Lowering of Blood Pressure for Recurrent Stroke Prevention

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Hypertension is the premier modifiable risk factor for stroke. Indeed, ≤50% of strokes may be attributable to hypertension, and the relationship of hypertension with stroke also comprises distinct independent links between both systolic and diastolic hypertension and the occurrence of both primary and recurrent strokes. Furthermore, the underlying pathophysiological rationale and clinical trial evidence for lowering blood pressure (BP) in people with hypertension to safely prevent a primary stroke of any type are overwhelmingly clear. However, when it comes to recurrent stroke prevention, questions surrounding BP treatment linger, including what exactly to do, when precisely to do it, and whether the approach should vary by type of patient. This comparative lack of clarity about the nature of the BP-lowering strategy after a stroke has arisen because of theoretical efficacy/safety concerns related to the acuity and type of index stroke, as well as the paucity of published hypertension treatment trials for recurrent stroke prevention. As such, expert consensus recommendations for BP lowering to avert vascular events either do not specifically or adequately address recurrent stroke prevention (Eighth Joint National Committee, American Heart Association guidelines for managing BP in coronary artery disease) or are largely based on a paucity of clinical trials or reviews that did not specifically address key issues of acuity, stroke type, or BP-lowering intensity. Nonetheless, some expert opinion suggests that management of high vascular risk patients with hypertension remains aggressive for now until specific compelling trial evidence is available. The importance of optimizing recurrent stroke prevention to lessen the personal and societal burden of stroke cannot be overemphasized. Approximately 25% of stroke cases are recurrent events, often occurring within the first year of a prior stroke or transient ischemic attack (TIA), and the case mortality rate is 41% after a recurrent stroke versus 22% after a primary stroke. Hypertension continually poses a major risk for recurrent stroke if the lifetime risk of elevated BP remains unattenuated, and presence of elevated systolic BP (SBP) at the time of hospital discharge after a stroke is a strong predictor of early recurrence. This topical review provides an update of pertinent issues and recent data concerning BP lowering for recurrent stroke prevention. It is broken down into 5 main sections that cover nature/type of published evidence, prevailing expert consensus guideline recommendations, and key literature gaps. Table I in the online-only Data Supplement describes BP-lowering trials, and Table II in the online-only Data Supplement describes current American Heart Association/American Stroke Association guidelines discussed in this review.

Effect of Antihypertensive Treatment for Recurrent Stroke Prevention

Observational Data
An analysis of the General Practitioner Research Database in the United Kingdom examined the effects of guideline-recommended antihypertensive use within 90 days of an index stroke on 1-year recurrence rates among first-ever stroke survivors without antihypertensive treatment before stroke. Compared with no antihypertensive treatment, guideline-recommended antihypertensive drug treatment was associated with a decrease in 1-year recurrent stroke risk (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71–0.96). Kaplan et al reported higher poststroke BP levels within first year after index stroke was associated with higher risk of recurrent stroke during a mean follow-up period of 5.4 years in adults aged ≥65 years with prior ischemic stroke (adjusted HR [AHR], 1.42; 95% CI, 1.03–1.99 per SD of SBP; \( P = 0.04 \) and AHR, 1.39; 95% CI, 1.01–1.91 per SD of diastolic BP [DBP]; \( P = 0.04 \)).

Clinical Trials
Few randomized controlled trials (RCTs) have focused on antihypertensive therapy for recurrent stroke prevention. The Post-stroke Antihypertensive Treatment Study (PATS) was a randomized, placebo-controlled trial conducted in 5665 patients in the United Kingdom examined the effects of guideline-recommended antihypertensive use within 90 days of an index stroke on 1-year recurrence rates among first-ever stroke survivors without antihypertensive treatment before stroke. Compared with no antihypertensive treatment, guideline-recommended antihypertensive drug treatment was associated with a decrease in 1-year recurrent stroke risk (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71–0.96). Kaplan et al reported higher poststroke BP levels within first year after index stroke was associated with higher risk of recurrent stroke during a mean follow-up period of 5.4 years in adults aged ≥65 years with prior ischemic stroke (adjusted HR [AHR], 1.42; 95% CI, 1.03–1.99 per SD of SBP; \( P = 0.04 \) and AHR, 1.39; 95% CI, 1.01–1.91 per SD of diastolic BP [DBP]; \( P = 0.04 \)).

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in which 6105 patients in Asia, Australasia,
and Europe with a history of any stroke or TIA within the previous 5 years (mean, 8 months) were randomized to add-on angiotensin-converting enzyme inhibitor–based (ACEI; perindopril) treatment with or without thiazide-type diuretic indapamide (addition of diuretic left up to the treating clinician) versus placebo, reported an overall relative risk reduction (RRR) in recurrent stroke of 28% (95% CI, 17%–38%; \( P<0.0001 \)) during a mean follow-up period of 3.9 years. This trial showed the benefits of BP lowering in both hypertensive (RRR, 32%; 95% CI, 17%–44%) and nonhypertensive (RRR, 27%; 95% CI, 8%–42%) patients. However, based on older definitions, presence of baseline hypertension in the trial was defined as \( \geq 160/90 \text{ mmHg} \) (mean BP in the nonhypertensive group was 136/79 mmHg, but SDs were not reported). The RRR for recurrent ischemic stroke was 24% (95% CI, 10%–35%) and for recurrent intracerebral hemorrhage (ICH) was 50% (95% CI, 26%–67%) for actively treated patients compared with placebo. For patients with a history of ICH at baseline in PROGRESS, add-on active BP treatment (versus placebo) was associated with an even greater magnitude of risk reduction (RRR, 49%; 95% CI, 18%–68%), thus underscoring the importance of BP control after ICH for recurrent stroke prevention. However, only 10% of the study population had ICH. The large treatment effect seen in patients with ICH could be due, in part, to the relatively stronger and more direct causative relationship of BP with ICH and the younger average age of patients with ICH (mean age, 61 years compared with 64 years for patients with ischemic stroke).

### Systematic Reviews and Meta-Analyses

A meta-analysis\(^a\) of 7 RCTs on patients with a recent history of ischemic stroke, TIA, or ICH in 2003—Dutch TIA trial,\(^{19}\) PATS,\(^{16}\) Heart Outcomes Prevention Evaluation (HOPE),\(^{20}\) PROGRESS,\(^{17}\) Hypertension-Stroke Cooperative Group,\(^{21}\) Carter,\(^{22}\) and Eriksson et al\(^{23}\)—showed that antihypertensive drug therapy was associated with a 24% reduction in recurrent stroke risk (RR, 0.76; 95% CI, 0.63–0.92). The reduction in recurrent stroke risk was seen in both hypertensive and normotensive (as defined by the respective trials) patients and was associated with the magnitude of reduction in SBP\(^5\).

An updated meta-analysis\(^\text{24}\) in 2009 included 10 RCTs that examined the role of BP reduction using antihypertensive agents to prevent recurrent stroke. This study found that BP-lowering agents reduced recurrent stroke (odds ratio, 0.71; 95% CI, 0.59–0.86; \( P=0.0004 \)) and cardiovascular events (odds ratio, 0.69; 95% CI, 0.57–0.85; \( P=0.0004 \)) in patients with a prior stroke or TIA; however, these agents did not affect the rate of myocardial infarction or all-cause mortality.

### Evidence Gaps

Although the aforementioned data clearly support the benefit of long-term use of antihypertensive therapy in patients with lower risk for recurrent stroke, given the heterogeneity of stroke pathophysiology and hemodynamic concerns that can accompany occurrence of a recent stroke, additional high-quality evidence pertaining to antihypertensive use for recurrent stroke prevention by index stroke acuity/type and antihypertensive treatment intensity/agent is warranted. Furthermore, although there is compelling evidence for the initiation of antihypertensive treatment for previously untreated stroke or TIA patients with an established SBP \( \geq 140 \text{ mmHg} \) or DBP \( \geq 90 \text{ mmHg} \), evidence for prescribing antihypertensive agents for previously untreated stroke or TIA patients with an established SBP \( \geq 140 \text{ mmHg} \) or DBP \( \geq 90 \text{ mmHg} \) remains much less clear and will require further investigation.

### Timing of Reduction of High BP for Recurrent Stroke Prevention

#### Observational Data

Elevations in SBP or DBP are seen in \( \leq 80\% \) of patients after an acute ischemic stroke, even among those previously established (before stroke) as being normotensive,\(^25\) with a spontaneous return to baseline within several days after stroke. Higher BP after stroke could be because of stress after the stroke or a physiological response to enhance compromised cerebral perfusion.\(^{26}\) Given a high early risk of recurrent stroke,\(^7,28\) evidence indicating that the presence of hypertension at the time of hospital discharge is a predictor of recurrent stroke risk\(^{29}\) and observations that in-hospital behavior strongly influences postdischarge community practice,\(^{30}\) the issue of promptly initiating as soon as possible after an index stroke is an important one. However, several studies have suggested that higher BP early in the setting of an acute ischemic stroke may be an independent predictor of favorable outcome at 90 days.\(^{26,31–33}\) Furthermore, recent observational data suggest that aggressive SBP reduction going beyond the early period after an ischemic stroke may have a differential impact on stroke prevention based on the timing of such treatment after an index ischemic stroke event. A post hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial comprising \( >20000 \) patients with a recent noncardioembolic ischemic stroke showed a J-shaped relationship between SBP with recurrent vascular risk after stroke to be most prominent in the first 90 to 180 days after the qualifying event;\(^{34}\) and a separate analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial comprising 3600 patients with a recent noncardioembolic ischemic stroke found that the adverse association of low-normal SBP with outcome was also more pronounced in the first 90 to 180 days after the qualifying event.\(^{35}\) Both these post hoc trial data align with those seen in an analysis of acute ischemic stroke where a J-shaped curve was observed and low-normal SBP was linked to a higher risk of early recurrence at 2 weeks and poor functional outcome at 6 months compared with high-normal SBP.\(^6\) However, it seems that moderate reductions in BP during the first week after admission may be associated with short-term functional improvement in patients with acute ischemic stroke.\(^7\)

The issue of lowering BP in patients with acute stroke remains controversial with epidemiological evidence supporting acute treatment, whereas physiological and clinical trial evidence suggesting this may provide no benefit or possibly cause harm, especially among patients with significant, especially bilateral, carotid stenosis.\(^38–40\) There are competing concerns about preventing recurrence versus reducing cerebral perfusion pressure with regard to initiating BP management in the acute setting after stroke.\(^41\)
Clinical Trials
Few trials have addressed the early initiation of treatment for secondary stroke prevention. In the PROFESSIONAL trial, treatment was initiated within a median of 15 days after ischemic stroke, which is the earliest time of treatment initiation in a large RCT reported to date. However, this trial did not find a significant difference between treatment and placebo groups, most likely as a result of the small BP reduction compared with placebo (3.8/2.0 mm Hg) and the short follow-up period in this study. The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) trial, however, reported improved outcomes among patients with ischemic stroke receiving antihypertensive therapy shortly after stroke onset (within 6–24 hours after admission), supporting the safety and efficacy of early implementation,43 especially because the risk of recurrence is highest in the first few weeks and months after initial stroke.44 In the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) trial, which examined whether immediate BP reduction in patients with acute ischemic stroke would reduce death and major disability at 14 days or hospital discharge, modest BP reduction by 10% to 25% within the first 24 hours after randomization and maintaining at <140/90 mm Hg for an average hospitalization period of 13 days showed a strong trend toward modest benefit in favor of the treatment group, amounting to a 35% RRR in stroke recurrence at 3 months.40 Because there was only a clinically negligible difference in mean SBP between 2 groups at 3 months (−2.7 [−3.7 to −2.2] mm Hg), it would be reasonable to postulate that this benefit likely came from the initial BP reduction (9.3 mm Hg difference at day 7). This trend toward recent stroke benefit was not observed in another clinical trial of early BP reduction in patients with acute stroke (ischemic or hemorrhagic) and elevated BP levels that revealed a trend toward higher risk of poor functional outcome at 6 months after BP-lowering treatment initiated within 30 hours of the index stroke,39 but the BP difference at day 7 was only 4.9 mm Hg.

Starting antihypertensive treatment in the initial 5 to 10 days after ICH may have a different outcome from that seen after an ischemic stroke because of secondary edema formation and hemodynamic changes.45 Two RCTs, the INTensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)46 and the Antihypertensive Therapy in Acute Cerebral Hemorrhage (ATACH)47 trial, conducted in patients with ICH offered proof of concept that early and aggressive BP lowering is feasible and potentially safe in the acute ICH period; however, the BP target, duration of therapy, and improvement in outcomes remain unclear.46 Some studies have suggested that high BP may promote hematoma expansion, and thus BP is often lowered in the acute setting, whereas other studies have argued against BP lowering in acute ICH because of possible occurrence of a perihematoma ischemic zone, which may in fact be as a result of reduced cerebral metabolism rather than reduction in BP around the hematoma.

Systematic Reviews and Meta-Analyses
A meta-analysis of 7 RCTs examined initiation of BP-lowering therapy after stroke, but timing of treatment ranged from <1 week to =1 year. Although the authors suggest that treatment should be initiated ≥1 week after the onset of stroke, no systematic review or meta-analysis has specifically examined the benefit or harm of taking such an approach.

Evidence Gaps
Controversy remains regarding early initiation and long-term treatment with antihypertensive agents in patients after stroke. Few trials, limited by small samples sizes, on BP management in patients with acute stroke, especially in patients with ICH, have been published. Uncertainty remains regarding the risks and benefits of treatment in patients with symptomatic carotid occlusive disease, especially among those with a carotid occlusion or bilateral ≥70% stenosis in whom cerebral perfusion may be compromised. Although ≥20% of patients with stroke have significant occlusion or stenosis placing them at increased risk of recurrent stroke, there are no specific hypertension guidelines for these patients, and little is reported on the extent or severity of carotid disease in poststroke BP-lowering trials. In a study examining the effect of carotid artery disease on the relationship between BP and recurrent stroke risk, Rothwell et al40 reported that the risk of recurrence increased with increasing BP in patients with symptomatic carotid artery disease and similarly in patients with unilateral stenosis; however, in patients with bilateral ≥70% stenosis, the relationship of BP and recurrent stroke risk was inverted, suggesting that aggressive BP treatment in such patients may be imprudent. In addition, long-term antihypertensive treatment may also compromise cerebral perfusion in poststroke patients, especially among elderly patients with carotid disease.5 Thus, RCTs focused on early initiation, and long-term maintenance of secondary prevention measures is needed.

Degree of Reduction of High BP for Recurrent Stroke Prevention
The classic debate of ‘lower is better and much lower is best’ versus J-curve association in BP management has again become a point of discussion in recent years. Several recently published large RCTs dispute the ‘lower is better’ argument, despite current American Heart Association/American Stroke Association and European Society of Cardiology guidelines recommending aggressive BP management.

Observational Data
Friday et al51 reported that a risk ratio of stroke recurrence for baseline DBP ≥80 versus <80 mm Hg was 2.4 (95% CI, 1.38–4.27) and for baseline SBP ≥140 versus <140 mm Hg was 2.4 (95% CI, 1.39–4.15). For isolated SBP (≥140/<90 mm Hg), the risk ratio was 2.2 (95% CI, 1.23–3.79) compared with BP <140/<90 mm Hg at baseline. A recurrent stroke risk reduction of 0.4 (95% CI, 0.21–0.88) was reported for patients who had ≥1 measured DBP <80 mm Hg during follow-up compared with those with DBP 80 to 90 mm Hg, even after controlling for possible confounding factors, thus supporting the ‘lower the better’ BP control for reducing recurrent stroke.51 Hier et al48 also reported an increased risk of recurrent stroke at 2 years with baseline DBP ≥100 mm Hg (RR, 1.012; 95% CI, 1.003–1.021). Alter et al39 report a continual reduction in recurrent stroke risk as quality of DBP control increased (RR, 8.4, 3.9, and 2.0 among those with poor, fair,
and good control, respectively, compared with nonhypertensive patients. However, Irie et al\textsuperscript{64} found that the recurrent stroke risk increased in patients with DBP <80 mm Hg, and Yoko et al\textsuperscript{65} found increased risk of stroke in elderly hypertensive patients with DBP ≤60 mm Hg. A report by Wang et al\textsuperscript{66} showed that BP >140/90 mm Hg on repeated measurements during hospitalization or patients treated with antihypertensive agents was specifically related to recurrent stroke at 3, 6, and 12 months in patients with small-vessel diseases, but not with other stroke subtypes.

In the PROGRESS trial,\textsuperscript{37} there was a reduction in BP of 9/4 mm Hg among those assigned active treatment compared with placebo, with no evidence of attenuation throughout the follow-up period. Combination therapy reduced BP by 12/5 mm Hg and stroke risk by 43% (95% CI, 30%–54%), whereas monotherapy only reduced BP by 5/3 mm Hg with no significant reduction in stroke risk (RRR, 5%; 95% CI, −19% to 23%). However, stratified analyses of the baseline SBP level among patients treated with combination perindopril and indapamide revealed that the significant reduction in recurrent stroke risk was seen only in patients with a baseline SBP ≥160 or 140 to 159 mm Hg, but not at the lower baseline SBP levels.\textsuperscript{57}

In post hoc analyses\textsuperscript{54} of the PROFESSION\textsuperscript{58} trial, a clinical trial that randomized recent noncardioembolic stroke patients to either angiotensin receptor blocker (ARB) telmisartan or placebo, investigators showed that patients with SBP in the high (140–149 mm Hg) and very high (≥150 mm Hg) range was associated with increased risk of recurrent stroke (AHR, 1.23; 95% CI, 1.07–1.41 and AHR, 2.08; 95% CI, 1.83–2.37, respectively) compared with the guideline-indicated SBP range of 130 to 139 mm Hg. In addition, they found that SBP in the very low-normal (<120 mm Hg) range was also significantly associated with an increased risk of recurrent stroke (AHR, 1.29; 95% CI, 1.07–1.56), thus indicating a threshold effect of benefit or harm for both short-term and long-term SBP levels after stroke. Therefore, BP management in the poststroke clinical setting needs to be well monitored to prevent adverse outcomes because of aggressive management. It was also noted that the effect of telmisartan on reducing recurrent outcomes may be time-dependent because the J-curve association of SBP and recurrent vascular risk was markedly present in the first 6 months after the index event, whereas the benefit of telmisartan only emerged later in follow-up period, however, did not reach statistical significance.

A recent analysis of participants in the North East Melbourne Stroke Incidence Study contacted at 5 years after stroke for a follow-up assessment showed that there was a greater risk of poor outcome in long-term survivors of stroke with low SBP.\textsuperscript{59} Compared with an SBP of 131 to 141 mm Hg, an SBP of ≤120 mm Hg was associated with a 61% greater risk of stroke, acute myocardial infarction, and death (95% CI, 1.08–2.41), but there were no differences in outcome in the patients with SBP 121 to 130 mm Hg or 142 to 210 mm Hg. These findings did not change even after adjusting for prescription of antihypertensive medications.

Recent studies have shown that BP variability may be an important contributing risk factor for stroke risk.\textsuperscript{60,61} Rothwell et al\textsuperscript{62} reported a high stroke risk among patients with high BP variability, independent of the absolute mean SBP.

### Clinical Trials

The recently published Secondary Prevention of Small Subcortical Stroke (SPS3)\textsuperscript{63} trial assessed 2 target ranges of SBP (130–149 versus <130 mm Hg) on the rate of recurrent stroke among patients with recent MRI-defined symptomatic lacunar infarctions. This study resulted in nonsignificant reductions in the rate of recurrence for all strokes (HR, 0.81; 95% CI, 0.64–1.03) and significant reductions in ICH recurrence. This study, although not significant, when viewed in light of prior BP-lowering randomized controlled trials after stroke,\textsuperscript{17,63} supports the lowering of SBP to below the normal range of <130 mm Hg to reduce recurrence risk among stroke survivors. Secondary analyses of the International Stroke Trial (IST)\textsuperscript{46} reported that for every 10 mm Hg increase in SBP the recurrent ischemic stroke rate within 14 days increased by 4.2%.

Although definitive data on optimal target BP for recurrent stroke prevention in patients with ICH are unavailable, experts suggest that a reasonable BP target of <140/90 mm Hg in uncomplicated patients and <130/80 mm Hg in patients with diabetes mellitus or chronic kidney disease is safe and tolerable.\textsuperscript{64}

### Systematic Reviews and Meta-Analyses

There is variability in the specific target BP goal for recurrent stroke prevention. A meta-analysis that looked at impact of achieving tight versus usual SBP control on stroke prevention of randomized controlled trials found that achieving an SBP ≤130 mm Hg compared with 130 to 139 mm Hg seemed to provide additional stroke protection only among people with known vascular risk factors (ie, primary prevention) but not those with established (or symptomatic) vascular disease.\textsuperscript{65}

### Evidence Gaps

The notion of the J-curve association of BP and poor outcomes remains unproven and will require dedicated clinical trials to answer this question. Although American Heart Association/American Stroke Association guidelines have based their recommendations on published trials, the recommended target of 130 mm Hg was not achieved in a substantial number of trials for which these recommendations were based.\textsuperscript{16,17,34,43} There is a significant lack of data on both the short- and long-term benefits of BP lowering in patients with ICH. Clinical trials that focused on the aggressive BP lowering to prevent recurrent vascular events after stroke are needed.

### Influence of Antihypertensive Drug Class on Recurrent Stroke Prevention

#### Observational Data

Data observed from several clinical trials raised the possibility of an additional mechanism, independent of BP lowering, through which selective antihypertensive agents may be beneficial for patients with stroke. Most of these studies suggested that modulators of the renin–angiotensin system may confer vascular protection beyond their primary mode of therapeutic action.\textsuperscript{20,43,66,67}
Clinical Trials
The varying results reported by antihypertensive treatment for secondary stroke prevention trials are mainly related to the different antihypertensive agents used.

Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES), the first trial to compare different antihypertensive drugs for recurrent stroke prevention, randomized patients with hypertension to 600 mg/d ARB eprosartan or 10 mg/d calcium channel blocker nitrendipine for a mean follow-up period of 2.5 years. By the end of the trial, BP reductions were similar between the treatment arms, and 75% of the patients reached the target BP goal of <140/90 mm Hg. BP was reduced by 13/3 mm Hg in the eprosartan arm and by 16/7 mm Hg in the nitrendipine arm. Combination therapy was necessary in 66% and 67% of the eprosartan- and nitrendipine-treated patients, respectively.

The PROFESSION trial randomized patients with ischemic stroke to 80 mg/d ARB telmisartan or placebo. Early initiation of telmisartan resulted in a 3.8/2.0 mm Hg lower BP compared with placebo; however, this reduction was not significantly associated with a risk reduction in recurrent stroke, major cardiovascular events, or diabetes mellitus. The impact of treatment may have been affected by the high rate of discontinuation of treatment medication because of hypotensive symptoms, syncope, diarrhea, and nausea experienced in the telmisartan arm and the more aggressive treatment with other standard antihypertensive therapies in the placebo arm. Thus, adverse side effects from treatment medications may affect quality of life and thus medication adherence after stroke.

Systematic Reviews and Meta-Analyses
A meta-analysis of the PROFESSION trial randomized assessment study in ACE intolerant subjects with cardiovascular disease (TRANSITION) studies did, however, show a significant reduction (odds ratio, 0.93; 95% CI, 0.86–0.99) in composite events (cardiovascular death, myocardial infarction, stroke, and heart failure) among patients treated with telmisartan compared with placebo, again with increasing significance after 6 months.

A meta-analysis of 7 RCTs performed through 2002 on patients with recent history of cerebrovascular disease with follow-up of 2 to 5 years showed significant reductions in recurrent stroke with diuretics alone and in combination with ACEI, but not with ACEI or β-blockers alone. Another meta-analysis evaluating the use of ACEI or ARBs to reduce the risk of future vascular events in patients with a prior history of stroke found that treatment only had a modest effect on reducing the risk of recurrent stroke (RR, 0.93; 95% CI, 0.86–0.99) and future vascular events (RR, 0.91; 95% CI, 0.87–0.97).

The effects of antihypertensive drugs on SBP variability are thought to be dose-dependent and persist when prescribed in combination. In a meta-analysis of BP-lowering drugs, calcium channel blockers were found to reduce SBP interindividual variability when used at a high dose alone or in combination with other agents, whereas high-dose β-blockers seem to increase SBP variability; thus, calcium channel blockers may play a protective role in the prevention of stroke. When examining drug comparison trials, a meta-analysis revealed that the average BP reduction was similar between the different classes of drugs; thus, the value of lowering BP to goal may be greater than the mechanism by which it is achieved for stroke prevention.

Evidence Gaps
Reduction in BP below the normal range has been associated with reduction in recurrent stroke risk; however, there is no definitive evidence of a drug class-specific treatment effect. The scarcity of trials limits the comparisons between different classes of antihypertensive medications; thus, the optimal BP-lowering drug treatment class for recurrent stroke prevention remains unclear. Guidelines have not adequately addressed the issues of hypertension management in patients with stroke, with more general recommendations including ACEI and/or ARB and diuretic therapy similar to other populations. However, because stroke is proposed as a cardiovascular risk equivalent, there is a significant view that management of high-risk patients with hypertension be aggressive and detailed until specific strong trial evidence is available. Beyond future head-to-head trials of antihypertensive drugs in different therapeutic classes, trials are also needed to assess the effects of lifestyle modification in reducing BP for the purposes of recurrent stroke prevention.

Although there is strong evidence to support antihypertensive treatment in elderly general populations, evidence for treatment of elderly patients with a history of stroke using a specific agent class is lacking. Future clinical trials testing the efficacy of a given antihypertensive agent class for secondary stroke prevention should make an effort to include elderly patients aged >70 years. Blacks and other race–ethnic minorities are also grossly under-represented in such trials, despite their excessively higher risk of stroke and other vascular diseases. Biological differences, such as salt-sensitive/low renin hypertension, among blacks may contribute to differential adverse stroke outcomes that may be amenable to treatment with specific agent classes. Other key factors that may influence the impact of agent class on recurrent stroke outcome such as existence/number/type of medical comorbidities and level of BP also warrant investigation.

Optimizing Reduction of High BP for Recurrent Stroke Prevention
Healthcare providers are often focused on the immediate management during the acute stroke hospitalization and thus may miss the opportunity to institute evidence-based prevention strategies. Healthcare providers should take advantage of the opportunity to institute evidence-based prevention strategies during acute stroke hospitalization; otherwise, long-term initiation of treatment may be deferred to the postdischarge clinical setting where the risk of loss of adequate follow-up of care is greater.

Observational Data
Although at least two thirds of patients hospitalized with acute ischemic cerebrovascular events may be discharged from the hospital on ≥1 antihypertensive medication, several lines of evidence from various registries in different countries suggest that BP remains poorly controlled and there is relatively poor...
adherence with antihypertensive treatment in a substantial number of patients in the postdischarge setting.74–76

In a post hoc analysis of the VISP trial, individuals with recent stroke, followed for 2 years, were divided according to proportion of visits in which BP was controlled (<140/90 mm Hg): <25%, 25% to 49%, 50% to 74%, and ≥75%.77 Multivariable models adjusting for demographic and clinical variables determined the association between consistency of BP control versus primary (stroke) and secondary (stroke, myocardial infarction, or vascular death) outcomes. Only 30% of participants had BP controlled ≥75% of the time. Among those with baseline SBP >75th percentile (>153 mm Hg), risks of primary and secondary outcomes were lower in those with BP controlled ≥75% versus <25% of visits (AHR, 0.46; 95% CI, 0.26–0.84 and AHR, 0.51; 95% CI, 0.32–0.82). Individuals with mean follow-up BP <140/90 mm Hg had lower risk of primary and secondary outcomes than those with BP ≥140/90 mm Hg (AHR, 0.76; 95% CI, 0.59–0.98 and AHR, 0.76; 95% CI, 0.62–0.92).

Clinical Trials
In-hospital initiation of antihypertensive therapies before stroke discharge has been shown to improve treatment utilization, adherence, as well as the risk of recurrent vascular events.28,30,78 However, we are unaware of any published clinical trials aimed at assessing the impact of an intervention targeting BP control for recurrent stroke prevention, but an ongoing trial is taking place in Los Angeles, CA.79

Systematic Reviews and Meta-Analyses
We are unaware of any systematic reviews or meta-analyses on the topic of implementing BP control strategies to optimize recurrent stroke prevention.

Evidence Gaps
Clinical trials evaluating dissemination and implementation of evidence-based strategies for BP control to prevent recurrent stroke in routine clinical practice are needed.

Recently, hypertension treatment guidelines have introduced ambulatory BP monitoring as a vital method to diagnose and manage hypertension. Some studies have suggested the intercorrelation of BP variability and diurnal or abnormal circadian BP patterns after stroke. The MOSES trial used ambulatory BP monitoring to confirm the efficacy of BP-lowering treatment in recurrent stroke prevention. However, data on BP measurements by ambulatory BP monitoring in stroke survivors are scarce. Ambulatory BP monitoring could play a pivotal role in addressing several unresolved questions, including the role of nocturnal BP dipping and stroke recurrence, the higher prevalence of unstable BP patterns in stroke patients with autonomic failure, and the necessity of chronic antihypertensive therapy after the acute stroke phase.80

Conclusions
Recurrent stroke risk is further compounded by elevated BP. Meta-analyses of RCTs have reported a 30% to 40% reduction in recurrent stroke risk with BP-lowering therapies.5,71 However, because of heterogeneous causes and hemodynamic consequences, the management of BP to reduce recurrent stroke is more complex and challenging than a meta-analysis across all stroke types and settings may suggest, especially in the early to short-term period after an index stroke. Clearly, the management of hypertension in the patient with stroke represents a complicated scheme as documented by this report and the recently published 2014 Secondary Stroke Prevention recommendations.9 However, a detailed focused evidence-based report on the treatment and management of high BP remains an essential need for both stroke neurologists and the primary care physicians tasked with the health care of patients with cerebrovascular disease. Similarly, several questions remain unanswered, but the way forward to resolving these issues will likely demand the conduct of clinical trials specifically aimed at incrementally boosting our current understanding of the pathophysiology, natural history, and care continuum of stroke. Future recurrent stroke prevention clinical trials may need to target more narrowly defined questions such as optimal BP reduction timing and target or ideal antihypertensive agent therapeutic class by patient type (elderly, black race, and so on) and event type (hemorrhagic or ischemic, large-vessel occlusive, TIA). Furthermore, developing and testing the best sustainable strategies for translating current and future evidence for efficacious BP treatment after stroke into clinical practice will become of increasing importance as the number of stroke survivors rises and the cost of caring for them soars.81

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Disclosures
None.

References


## SUPPLEMENTAL MATERIAL

### SUPPLEMENTAL TABLES

### Table I. BP Lowering Trials for Recurrent Stroke Prevention

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects (Centers)</th>
<th>Age, y/ Female, %</th>
<th>Qualifying Event, %</th>
<th>Median Enroll Months</th>
<th>Mean Follow-up Years</th>
<th>Treatment Drug (daily dose); Control</th>
<th>Baseline BP, mm Hg (% HTN)</th>
<th>BP Reduction, mm Hg</th>
<th>Treatment v. Control Recurrent Event; Risk Reduction* (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>PATS 1995¹</td>
<td>5,665 (44)</td>
<td>60/ 28</td>
<td>IS: 71; TIA: 12; HS: 16</td>
<td>14</td>
<td>2</td>
<td>Indapamide (2.5mg); placebo</td>
<td>154/93 (84)</td>
<td>5/2</td>
<td>9.4% v. 12.3%; RR 29% (12-42)</td>
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<tr>
<td>PROGRESS 2001² (Single-drug)</td>
<td>2,561 (172)</td>
<td>65/ 32</td>
<td>IS: 70; TIA: 23; ICH: 11</td>
<td>9</td>
<td>3.9</td>
<td>Perindopril (4mg); placebo</td>
<td>144/84 (40)</td>
<td>5/3</td>
<td>12.3% v. 12.9%; RR 5% (-19-23)</td>
</tr>
<tr>
<td>PROGRESS 2001² (Combination)</td>
<td>3,544 (172)</td>
<td>63/ 29</td>
<td>IS: 71; TIA: 22; ICH: 11</td>
<td>7</td>
<td>3.9</td>
<td>Perindopril (4mg) + Indapamide (2.5mg); double-placebo</td>
<td>149/87 (54)</td>
<td>12/5</td>
<td>8.5% v. 14.4%; RR 43% (30-54)</td>
</tr>
<tr>
<td>MOSES 2005³</td>
<td>1,405 (330)</td>
<td>68/ 46</td>
<td>IS: 61; TIA: 27; PRIND: 6; ICH: 6</td>
<td>12</td>
<td>2.5</td>
<td>Eprosartan (600mg); Nitrendipine (10mg)</td>
<td>151/87 (100) in both groups</td>
<td>13/3</td>
<td>6.6 ID Eprosartan v. 8.8 ID Nitrendipine; RR 25% (3-42)</td>
</tr>
<tr>
<td>PRoFESS 2008⁴</td>
<td>20,332 (695)</td>
<td>66/ 36</td>
<td>IS: 100</td>
<td>0.5</td>
<td>2.5</td>
<td>Telmisartan (80mg); placebo</td>
<td>144/84 (74)</td>
<td>3.8/2.0</td>
<td>8.7% v. 9.2%; RR 5% (-4-14)</td>
</tr>
</tbody>
</table>

IS, ischemic stroke; TIA, transient ischemic attack; HS, hemorrhagic stroke; ICH, intracerebral hemorrhage; PRIND, prolonged reversible ischemic neurological disorder; BP, blood pressure, given as systolic/diastolic; HTN, prior hypertension, RR, risk reductions; ID, incidence density per 100 person-years; CI, confidence interval.

* Recurrent stroke relative risk reduction estimates for treatment versus placebo were based on proportional hazards regression for all studies except for MOSES where risk reduction was estimated from the incidence density ratio (ID ratio: 0.75 (0.58-0.97)) between two treatment groups.
Table II. ASA/AHA Guideline Recommendations for BP Management for Recurrent Stroke Prevention

Ischemic Stroke and Transient Ischemic Attack

1. Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP $\geq 140$ mm Hg systolic or $\geq 90$ diastolic (Class I; LOV B). Initiation of therapy for patients with BP $<140$ mm Hg systolic and $<90$ mm Hg diastolic is of uncertain benefit (Class IIb; LOV C).*

2. Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days (Class I; LOV A).*

3. Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure $<140$ mm Hg and a diastolic pressure $<90$ mm Hg (Class IIa; LOV B). For patients with a recent lacunar stroke, it might be reasonable to target an SBP $<130$ mm Hg (Class IIb; LOV B).*

4. Several lifestyle modifications have been associated with BP reduction and are a reasonable part of a comprehensive antihypertensive therapy. These modifications include salt restriction; weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption. (Class IIa; LOV C)

5. The optimal drug regimen to achieve the recommended level of reductions is uncertain because direct comparisons between regimens are limited. The available data indicate that diuretics or the combination of diuretics and an ACEI is useful. (Class I; LOV A)

6. The choice of specific drugs and targets should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes). (Class IIa; LOV B)

Intracerebral Hemorrhage

1. After the acute ICH period, absent medical contraindications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy. (Class I; LOV A)*

2. After the acute ICH period, a goal target of a normal BP of $<140/90$ ($<130/80$ if diabetes or chronic kidney disease) is reasonable. (Class IIa; LOV B)*

Class, class of recommendation; LOV, level of evidence; BP, blood pressure, given as systolic/diastolic mm Hg; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; ACEI, angiotensin-converting enzyme inhibitor.

* New or revised recommendation from previously published guidelines
SUPPLEMENTAL REFERENCES


### Table I. BP Lowering Trials for Recurrent Stroke Prevention

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects (Centers)</th>
<th>Age, yrs/ Female, %</th>
<th>Qualifying Event, %</th>
<th>Median Enroll Months</th>
<th>Mean Follow-up Years</th>
<th>Treatment Drug (daily dose); Control</th>
<th>Baseline BP, mm Hg (% HTN)</th>
<th>BP Reduction, mm Hg</th>
<th>Treatment v. Control Recurrent Event; Risk Reduction* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATS 1995¹</td>
<td>5,665 (44)</td>
<td>60/ 28</td>
<td>IS: 71; TIA: 12; HS: 16</td>
<td>14</td>
<td>2</td>
<td>Indapamide (2.5mg); placebo</td>
<td>154/93 (84)</td>
<td>5/2</td>
<td>9.4% v. 12.3%; RR 29% (12-42)</td>
</tr>
<tr>
<td>PROGRESS 2001²</td>
<td>2,561 (172)</td>
<td>65/ 32</td>
<td>IS: 70; TIA: 23; ICH: 11</td>
<td>9</td>
<td>3.9</td>
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