Implications of Recent Clinical Trials and Hypertension Guidelines on Stroke and Future Cerebrovascular Research

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The decline in stroke mortality observed over the past 50 years has been attributed, in part, to improved implementation of high blood pressure (BP) treatment and control strategies based on the most current evidence from clinical research studies and randomized controlled trials (RCTs).[1] The reduction in stroke risks coincides with the shift to lower systolic BP (SBP) distributions in the US adult population for all age groups.[1] However, critical clinical questions remain about the treatment, control, and prevention of high BP. New evidence from RCTs and meta-analyses[2–6] is expected to have an important positive impact on hypertension guidelines, clinical practice, and future research. Because stroke risk is substantially associated with BP levels and hypertension treatment and control, raised BP and stroke reduction is so heavily tied to BP control, stroke prevention is a key driving force for clinical practice decisions. As a component of the 2017 International Stroke Conference, the American Heart Association, American Stroke Association, and World Hypertension League cosponsored session focused on impact of recent hypertension studies, meta-analyses and new clinical guidelines on stroke risk reduction, and implications for future research.

Post Hoc Analyses of Stroke Risks and Reduction BP Treatment and Control

The Prospective Studies Collaboration[7] showed a log-linear relationship between BP and stroke declining with lower BP values right down to <120 mm Hg systolic and <70 mm Hg diastolic. Further, a meta-analysis of 147 RCTs of antihypertensive therapy the percentage reduction in stroke with BP reduction down to a mean of 110/70 mm Hg regardless of their BP before treatment.[8] Another systematic review in patients with diabetes mellitus reported a decrease of 13% in the risk of stroke for each 5 mm Hg reduction in SBP, and by 11.5% for each 2 mm Hg reduction in diastolic BP.[9] In another meta-analysis of 123 studies, Ettehad et al[4] provided support for lowering SBP to <130 mm Hg. All of these reports suggest that there is no J-shaped curve at least at BP levels within these ranges.

However, all of these data were derived from post hoc analyses, usually from studies of the efficacy of antihypertensive drugs, and there were no convincing RCTs addressing the specific question of BP targets for the prevention of cardiovascular disease (CVD) events, including stroke, until the ACCORD (Action to Control Cardiovascular Risk in Diabetes) and the SPRINT (Systolic Blood Pressure Intervention Trial).

Implications of ACCORD and SPRINT Results and Stroke Outcomes

ACCORD[10] was 1 designed to evaluate the overall effects intensive BP lowering in patients with type 2 diabetes mellitus on CVD and stroke. The composite primary outcome included nonfatal stroke. The study randomized 4733 patients to intensive therapy, SBP target <120 mm Hg or to standard therapy, SBP <140 mm Hg. BP at each visit was measured using an automated measurement system (Model 907, Omron Healthcare). At each clinic visit BP was recorded as the mean of 3 measurements while patients were seated.

In ACCORD, the mean SBP after 1 year was 119.3 mm Hg in the intensive-treatment group and 133.5 mm Hg in the standard-treatment group. Equivalent values for SPRINT were 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group, for an average difference of 14.8 mm Hg. In ACCORD during a mean follow-up of 4.7 years, there was no significant difference between the 2 groups with respect to the primary composite outcome or of most of its individual components, although there was a trend favoring the intensive-treatment arm (suggesting that the study was underpowered). There was a significantly lower incidence of stroke in the intensive therapy group than in the

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standard therapy group (36 or 0.32% per year versus 62 or 0.53% per year; hazard ratio [HR], 0.59 [95% CI, 0.39–0.89; $P<0.01$; Table; Figure). Because patients with prior stroke were not excluded from ACCORD, the stroke outcome in ACCORD could be regarded as relating to both primary and secondary prevention.

The design of SPRINT[11] was almost a mirror image of that of ACCORD. A total of 9361 adults with a SBP of 130 to 180 mm Hg and a high risk of CVD, were randomized to SBP target groups, <120 mm Hg and <140 mm Hg. The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. As in ACCORD, BP at each visit was measured using an automated measurement system (Model 907, Omron Healthcare). The mean of 3 measurements was recorded. Thus, both ACCORD and SPRINT may have set a new standard for office BP measurement. Subjects with prior strokes were excluded from SPRINT. After 1 year, the mean SBP was 136.2 mm Hg in the standard-treatment group and 121.4 mm Hg in the intensive-treatment group, with an average difference of 14.8 mm Hg. The study was stopped early after a median follow-up of 3.26 years, because the rate of the primary composite outcome was 25% lower in the intensive-treatment group than the standard-treatment group (HR with intensive treatment, 0.75; 95% CI, 0.64–0.89; $P<0.001$). All-cause mortality was significantly reduced by 27%. One unexpected finding was that the difference between the 2 groups was driven primarily by a decrease in heart failure and cardiovascular death but there was no significant difference in stroke (intensive treatment, 0.41% per year; standard treatment, 0.47% per year). Although not statistically significant, the HR for stroke with intensive treatment was 0.89, a decrease of 11%. (Table). Because patients with prior stroke were excluded from SPRINT, the lower stroke rate reflects inclusion of a primary prevention patient sample.

In the elderly (≥75 years), there was a 28% lower incidence of stroke in the intensive-treatment group which was also not statistically significant (HR, 0.72; 5% CI, 0.43–1.21; $P=0.22$).[12] This result does support lower BP targets in the elderly, although, in these patients, the BP should be lowered slowly and they should be closely monitored for any untoward effects including dizziness, syncope, any neurological symptoms, angina, or worsening cardiac or renal function. Elderly persons are prone to isolated systolic hypertension and arterial stiffness. Thus, aggressive or substantial lowering of BP may result in the potential for loss of cerebral autoregulation as their autoregulatory curves are shifted to the right, and the possibility of borderzone brain infarcts associated in some with relative or absolute hypotension. Thus, in individual cases there may be a need to seek less aggressive BP treatment targets, especially if dizziness, syncope or neurological or cardiac symptoms ensue or if there is development of renal dysfunction.

A reasonable conclusion from these studies is that there is now support for more intensive BP lowering in both diabetic and nondiabetic patients, and that a SBP target of <120 mm Hg is a reasonable option for adults with high CVD risk This conclusion is also supported by a SPRINT substudy demonstrating that patients with prediabetes derived a similar cardiovascular benefit from intensive BP lowering as those with normoglycemia.[13]

Responses to Criticisms of SPRINT in Consideration of Stroke

Although the SPRINT results are strong with high impact, there are several criticisms and questions that are frequently evoked by clinicians that have implications for stroke.

There Was an Unacceptable Incidence of Side-Effects

These included an increased incidence of a ≥30% reduction in estimated glomerular filtration rate in SPRINT intensive compared with standard-treatment participants without chronic kidney disease at baseline. However, even in those with chronic kidney disease at baseline the average difference in estimated glomerular filtration rate between groups was only ≈3 mL/min per m2.[14] An explanation, yet to be verified in a more detailed analysis of the renal data, is that subjects in the intensive group were more likely to be treated with blockers of the renin–angiotensin system, and at higher doses. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers dilate the efferent arterioles of the kidney, reducing glomerular filtration pressure and thus glomerular filtration rate, a benign hemodynamic effect. Also, as expected, hypotension (2.4% versus 1.4%) and syncope (2.3% versus 1.7%) were more frequent in the intensive versus the standard-treatment group, as was hyponatremia and hypokalemia (possibly related to more intensive diuretic dosing).[12] However, orthostatic hypotension was more common in the standard group ($P=0.13$) and there was no significant difference in the incidence of orthostatic hypotension with symptoms. There was a significant difference in serious adverse events (hospitalizations) associated with hypotension (the 2.4% versus 1.4%) and syncope (2.3% versus 1.7%) but no overall difference in serious adverse events between the 2 treatment groups.

I Would Not Apply These Findings to My Elderly, Frail Patients

In a prespecified subgroup analysis of SPRINT participants ≥75 years, the incidence of the primary outcome was significantly lower in the intensively treated group in the fit elderly, the less fit elderly, and even in the frail elderly,[6] and also in those with diminished gait speed and mobility.[12,15]

Table. Comparison of Data and Stroke Outcomes From the ACCORD and SPRINT Trials

	Mean Age, y	Body Mass Index	Years of Follow-Up	Intensive Treatment, n (%/y)	Standard Treatment, n (%/y)	Hazard Ratio (95% CI)	*P* Value
ACCORD	62.2±6.9	32.1±5.6	4.7 (mean)	36 (0.32)	62 (0.53)	0.59 (0.39–0.89)	<0.01
SPRINT	67.9±9.4	Not reported	3.2 (median)	62 (0.41)	70 (0.47)	0.89 (0.63–1.25)	0.19

ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; and SPRINT, Systolic Blood Pressure Intervention Trial.

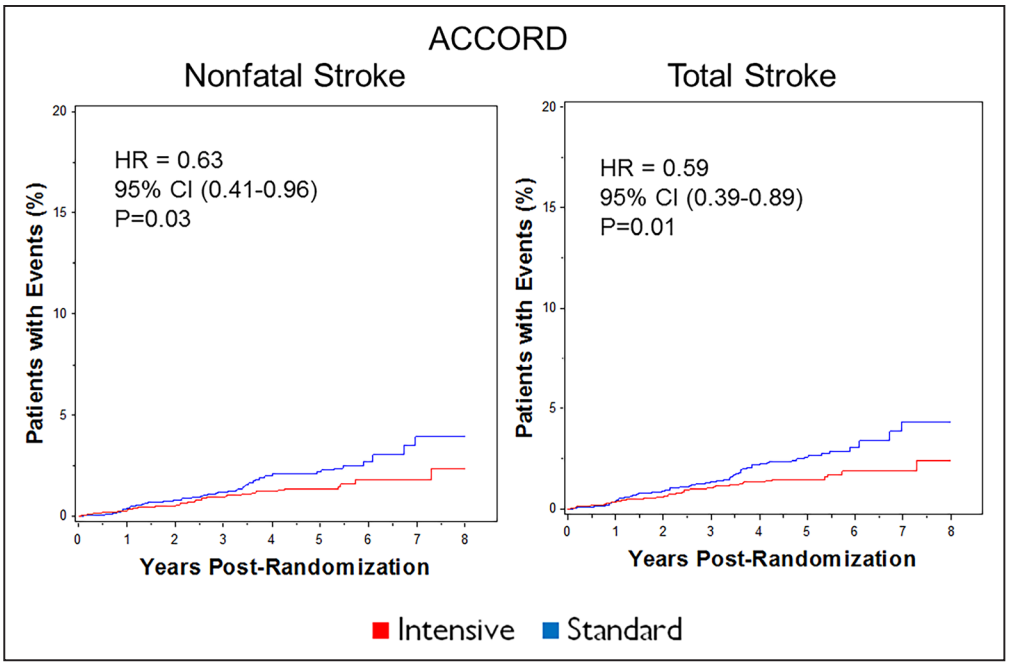

Figure. Results from ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) showing the reduction in stroke risks with intensive hypertension treatment with the Kaplan–Meier curves for stroke starting to diverge at about 3.5 y. Data derived from Cushman et al[10]. HR indicates hazard ratio.

Absolute Risk Reduction Is Small

The rate of the primary outcome was 1.65% per year for the intensive group and 2.19% per year for the standard group, so the absolute risk reduction is only 0.54% per year. However, hypertension is such a common risk factor for stroke and CVD that the benefit of applying the SPRINT target to the population at large is substantial.[16] It can be calculated that, in the United States alone, there would be 90 000 fewer cardiovascular events, 62 000 fewer deaths, and 10 100 fewer strokes, per year based on the SPRINT results.

There Was No Statistically Significant Benefit in Reducing Stroke

Although true but the stroke rates were intensive treatment 0.41% per year and standard treatment 0.47% per year, with a HR of 89% and a relative risk reduction 11%. This, together with the ACCORD stroke data, with its 41% relative reduction, and the vast preponderance of the evidence supports aggressive BP reduction to prevent strokes.

Patients With Prior Stroke Were Excluded From SPRINT, So SPRINT Tells Us Nothing About Secondary Stroke Prevention

These patients were excluded as the SPS3 trial (Secondary Prevention of Small Subcortical Strokes)[17] was implemented, which included 3020 patients with magnetic resonance imaging-defined symptomatic lacunar infarctions. Patients were randomized to a target SBP of 130 to 149 mm Hg, or to <130 mm Hg. At 1 year, mean SBP was 138 mm Hg (95% CI, 137–139) in the higher target group and 127 mm Hg (95% CI, 126–128) in the lower target group. Nonsignificant rate reductions were seen for all stroke (HR, 0·81; 95% CI, 0·64–1·03; *P*=0·08) and disabling or fatal stroke (HR, 0.81; 95% CI, 0.53–1.23; *P*=0.32) with the lower target. The rate of intracerebral hemorrhage, however, was reduced significantly (HR, 0.37; 95% CI, 0.15–0.95; *P*=0·03). The authors concluded that although the reduction in total stroke was not statistically significant, the results support the conclusion that in patients with recent lacunar stroke, a SBP target of <130 mm Hg is likely to be beneficial.

Why Were the Stroke Outcomes in ACCORD and SPRINT So Different?

The ACCORD Kaplan–Meier curves for stroke start to diverge at ≈3.5 years (Figure). SPRINT was stopped before that (median follow-up, 3.26 years). So, a reasonable hypothesis is that the SPRINT 11% relative risk reduction for stroke might have increased to significant levels had the study been extended for a longer time period.

Watershed infarcts can occur because of hypoperfusion in patients with significant arterial stenosis in cervicocephalic arteries, and none of the trials assessed the presence/degree of arterial lesions. In the SAMMPRIS trial (Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis) aggressive medical treatment alone with aggressive medical treatment and percutaneous transluminal angioplasty and stenting) in patients with transient ischemic attack or nondisabling stroke caused by stenosis of 70% to 99% of intracranial arteries, the target SBP was <140 mm Hg for nondiabetics and <130 mm Hg for diabetics.[18] Stroke recurrence was less frequent than in previous studies and this result contributed to change the paradigm of treatment in patients with large-artery intracranial atherosclerosis. Aggressive medical treatment included control of other risk factors and lifestyle changes, and it is not possible to determine which component of the treatment (BP target or other measures) played the most beneficial role on secondary stroke prevention). Still, the success of medical treatment decreased fears about risks of provoking strokes by treating hypertension to the chosen

targets in patients with large-artery disease at risk of hypoperfusion. Whether a lower target (BP<120 mm Hg) can also be safely applied to all patients with large-artery stenosis remains unknown.

Recent Meta-Analyses of RCTs on Intensive BP Reduction and Stroke Prevention

Prediction models from the 1980s indicated that a 10 mm Hg lower SBP would predict a 40% reduction in stroke risk with stroke risk reduced even with as little as a 2 mm Hg SBP reduction.[1] These models were accurate with stroke mortality rates lowered with the shifts in SBP distribution in the United States from 1960 to 2005.[1] On a population basis, therefore, every mm Hg in BP lowering can be of potential clinical importance, especially in reducing stroke risk.

Recently, 5 meta-analyses have used different analytic approaches comparing more versus less intense BP targets on the risk of stroke outcomes.[2,3,19–21] In each, the risk of stroke was significantly improved with more intense over less intense BP reduction. Xie et al[3] analyzed 19 RCTs (not including SPRINT) in 44 989 participants during 3.8 years of follow-up. BP levels in the more intensive BP group achieved 133/76 mm Hg compared with 140/81 mm Hg in the less intensive group. This BP difference resulted in a 22% risk reduction (P<0.001) for stroke in the more intensive over less intensive group. Thomopoulos et al[2] analyzed 16 RCTs (including SPRINT) comparing more versus less intense BP targets. The trials were stratified by achieved SBP. In all 3 tiers of achieved SBP reduction, there were significant reductions in risk reduction (all P<0.001). The standardized stroke risk reduction (95% CI were 0.68 [0.60–0.79] for 140 to 149 versus ≥150 mm Hg; 0.62 [0.51–0.76] for 130 to 139 versus ≥140 mm Hg; and 0.71 [0.61–0.84] for <130 versus ≥130 mm Hg). Verdecchia et al[19] used a cumulative and sequential meta-analysis of 18 RCTs (including SPRINT) with random allocation of 53 405 participants to more versus less intensive BP targets. Consistent with the results of the aforementioned studies, the more intense BP-lowering strategy was associated with a significant reduction in the cumulative risk of stroke: odds ratio, 0.802 (0.676–0.952). Bangalore et al[20] performed a network meta-analysis involving 17 RCTs in 55 163 participants. There was a significant reduction in the risk of stroke with lower on-treatment SBP targets. SBP targets of <120 and <130 mm Hg ranked as number 1 and number 2, respectively, as the most efficacious targets for the prevention of stroke, whereas the target of <120 mm Hg ranked worst in terms of adverse events. Cluster analysis for combined efficacy and safety outcomes showed that a SBP target of <130 mm Hg achieved the best balance between efficacy and safety.[20] Bundy et al[21] used a network meta-analysis to pool information from 44 clinical trials, providing substantial statistical power for randomized comparisons of SBP during treatment. The analyses demonstrated a reduction in risk of major CVD at lower levels of achieved SBP (eg, SBP, 120–124 mm Hg was significantly better than 125–129 mm Hg). There were similar findings for stroke. Taken together, the evidence from these 5 meta-analyses suggests that SBP <130 mm Hg may be most clinically advantageous BP target in the prevention of stroke.

Implications of the Hypertension Guidelines on Stroke Risks

The first US national guideline for detection, evaluation, and treatment of hypertension Joint National Committee (JNC) 1 was published in 1977.[22] Subsequently, updated JNC reports, as well as guidelines from national, regional, and global organizations were developed for BP management. Although many of the core recommendations have been similar, considerably more attention has been paid to disagreements than similarities between different guidelines.[23] This has led to confusion for practitioners and the general public.[24,25] Between 2013 and 2017, 5 clinical practice guidelines that specifically focused on BP management have been published.[26–30] Two of the 5 were US-based reports[27,30], whereas the other 3 were from Europe,[26] Canada,[29] and Australia.[28] (Table I in the online-only Data Supplement) The European, Canadian, and Australian guidelines reports were comprehensive documents that provided recommendations dealing with prevention, diagnosis, evaluation, and management of high BP.[26,28,29] In contrast, one of the US guidelines was restricted to recommendations related to pharmacological treatment questions in adults[27] and the other was restricted further to pharmacological treatment questions in adults ≥60 years.[30] Although automated office BP measurements were recommended as the preferred means to assess level of BP in the Hypertension Canada report,[29] all 5 of the guidelines based the diagnosis of hypertension on traditional office measurements with an average SBP ≥140 mm Hg or a diastolic BP ≥90 mm Hg.

Use of CVD risk as a guide for pharmacological treatment of hypertension was first recommended in 1993.[31,32] The rationale is that treatment is unlikely to prevent CVD events in settings where events are likely to be infrequent. Specifically, the absolute benefit of drug treatment as a means to prevent CVD and stroke events or death is modest and the number needed to treat to prevent a CVD event or death is quite high in adults with a low risk for CVD.[33,34] The JNC 5 guideline[35] suggested that target organ damage or multiple risk factors should influence the decision to initiate antihypertensive drug therapy. The importance of underlying CVD risk was further emphasized in the JNC 6 report.[36] In contrast to JNC 5 and 6, the JNC 7 guideline[37] and the 2014 report from the panel members appointed to the Eight Joint National Committee (JNC 8 panel)[27] provided recommendations for drug treatment of hypertension that were primarily based on level of BP, with indicators of CVD risk only playing an indirect role. The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP), European Society of Hypertension (ESH) and European Society of Cardiology (ESC), Canadian Hypertension Education Program (CHEP) and the National Heart Foundation of Australia (NHFA) guidelines all emphasize the role of CVD risk in BP treatment decision-making.

The 3 comprehensive guideline reports provide recommendations for nonpharmacological interventions, with the 2016 CHEP guideline adding a recommendation for increased dietary potassium intake in those not at risk for hyperkalemia.[29] The recommendation was based on meta-analyses that document a BP-lowering effect of increased potassium

intake.[38] This is an intervention that seems to be especially useful in those consuming a high intake of dietary sodium[39,40] and in Blacks.[39] It also may reduce the risk of strokes.[41]

All 5 guidelines recommended use of either a diuretic, calcium channel blocker, ACEI, or angiotensin receptor blocker for first-step monotherapy of hypertension, with further specification of class type in some of the reports. Use of a β-blocker for first-step monotherapy was also recommended in the ESH/ESC and CHEP guidelines but not in the JNC 8 panel or NHFA reports. The ESH/ESC, CHEP, and NHFA guidelines all endorse combination drug therapy as an alternative to monotherapy, especially in patients with a higher BP[26,29] or at high risk for CVD[26] but specifically recommend against concurrent use of an ACEI and angiotensin receptor blocker combination[28,29] or 2 drugs that block the renin–angiotensin system.[26] There was considerable diversity on recommendations for drug choice in patients with a prior history of a stroke or transient ischemic attack, with an ACEI or diuretic being recommended in the CHEP guideline, any first-line drug in the NHFA guideline, no definitive recommendation in the ESH/ESC guideline (but an apparent preference for a calcium channel blocker, diuretic, or an ACEI-diuretic combination). Choice of antihypertensive medication for long-term management in stroke survivors was not addressed in the other 2 guidelines.

The 2017 guidelines, sponsored by the American College of Cardiology/American Heart Association and 9 other professional societies, represent some of the latest evidence-based recommendations with specific consideration of BP reduction for lower stroke risks.[42,43] Although the impact of these guideline for the prevention, detection, evaluation, and management of high BP has not been quantified, it would be expected that significant effects on stroke reduction will be found, similar to the previous robust recommendations.

Questions for Future Research Related to Hypertension and Stroke Risks

During the past 50 years, enormous advances were made in the pharmacological treatment of hypertension.[44] Multiple trials demonstrated that treatment of hypertension consistently decreases stroke risk. Still, large gaps remain in the evidence-base of SBP targets for primary and secondary stroke prevention. Evidence specific for SBP targets for reduction of stroke risks has been limited to a few reports,[45,46] and the SPRINT results with the early ending, was unable to add critical information for stroke.[12] Further, SPRINT results did not contribute to define targets for secondary prevention because patients with stroke were excluded from the study.[12] The lack of significant stroke reduction has typically been explained by the design and statistical power of the study. The expected incidence of stroke was only 0.47% per year in SPRINT and few strokes (62 in the intensive-treatment group and 70 in the standard-treatment group) occurred during the trial at a median follow-up of 3.26 years.[47] The focus on evidence for BP targets for stroke remains a critical global need.[48]

The selection of subjects at high risk of cardiovascular events either by definition of clinical CVD or high estimated 10-year risk as inclusion criteria has advantages and drawbacks. This high-risk strategy can maximize absolute benefits or benefit-to-risk ratios and increase the probability of finding differences between groups in which rates of events are expected to be high, thus representing potential advantages considering that numbers of patients and durations of follow-up represent challenges for the design of clinical trials in stroke prevention. Also, this approach is consistent with a prevention paradigm that focuses on providing intensive clinical care for high-risk individuals.[49] However, there are disadvantages in the exclusion of subjects based on 10-year cardiovascular risk. Age is a strong predictor of 10-year risk, therefore, middle-age or younger subjects considered to be at low or intermediate may be excluded from prevention trials in spite of a substantial lifetime risk.[50] This is particularly relevant for stroke prevention because hypertension may be undertreated in younger individuals. For instance, only 40.1% of US hypertensive individuals aged 20 to 39 years had their BP under control.[51] Meta-analyses showed that intensive BP treatment was able to decrease stroke risk in groups at low, intermediate, or high 10-year cardiovascular death risk,[51] with mean achieved SBP targets (130.8–140.8 mm Hg in the intensively treated groups) consistent with intensive treatment in SPRINT.[52]

Still, it remains to be determined whether intensive treatment of hypertensive patients regardless of cardiovascular risk can further decrease stroke without increasing serious adverse events, compared with standard treatment. In the HOPE-3 study (Heart Outcomes Prevention Evaluation–3),[53] subjects at intermediate cardiovascular risk but without stroke or other CVDs were randomized to treatment with a fixed-dose combination of candesartan and hydrochlorotiazide or candesartan and placebo. The difference in stroke risk was not significant between the 2 groups after follow-up of 5.6 years. However, HOPE-3 was not able to determine whether more intensive treatment of hypertensive subjects decreases stroke risk because only 38% of the subjects included in the study were hypertensive at baseline, the difference attained in SBP between the 2 groups was small (6 mm Hg) and the study did not apply a target-to-treatment approach. However, post hoc analysis from the China Stroke Primary Prevention Trial[54] indicated that in subjects without stroke, an SBP goal of 120 to 130 mm Hg was associated with a lower risk of stroke compared with targets of 130 to 140 or <120 mm Hg. Further trials are necessary to answer this question worldwide. An important point is that an SBP <120 mm Hg measured according to the unattended automated protocol used in SPRINT may correspond to an SBP <130 to 136 mm Hg according to auscultatory methods used in other trials.[55]

For secondary prevention, the ongoing ESH-CHL-SHOT (Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensives) is testing 3 different targets (<120 mm Hg, 125 to <135 mm Hg, and 135 to 145 mm Hg) in patients with history of stroke or transient ischemic attack. In contrast to other treatment-to-target trials of hypertension, the primary outcome is recurrent fatal or nonfatal stroke.[47] Secondary outcomes include cognitive impairment and dementia, of major relevance considering the devastating effects of hypertension on cerebrovascular damage and the inconclusive evidence about effects of antihypertensive treatment on cognition.[56] Results of the SPRINT MIND (The SPRINT Memory and Cognition in Decreased Hypertension)

and SPRINT MIND MRI (The SPRINT Memory and Cognition in Decreased Hypertension Magnetic Resonance Imaging) substudies[57] may also provide valuable information about whether a more intensive BP target can prevent cognitive decline or subclinical brain lesions.

Finally, when trials aiming to decrease stroke risk are designed, absolute BP targets may not be the only relevant goals of treatment. Variability in BP, night-time SBP, and other measures obtainable through ambulatory BP monitoring[58] may be of value for the prevention of stroke[59] or cognitive deterioration[60] but optimal evidence-based targets for these measures are not yet available.

Implementing Hypertension Guidelines for the Reduction of Stroke Risks

Implementation of more intense BP control will require new approaches both by individual physicians and importantly by health systems throughout the world. Strategies will include improvement of lifestyle modification using behavioral and motivational strategies, addressing drug nonadherence, employment of team-based care, greater utilization of health information technology, including electronic health records and patient registries, and forming new connections for patients to their healthcare teams by telehealth. Great success has recently been demonstrated by Kaiser Permanente of Northern California, which used of these strategies to improve the control of hypertension from 44% to 90% over a 14 year period with a concomitant reduction in death from stroke by 42%.[61]

Strategies to achieve BP control require medication nonadherence. Berra et al[62] have reported one-quarter of patients newly initiated on antihypertensive therapy fail to fill their initial prescription. During the first year of treatment, the average patient has possession of antihypertensive medication only 50% of the time. Only 1 in 5 patients has sufficiently high adherence to achieve the benefits observed in RCTs. Thus, lack of adherence to antihypertensive drug therapy is often a major barrier to the achievement of target BP goals and consequently the prevention of stroke.

Methods for assessment of possible medication nonadherence can be divided into indirect (self-report: questionnaire, diary, and interview; pill count: manual, electronic monitoring device, and prescription registries) and direct (directly observed therapy and therapeutic drug monitoring) methods.[63] Clarification of the optimal method(s) for detection and treatment of nonadherence to antihypertensive drugs is vital to the prevention of stroke in the future.

Summary and Conclusions

Although stroke risks have been long recognized as associated with BP levels, recent trial results provide detailed evidence for the benefit of hypertension treatment and control.[64] Further, as stroke represents a particular global burden for many of the larger world populations including China, India, and Brazil, high BP is at a critical point in time.[65] Thus, the implications of the new study results and subsequent recommendations based on the evidence can have significant impact.[66]The information presented as part of the International Stroke Conference Session was timely and detailed and focused on the implications of the current study results building on the previous trials with a targeted interdisciplinary clinical audience. These data are particularly relevant given the recent report that the prior declines in stroke death rates have not continued in recent years, and the importance of strategically identifying opportunities for hypertension treatment and control.[67]

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KEY WORDS: dizziness ■ incidence ■ myocardial infarction ■ prospective studies ■ secondary prevention

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Implications of Recent Clinical Trials and Hypertension Guidelines on Stroke and Future Cerebrovascular Research

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Comparison of recent hypertension guidelines

	European Society of Hypertension and European Society of Cardiology	Panel members appointed to the Eight Joint National Committee	Canadian Hypertension Education Program	National Heart Foundation of Australia	American College of Physicians and American Academy of Family Physicians
Year	2013	2014	2016	2016	2017
Target population	Adults	≥18 years	Adults	≥18 years	≥60 years
Focus	Comprehensive	Treatment -BP threshold -BP goal -Drug class differences	Comprehensive	Comprehensive	Treatment -BP target during drug treatment of hypertension
BPs for diagnosis of hypertension	Office BPs -SBP ≥140 mm Hg or -DBP ≥90 mm Hg	Not defined	Clinic BPs* -SBP ≥140 mm Hg or -DBP ≥90 mm Hg	Office BPs -SBP ≥140 mm Hg or -DBP ≥90 mm Hg	Not defined
Assessment of cardiovascular disease risk	Prominent	Focus on level of BP but CVD risk elements inform recommendations	Prominent	Prominent	Focus on levels of BP but CVD risk and CVD risk elements inform recommendations
Nonpharmacological interventions	Lifestyle changes	Not covered	Health behavior management	Lifestyle modification	Mentioned in introduction
Drug therapy choice	Diuretics, β-blockers, CCB, ACEI, or ARB Consider combination therapy in patients at high risk or with a markedly high BP (combination of two different agents that block the renin-angiotensin system not recommended) Prior stroke or TIA:	Main objective -attain and maintain goal BP Initial therapy: General non-Black: -Thiazide-type diuretic, CCB, ACEI or ARB General Black: -Thiazide-type diuretic or CCB -β-blockers and α-blockers not recommended for initial treatment -ACEI and ARB should not be used in combination	Initial monotherapy with a thiazide/thiazide-like diuretic, β-blocker (< 60 years), ACEI (non-Black), long acting CCB, or ARB Consider initial combination therapy, especially with higher BP (combination of ACEI and ARB not recommended; caution for combination of nondihydropyridine CCB and β-blocker) Prior stroke or TIA:	Uncomplicated hypertension: -ACEI or ARB, CCB or thiazide diuretic -β-blockers not recommended for first-line therapy in patients with uncomplicated hypertension Usually >1 drug required (combination of ACEI and ARB not recommended) Prior stroke or TIA:	Mentioned in introduction -thiazide type diuretics, ACEI, ARB, CCB and β-blockers

Drug choice in patients with a prior stroke or TIA	No definitive recommendation but seemed to prioritize use of CCB, followed by diuretic or diuretic-ACEI combination	Not specifically addressed	ACEI or diuretic	Any first-line drug	Not addressed
Treatment target BP target in patients with prior stroke or TIA	Generally, <140/90 mm Hg If elderly but <80 years with SBP ≥160 mm Hg -SBP 140-150 mm Hg If >80 years - If fit, SBP 140-150 mm Hg - If fragile, individualize SBP target based on tolerance In patients with diabetes -DBP <85 mm Hg "General" target (SBP/DBP <140/90 mm Hg) --- ensure effective reduction in BP	≥60 years: SBP/DBP <150/90 mm Hg 30-59 years: SBP/DBP <140/90 mm Hg In patients with diabetes but no CKD: SBP/DBP <140/90 mm Hg In patients with CKD: SBP/DBP <140/90 mm Hg Targets as above	Generally, SBP/DBP <140/90 mm Hg, In patients with diabetes (SBP/DBP <130/80 mm Hg) In adults ≥80 years (SBP <150 mm Hg) In selected high risk patients, consider AOBP SBP <120 mm Hg (with careful monitoring) "General" target (SBP/DBP <140/90 mm Hg) --- ensure effective reduction in BP	Influenced by underlying CVD risk In uncomplicated hypertension: SBP/DBP <140/90 mm Hg In selected high risk patients (including patients with CKD, diabetes and >75 years): consider SBP<120 mm Hg (with careful monitoring) "General" target (SBP/DBP <140/90 mm Hg)	Adults ≥60 years and SBP ≥150 mm Hg: SBP <150 mm Hg Adults ≥60 years at high risk for CVD (not defined): -SBP <140 mm Hg Adults ≥ 60 years: -SBP <140 mm Hg (moderate evidence for < 130-139 mm Hg)

Table 2. Selected features of five blood pressure guidelines published between 2013 and 2017

*Automated office blood pressure (AOBP) endorsed as preferred method for measuring blood pressure in the office but recommendations based on traditional measurement methods.

BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CVD=cardiovascular disease; CCB=calcium channel blocker (calcium antagonist); ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; TIA=transient ischemic attack.