Published in final edited form as:
Stroke. 2014 August ; 45(8): 2506–2513. doi:10.1161/STROKEAHA.114.003666.

Lowering of Blood Pressure for Recurrent Stroke Prevention: Topical Review

Andrea D. Boan, PhD, MSCR[1], **Daniel T. Lackland, DrPH, FAHA**[1], and **Bruce Ovbiagele, MD, MSc, MAS, FAHA**[1]

[1]Department of Neurosciences, Medical University of South Carolina, Charleston, SC

Keywords

Stroke prevention; Hypertension; Blood pressure treatment

I. Introduction

Hypertension is the premier modifiable risk factor for stroke.[1, 2] Indeed, up to 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.[3] Furthermore, the underlying pathophysiologic rationale and clinical trial evidence for lowering blood pressure (BP) in people with hypertension to safely prevent a primary stroke of any type is overwhelmingly clear.[4] 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 due to 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.[5, 6] As such, expert consensus recommendations for BP-lowering to avert vascular events either do not specifically and/or adequately address recurrent stroke prevention (JNC-8,[7] AHA guidelines for managing BP in CAD[8]), 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.[9] Nonetheless, some expert opinion suggests that management of high vascular risk patients with hypertension remain aggressive for now until specific compelling trial evidence is available.[10]

The importance of optimizing recurrent stroke prevention to lessen the personal and societal burden of stroke cannot be overemphasized. Nearly 25% of stroke cases are recurrent events, often occurring within the first year of a prior stroke or transient ischemic attack (TIA),[11] and the case mortality rate is 41% after a recurrent stroke vs. 22% following a primary stroke.[12] Hypertension continually poses a major risk for recurrent stroke if the

Address for Correspondence: Bruce Ovbiagele, MD MSc MAS, Department of Neurosciences, Medical University of South Carolina, 96 Jonathan Lucas Street, CSB 301, MSC 606, Charleston, SC 29425, Fax: 843-792-6995.

Disclosure(S): None.

lifetime risk of elevated BP remains unattenuated,[5] and presence of elevated systolic blood pressure (SBP)at the time of hospital discharge following a stroke, is a strong predictor of early recurrence.[13] This topical review article provides an update of pertinent issues and recent data concerning BP-lowering for recurrent stroke prevention. It is broken down into five main sections that cover nature/type of published evidence, prevailing expert consensus guideline recommendations, and key literature gaps. Please see http://stroke.ahajournals.org for supplemental table I describing BP-lowering trials and table II current AHA/ASA guidelines discussed in this review.

II. Effect of Antihypertensive Treatment for Recurrent Stroke Prevention

1. 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 prior to stroke. When compared to no antihypertensive treatment, guideline-recommended antihypertensive drug treatment was associated with a decrease in 1-year recurrent stroke risk (hazards ratio [HR], 0.82; 95% confidence interval [CI], 0.71-0.96).[14] Kaplan et al[15] reported higher post stroke BP levels within first year after index stroke was associated with higher risk of recurrent stroke over mean follow-up period of 5.4 years in adults ≥65 years with prior ischemic stroke (adjusted hazards ratio [AHR], 1.42; 95% CI, 1.03-1.99 per standard deviation [SD] of SBP; p=.04 and AHR, 1.39; 95% CI, 1.01-1.91 per SD of diastolic blood pressure [DBP]; p=.04).

2. Clinical trials

Few randomized controlled trials (RCTs) have focused on antihypertensive therapy for recurrent stroke prevention. The Post-stroke Antihypertensive Treatment Study (PATS),[16] trial was a randomized, placebo-controlled trial in 5,665 patients in China to assess risk reduction of fatal and non-fatal stroke in patients with a prior history of any stroke or TIA, using a thiazide-type diuretic (indapamide) monotherapy compared to placebo. Findings showed that thiazide-type diuretic treatment reduced the incidence of fatal and non-fatal recurrent stroke by 29% over a mean follow-up period of 2 years.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[17] trial, in which 6,105 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 (ACEI) (perindopril) based treatment with or without thiazide-type diuretic indapamide (addition of diuretic left up to treating clinician)versus placebo, reported an overall relative risk reduction (RRR) in recurrent stroke of 28% (95% CI, 17-38%; p<.0001) over 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 non-hypertensive (RRR, 27%; 95% CI, 8-42%) patients. However, based on older definitions, presence of baseline hypertension in the trial was defined as ≥160/90 mm Hg (mean BP in the “non-hypertensive” group was 136/79 mm Hg, but standard deviations 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 to placebo. For patients with a history of ICH at baseline in PROGRESS, add-on active BP treatment (vs. placebo)was associated with an even greater magnitude of risk reduction (RRR, 49%; 95% CI, 18-68%);[18] thus under scoring 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 ICH patients could be due in part to the relatively stronger and more direct causative relationship of BP with ICH, and the younger average of ICH patients (mean age 61 years compared to 64 years for ischemic stroke patients).[18]

3. Systematic Reviews and Meta-analyses

A meta-analysis[6] of seven 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] Cater *et. al*,[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.[6]

An updated meta-analysis[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 [OR], 0.71; 95% CI, 0.59-0.86; p= 0.0004) and cardiovascular events (OR, 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 (MI) or all-cause mortality.

4. Evidence Gaps

While the aforementioned data clearly support the benefit of long-term use of antihypertensive therapy in patients to 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 are warranted. Furthermore, while there is compelling evidence for the initiation of antihypertensive treatment for previously untreated stroke or TIA patients with an established systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, evidence for prescribing antihypertensive agents in previously untreated stroke or TIA patients with an established systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg diastolic remains much less clear and will require further investigation.

III. Timing of Reduction of High Blood Pressure for Recurrent Stroke Prevention

1. Observational Data

Elevations in SBP or DBP are seen in up to 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 post stroke. Higher BP after stroke could

be due to stress after the stroke or a physiologic response to enhance compromised cerebral perfusion.[26] Given a high early risk of recurrent stroke,[27, 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 post-discharge 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 very early period after an ischemic stroke, may have a differential impact on stroke prevention based on the timing of such treatment following an index ischemic stroke event. A post-hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial comprising >20,000 patients with a recent non-cardioembolic 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 3,600 patients with a recent non-cardioembolic ischemic stroke, found that the adverse association of low-normal SBP with outcome was also more pronounced in the first 90-180 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.[36] On the other hand, it appears 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.[37]

The issue of lowering BP in acute stroke patients remains controversial with epidemiological evidence supporting acute treatment; whereas physiologic 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 in regards to initiating BP management in the acute setting after stroke.[41]

2. Clinical trials

Few trials have addressed the early initiation of treatment for secondary stroke prevention. In the PRoFESS[42] 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 ischemic stroke patients receiving antihypertensive therapy shortly after stroke onset (within 6-24 hours after admission), supporting the safety and efficacy of early implementation,[43] especially since 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 10-25% within the first 24 hours after randomization and maintained at <140/90 mm Hg for an average hospitalization period of 13 days showed a strong trend towards modest benefit in favor of the treatment group, amounting to a 35% relative risk reduction in stroke recurrence at 3 months. [40] Since there was only a clinically negligible difference in mean SBP between two groups at 3 months (−2.7 mm Hg (−3.7 to −2.2)), 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 towards recurrent 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 following 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 5-10 days after ICH may have a different outcome from that seen following an ischemic stroke due to secondary edema formation and hemodynamic changes.[45] Two RCTs, the INTensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)[46] and the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH)[47] trial, conducted in ICH patients 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 remains unclear.[48] 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 due to possible occurrence of a perihematomal ischemic zone, which may in fact be due to reduced cerebral metabolism rather than reduction of BP around the hematoma.

3. Systematic Reviews and Meta-analyses

A meta-analysis[6] of seven RCTs, examined initiation of BP-lowering therapy after stroke but timing of treatment ranged from less than one week to approximately one year. While the authors suggest treatment should be initiated at least 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.

4. 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 acute stroke patients, especially in ICH patients, 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 approximately 20% of stroke patients 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 post-stroke BP lowering trials. In a study examining the effect of carotid artery disease on the relationship between BP and recurrent stroke risk, Rothwell et al 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 aggressive BP treatment in such patients may be imprudent.[49] In addition, long-term antihypertensive treatment may also compromise cerebral perfusion in post-stroke patients, especially among elderly patients with carotid disease.[9] Thus, RCTs focused on early initiation and long-term maintenance of secondary prevention measures are need.

IV. Degree of Reduction of High Blood Pressure for Recurrent Stroke Prevention

The classic debate of 'lower is better and much lower is best' vs. 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 AHA/ASA[9] and ESH/ESC[50] guidelines recommending aggressive BP management.

1. Observational Data

Friday et al[51] reported a risk ratio of stroke recurrence for baseline DBP ≥80 mm Hg vs.<80 mm Hg was 2.4 (95% CI, 1.38-4.27) and for baseline SBP ≥140 mm Hg vs.<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 to 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 at least 1 measured DBP <80 mm Hg during follow-up compared to those with DBP 80-90 mm Hg, even after controlling for possible confounding factors; thus supporting the 'lower the better' BP control for reducing recurrent stroke.[51] Hier et al[52] also reported an increased risk of recurrent stroke at 2-years with baseline DBP ≥ 100 (RR, 1.012; 95% CI, 1.003-1.021). Alter et al[53] 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 non-hypertensive patients. However, Irie et al[54] found that the recurrent stroke risk increased in patients with DBP <80 mm Hg and Voko et al[55] found increased risk of stroke in elderly hypertensive patients with DBP <60 mm Hg. A report by Wang et al[56] 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 sub-types.

In the PROGRESS trial,[17] 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, -19-23%). 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 of ≥160 or 140-159 mm Hg, but not at the lower baseline SBP levels.[57]

In post-hoc analyses[34] of the PRoFESS[58] trial, a clinical trial that randomized recent non-cardioemobolic 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) when compared to the guideline indicated SBP range of 130-139 mm Hg. In addition, they found that SBP in the very low-normal (<120 mm Hg) 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 post stroke. Therefore, BP management in the post-stroke clinical setting needs to be well monitored to prevent adverse outcomes due to aggressive management. It was also noted that the effect of the telmisartan on reducing recurrent outcomes may be time-dependent as 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.[59] Compared to a SBP of 131-141 mm Hg, a SBP of 120 mm Hg or less was associated with a 61% greater risk of stroke, acute MI and death (95% CI: 1.08-2.41), but there were no differences in outcome in the patients with SBP 121-130 mm Hg or 142-210 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.[60, 61] Rothwell et al reported a high stroke risk among patients with high BP variability, independent of the absolute mean SBP.[60]

2. Clinical Trials

The recently published Secondary Prevention of Small Subcortical Stroke (SPS3)[62] trial assessed two target ranges of SBP (130-149 vs. <130 mm Hg) on the rate of recurrent stroke among patients with recent MRI-defined symptomatic lacunar infarctions. This study resulted in non-significant reductions in the rate of recurrence for all strokes (HR, 0.81; 95% CI, 0.64-1.03) and significant reductions for intracerebral hemorrhage recurrence. This study, although not significant, when viewed in light of prior BP-lowering randomized controlled trials after stroke,[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)[36] 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 ICH patients are unavailable, experts suggest a reasonable BP target of <140/90 mm Hg uncomplicated patients and <130/80 mm Hg in patients with diabetes or chronic kidney disease, is safe and tolerable.[64]

3. 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 to 130-139 mm Hg appeared to provide additional stroke protection only among people with known vascular risk factors (i.e. primary prevention) but not those with established (or symptomatic) vascular disease.[65]

4. 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 AHA/ASA guidelines have based their recommendations on published trials, the recommended target of 130 mm Hg was not achieved in a substantial number of the trials for which these recommendations were based.[16, 17, 34, 43] There is a significant lack of data regarding both the short- and long-term benefits of BP-lowering in ICH patients. Clinical trials focused on the aggressive BP-lowering to prevent recurrent vascular events after stroke are needed.

V. Influence of Antihypertensive Drug Class on Recurrent Stroke Prevention

1. Observational Data

Data observed from several clinical trials raised the possibility of an additional mechanism, independent of BP-lowering, through which select 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.[20, 43, 66, 67]

2. 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),[67] the first trial to compare different antihypertensive drugs for recurrent stroke prevention, randomized patients with hypertension to 600 mg/day ARB eprosartan or 10 mg/day calcium channel blocker (CCB)nitrendipine for a mean follow-up period of 2.5 years. By the end of the trial, BPs reductions were similar between the treatment arms, and approximately 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 PRoFESS[58] trial randomized ischemic stroke patients to 80 mg/day ARB telmisartan or placebo. Early initiation of telmisartan resulted in a 3.8/2.0 mm Hg lower BP as compared to placebo; however, this reduction was not significantly associated with a risk reduction in recurrent stroke, major cardiovascular events, or diabetes. The impact of treatment may have

been affected by the high rate of discontinuation of treatment medication due to 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 impact quality of life and thus medication adherence post stroke.

3. Systematic Reviews and Meta-analyses

A meta-analysis of the PRoFESS58 and Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND)68 studies, did however show a significant reduction (OR, 0.93; 95% CI, 0.86-0.99) in composite events (cardiovascular death, MI, stroke, and heart failure) among patients treated with telmisartan as compared to placebo; again with increasing significance after 6 months.

A meta-analysis[6] of seven RCTs performed through 2002 on patients with recent history 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 beta-blockers alone. Another meta-analysis[69] evaluating the use of ACEI or ARBs to reduce the risk of future vascular events in person 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.[70] In a meta-analysis of BP-lowering drugs, CCBs were found to reduce SBP inter-individual variability when used at a high does alone or in combination with other agents; whereas high dose beta-blockers appear to increase SBP variability; thus CCBs may play a protective role in the prevention of stroke.[70] 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.

4. Evidence Gaps

Reduction in BP below the normal range has been associated with reduction in recurrent stroke risk; however, there's no definitive evidence of a drug class-specific treatment effect.[71] 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 stroke patients, with more general recommendations including ACEI or ARB and/or diuretic therapy similar to other populations.[7] However, as stroke is proposed as a cardiovascular risk equivalent,[72] there is a significant view that management of high risk hypertensive patients be aggressive and detailed until specific strong trial evidence is available.[10] 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 the 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 >70 years. Blacks and other race-ethnic minorities are also grossly underrepresented 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 impact of agent class on recurrent stroke outcome such as existence/number/type of medical co-morbidities and level of blood pressure also warrant investigation.

VI. Optimizing Reduction of High Blood Pressure 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 the acute stroke hospitalization; otherwise, long-term initiation of treatment may be deferred to the post discharge clinical setting where the risk of loss of adequate follow-up of care is greater.[30]

1. Observational Data

While at least two-thirds of patients hospitalized with acute ischemic cerebrovascular events may be discharged from the hospital on ≥1 antihypertensive medication,[73] several lines of evidence from various registries in different countries suggest that BP remains poorly controlled and relatively poor adherence with antihypertensive treatment in a substantial number of patients in the post-discharge 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%, 25-49%, 50-74%, and ≥75%.[77] Multivariable models adjusting for demographic and clinical variables determined the association between consistency of BP control vs. primary (stroke) and secondary (stroke, MI 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% vs. <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 (AHR, 0.76;95% CI, 0.59-0.98 and AHR, 0.76;95% CI, 0.62-0.92).

2. Clinical Trials

In-hospital initiation of antihypertensive therapies prior to stroke discharge has been shown to improve treatment utilization, adherence, as well as the risk of recurrent vascular events.[18, 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, California.[79]

3. 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.

4. 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 blood pressure monitoring (ABPM) 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 utilized ABPM to confirm the efficacy of BP lowering treatment in recurrent stroke prevention. However, data on BP measurements by ABPM in stroke survivors is scarce. ABPM 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]

VII. 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, due to heterogeneous causes and hemodynamic consequences, the management of BP to reduce recurrent stroke is more complex and challenging than a meta-analyses 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 stroke patient 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. Likewise, 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, etc.) 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]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: Andrea D Boan and Daniel T Lackland were supported by Southeastern Virtual Institute for Heath Equality and Wellness:W81XWH-10-2-0057 from the Department of Defense. Bruce Ovbiagele was supported by U01 NS079179 and U54 HG007479 from the National Institute of Health.

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