemic and hemorrhagic strokes, respectively) was the lowest in those with an SBP in the range of 130–139 mmHg, and the risk was significantly higher in those with an SBP between <120 mmHg and >140 mmHg, which suggests a J-shaped association between achieved SBP and recurrent stroke. A subgroup analysis of incident ICH in the PRoFESS trial [19] showed that the incidence of ICH increased with an increase in SBP in the range between <120 mmHg and >160 mmHg with no evidence of a J-curve. A post hoc analysis of the Vitamin Intervention for Stroke Prevention trial (index stroke: 100% ischemic stroke) [20] showed that the risk of recurrent stroke (subtypes not described) was the lowest in the range of an achieved BP between 120 and 139 mmHg and was higher in those with a BP level <120 mmHg than those with a BP level between 120 and 139 mmHg, which suggests a J-curve phenomenon. A post hoc analysis of the SPS3 trial [21] (index stroke: 100% LI) (77.0% and 8.0% of recurrent strokes classified as ischemic stroke and ICH, respectively) showed a J-shaped association between achieved BP and all recurrent strokes or ischemic stroke, with the lowest risk at SBP and DBP levels of approximately 124/87 mmHg, respectively. The association between the risk of ICH and achieved BP was not described, perhaps because of the small number of ICH patients included in the study. An observational study of 1145 patients who survived at least 90 days after the index ICH [22] showed that the lowest risk of recurrent ICH was observed in those with a BP level <120/80 mmHg, without any evidence of the J-curve phenomenon. Therefore, it can be concluded that the J-curve may be relevant for recurrent ischemic stroke in cases of BP levels <120 mmHg; however, no such association was observed between achieved BP and ICH risk. The PRoFESS trial [23] and the Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic Attack (PERFORM) study [24] showed that compared with other ethnicities, Asian patients with a history of ischemic stroke showed a significantly higher risk of hemorrhagic stroke following the administration of antiplatelet drugs; therefore, the prevention of ICH is important in the Asian patient population. To summarize the current findings, it is reasonable to conclude that the optimal BP level should be <130/80 mmHg; however, more aggressive BP lowering (values <120/80 mmHg) should be considered in patients at a high risk of ICH, such as in those with a history of ICH, a history of administration of >two antiplatelet or anticoagulant medications [25], older age, a history of renal disease, and documented cerebral microbleeds [26].

Intensive BP lowering to values <130/80 mmHg is acceptable for secondary stroke prevention in the chronic stage in most cases. However, patients with severe stenosis or occlusion of the major cerebral arteries require close monitoring. A post hoc analysis of the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial showed significant negative associations between SBP and recurrent stroke risk in patients with bilateral carotid stenosis >70% and a higher risk of recurrence in patients with an SBP < 140 mmHg than in those with an SBP > 140 mmHg [27]. However, a positive association was observed between SBP and stroke risk in patients with carotid stenosis <70% and >70% [27]. A post hoc analysis of the Warfarin-Aspirin Symptomatic Intracranial Disease trial, which included patients with intracranial stenosis, showed that a high SBP was associated with a high risk of recurrent stroke and stroke in the territory, and an increased risk in patients with an SBP > 160 mmHg; no increase in risk was shown in those with an SBP < 120 mmHg [28]. Therefore, except for rare cases with severe bilateral carotid stenosis, the optimal SBP was <140 mmHg or <130 mmHg for most patients, and no J-shaped curve was observed in patients with BP values <140 mmHg. However, patients with major cerebral artery disease and impaired perfusion require close monitoring. The risk of ischemic stroke in the territory was higher in patients with an SBP < 130 mmHg than in those with an SBP > 130 mmHg among 130 patients with symptomatic extracranial carotid occlusion or intracranial stenosis or occlusion of the carotid artery or middle cerebral artery, particularly in those with impaired cerebral perfusion documented by positron emission tomography [29].

Perspectives in Asia

Asian people with a history of ischemic stroke have a higher risk of intracerebral hemorrhage under antithrombotic treatment than Caucasian people [23, 24]. Therefore, the benefit of intensive BP treatment on the prevention of

intracerebral hemorrhage is much greater in Asian people than in Caucasian people. Compared with other medical vascular risk factors, BP management would be more important in Asian people than in Caucasian people for secondary stroke prevention.

Conclusion

BP lowering is an effective strategy for secondary stroke prevention; the optimal BP level is <130/80 mmHg in most cases. With regard to recurrent ischemic stroke, the risks appear similar in patients with an SBP in the range of 120–140 mmHg and may be higher in patients with an SBP < 120 mmHg (J-curve phenomenon). In contrast, the risk of hemorrhagic stroke increased in a linear manner in patients with an SBP in the range from <120 mmHg to > 160 mmHg (no J-curve phenomenon was observed). Therefore, an SBP < 130 mmHg and <120 mmHg is considered the target SBP for the prevention of total and ischemic and hemorrhagic strokes, respectively. However, patients with severe bilateral carotid stenosis, intracranial stenosis, or occlusion with impaired cerebral perfusion warrant close monitoring; a stepped-care approach with cautious BP lowering aimed at BP levels <140/90 mmHg or 130/80 mmHg is essential to prevent ischemic stroke recurrence.

Compliance with ethical standards

Conflict of interest KK reports grants and personal fees from Daiichi Sankyo, Bayer Inc., grants and personal fees from Nippon Boehringer Ingelheim, Kyowa Kirin, Sumitomo Dainippon Pharma, Astellas Pharma, and Sanofi, and personal fees from Takeda Pharmaceutical outside of the submitted work.

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