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Blood Pressure Management in Stroke: Viewpoint

Philip B. Gorelick, MD MPH [Adjunct Professor of Neurology],
Northwestern University Davee Department of Neurology and Feinberg School of Medicine, Division of Stroke and Neurocritical Care

Paul K. Whelton, MB MD MSc [Snow Chwan Professor of Global Public Health],
Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, Tulane University of Medicine, Department of Epidemiology, #8318, Tulane University School of Public Health and Tropical Medicine, 1440 Canal Street, Room 2015, New Orleans, LA 70112

Farzaneh Sorond, MD PhD [Professor of Neurology],
Northwestern University Davee Department of Neurology and Feinberg School of Medicine, Department of Neurology, 625 N. Michigan Avenue, 11th Floor, Chicago, Illinois 60611

Robert M. Carey, MD [Professor of Medicine]
Dean Emeritus, School of Medicine, Division of Endocrinology and Metabolism, Department of Medicine

Abstract

Hypertension is a well-established and modifiable risk factor for stroke and other cardiovascular diseases. Notably, stroke is the second leading cause of death worldwide and the second most common cause of disability-adjusted life years. As such, we provide a viewpoint on blood pressure management in stroke and emphasize blood pressure control or management for first and recurrent stroke prevention, acute stroke treatment, and for prevention of cognitive impairment or dementia.

Keywords

hypertension; stroke; intracranial hemorrhage; blood pressure

Introduction

Proper management of blood pressure (BP) is a cornerstone of stroke prevention and acute treatment [1]. Hypertension is common, has a high attributable risk for stroke (25%-50%), and both clinical trials and observational studies have shown a reduction in the risk of first and recurrent stroke with BP-lowering therapy. Recently, intensive BP lowering has been associated with reduction in the combined risk of dementia and mild cognitive impairment

Corresponding and Lead Author Address: Department of Neurology, 625 N. Michigan Avenue, 11th Floor, Chicago, Illinois 60611, Telephone: 773-975-1126, pgorelick@thorek.org.

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[2]. In addition, the study of BP now includes elucidation of BP trajectory and variability metrics and their predictive implications for acute stroke treatment and prevention [3, 4].

This viewpoint emanates from a 2019 American Heart Association/American Stroke Association (AHA/ASA) debate on BP management in stroke by authors PBG and PKW during which we concluded that our positions on BP management for prevention and acute treatment of stroke had many more similarities than differences. During the past several years important new studies and guidance statements have been published. As a result, the field is well positioned for an update on BP management to prevent and treat stroke. Our discussion emphasizes BP control or management for first and recurrent stroke prevention, and acute stroke treatment. In addition, because BP and cognition are so highly correlated, we discuss BP and prevention of cognitive impairment.

Methods (Search Strategy)

Rather than carry out a formal review or search strategy, we subjectively chose key articles available in our clinical files on: 1. Randomized clinical trials (RCTs), meta-analyses and observational study results on the topic primarily from the past 5-10 years; and 2. Recent guidance statements from the United States published during the past 3-5 years.

Review of Select Studies

Observational studies

Observational studies have repeatedly identified a relationship between BP and stroke. In 347, 978 men screened for participation in the Multiple Risk Factor Intervention Trial (MRFIT), a strong direct relationship was noted between BP and stroke mortality, with no evidence of a BP threshold for risk [5]. Systolic BP (SBP) was a better predictor of risk compared to diastolic BP (DBP), especially at higher levels of BP. Following adjustment for other cardiovascular disease (CVD) risk factors, the relative risks (RRs) of stroke mortality for ≥151 mm Hg, 142-150, 137-141 and 132-136 compared to <112 mmHg were 6.2, 4.44, 3.60 and 3.06, respectively. The BP-stroke relationship was true for subarachnoid hemorrhage, intracranial hemorrhage and non-hemorrhagic strokes [6]. A similar association between BP and both transient ischemic attack and stroke (fatal and non-fatal ischemic, subarachnoid hemorrhage, and intracerebral hemorrhage) was noted in a large electronic health record study [7]. Again, there was no evidence of a threshold for risk above the lowest categories of SBP (90-114 mmHg) or DBP (60-74 mmHg). In the Prospective Studies Collaboration meta-analysis of 61 cohort studies, stroke risk increased continuously, with no evidence for a threshold in risk, at progressively higher levels of usual BP above SBP 115 and DBP 75 mmHg in each age category (50-59, 60-69, 70-79, and 80-89 years) studied [8]. The slope for BP-stroke mortality was steepest at younger age but the BP-related difference in stroke mortality was largest at older age due to the high stroke rate in older adults. In middle age, the RR for stroke mortality was approximately two-fold less for a 20 mmHg lower level of SBP.

Elevated BP and fluctuation in BP are very common immediately following a stroke. Observational studies have identified a U-shaped curve between admission or early phase

change in BP and adverse outcomes, including mortality. Whether the excess mortality is a consequence or cause of the extremes of BP cannot be determined from the available observational reports.

Blood pressure lowering following acute stroke

The effect of rapid BP lowering has been studied in six RCTs conducted in patients with stroke due to intracerebral hemorrhage (ICH). In the largest trial (N=2829), intensive BP lowering did not result in a significant beneficial outcome for the primary outcome of death or severe disability at 90 days (odds ratio 0.87, 95% confidence interval [CI] 0.75-1.01) but a prespecified secondary ordinal analysis suggested better outcomes with intensive treatment (odds ratio 0.87. 95% CI 0.77-1.00) [9]. A subsequent trial (N=1000) failed to demonstrate the benefit of rapid BP lowering and was stopped early due to futility [10]. A systematic review and meta-analysis of the six RCTs documented neither harm nor benefit from acute BP lowering [11]. Overall, clinical trial results suggest lowering of SBP to <140 mm Hg in patients with acute ICH may be safe in some patients, but of uncertain value.

The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) [12] has been the largest RCT (N=4071) to study the effect of immediate BP treatment following acute ischemic stroke. Within 24 hours, the active treatment group had an average SBP that was 9.1 mm Hg lower compared to control and 137.3 mmHg at day 7. There was no difference between the treatment groups in death or major disability at day 14 or hospital discharge (primary outcome) or at three months. Generally consistent results have been noted in several smaller acute ischemic stroke RCTs [13]. As with ICH, rapid reduction in BP is generally safe, and may be desirable in those with an acute ischemic stroke who present with a very high level of BP.

Blood pressure lowering for primary prevention of stroke

In ambulatory patients with high BP, RCTs have repeatedly demonstrated that antihypertensive drug therapy is effective for primary and secondary prevention of stroke. In the Systolic Hypertension in the Elderly Program (SHEP) RCT (N=4736), SBP/DBP was 11-12/3-4 mm Hg lower during active treatment compared to placebo, with a final active treatment average SBP/DBP of 144/68 mm Hg [14]. Stroke incidence, the primary outcome, was 36% less common in the active treatment group compared to placebo. In a meta-analysis of 45 RCTs, 10 mm Hg lowering of SBP resulted in 41% reduction in stroke incidence [15]. This level of benefit was similar to the 36% reduction predicted based on the risk associated with the achieved difference in BP. A more recent meta-analysis, based on 54 RCTs, reported a 27% reduction in stroke incidence for every 10 mm Hg decrement in SBP (RR and 95% CI: 0.73, 0.68-0.77) [16]. Benefit was independent of baseline SBP and similar for those with and without prior CVD.

Blood pressure lowering for secondary prevention of stroke

The effect of intensive antihypertensive therapy for secondary prevention of stroke has been evaluated, as a primary outcome, in the Secondary Prevention of Small Cortical Strokes (SPS3) and Recurrent Stroke Prevention Clinical Outcome (RESPECT) trials [17, 18] and, as a secondary outcome, in the Prevention After Stroke-Blood Pressure (PAST-BP) trial [19]

and Prevention of Decline in Cognition after Stroke Trial (PODCAST) [20]. Selected Information from these four trials, including sample size, is presented in Table 1. SPS3, which accounts for almost 70% of the participants and 74% of the stroke events in Table 1, was conducted in adults with recent symptomatic MRI-proven lacunar infarctions. In each trial, the average achieved intensive treatment SBP was ≤130 mm Hg, and less stroke recurrence was noted in those randomized to more compared to less intensive treatment, with an overall RR 0.78, 95% CI 0.64-0.94 [18]. In aggregate, these results provide substantial evidence that a SBP treatment target <130 mm Hg, if tolerated, is warranted for secondary stroke prevention. Although not designed as an "intensive therapy" investigation, the PROGRESS study (baseline SBP/DBP 147/86 mmHg) was a stroke secondary prevention RCT that yielded a net SBP/DBP difference of 9.0/4.0 mm Hg between the 3051 participants assigned to active therapy compared to the 3054 assigned to placebo (12.3/5.0 mm Hg in the 3544 treated with both perindopril and indapamide) [21]. Compared to placebo, active therapy reduced stroke incidence by 28% (95% CI, 17-38%), with most of the benefit accruing to those assigned to combined perindopril and indapamide therapy (43%; 95% CI, 30-54%).

Concern for a potential complication should not be an impediment to initiating a treatment that is likely to prevent stroke, other serious CVD events and mortality. Generally, intensive antihypertensive drug treatment has been well tolerated in RCTs. On-treatment observational analyses demonstrating a J-or U-shaped relationship between achieved BP and CVD (primarily CHD) events are difficult to interpret but have led to recommendations for less intensive treatment in older adults [22]. A U-shaped BP-CVD risk relationship was noted in both the intensive and standard SPRINT treatment groups but randomized comparisons demonstrated a significant CVD and mortality benefit for more compared to less intensive treatment at every level of baseline BP [23].

Comparison of different antihypertensive drug classes for prevention of stroke

The Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) was a superiority RCT (N=33357) that compared double-blind first-step treatment with the calcium channel blocker (CCB) amlodipine or angiotensin converting enzyme inhibitor (ACEI) lisinopril to treatment with the long-acting diuretic chlorthalidone [24]. Additional antihypertensive drugs, that were used to target an SBP/DBP <140/90 mm Hg, were similar across the three treatment groups. There was no significant primary outcome (CHD) benefit for amlodipine or lisinopril compared to chlorthalidone. There was no difference in stroke incidence, a secondary outcome, between the chlorthalidone and amlodipine groups but stroke was significantly more common in the lisinopril compared to chlorthalidone group (RR 1.15, 95% CI 1.02-1.30). In a pre-specified subgroup analysis, the stroke difference was most apparent in Black participants and some, but not all, of this difference could be explained by higher BP levels in the Black patients treated with lisinopril compared to chlorthalidone. In a meta-analysis of 58 two-arm comparisons, diuretics, CCBs, ACEIs, angiotensin receptor blockers (ARBs), and β-blockers were superior to placebo for prevention of stroke [25]. In the same meta-analysis, diuretics were superior to renin-angiotensin system (RAS) blockers for prevention of stroke and to CCBs, RAS blockers and all other drug classes together for prevention of heart failure – an outcome that is common at

older age. Most adults with hypertension, especially Black patients and those with a high starting level of BP, should be treated with two or more antihypertensive drugs, in combination with lifestyle modification, to control their BP [26]. Drugs with complementary mechanisms of action, such as a diuretic and RAS blockers, are preferred for combinations and should be administered as a single pill combination when possible.

More compared to less intensive blood pressure reduction for prevention of stroke

Clinical trials have demonstrated that more intensive treatment, if tolerated, is better for prevention of CVD, including stroke. Several RCT meta-analyses have specifically demonstrated a stroke prevention benefit down to a target SBP of <130 mm Hg [27-30] and the two analyses with the greatest statistical power to <120 mm Hg [28, 30]. History of stroke was an exclusion in the Systolic Blood Pressure Intervention Trial (SPRINT) [31] (N=9361) and the trial was not powered to assess a difference in stroke incidence (a secondary outcome). However, the stroke outcome 95% confidence interval included the possibility of a 37% reduction for primary prevention of stroke. History of stroke was permitted in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) trial (N=4733) [32]. Stroke, a secondary outcome, was significantly less common (Hazard Ratio [HR] 0.59, 95% CI 0.39-0.89) in those randomized to the SBP target of <120 mm Hg compared to <140 mm Hg. In Table 2 we provide a brief overview of select observational, RCT and meta-analysis studies addressed in the viewpoint.

Blood pressure lowering to prevent cognitive impairment and dementia

Several cohort studies have identified an association between elevated BP in mid-life and subsequent dementia [33]. Worsening of cognitive function has not been a feature of BP lowering in RCTs. The 2017 ACC/AHA BP Guideline concluded that “In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia” [26]. In SPRINT, a trial that excluded stroke survivors, mild cognitive impairment (MCI) was significantly less common in the intensive compared to standard treatment group during trial follow-up (HR 0.83, 95% CI 0.70-0.99) and the combination of dementia and MCI was less common during extended (trial and post-trial) follow-up (HR 0.85, 95% CI 0.74-0.97) [2]. There were small but statistically significant differences favoring intensive BP control for a smaller increase in cerebral white matter lesion volume, but a greater decrease in total brain volume [34]. In the PRESERVE RCT, conducted in patients with a lacunar stroke and hypertension, there was no evidence of cerebral hypoperfusion in an analysis that compared 29 participants randomized to intensive antihypertensive treatment (target SBP <125 mm Hg) and 33 randomized to standard treatment (target SBP 130-140 mm Hg) [35]. In a meta-analysis of eight BP lowering trials, including SPRINT, the RR (95% CI) for dementia incidence was 0.93 (0.86-1.00) and 0.88 (0.78-0.98) in the subset of RCTs with an achieved SBP difference ≥10 mm Hg [36]. In another meta-analysis of 12 RCTs, BP lowering was associated with a significant reduction in the odds ratio (OR) of dementia or cognitive impairment (OR [95% CI]: 0.93 [0.88-0.98]) [37]. In a meta-analysis based on four RCTs and 23 cohort analyses, there was no definitive evidence for a preferred class of antihypertensive medication but some suggestive evidence favored diuretics for prevention of cognitive impairment or dementia [38].Ongoing trials are testing the efficacy of SPRINT-like SBP targets on CVD outcomes, all-cause mortality and brain function. One RCT

(OPTIMAL Stroke) is being conducted in approximately 7000 Brazilian adults with high BP and a history of ischemic stroke or transient ischemic attack (ClinicalTrials.gov Identifier: NCT04036409). These trials will help to clarify optimal SBP targets during antihypertensive drug therapy and enhance our understanding of BP lowering effects on brain function in participants with a history of stroke as there is uncertainty about proper BP targets.

Blood Pressure Variability in Stroke and Cognition

SBP elevation is an important risk factor for stroke and other CVD events [39]. In a recent National Health and Nutrition Examination Survey (2013-2016) analysis, isolated diastolic hypertension based on the 2017 ACC/AHA BP Guideline definition of DBP ≥80 mm Hg and SBP <130 mm Hg was not significantly associated with an increased risk of CVD events [40]. Beyond the conventional measures of SBP and DBP, BP variability is a predictor of stroke and related CVD events. In 2010, Rothwell and colleagues reported that visit-to-visit SBP variability, beyond mean BP, predicted stroke, and also noted certain BP-lowering medications that tend to reduce BP variability (e.g., CCBs and diuretics) were associated with more efficacious stroke prevention compared to medications that seem to do the opposite (e.g., non-selective beta blockers) [41-43]. BP variability has been measured in different ways, including standard deviation, coefficient of variation, and maximum-minimum of SBP or DBP [43].

A series of observational studies from South Korea identified BP variability as being associated with poor functional outcome at 90 days after acute ischemic stroke and with early neurological deterioration [44-46]. In a prospective analysis of 8376 patients with acute ischemic stroke, acutely high and persistent SBP was the BP trajectory best associated with risk of subsequent vascular events [44-46].BP variability early after *acute* ICH has been associated with unfavorable inpatient modified Rankin Scale disability scores [47, 48]. The literature on recurrent and first stroke prevention supports the concept that BP variability, instability and episodic hypertension may explain risk of stroke beyond traditional mean SBP or DBP [4, 41].

Cognitive impairment may also be predicted by BP variability [49]. With BP variability there may be accompanying brain atrophy, subcortical ischemic lesions and cognitive impairment [50]. If indeed certain classes of BP-lowering drugs such as calcium-channel blockers and diuretics are superior to others for reducing BP variability in addition to mean BP, use of these agents may provide an opportunity to preserve the brain and reduce stroke risk.

Recently, there have been recommendations to treat diurnal variation in BP [39]. CVD events such as stroke, for example, may be associated with an early morning surge of BP [51]. Factors that may explain the occurrence of stroke with a BP surge include heightened sympathetic nervous system and RAS activity, increase in platelet aggregation, and plasminogen activator inhibition [39]. In addition, night time BP non-dipping or extreme dipping may also be associated with ischemic brain injury [52, 53].

In a commentary, Whelton and Pollock concluded that although significant associations between BP variability and CVD outcomes have been observed in some studies, the findings have been inconsistent, and add little to CVD prediction equations [54]. However, they identified BP variability as an important research topic that could yield clinically meaningful findings in the future.

Guidance Statements on Blood Pressure Management in Stroke

According to the 2017 ACC/AHA BP Guideline the definition of a BP treatment threshold of 140/90 mm Hg has been shifted downward to 130/80 mm Hg [26]. In this section we review AHA and ACC/AHA guidance including AHA class/levels of evidence (in parentheses) on BP targets for acute ischemic stroke, prevention of recurrent and first stroke, ICH, and for prevention of cognitive impairment.

Ischemic Stroke

Acute Stroke Management. The reference guidance for this section is the 2019 AHA Powers et al statement on early management of patients with acute ischemic stroke that contains the following recommendations [55]:

1. Hypotension and hypovolemia should be avoided to facilitate systemic perfusion (I/C-EO);
2. Before intravenous fibrinolytic therapy is administered, BP should be <185/110 mm Hg, and <180/105 mm Hg in the first 24 hours after such treatment (specific BP-lowering agents and strategies are discussed in the Powers et al source) (I/B-NR) [55].
3. If mechanical thrombectomy is planned and intravenous thrombolytic therapy has not been given, BP should be </=185/110 mm Hg before the procedure and </=180/105 mm Hg in the first 24 hours after the procedure (IIa/B-NR);
4. In patients who undergo successful reperfusion with mechanical thrombectomy, it may be reasonable to maintain BP <180/105 mm Hg (I/B-R);
5. Early treatment of hypertension may be indicated in the presence of certain co-morbid conditions (e.g., heart failure, aortic dissection, acute myocardial infarction) (I/C-EO);
6. The usefulness of BP augmentation in acute ischemic stroke remains uncertain (IIb/B-R); and
7. For patients who are *not* treated with intravenous fibrinolytic therapy or mechanical thrombectomy:
    A. If BP is >/=220/120 mm Hg and there are no comorbid conditions requiring acute BP-lowering treatment, it is reasonable to initially lower BP by 15% although the benefit of lowering or re-instituting BP therapy in the first 48-72 hours is uncertain (IIb/C-EO).

B. Lowering BP when it is <220/120 mm Hg in the first 48 to 72 hours seems to be a safe strategy but does not lower mortality or improve functional outcome (III: no benefit/A).

Finally, it is reasonable to re-start BP-lowering medication in patients who have BP>140/90 mm Hg once the patient is neurologically stable [55]. The 2017 ACC/AHA BP Guideline recommendations are consistent with the 2019 AHA early management of acute ischemic stroke BP targets and strategies [26, 55].

Recurrent Stroke Prevention. The AHA guidance for recurrent stroke prevention dates back to 2014 and is being updated. Key BP-lowering recommendations from the 2014 guidance statement include [56]:

1. For those with SBP >/=140 mm Hg or DBP >/=90 mm Hg, BP-lowering therapy is reasonable, and a target for BP-lowering of <140/90 mm Hg is reasonable (I/B); and
2. For those with small vessel (i.e., lacunar) cerebral ischemia, a SBP-lowering target of <130 mm Hg is reasonable (IIb/B).

The 2017 ACC/AHA BP Guideline supports the above recommendations with the following update [26]:

1. For those with a stroke or TIA, a BP-lowering goal of <130/80 mm Hg may be reasonable (IIb/B-R).

The 2017 ACC/AHA BP Guideline and the 2014 AHA guidance are generally consistent on the following points in relation to BP-lowering therapy [26, 56].

1. Restart BP-lowering medications within several days after the index stroke or transient ischemic attack to reduce the risk of subsequent major vascular events (I/A);
2. Any of a number of medication classes may be used to lower BP, however, a thiazide diuretic, ACEI or ARB or a combination of the first two medication choices may be administered (I/A);
3. Individualize the choice of BP-lowering medication based on patient comorbidities (I/B-NR); and
4. The usefulness of BP-lowering in persons with stroke or transient ischemic attack and SBP <140 mm Hg or DBP <90 mm Hg is not well established (IIb/C-LD).

First Stroke Prevention. The AHA guidance for first stroke prevention dates back to 2014 and is also being updated [57]. Key BP-lowering recommendations from this guidance statement include [57]:

1. Regular screening of BP and treatment of elevated BP by lifestyle and pharmacologic measures (I/A);
2. Lower BP to a target of <140/90 mm Hg (I/A);

3. Based on patient comorbidities choose appropriate BP-lowering medications, however, successful lowering of BP is emphasized over specific classes of BP-lowering medications save for those with specific comorbidities requiring a specific BP-lowering medication class (I/A); and

4. Self-measurement of BP is recommended (I/A).

The 2017 ACC/AHA BP Guideline sets a new target for BP lowering for first stroke prevention: <130/80 mm Hg (guidance for class/level varies by risk status) [26].

Intracerebral Hemorrhage

Guidance for BP targets and management of ICH emanate from a 2015 AHA statement and include two primary recommendations [58]:

1. When SBP is between 150 to 220 mm Hg, acute BP lowering may be effective in relation to improvement of functional outcome and is safe (I/A); and

2. When SBP is >220 mm Hg, it may be reasonable to lower BP by administration of a continuous intravenous infusion medication with initiation of frequent BP monitoring (IIb/C).

The 2017 ACC/AHA BP Guideline included additional available clinical trial data results (e.g., ATACH-2 Trial) and updated the aforementioned first recommendation from the 2015 AHA guidance and concluded that BP lowering to a SBP of <140 mm Hg within 6 hours of the index brain hemorrhage did not reduce death or disability, and could be harmful [26]. We believe that it is reasonable to aim for a target SBP of 140-160 mm Hg early after the onset of ICH. Based on pooled analyses of ATACH-II and INTERACT2, achieving an early and stable mean SBP of ~147 mmHg in ICH of mild-to-moderate severity is safe and associated with improvement in functional status [59].

Future Studies of Interest

In addition to ongoing research, there is need to better understand the role of nighttime BP and BP variability on stroke risk, to determine the consequence of high lifetime risk for CVD and for stroke in those under age 40, to determine the value of out-of-office BP monitoring, telemetry and other approaches to achieve guideline recommended levels of BP, and to confirm the value of intensive BP lowering for prevention of cognitive impairment and dementia in stroke survivors. Further study of brain small vessel disease neuroimaging biomarkers (e.g., white matter lesions, cerebral microbleeds) may prove useful in the evaluation of intensive BP treatment strategies.

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Table 1.

Selected characteristics and findings in three trials that evaluated intensive blood pressure lowering in stroke survivors.

					Intensive Therapy			Standard Therapy		
Trial	**Sample size**	**Mean Age, y**	**Follow-up, y**	**Primary outcome**	**Target BP**	**Achieved BP**	**Stroke events**	**Target BP**	**Achieved BP**	**Stroke events**
SPS3 *[17]*	3020	63	3.7	Stroke	<130	12/7	125	130-149	138	152
RESPECT [18]	1263	67	3.9	Stroke	<120/80	127/77	39	<140/90	133/78	52
PAST-BP [19]	83	72	1.0	BP	<130*	127/72	0	<140	129/74	3
PODCAST [20]	83	74	2.0	Cognitive function	<125	130/73†	1	<140	140/77†	3
					Total strokes		165	Total strokes		210

SPS3=Secondary Prevention of Small Cortical Strokes; RESPECT=Recurrent Stroke Prevention Clinical Outcome; PAST-BP=Prevention After Stroke-Blood Pressure.

*or SBP reduction >10 mm Hg if starting SBP was <140 mm Hg.

**at the six-month visit

Table 2:

Brief Overview of Select Observational, Randomized Controlled Trial and Meta-Analysis Studies Addressed in the Viewpoint*

Observational Cohort Analysis

Adults Screened for Participation in the Multiple Risk Factor Intervention Trial (MRFIT) [6]

Overview: Non-concurrent prospective analysis of the association between blood pressure (BP) and mortality from coronary heart disease (CHD) and stroke during an average follow-up of 11.6 years in a cohort of 347,978 men with no history of hospitalization for myocardial infarction who were screened for possible participation in MRFIT.

Primary outcomes: mortality from CHD or stroke, including subarachnoid hemorrhage, intracranial hemorrhage, non-hemorrhagic strokes, and transient ischemic attacks (TIAs).

Demographics: men aged 35-57 years (average 46 years) at baseline; 312,998 White, 22,471 Black, 8,511 Hispanic, 4,257 Asian participants.

Randomized Controlled Trials

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT2) [9]

Overview: 2,839 participants with spontaneous intracranial hemorrhage (ICH) within 6 hours of onset who had elevated BP (150 to 220 mmHg) were randomized to open-treatment (blinded end point) with either intensive BP lowering (goal <140 mmHg) within 1 hour or guideline-recommended treatment (goal <180 mmHg) using BP lowering agents according to the physician's choice.

Primary outcome: death or major disability (modified Rankin Scale [mRS] score of 3-6) at 90 days.

Secondary outcome: A pre-specified mRS ordinal analysis.

Demographics: mean age 63.5 years, men 62.9%, and Chinese enrollees 67.7%.

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2) [10]

Overview: 1,000 participants with ICH (volume <60cm^3) and a Glasgow Coma Score of 5 or more were randomized to open-label treatment with a systolic blood pressure (SBP) goal of either 110-139 mmHg (intensive therapy) or 140-179 mmHg (standard therapy) within 4.5 hours of symptom onset to test the superiority of intensive BP lowering over standard BP lowering. Participants had a SBP measurement after symptom onset and before study treatment of 180 mmHg or greater. Intravenous nicardipine was the main intervention for intensive BP lowering.

Primary outcome: death or disability (defined as mRS of 4-6) at 3 months.

Demographics: mean age 61.9 years, men 60.8%, and Asian enrollees 56.2%.

China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) [12]

Overview: 4,071 participants enrolled in a single-blind (blinded end points) RCT to evaluate immediate BP lowering in acute ischemic stroke (AIS) within 48 hours of stroke onset by achieving BP lowering of 10% to 25% within 24 hours, <140/90 mmHg within 7 days, and maintenance of the BP level during hospitalization compared to discontinuation of all antihypertensives (control) during hospitalization. Several antihypertensive agents, including intravenous enalapril (1st), a calcium channel blocker (2nd), and a diuretic (3rd) could be used individually or in combination to achieve the BP target.

Primary outcome: death and major disability (mRS score 3 or higher) at 14 days or at hospital discharge.

Demographics: mean age 62.0 years, men 64%, and Chinese enrollees 100%.

Systolic Hypertension in the Elderly Program (SHEP) [14]

Overview: 4,736 participants with isolated systolic hypertension were enrolled if SBP was 160 to 219 mmHg and diastolic BP <90 mmHg and randomized to receive double-blinded treatment with either chlorthalidone (step 1)/atenolol (step 2) to reach the BP lowering goal (reduction of at least 20 mm Hg from baseline and to below 160 mm Hg) or placebo.

Primary outcome: nonfatal and fatal (total) stroke.

Demographics: mean age 71.6 years, men 43.2%, and black enrollees 13.9%.

Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [21]

Overview: 6,105 hypertensive and non-hypertensive participants with a history of stroke or TIA were randomized to double-blind therapy with perindopril, alone or combined with indapamide, or placebo with a BP reduction goal of 8-9/4-5 mmHg in the active treatment arm.

Primary outcome: fatal or nonfatal stroke.

Demographics: mean age 64 years, women 30%, and Asian enrollees 39%.

Systolic Blood Pressure Intervention Trial (SPRINT) [23]

Overview: 9,361 non-diabetic participants without a history of stroke who had a SBP 130 mmHg or greater were enrolled and randomized to open-label intensive antihypertensive therapy with a SBP goal of <120 mmHg or standard treatment with a SBP goal of <140 mmHg. BP lowering agents were chosen according to the most robust medical evidence, and specific agents were encouraged but not mandated.

Primary outcome: myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death of cardiovascular causes.

Demographics: mean age 67.9 years, women ~36% and black enrollees ~30%.

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) [24]

Overview: 33,357 participants 55 years of age or older with hypertension and at least 1 other CHD risk factor were randomized to double-blind therapy with chlorthalidone, amlodipine or lisinopril to determine the best 1st step BP lowering therapy.

Primary outcome: fatal CHD or non-fatal MI.

Secondary outcomes: all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization or angina with hospitalization) and combined CVD (CHD, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease).

Demographics: mean age 67 years, women 47%, and enrollees who were black (35%) and Hispanic (19%).

Meta-analyses

Prospective Studies Collaboration [8]

Overview: A meta-analysis that included 61 prospective observational studies of BP and mortality covering 12.7 million person-years at risk with 56,000 vascular deaths (12,000 stroke, 34,000 ischemic heart disease [IHD], 10,000 other vascular) and 66,000 other vascular deaths in adults aged 40-89 years. Time-dependent correction for regression dilution bias related to mortality during each decade of age of death was used to estimate the usual BP at the start of each decade.

Meta-analysis of 6 Randomized Controlled Trials (ATACH2, Gong et al., INTERACT2, ADAPT, INTERACT and Koch et al.) by Shi L et al [11]

Overview: A meta-analysis of six BP lowering trials that included 4,412 participants with acute ICH to assess hematoma growth and neurological improvement at 24 hours, hypotension at 72 hours, death or dependency at 90 days, mortality at 90 days, and serious adverse events at 90 days by comparing intensive and more conservative BP lowering.

Meta-analysis of 147 Randomized Controlled Trials of Blood Pressure Lowering Drugs in Prevention of Coronary Heart Disease and Stroke by Law MR et al [15]

Overview: 108 trials addressing differences in BP between drug and placebo or control; 46 compared drugs; and 7 fell into both groups. The observed results were interpreted in relation to expected results based on the Prospective Studies Collaboration meta-analysis of cohort studies that included 958,000 participants. There were 3 exclusive study groups: no history of vascular disease; a history of CHD; or a history of stroke.

Meta-analysis and Systematic Review of 123 Studies of Blood Pressure Lowering in 613,815 Participants by Ettehad D et al [16]

Overview: Inclusion was restricted to trials with at least 1,000 patient-years of follow-up in each study arm. Baseline comorbidities and use of antihypertensive therapy for indications other than hypertension were not exclusions. Summary level data was presented for baseline characteristics and key outcomes (major CVD events, CHD, stroke, heart failure, and all-cause mortality).

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* If stroke or stroke-related disability or death is not included in the primary outcome, secondary outcomes that include stroke are listed