4-1-2021

Effect of Intensive Versus Standard Blood Pressure Control on Stroke Subtypes

Clinton B. Wright

Alexander P. Auchus

Alan Lerner

Walter T. Ambrosius

Hakan Ay

See next page for additional authors

Recommended Citation

Wright CB, Auchus AP, Lerner A, Ambrosius WT, Ay H, Bates JT, Chen J, Meschia JF, Pancholi S, Papademetriou V, Rastogi A, Sweeney M, Willard JJ, Yee J, and Oparil S. Effect of Intensive Versus Standard Blood Pressure Control on Stroke Subtypes. Hypertension 2021.

Authors

Clinton B. Wright, Alexander P. Auchus, Alan Lerner, Walter T. Ambrosius, Hakan Ay, Jeffrey T. Bates, Jing Chen, James F. Meschia, Suchita Pancholi, Vasilios Papademetriou, Anjay Rastogi, Mary Sweeney, James J. Willard, Jerry Yee, and Suzanne Oparil

Hypertension

SPRINT

Effect of Intensive Versus Standard Blood Pressure Control on Stroke Subtypes

Clinton B. Wright, Alexander P. Auchus, Alan Lerner, Walter T. Ambrosius, Hakan Ay, Jeffrey T. Bates, Jing Chen, James F. Meschia, Suchita Pancholi, Vasilios Papademetriou, Anjay Rastogi, Mary Sweeney, James J. Willard, Jerry Yee, Suzanne Oparil; for the SPRINT Research Group

ABSTRACT: In the SPRINT (Systolic Blood Pressure Intervention Trial), the number of strokes did not differ significantly by treatment group. However, stroke subtypes have heterogeneous causes that could respond differently to intensive blood pressure control. SPRINT participants (N=9361) were randomized to target systolic blood pressures of <120 mm Hg (intensive treatment) compared with <140 mm Hg (standard treatment). We compared incident hemorrhage, cardiac embolism, large- and small-vessel infarctions across treatment arms. Participants randomized to the intensive arm had mean systolic blood pressures of 121.4 mm Hg in the intensive arm (N=4678) and 136.2 mm Hg in the standard arm (N=4683) at one year. Sixty-nine strokes occurred in the intensive arm and 78 in the standard arm when SPRINT was stopped. The breakdown of stroke subtypes across treatment arms included hemorrhagic (intensive treatment, n=6, standard treatment, n=7) and ischemic stroke subtypes (large artery atherosclerosis: intensive treatment n=11, standard treatment, n=13; cardiac embolism: intensive treatment n=11, standard treatment n=15; small artery occlusion: intensive treatment n=8, standard treatment n=8; other ischemic stroke: intensive treatment n=3, standard treatment n=1). Fewer strokes occurred among participants without prior cardiovascular disease in the intensive (n=43) than the standard arm (n=61), but the difference did not reach predefined statistical significance level of 0.05 (*P*=0.09). The interaction between baseline cardiovascular risk factor status and treatment arm on stroke risk did not reach significance (*P*=0.05). Similar numbers of stroke subtypes occurred in the intensive BP control and standard control arms of SPRINT. **(*Hypertension*.2021;77:1391-1398. DOI: 10.1161/HYPERTENSIONAHA.120.16027.)**

Key Words: atherosclerosis ■ blood pressure ■ hemorrhagic stroke ■ hypertension ■ ischemic stroke

Stroke is the fifth leading cause of death in the United States and the leading cause of adult disability. The estimated annual cost of stroke is expected to increase by $240 billion by 2030.[1] The most recent American Heart Association/American Stroke Association statement on the primary prevention of stroke states, "The relationship between blood pressure (BP) and stroke risk is strong, continuous, graded, consistent, independent, predictive, and etiologically significant".[2] Observational studies show a benefit of lower BP down to 115/75 for both men and women aged 40 to 89 years in relation to risk of first fatal or nonfatal stroke.[3,4] Multiple randomized controlled trials have also shown a benefit of moderate BP lowering in primary stroke prevention, and some have shown a benefit of more intensive BP lowering to various targets as well, but the issue of what BP target is optimal for stroke prevention remains unsettled.[5]

The SPRINT (Systolic Blood Pressure Intervention Trial) randomized 9361 participants with an increased cardiovascular risk, but without diabetes or a history of stroke, to a systolic BP target of <120 mm Hg (intensive treatment) or a target of <140 mm Hg (standard treatment) and was stopped early when the combined primary end point was reached. The combined primary outcome favored the intensive BP arm, with significantly fewer fatal and nonfatal major cardiovascular events (including stroke) and death from any cause. However, although fewer strokes occurred in the intensive arm, only 147 stroke events had accrued by study

Correspondence to: Clinton B. Wright, 6001 Executive Blvd, Rockville, MD 20852. Email wright.clinton@gmail.com
For Sources of Funding and Disclosures, see page 1397.

Hypertension is available at www.ahajournals.org/journal/hyp

Novelty and Significance

What Is New?

- SPRINT (Systolic Blood Pressure Intervention Trial) provided a unique opportunity to compare intensive blood pressure control to standard blood pressure control in relation to the risk of hemorrhagic and ischemic stroke and their subtypes.

What Is Relevant?

- Hypertension is a strong risk factor for stroke through its effects on the heart and systemic arteries.
- Intensive blood pressure lowering could halt the deleterious effects of hypertension and lower the risk of stroke or cause brain ischemia in the setting of long-standing hypertension.

Summary

The number of hemorrhagic and ischemic stroke subtypes were similar across the intensive and standard blood pressure arms of SPRINT. Intensive blood pressure lowering was not associated with an elevated risk of cerebral small vessel strokes compared with standard control.

Nonstandard Abbreviation and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
BP	blood pressure
CCS	Causative Classification System
CE	cardiac embolism
HOPE	Heart Outcomes Prevention Evaluation
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes

termination.[6] Since stroke is a broad term referring to events caused by multiple mechanisms, most of them modifiable by treatment of hypertension, it is important to examine the effect of intensive BP lowering on different stroke subtypes to better understand the mechanisms that link hypertension with different types of brain damage. BP-lowering appears to be beneficial for preventing both ischemic and hemorrhagic stroke, but only limited data are available on the effects of BP treatment on different types of stroke, especially ischemic stroke subtypes.[3,4] Cerebral small vessel disease due to hypertensive vasculopathy can manifest as small subcortical (ie, lacunar) infarctions and intraparenchymal hemorrhages and may be the most direct link between high BP and stroke. Hypertension also leads to heart disease, including myocardial infarction, nonvalvular atrial fibrillation, and heart failure predisposing to cardiac embolism (CE) that results in stroke. Large vessel atherosclerosis leads to local thrombosis or artery to artery embolism. Given the established links between hypertension and small vessel stroke, and the reductions in heart failure and cardiovascular mortality due to intensive BP lowering seen in SPRINT, we hypothesized that intensive BP lowering would also result in fewer strokes attributable to cerebral small vessel disease or those attributable to a cardiogenic mechanism.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

Stroke subtyping was a prespecified outcome. The design and cardiovascular outcome results for SPRINT have been described previously.[6,7] Adults 50 years of age or older with systolic BP between 130 and 180 mm Hg at screening were enrolled. Participants were at elevated cardiovascular risk, defined as either having chronic kidney disease with an estimated glomerular filtration rate of 20 to <60 mL/(min·1.73 m^2), a 10-year Framingham cardiovascular disease risk ≥15%, or being 75 years of age or older. Exclusions included having diabetes, a history of prior stroke or dementia, or living in a nursing home. Enrolled participants were randomly assigned to either an intensive treatment strategy with a systolic BP goal of <120 mm Hg or a standard treatment strategy with a systolic BP goal of <140 mm Hg. SPRINT was funded by the National Heart, Lung, and Blood Institute and co-funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging. An independent data and safety monitoring board monitored unblinded trial results and safety events. The study was approved by the institutional review board at each participating study site (URL: https://www.clinicaltrials.gov; Unique identifier: NCT01206062).

Stroke Adjudication and Subtyping

Randomization was stratified by clinical site and participants, and study personnel were aware of study-group assignments, but outcome adjudicators were blinded and did not adjudicate cases from their home networks. Medical records and electrocardiograms were obtained for documentation of events and whenever clinical site staff became aware of a stroke, the approved protocol was followed to obtain information on the

event.[7] A member of the Stroke Subcommittee (C. Wright) of the Morbidity and Mortality Committee of SPRINT adjudicated stroke subtypes using the Causative Classification System (CCS), a standardized, automated, evidence-based, and web-based subtype classification system adapted for use in SPRINT as specified in the design and rationale publication.[7,8] The CCS generated 5 mutually exclusive categories for each case: large artery atherosclerosis (supra-aortic), CE, small artery occlusion, other uncommon causes, and undetermined causes.[8–10] The undetermined category was further divided into cryptogenic, multiple competing causes, and incomplete evaluation.[8,9] We also stratified CE into major-CE and minor-CE where major CE denotes cardio-embolic sources with high potential to cause a stroke such as atrial fibrillation, and minor CE indicates sources with a low- or uncertain potential to cause a stroke such as mitral annulus calcification (1–4).[8–11] Finally, we generated an additional cryptogenic group that also included low- or uncertain-risk cardiac sources. The CCS software stratified each CCS category into 3 confidence levels as evident, probable, and possible depending on the level of causal evidence. Because of the small number of strokes, we determined the effects of the intervention by aggregating the confidence levels.

Statistical Analysis

We compared the number of participants with stroke types and subtypes across treatment arms using χ^2 tests or Fisher exact tests (for expected cell counts <5). The 3 major stroke types were hemorrhagic, ischemic, and unknown. Hemorrhagic strokes were classified as subarachnoid, intraparenchymal, or other. We then used Cox proportional hazard models stratified by clinical site to estimate hazard ratios and 95% CIs comparing stroke rates across prespecified subgroups using tests of interaction with significance defined as Hommel-adjusted alpha levels smaller than 0.05.[12]

RESULTS

Characteristics of the SPRINT participants are shown in Table 1 and were well balanced across BP treatment arms. Of 9361 participants randomized to intensive (N=4678) or standard (N=4683) BP control, 69 participants in the intensive arm versus 78 participants in the standard arm had strokes during a mean follow-up of 3.33 years (Figure 1). There was no significant difference in the number of strokes overall by treatment arm.[6] Likewise, baseline cardiovascular risk factor status did not significantly modify the effect of the intervention. However, for those having no prior history of cardiovascular disease at baseline, results favored intensive BP control, but this did not reach significance (*P*=0.05, Figure 2).

Hemorrhagic and ischemic strokes and their subtypes across treatment arms are shown in Table 2. There were 32 events that could not be classified as to type, and 5 with incomplete stroke evaluations that prevented subtype classification. Roughly 70% of strokes were ischemic, with cryptogenic (31%) and cardioembolic (25%) being the most common subtypes. The treatment effects of intensive BP were consistent for the different stroke subtypes with generally fewer strokes in the intensive arm regardless of subtype. Likewise, treatment effects were similar across arms when the undetermined category was broken into subgroups, when the CE category was stratified into major and minor, and when minor CE was combined with the cryptogenic category. The number of ischemic and hemorrhagic stroke subtypes was similar across age (<75 versus ≥75 years), sex, and race/ethnic strata (*P*=0.05, Figure 2).

DISCUSSION

In this prespecified analysis of SPRINT data, intensive BP lowering resulted in similar numbers, types, and subtypes of strokes compared with standard BP control during follow-up. The numbers of hemorrhagic and ischemic stroke subtypes were similar across arms.

As indicated in the primary outcomes report, intensive BP control in SPRINT participants reduced the risk of heart failure and death from cardiovascular causes, with a nonsignificant decrease in the number of myocardial infarctions as well.[6] Given these findings, a lower risk of ischemic strokes caused by CE in the intensive BP control group than the standard control group might be expected. However, the number of stroke events was small, and SPRINT was not powered to detect these differences. Although the anticipated difference in systolic BP between randomized arms (>10 mm Hg) was achieved, it is possible a difference in strokes may have been observed if greater systolic BP differences across arms had been attained.

Hypertension is a major risk factor for small vessel arteriopathies that lead to end-organ damage affecting the brain, heart, kidney, and eye.[13–16] Intensive BP lowering could limit such damage in patients with hypertension, thereby protecting against stroke. In the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial that enrolled participants with recent lacunar strokes who were thus at greater risk of stroke than those in SPRINT, maintaining systolic BP below 130 mm Hg compared with 130 to 139 mm Hg resulted in significantly fewer incident intraparenchymal hemorrhages but not new ischemic strokes.[17] Since intraparenchymal hemorrhage often results in severe morbidity and mortality, it is notable that intensive BP lowering did not result in fewer hemorrhages compared with standard control in the current study.

Intensive lowering of BP in patients with longstanding hypertension could also place some organs at risk of ischemia should BP be lowered too aggressively. In the brain, longstanding hypertension has been hypothesized to require greater BPs to maintain adequate cerebral perfusion pressures and avoid ischemia due to a rightward shift in the autoregulatory curve.[18] Data are limited, but a small study showed cerebral hemodynamic responses were

Table 1. Baseline Clinical Characteristics by Treatment Arm

Characteristic	Intensive treatment (N=4678)	Standard treatment (N=4683)
Criterion for increased cardiovascular risk, n (%)		
Age ≥75 y	1317 (28.2%)	1319 (28.2%)
Chronic kidney disease	1329 (28.5%)	1316 (28.3%)
Cardiovascular disease, n (%)	940 (20.1%)	937 (20.0%)
Clinical	779 (16.7%)	783 (16.7%)
Subclinical	247 (5.28%)	246 (5.3%)
Framingham 10-y cardiovascular disease risk score ≥15%	3556 (76.0%)	3547 (75.7%)
Female sex, n (%)	1684 (36.0%)	1648 (35.2%)
Age, y		
Overall	67.9±9.4	67.9±9.5
Among those ≥75 y of age	79.8±3.9	79.9±4.1
Race or ethnic group, n (%)		
Non-Hispanic Black	1379 (29.5%)	1423 (30.4%)
Hispanic	503 (10.8%)	481 (10.3%)
Non-Hispanic White	2698 (57.7%)	2701 (57.7%)
Other	98 (2.1%)	78 (1.7%)
Black race*	1454 (31.1%)	1493 (31.9%)
Baseline blood pressure, mm Hg		
Systolic	139.7±15.8	139.7±15.4
Diastolic	78.2±11.9	78.0±12.0
Distribution of systolic blood pressure, n (%)		
≤132 mm Hg	1583 (33.8%)	1553 (33.2%)
>132 to <145 mm Hg	1489 (31.8%)	1549 (33.1%)
≥145 mm Hg	1606 (34.3%)	1581 (33.8%)
Serum creatinine, mg/dL	1.07±0.34	1.08±0.34
Estimated GFR, mL/(min·1.73 m^2)		
Among all participants	71.8±20.7	71.7±20.5
Among those with estimated GFR ≥60 mL/(min·1.73 m^2)	81.3±15.5	81.1±15.5
Among those with estimated GFR <60 mL/(min·1.73 m^2)	47.8±9.5	47.9±9.5
Ratio of urinary albumin (mg) to creatinine (g)	44.1±178.7	41.1±152.9
Fasting total cholesterol, mg/dL	190.2±41.4	190.0±40.9
Fasting HDL cholesterol, mg/dL	52.9±14.3	52.8±14.6
Fasting total triglycerides, mg/dL	124.8±85.8	127.1±95.0
Fasting plasma glucose, mg/dL	98.8±13.7	98.8±13.4
Statin use, n/total n (%)	1978/4646 (42.6%)†	2076/4640 (44.7%)†
Aspirin use, n/total n (%)	2406/4662 (51.6%)†	2350/4666 (50.4%)†
Smoking status, n (%)		
Never smoked	2051 (43.8%)	2072 (44.2%)
Former smoker	1977 (42.3%)	1996 (42.6%)
Current smoker	639 (13.7%)	601 (12.8%)
Missing data	11 (0.2%)	14 (0.3%)
Atrial fibrillation, n/total n (%)	390/4661 (8.4%)†	364/4666 (7.8%)†
Framingham 10-y CVD risk score, %	24.8±12.6	24.8±12.5
Body mass index	29.9±5.8	29.8±5.7
Antihypertensive medications prescribed, no/patient	1.8±1.0	1.8±1.0
Not using antihypertensive agents, n (%)	432 (9.2%)	450 (9.6%)

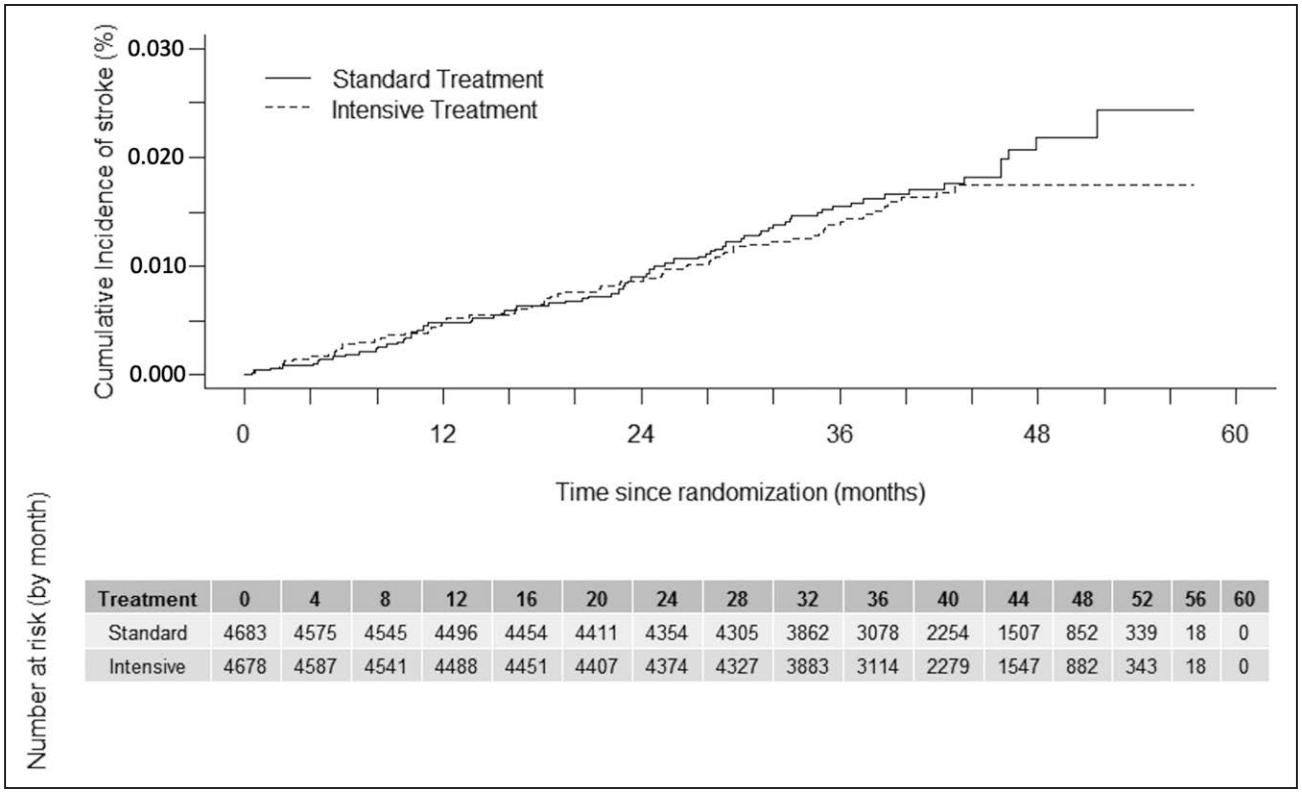
CVD indicates cardiovascular disease; HDL, high density lipoprotein; and GFR, glomerular filtration rate. Black race includes Hispanic Black and Black as part of a multiracial identification.

Black race includes Hispanic Black and Black as part of a multiracial identification.

†Denominator smaller than overall treatment arm totals due to missing data.

stable acutely and up to four months later after initiating treatment of mild and moderate hypertension.[19] In SPRINT, intensive BP lowering also did not increase the risk of stroke subtypes usually attributable to cerebral small vessel disease such as intracerebral hemorrhage and lacunar stroke. These findings are consistent with the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) where intensive BP control targeted below 130 mm Hg significantly lowered stroke risk and with pooled data from SPRINT and ACCORD that showed no increase in stroke risk from intensive BP lowering.[20,21] Further, the SPRINT MIND study found intensive BP control lowered the risk of mild cognitive impairment and the combined outcome of mild cognitive impairment and probable dementia.[22] Intensive BP control did not prevent probable dementia alone (the primary outcome) compared with standard BP control, but there were only about half as many dementia as mild cognitive impairment events due to early termination.

In the current study, we did not find a notable difference between treatment arms in the number of hemorrhagic or ischemic strokes usually attributed to small vessel arteriopathies, namely intraparenchymal hemorrhages and lacunar infarctions. However, the SPRINT-MIND MRI sub-study showed that participants in the intensive BP treatment arm had less progression of white matter hyperintensities than those in the standard arm and that this effect did not differ across various subgroups (those with and without prior cardiovascular disease; those with and without a history of orthostatic hypertension; those older versus younger than 75; and across baseline BP levels).[23] Since there was reason to be concerned about the possible detrimental effects of intensive BP control in all of these subgroups, these findings are reassuring. In addition, since only 22 strokes in the small vessel subtype categories occurred during follow-up, lack of concordance with the MRI sub-study findings could be attributable to the small number of events. In addition, white matter hyperintensities are areas of extracellular water detected on T2-weighted MRI sequences and, though strongly associated with small vessel damage, are nonspecific.



Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Standard	4683	4575	4545	4496	4454	4411	4354	4305	3862	3078	2254	1507	852	339	18	0
Intensive	4678	4587	4541	4488	4451	4407	4374	4327	3883	3114	2279	1547	882	343	18	0

Figure 1. Cumulative incidence plot of stroke events by treatment arm in SPRINT (Systolic Blood Pressure Intervention Trial).
The cumulative incidence of stroke events (*y* axis) in each SPRINT study arm is plotted for the number of participants at risk by month of follow-up (*x* axis).

SPRINT was not designed to examine hypertensive medication class effects, and the small number of ischemic strokes does not allow for a meaningful analysis of the potential class effects of different BP agents. Some classes have been posited to provide additional benefits beyond BP lowering. For example, the HOPE

Subgroup	Intensive Treatment	Standard Treatment	Hazard Ratio	Int P
Overall	69/4678 (1.5)	78/4683 (1.7)	0.89 (0.64, 1.23)	
No Prior CKD	40/3326 (1.2)	49/3336 (1.5)	0.82 (0.54, 1.25)	0.60
Prior CKD	29/1329 (2.2)	29/1316 (2.2)	0.98 (0.58, 1.66)	
Age < 75	38/3361 (1.1)	40/3364 (1.2)	0.97 (0.62, 1.51)	0.53
Age >= 75	31/1317 (2.4)	38/1319 (2.9)	0.75 (0.46, 1.22)	
Male	38/2994 (1.3)	53/3035 (1.7)	0.72 (0.47, 1.09)	0.13
Female	31/1684 (1.8)	25/1648 (1.5)	1.24 (0.73, 2.11)	
Non-Black	54/3224 (1.7)	54/3190 (1.7)	0.95 (0.65, 1.39)	0.33
Black	15/1454 (1.0)	24/1493 (1.6)	0.65 (0.33, 1.22)	
No Prior CVD	43/3738 (1.2)	61/3746 (1.6)	0.71 (0.48, 1.05)	0.05
Prior CVD	26/940 (2.8)	17/937 (1.8)	1.56 (0.84, 2.96)	
SBP <= 132	17/1583 (1.1)	19/1553 (1.2)	0.85 (0.44, 1.65)	0.45
132 < SBP < 145	22/1489 (1.5)	19/1549 (1.2)	1.24 (0.66, 2.33)	
SBP >= 145	30/1606 (1.9)	40/1581 (2.5)	0.76 (0.47, 1.22)	

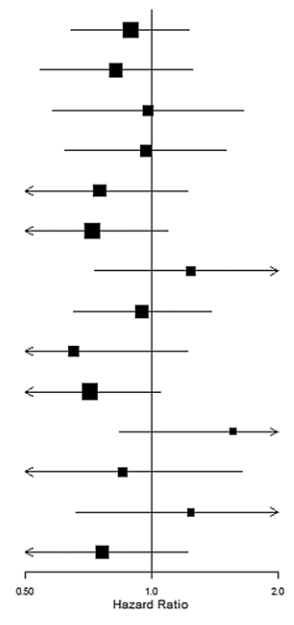


Figure 2. Forest plot of stroke outcome by subgroups.
The forest plot for the groups of interest. Note that all interactions between covariate and treatment arm are nonsignificant for stroke as an outcome at the <0.05 significance level. CKD, chronic kidney disease; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Table 2. Stroke Subtypes in the SPRINT

Stroke Outcome	Overall (N=9361)	Intensive (N=4678)	Standard (N=4683)	*P* value
Absolute overall, n (%)	147 (1.6)	69 (1.5)	78 (1.7)	0.51
Hemorrhagic stroke, n (%)	13 (0.1)	6 (0.1)	7 (0.2)	1.00
Subarachnoid hemorrhage	3 (0.0)	2 (0.0)	1 (0.0)	0.65*
Intraparenchymal hemorrhage	6 (0.1)	3 (0.1)	3 (0.1)	1.00*
Other hemorrhage	4 (0.0)	1 (0.0)	3 (0.1)	0.62*
Ischemic stroke, n (%)	102 (1.1)	48 (1.0)	54 (1.2)	0.62
Large artery atherosclerosis	24 (0.3)	11 (0.2)	13 (0.3)	0.84
Cardiac embolism	26 (0.3)	11 (0.2)	15 (0.3)	0.56
Major cardiac embolism	13 (0.1)	5 (0.1)	8 (0.2)	0.58
Minor cardiac embolism	13 (0.1)	6 (0.1)	7 (0.2)	1.00
Small artery occlusion	16 (0.2)	8 (0.2)	8 (0.2)	1.00
Other uncommon causes	4 (0.0)	3 (0.1)	1 (0.0)	0.38*
Undetermined cause	32 (0.3)	15 (0.3)	17 (0.4)	0.86
Unknown: cryptogenic embolism	19 (0.2)	8 (0.2)	11 (0.2)	0.65
Multiple competing causes	8 (0.1)	4 (0.1)	4 (0.1)	1.00*
Incomplete evaluation	5 (0.1)	3 (0.1)	2 (0.0)	0.69*
Unknown stroke type, n (%)	32 (0.3)	15 (0.3)	17 (0.4)	0.86

SPRINT indicates Systolic Blood Pressure Intervention Trial.
*Denotes Fisher exact test.

trial (Heart Outcomes Prevention Evaluation) showed a benefit to adding ramipril to standard BP treatment for both ischemic and hemorrhagic stroke, and the Systolic Hypertension in the Elderly Program showed a benefit of chlorthalidone versus placebo for various stroke subtypes.[24,25]

The CCS was used for ischemic stroke subtype classification in this study and differs from conventional systems in that it is fully rule- and evidence-based as an algorithm, using objective criteria to assign stroke causes into easily replicable subtypes.[26] The reported κ values for CCS range between 0.75 and 0.90 depending on the data source, number of cases, and number of raters.[8–11] In contrast, reports from independent investigators demonstrate only moderate reliability with κ values ranging between 0.42 and 0.54 for conventional etiologic classification systems.[27–31] Likewise, CCS provides higher discriminative validity compared with other classification systems, because the CCS generates more distinct subtypes with discrete clinical, genetic, and prognostic features.[26,32] However, the ability of etiologic classification, regardless of the system used, to unambiguously assign the cause of stroke is limited because of the absence of pathology data. This problem is greater for the category of CE as this category includes several abnormalities with discrete embolic potential. The CCS provided the flexibility to examine the effect of intensive BP reduction across a wide range of causes generated based on the strength of causal evidence. For instance, we stratified cardiac sources into high risk and low- or uncertain-risk CE. Likewise, we generated a new cryptogenic category that included low- or uncertain-risk cardiac pathologies. We found that the intervention effect was similar across such categories, suggesting that the etiologic mechanism of stroke is not a strong determinant of benefit from intensive BP reduction, with the caveat noted above about the small number of strokes in each category.

Limitations

This study was not powered to detect differences in stroke subtypes. The generalizability of these findings is limited to people with higher cardiovascular risk than the general population due to the enrollment criteria that excluded those with diabetes mellitus, prior stroke, and nursing home residents. A single adjudicator did the ischemic stroke subtype classifications using the CCS system, and intrarater reliability was not measured during the adjudication process.

In summary, we found similar numbers of stroke subtypes in the intensive BP control and standard control arms of SPRINT.

Perspectives

Hypertension leads to stroke through heart disease, especially atrial cardiopathy and atrial fibrillation, as well as large vessel atherosclerosis and small vessel arteriolosclerosis. In addition, longstanding hypertension may place the brain at elevated risk of ischemia if BP is treated aggressively. It is important to understand if intensive BP control affects the risk of certain types of stroke. In SPRINT, intensive BP control did not reduce the risk of stroke overall, but the study was stopped early and the number of strokes was

small. Different kinds of damage lead to diverse types of stroke, and intensive BP control could affect them in different ways. In this study, we compared the effect of intensive BP control to standard BP control on the risk of different types of stroke and found that hemorrhagic and ischemic subtypes were similar across treatment arms and neither BP control strategy showed greater benefits or harms. Future well-powered stroke studies are needed to understand the role of intensive BP control on different types of stroke in those at high risk of cardiovascular disease and longstanding hypertension.

ARTICLE INFORMATION

Received July 21, 2020; accepted January 10, 2021.

Affiliations

From the Division of Clinical Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (C.B.W.); Department of Neurology, University of Mississippi Medical Center, Jackson (A.P.A.); Department of Neurology, Case Western Reserve University, Cleveland, OH (A.L.); Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC (W.T.A., J.J.W.); Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School, Boston (H.A.); Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX (J.T.B.); Department of Medicine, Tulane School of Medicine, New Orleans, LA (J.C.); Department of Neurology, Mayo Clinic, Jacksonville, FL (J.F.M.); Department of Medicine, University of South Carolina School of Medicine, Columbia (S.P.); Department of Medicine, Georgetown University School of Medicine, Washington, DC (V.P.); Department of Medicine, UCLA School of Medicine, Los Angeles, CA (A.R.); Department of Medicine, Emory University School of Medicine, Atlanta, GA (M.S.); Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI (J.Y.); and Department of Medicine, University of Alabama at Birmingham (S.O.).

Sources of Funding

Supported by contracts (HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, and HHSN268200900049C) and an interagency agreement (A-HL-13-002-001) from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke. Several study sites were supported by Clinical and Translational Science Awards funded by the National Center for Advancing Translational Sciences of the NIH (Case Western Reserve University: UL1TR000439; Ohio State University: UL1RR025755; University of Pennsylvania: UL1RR024134 and UL1TR000003; Boston University: UL1RR025771; Stanford University: UL1TR000093; Tufts University: UL1RR025752, UL1TR000073, and UL1TR001064; University of Illinois: UL1TR000050; University of Pittsburgh: UL1TR000005; University of Texas Southwestern: 9U54TR000017-06; University of Utah: UL1TR000105-05; Vanderbilt University: UL1TR000445; George Washington University: UL1TR000075; University of California, Davis: UL1TR000002; University of Florida: UL1TR000064; University of Michigan: UL1TR000433; and Tulane University: P30GM103337 COBRE Award NIGMS). The trial was also supported in part with respect to resources and the use of facilities by the Department of Veterans Affairs.

Disclosures

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH), the Department of Veterans Affairs, or the US Government. The Systolic Blood Pressure Intervention Trial was funded by the National Institutes of Health (including the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke) under contracts HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, and HHSN268200900049C and interagency agreement A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. Azilsartan and chlorthalidone (combined with azilsartan) were provided by Takeda Pharmaceuticals International Inc. Additional support was provided through the following National Center for Advancing Translational Sciences clinical and translational science awards: UL1TR000439 (awarded to Case Western Reserve University); UL1RR025755 (Ohio State University); UL1RR024134 and UL1TR000003 (University of Pennsylvania); UL1RR025771 (Boston University); UL1TR000093 (Stanford University); UL1RR025752, UL1TR000073, and UL1TR001064 (Tufts University); UL1TR000050 (University of Illinois); UL1TR000005 (University of Pittsburgh); 9U54TR000017-06 (University of Texas Southwestern Medical Center); UL1TR000105-05 (University of Utah); UL1 TR000445 (Vanderbilt University); UL1TR000075 (George Washington University); UL1 TR000002 (University of California, Davis); UL1 TR000064 (University of Florida); and UL1TR000433 (University of Michigan); and by National Institute of General Medical Sciences, Centers of Biomedical Research Excellence award NIGMS P30GM103337 (awarded to Tulane University). Additional support also provided by R01AG055606, K01HL133468 (Dr Bress), K23NS107645 (Dr Miller), the Wake Forest Claude Pepper Center (P30AG021332), and the Alzheimer's Association. C.B. Wright reports royalties from UpToDate. A. Lerner reports grants from the National Institutes of Health and from the American Heart Association. H. Ay receives authorship royalties from UpToDate. H. Ay was involved in the design and development of the CCS algorithm. The CCS is a web-based algorithm licensed by the Massachusetts General Hospital that is free for academic use. H. Ay is an employee of Takeda Pharmaceutical Company Limited. J.F. Meschia receives payment for serving on the Editorial Board of the European Journal of Neurology. His work on the Carotid Revascularization Endarterectomy Versus Stenting Trial-2 trial and the DISCOVERY study are covered by grants from the NINDS. S. Oparil reports personal fees from 98point6, Inc, CinCor Pharma, Inc, Novo Nordisk, Inc, Pfizer, Inc, and ROX Medical, Inc., and research support from Bayer, Idorsia Pharmaceuticals, Ltd, and Novartis, outside of the area of this work; she serves as Editor-in-Chief of Current Hypertension Reports. A. Rastogi reports being on the following speaker's bureaus: Amgen, Fresenius Medical Care, Sanofi, Otsuka, Relypsa, Inc, Astrazeneca; advisory boards: Astrazeneca, Fresenius Medical Care-Vifor, GlaxoSmithKline, Otsuka, Relypsa, Rockwell Medical, Inc, Sanofi S.A; research support: Astrazeneca PLC, Bayer, GlaxoSmithKline, Kadmon Corporation, LLC, NIH, Omeros Inc., Pfizer, Protalix Biotherapeutics, Ltd, Reata Pharmaceuticals, Inc, Sanofi S.A. J. Yee reports honoraria from Baylor Scott and White Health, International Society of Hemodialysis, Washington University, St. Louis; consulting fees from Vasc-Alert, LLC., EBSCO, Fallon Medica, Pharma 1798, and Reata Pharmaceuticals; royalty payments from Elsevier and Vasc-Alert, LLC; and stock from Vasc-Alert, LLC. The other authors report no conflicts.

REFERENCES

1. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, Lackland DT, Lichtman JH, Mohl S, Sacco RL, et al; American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke*. 2013;44:2361–2375. doi: 10.1161/STR.0b013e31829734f2
2. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration.Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
4. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S; Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707–716. doi: 10.1097/00004872-200304000-00013
5. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
6. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939

7. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, Fine LJ, Goff DC Jr, Johnson KC, Killeen AA, et al; SPRINT Study Research Group. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014;11:532–546. doi: 10.1177/1740774514537404
8. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, et al. A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. *Stroke*. 2007;38:2979–2984. doi: 10.1161/STROKEAHA.107.490896
9. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688–697. doi: 10.1002/ana.20617
10. Arsava EM, Ballabio E, Benner T, Cole JW, Delgado-Martinez MP, Dichgans M, Fazekas F, Furie KL, Illoh K, Jood K, et al; International Stroke Genetics Consortium. The causative classification of stroke system: an international reliability and optimization study. *Neurology*. 2010;75:1277–1284. doi: 10.1212/WNL.0b013e3181f612ce
11. Ay H, Arsava EM, Andsberg G, Benner T, Brown RD Jr, Chapman SN, Cole JW, Delavaran H, Dichgans M, Engström G, et al. Pathogenic ischemic stroke phenotypes in the NINDS-stroke genetics network. *Stroke*. 2014;45:3589–3596. doi: 10.1161/STROKEAHA.114.007362
12. Hommel G. A stagewise rejective multiple test procedure based on a modified bonferroni test. *Biometrika*. 1988;75:383–386.
13. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH Jr. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2010;41:3–8. doi: 10.1161/STROKEAHA.109.566992
14. Clark D 3rd, Nicholls SJ, St John J, Elshazly MB, Ahmed HM, Khraishah H, Nissen SE, Puri R. Visit-to-visit blood pressure variability, coronary atheroma progression, and clinical outcomes. *JAMA Cardiol*. 2019;4:437–443. doi: 10.1001/jamacardio.2019.0751
15. Coresh J, Wei GL, McQuillan G, Brancati FL, Levey AS, Jones C, Klag MJ. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med*. 2001;161:1207–1216. doi: 10.1001/archinte.161.9.1207
16. Wong TY, Hubbard LD, Klein R, Marino EK, Kronmal R, Sharrett AR, Siscovick DS, Burke G, Tielsch JM. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002;86:1007–1013. doi: 10.1136/bjo.86.9.1007
17. Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM; Seconary Prevention of Small Subcortical Strokes Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382:507–515.
18. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. *Circulation*. 1975;53:720–727.
19. Zhang R, Witkowski S, Fu Q, Claassen JA, Levine BD. Cerebral hemodynamics after short- and long-term reduction in blood pressure in mild and moderate hypertension. *Hypertension*. 2007;49:1149–1155. doi: 10.1161/HYPERTENSIONAHA.106.084939
20. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585. doi: 10.1056/NEJMoa1001286
21. Beddhu S, Chertow GM, Greene T, Whelton PK, Ambrosius WT, Cheung AK, Cutler J, Fine L, Boucher R, Wei G, et al. Effects of intensive systolic blood pressure lowering on cardiovascular events and mortality in patients with Type 2 diabetes mellitus on standard glycemic control and in those without diabetes mellitus: reconciling results from ACCORD BP and SPRINT. *J Am Heart Assoc*. 2018;7:e009326. doi: 10.1161/JAHA.118.009326
22. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, et al; Sprint Mind Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321:553–561.
23. Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, et al; Sprint Mind Investigators for the SPRINT Research Group. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA*. 2019;322:524–534.
24. Perry HM Jr, Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, Kuller L, Pressel S, Stamler J, Probstfield JL. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 2000;284:465–471. doi: 10.1001/jama.284.4.465
25. Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, Davies R, Ostergren J, Probstfield J; HOPE Investigators. Heart outcomes prevention evaluation. Use of ramipril in preventing stroke: double blind randomised trial. *BMJ*. 2002;324:699–702. doi: 10.1136/bmj.324.7339.699
26. Arsava EM, Helenius J, Avery R, Sorgun MH, Kim GM, Pontes-Neto OM, Park KY, Rosand J, Vangel M, Ay H. Assessment of the predictive validity of etiologic stroke classification. *JAMA Neurol*. 2017;74:419–426. doi: 10.1001/jamaneurol.2016.5815
27. Goldstein LB, Jones MR, Matchar DB, Edwards LJ, Hoff J, Chilukuri V, Armstrong SB, Horner RD. Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. *Stroke*. 2001;32:1091–1098. doi: 10.1161/01.str.32.5.1091
28. Gordon DL, Bendixen BH, Adams HP Jr, Clarke W, Kappelle LJ, Woolson RF. Interphysician agreement in the diagnosis of subtypes of acute ischemic stroke: implications for clinical trials. The TOAST Investigators. *Neurology*. 1993;43:1021–1027. doi: 10.1212/wnl.43.5.1021
29. Atiya M, Kurth T, Berger K, Buring JE, Kase CS; Women's Health Study. Interobserver agreement in the classification of stroke in the Women's Health Study. *Stroke*. 2003;34:565–567. doi: 10.1161/01.str.0000054159.21017.7c
30. Meschia JF, Barrett KM, Chukwudelunzu F, Brown WM, Case LD, Kissela BM, Brown RD Jr, Brott TG, Olson TS, Rich SS, et al; Siblings with Ischemic Stroke Study (SWISS) Investigators. Interobserver agreement in the trial of org 10172 in acute stroke treatment classification of stroke based on retrospective medical record review. *J Stroke Cerebrovasc Dis*. 2006;15:266–272. doi: 10.1016/j.jstrokecerebrovasdis.2006.07.001
31. Selvarajah JR, Glaves M, Wainwright J, Jha A, Vail A, Tyrrell PJ. Classification of minor stroke: intra- and inter-observer reliability. *Cerebrovasc Dis*. 2009;27:209–214. doi: 10.1159/000196817
32. NINDS Stroke Genetics Network (SiGN); International Stroke Genetics Consortium (ISGC). Loci associated with ischaemic stroke and its subtypes (sign): a genome-wide association study. *Lancet Neurol*. 2016;15:174–184.