The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 23, 2026 VOL. 394 NO. 16

Three Low-Dose Antihypertensive Agents in a Single Pill after Intracerebral Hemorrhage

The Trident Research Group*

ABSTRACT

BACKGROUND

Blood-pressure reduction is the only proven treatment to prevent stroke. Whether a single pill that combines three antihypertensive drugs at low doses, in addition to standard antihypertensive treatment, can lower blood pressure more than standard care alone and reduce the risk of recurrent stroke after intracerebral hemorrhage is uncertain.

METHODS

We conducted a multinational, double-blind, randomized, placebo-controlled trial involving patients with a history of intracerebral hemorrhage. Patients were eligible for the trial if they had a systolic blood pressure of 130 to 160 mm Hg at baseline and were in clinically stable condition. After a 2-week active run-in phase during which all the patients received a once-daily pill containing three antihypertensive agents at low doses (telmisartan at 20 mg, amlodipine at 2.5 mg, and indapamide at 1.25 mg; the triple pill), the patients were randomly assigned to continue receiving the triple pill or to receive matching placebo. The primary outcome was the first recurrent stroke. Secondary outcomes included blood-pressure control, major cardiovascular events, death from cardiovascular causes, and safety.

RESULTS

Of 1670 patients who underwent randomization, 833 were assigned to receive the triple pill and 837 to receive placebo. The mean age of the patients was 58 years. At a median follow-up of 2.5 years, recurrent stroke had occurred in 38 patients (4.6%) in the triple-pill group and 62 (7.4%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.41 to 0.92; P=0.02). The mean systolic blood pressure during follow-up was 127 mm Hg and 138 mm Hg, respectively. The incidence of major cardiovascular events was lower with the triple pill than with placebo (6.6% vs. 9.8%; P=0.04). Serious adverse events occurred in 23.2% of the patients in the triple-pill group and 26.0% of those in the placebo group. Early discontinuation of the trial regimen due to an adverse event occurred in 13.6% and 6.0%, respectively. The most common adverse event leading to discontinuation was an increase of 20% or more in the serum creatinine level.

CONCLUSIONS

Among patients with intracerebral hemorrhage, treatment with a combination of three low-dose antihypertensive agents in a single pill, in addition to standard care, was associated with a lower incidence of recurrent stroke and major cardiovascular events than placebo. (Funded by the National Health and Medical Research Council of Australia and the Brazilian Ministry of Health; TRIDENT ClinicalTrials.gov number, NCT02699645; Australian New Zealand Clinical Trials Registry number, ACTRN12616000327482.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Craig S. Anderson can be contacted at canderson@georgeinstitute.org.au or at the George Institute for Global Health, University of New South Wales, P.O. Box 6366, Sydney, NSW 1466, Australia. Lili Song can be contacted at lili_song@fudan.edu.cn or at the Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Zhangheng Rd., Pudong District, Shanghai 201203, China.

*A complete list of members of the TRIDENT Research Group is provided in the Supplementary Appendix, available at NEJM.org.

John Chalmers and Anthony Rodgers contributed equally to this article.

N Engl J Med 2026;394:1571-82.
DOI: 10.1056/NEJMoa2515043

CME

A Quick Take is available at NEJM.org

Spontaneous intracerebral hemorrhage is a serious form of stroke with limited therapeutic options.[1] The only proven treatment to prevent first and recurrent intracerebral hemorrhage is effective blood-pressure reduction.[2,3] However, the benefits of intensive blood-pressure lowering and the preferred approach to treatment are uncertain.[2-5]

Although most survivors of stroke are discharged from the hospital with a prescription for medications to lower blood pressure, long-term blood-pressure control is generally inadequate owing to poor adherence to treatment, uncertainty surrounding the degree of benefit, varying guideline recommendations, insufficient intensification of treatment when blood pressure remains elevated, and therapeutic inertia.[6-11] Combination antihypertensive therapy delivered in a single pill holds considerable promise as a strategy to improve blood-pressure control.[12-14] We undertook the Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT) to evaluate the efficacy and safety of a single pill containing three antihypertensive drugs at low doses (telmisartan at 20 mg, amlodipine at 2.5 mg, and indapamide at 1.25 mg; hereafter referred to as the triple pill), in addition to standard care, in patients with a history of intracerebral hemorrhage.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this double-blind, randomized, placebo-controlled trial at 61 sites in 12 countries (Australia, Brazil, Georgia, Malaysia, the Netherlands, Nigeria, Singapore, Sri Lanka, Switzerland, Taiwan, the United Kingdom, and Vietnam). Details of the rationale and design of the trial, as well as the trial protocol and statistical analysis plan (available with the full text of this article at NEJM.org), have been published previously.[15,16] Funding was received through grants from the National Health and Medical Research Council of Australia and the Brazilian Ministry of Health. The trial was approved by a central ethics committee, by the ethics committee at each participating hospital, and by relevant national and local regulatory bodies. All the patients provided written informed consent. The George Institute for Global Health coordinated the trial in accordance with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice and performed the analyses. An independent data and safety monitoring committee oversaw the trial. The first author wrote the first draft of the manuscript with input from the last author. All the authors commented on drafts of the manuscript, approved the final version, and agreed to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

ELIGIBILITY

Adult patients (≥18 years of age) with a history of spontaneous (nontraumatic) intracerebral hemorrhage were recruited from academic hospitals, either from inpatient wards or outpatient clinics. Patients were eligible for inclusion if they were in clinically stable condition, had a systolic blood pressure of 130 to 160 mm Hg while seated and at rest (with the use of any blood-pressure–lowering therapy as appropriate), and had no contraindication to any individual component of the triple pill used in the trial. Patients who were taking an angiotensin-converting–enzyme inhibitor that could not be replaced with a suitable alternative, were unable to complete the trial procedures, or had abnormal test results for renal function, liver function, or both were ineligible for the trial.

All the patients who underwent screening for eligibility entered an active, single-blind run-in phase, during which the patients continued to receive background medical therapies as indicated, with the addition of a once-daily triple pill. The run-in phase lasted for 2 weeks, with the option to continue for another 2 weeks as needed to evaluate adherence to the trial regimen. This period was designed to ensure that the patients had at least 80% adherence to treatment, that the trial procedures and the side-effect profile of the triple pill were acceptable to the patients, and that the patients had no substantial change in tests of renal function. Patients whose serum creatinine level at the end of the run-in period and during follow-up was at least 20% higher than the level at the time of screening were excluded in accordance with a regulatory requirement.

RANDOMIZATION AND PROCEDURES

After the run-in period, eligible patients who had provided consent underwent centralized randomization in a 1:1 ratio, with stratification according to country, age, and systolic blood pressure at baseline, to receive the triple pill or matching placebo. Two different formulations of the triple pill and of matching placebo were used during different periods of the trial; details are provided in the Supplementary Appendix, available at NEJM.org. The trial protocol recommended adherence to local prescribing guidelines for hypertension, with a target for systolic blood pressure of less than 130 mm Hg or less than 140 mm Hg, for all the patients in both groups and provided options to achieve this target with additional concomitant medications.

Data about demographic characteristics, medical history, lifestyle factors, and medication use were collected at baseline (the time of randomization). Follow-up data were collected at 6 weeks and at 6 months after randomization and every 6 months thereafter for up to 72 months. Patients were assessed for any serious adverse events, adverse events of special interest occurring within the first 6 weeks, adherence to the trial regimen, and resting blood pressure as measured in the clinic. Protocol-specified blood tests were performed at 6 weeks and at the end of the trial. Patients received supplies of the triple pill or placebo every 6 months, with home delivery provided during the coronavirus disease 2019 (Covid-19) pandemic.

OUTCOMES

The primary outcome was the first recurrent stroke, assessed in a time-to-event analysis. The key secondary outcomes were blood-pressure control (defined as a systolic blood pressure of <130 mm Hg) at 6 months after randomization, a composite of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, whichever occurred first), and death from cardiovascular causes. Major cardiovascular events and death from cardiovascular causes were assessed in time-to-event analyses. Cardiovascular outcomes were adjudicated according to prespecified definitions by an independent committee whose members were unaware of the trial-group assignments.

Other cardiovascular outcomes included recurrent intracerebral hemorrhage, ischemic stroke, stroke of unknown type (no brain imaging or autopsy performed), and nonfatal myocardial infarction, assessed in time-to-event analyses; death related to stroke; death from any cause; and various other measures of blood-pressure control. Adherence to the trial regimen was assessed according to numbers of missed doses and pill counts, with an acceptable level of adherence defined as missing a dose on no more than 1 of 7 days in the week preceding the trial visit for at least 80% of follow-up visits. Safety outcomes included serious adverse events and adverse events of special interest (hypotension, syncope, headache, hyponatremia, hyperkalemia, injurious falls, and acute kidney injury), which were defined according to standard definitions.

STATISTICAL ANALYSIS

The trial was designed to recruit 3782 patients (1891 per group), which was expected to allow for the occurrence of 230 first recurrent strokes on the basis of a 2.5% annual incidence and a hazard ratio of 0.65. In early 2020, the steering committee made the decision to reduce the sample size to a total of 1500 patients owing to challenges in recruitment, as well as the publication of the results of the Japanese Recurrent Stroke Prevention Clinical Outcome (RESPECT) trial,[17] in which the large effect of intensive blood-pressure lowering on the incidence of intracerebral hemorrhage was consistent with that seen in the Perindopril Protection against Recurrent Stroke Study (PROGRESS).[18,19] This decision was made without any knowledge of the evolving treatment effect in the present trial. The revised sample size was estimated to provide the trial with 90% power to detect a hazard ratio of 0.50 when 100 primary-outcome events were accrued over a mean follow-up of 3 years with 5% loss to follow-up and 10% crossover between trial groups. In early 2024, the steering committee estimated that the target of at least 100 primary-outcome events would be reached in 2025 and planned to stop the trial at that point.

Efficacy analyses were conducted according to the intention-to-treat principle. The effect of the intervention on the primary outcome was estimated as a cause-specific hazard ratio and

95% confidence interval in a Cox proportional-hazards model, with the stratification factors used for randomization included as fixed covariates. Sensitivity analyses included the use of a Fine and Gray competing-risks model[20] and an extended adjusted analysis. Log-rank tests and analyses of differences in restricted mean survival time at multiple time points were undertaken if the proportional-hazards assumption was violated. For blood-pressure control at 6 months, a logistic-regression model was used with the randomization stratification factors as fixed covariates.[21] The primary analysis was performed with all missing blood-pressure data imputed as uncontrolled hypertension (systolic blood pressure ≥130 mm Hg); a sensitivity analysis used multiple imputations under the assumption that these data were missing at random (see the Supplementary Appendix).

All the tests were two-sided with a nominal level set at 5%. For the three key secondary efficacy outcomes, the familywise error rate was controlled with a sequential Holm–Šídák correction, whereby the P values were ordered and sequentially compared from smallest to largest with adjusted significance levels, with the process stopped at the first result that was nonsignificant.[22] No multiplicity adjustment was applied to the other outcomes, which were to be considered exploratory. For these outcomes, only point estimates of effect are presented with 95% confidence intervals, from which causal inference should not be made. The heterogeneity of treatment effects for the primary outcome and blood-pressure control was to be assessed across 10 prespecified subgroups, but this analysis was not possible for groups stratified according to race or ethnic group owing to small numbers of patients in the groups. The statistical analyses were performed with SAS software, version 8.3 or above (SAS Institute), and R software, version 4.0 or above (R Foundation).

RESULTS

PATIENTS AND TRIAL COHORTS

From September 28, 2017, to November 30, 2024, a total of 2206 patients with intracerebral hemorrhage were assessed for eligibility and entered the active run-in phase at 61 sites in 12 countries. At the end of the run-in period, 1670 patients at 57 sites in 10 countries underwent randomization, with 833 assigned to continue receiving the triple pill and 837 assigned to receive placebo. Patients in Switzerland and Vietnam who entered the active run-in phase did not undergo randomization. Randomization occurred at a median of 54 days (range, 27 to 127) after the index intracerebral hemorrhage (Table S1 and Figs. S1 and S2 in the Supplementary Appendix). Among the 536 patients (24.3%) who entered the run-in phase but did not undergo randomization, the most common reason was an increase of 20% or more in the serum creatinine level from baseline, which affected 147 patients (27.4%), with 68 (12.7%) having an increase of 30% or more. Other key reasons for exclusion were an investigator decision (17.2%), withdrawal of consent (14.7%), an unacceptable side-effect profile (4.9%), and poor adherence to the trial regimen (4.9%) (Table S2).

Among the patients who underwent randomization, the mean (±SD) age was 57.8±11.4 years, 563 (33.7%) were women, and 1213 (72.6%) were Asian, with 1114 (66.7%) residing in Sri Lanka. Patient characteristics were balanced between the two trial groups and were similar among the patients who underwent randomization and those who did not. The trial population was representative of patients with intracerebral hemorrhage with respect to age, sex, coexisting conditions, and ethnic group (Tables S3 through S14). The mean systolic blood pressure was 143±10 mm Hg at the beginning of the active run-in phase and 127±16 mm Hg at the end of the run-in. At the time of randomization, the mean number of blood-pressure–lowering drugs being used per patient was 1.2±1.1, with 57.8% of the patients using 2 drugs or more. An angiotensin-receptor blocker at a submaximal dose was the most common background therapy (used by 43.6% of the patients) (Table 1 and Table S15).

A total of 1401 patients (83.9%) were alive at the completion of the trial after a median follow-up of 2.5 years (interquartile range, 1.6 to 4.4) (Tables S16 and S17). Of 269 patients (16.1%) who did not complete the trial, 86 (5.1%) were lost to follow-up; the loss to follow-up was similar in the two trial groups (Table S18). Of 1524 patients for whom an assessment was possible,

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Triple Pill (N=833)	Placebo (N=837)
Age — yr	57.5±11.2	58.0±11.5
Female sex — no. (%)	275 (33.0)	288 (34.4)
Race — no. (%)†		
Asian	610 (73.2)	603 (72.0)
White	102 (12.2)	109 (13.0)
Black	96 (11.5)	100 (11.9)
Other	25 (3.0)	25 (3.0)
Medical history — no. (%)		
Hypertension	667 (80.1)	680 (81.2)
Previous ischemic stroke	33 (4.0)	33 (3.9)
Previous intracerebral hemorrhage before index event	56 (6.7)	56 (6.7)
Diabetes	181 (21.7)	188 (22.5)
Coronary artery disease	47 (5.6)	55 (6.6)
Current smoker	43 (5.2)	47 (5.6)
Median time from onset of symptoms (IQR) — days	52 (27–129)	54 (28–126)
Median volume of hematoma (IQR) — ml‡	12 (6–24)	11 (5–21)
Deep location of intracerebral hemorrhage — no. (%)§	653 (78.4)	635 (75.9)
BP management at baseline		
Single antihypertensive drug — no. (%)	252 (30.3)	262 (31.3)
Multiple antihypertensive drugs — no. (%)	488 (58.6)	478 (57.1)
Antihypertensive drugs per patient	1.2±1.1	1.2±1.1
Systolic BP at beginning of run-in phase	143±10	143±10
Diastolic BP at beginning of run-in phase	88±10	88±10

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Data are shown for the intention-to-treat population (all the patients who underwent randomization). BP denotes blood pressure, and IQR interquartile range.
† Race was reported by the patients.
‡ Data were reported by the investigators and were available for 192 patients in the triple-pill group and 200 patients in the placebo group (further details are provided in Table S3 in the Supplementary Appendix).
§ Data were reported by the investigators.

1317 (86.4%) had a level of adherence to the trial regimen that was considered to be acceptable (Table S19). Few protocol violations occurred, and those that did were mainly errors in dispensing of medication or placebo (Table S20). Over the entire time of follow-up, the mean systolic blood pressure was 127 mm Hg in the triple-pill group and 138 mm Hg in the placebo group; the modeled between-group difference in mean systolic blood pressure was 9 mm Hg (95% confidence interval [CI], 7 to 10) (Fig. 1 and Table S21). The mean diastolic blood pressure during follow-up was 82 mm Hg in the triple-pill group and 86 mm Hg in the placebo group (Fig. S3). Blood-pressure differences attenuated over time owing to increased use of concomitant antihypertensive drugs in the placebo group (Fig. 1).

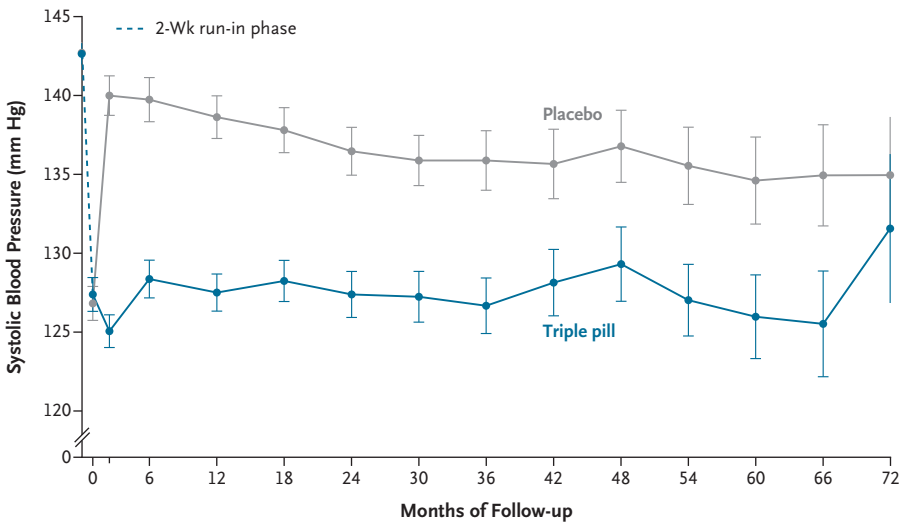
PRIMARY EFFICACY OUTCOME

A recurrent stroke occurred in 38 patients (4.6%) in the triple-pill group and in 62 patients (7.4%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.41 to 0.92; P=0.02) (Table 2 and Fig. 2). Despite

modest deviation in the proportional-hazards assumption that was related to the occurrence of few early events (Fig. S4), the result was unchanged after log-rank tests and analyses of differences in restricted mean survival time at multiple time points (Table S22). Similarly, the effect remained consistent when death from any cause was treated as a competing risk, as well as in a fully adjusted model (Table S23). The primary outcome appeared to be driven by effects on recurrent intracerebral hemorrhage, which occurred in 15 patients (1.8%) in the triple-pill group and 37 (4.4%) in the placebo group (hazard ratio, 0.40; 95% CI, 0.22 to 0.73) (Table 2 and Fig. S5). The effect was consistent across eight prespecified subgroups. Only the subgroups stratified according to blood pressure at baseline showed a degree of heterogeneity: the group with higher baseline blood pressure appeared to have a greater reduction in the risk of stroke with the triple pill than the group with lower baseline blood pressure (Fig. 3).

SECONDARY AND OTHER EFFICACY OUTCOMES

Blood-pressure control (systolic blood pressure <130 mm Hg) at 6 months was achieved in 416 patients (49.9%) in the triple-pill group and 221 (26.4%) in the placebo group (odds ratio, 3.15; 95% CI, 2.53 to 3.92; P<0.001). All other measures of blood-pressure control at different time points appeared to favor the triple-pill group (Tables S24 through S28). A major cardiovascular event occurred in 55 patients (6.6%) in the triple-pill group and 82 (9.8%) in the placebo group (hazard ratio for nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, 0.67; 95% CI, 0.47 to 0.94; P=0.04) (Table 2). Other cardiovascular outcomes, including death from cardiovascular causes, did not appear to differ substantially between the groups. The effects on mean systolic blood pressure during follow-up did not appear to differ among patients who received different formulations of the triple pill or placebo, and the results for blood-pressure control



Mean No. of Background Antihypertensive Drugs per Patient													
Placebo	1.2	1.5	1.7	1.8	1.8	1.9	1.9	2.0	2.0	2.0	1.9	2.0	2.1
Triple pill	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
No. of Patients													
Placebo	837	748	686	613	497	399	316	261	218	187	123	85	61
Triple pill	833	746	695	623	504	412	323	265	230	189	136	82	63

Figure 1. Mean Systolic Blood Pressure over Time.

I bars indicate 95% confidence intervals.

Table 2. Efficacy Outcomes and Safety.*

Outcome	Triple Pill (N=833)	Placebo (N=837)	Measure of Effect (95% CI)†	P Value
	no. of patients (%)			
Primary outcome				
Recurrent stroke	38 (4.6)	62 (7.4)	0.61 (0.41–0.92)‡	0.02§
Secondary outcomes¶				
BP control (SBP <130 mm Hg) at 6 mo	416 (49.9)	221 (26.4)	3.15 (2.53–3.92)‖	<0.001
Major cardiovascular event**	55 (6.6)	82 (9.8)	0.67 (0.47–0.94)	0.04
Death from cardiovascular causes	17 (2.0)	25 (3.0)	0.67 (0.36–1.25)	0.21
Other cardiovascular outcomes††				
Intracerebral hemorrhage	15 (1.8)	37 (4.4)	0.40 (0.22–0.73)	
Ischemic stroke	25 (3.0)	28 (3.3)	0.90 (0.52–1.54)	
Stroke of unknown type	0 (0.0)	2 (0.2)	NA	
Fatal stroke	3 (0.4)	12 (1.4)	0.25 (0.07–0.89)	
Nonfatal stroke	35 (4.2)	51 (6.1)	0.68 (0.44–1.05)	
Nonfatal myocardial infarction	5 (0.6)	7 (0.8)	0.69 (0.22–2.19)	
Death from any cause	54 (6.5)	72 (8.6)	0.75 (0.53–1.07)	
Safety				
Any adverse event of special interest by 6 wk‡‡	56 (6.7)	55 (6.6)		
Any serious adverse event§§	193 (23.2)	218 (26.0)	0.90 (0.74–1.09)¶¶	
Any adverse event leading to discontinuation of triple pill or placebo‖‖	113 (13.6)	50 (6.0)		

* Data are shown for the intention-to-treat population. NA denotes not assessed, and SBP systolic blood pressure.
† Values are hazard ratios unless otherwise noted.
‡ In sensitivity analyses, the hazard ratios were 0.61 (95% CI, 0.41 to 0.92) in a competing-risks model and 0.62 (95% CI, 0.41 to 0.93) in a fully adjusted model that included age, sex, level of functionality before symptom onset, level of education (<12 vs. ≥12 years), and history of hypertension, cardiac disease, and diabetes.
§ The P value from both the primary model analysis and a log-rank test was 0.02.
¶ Secondary outcomes are presented according to ordered level of significance with the use of Holm–Šídák correction to control the familywise error rate.
‖ The value shown is an odds ratio from a binomial-regression model with the stratification factors used at randomization included as fixed covariates and all missing data imputed as poor blood-pressure control (systolic blood pressure ≥130 mm Hg). Data were missing for 87 patients (10.4%) in the triple-pill group and 89 (10.6%) in the placebo group. Results of a sensitivity analysis with missing data imputed at random are shown in Table S23.
** Major cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes, whichever occurred first.
†† The total number of patients with a first occurrence of stroke of the indicated subtypes is greater than the number for the primary outcome because a single patient could have multiple different types of stroke.
‡‡ Adverse events of special interest were hypotension, syncope, headache, hyponatremia, hyperkalemia, injurious falls, and acute kidney injury.
§§ Serious adverse events were prespecified to include events that may be considered related to the trial regimen and that were life-threatening or resulted in hospitalization or prolongation of existing hospitalization, persistent or clinically significant disability or incapacity, medical or surgical intervention to prevent permanent impairment to bodily structure or function, or death. A patient could have more than one event. In all, 338 serious adverse events were reported in the triple-pill group and 399 in the placebo group.
¶¶ The value shown is the risk ratio for a serious adverse event in the triple-pill group as compared with the placebo group.
‖‖ The numbers include 59 patients in the triple-pill group and 21 in the placebo group who had a change in the serum creatinine level of 20% or more from the baseline value and discontinued the trial regimen according to a protocol requirement.

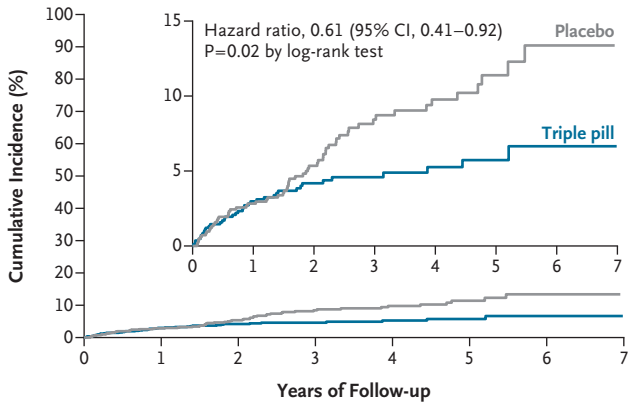


Figure 2. Cumulative Incidence of First Recurrent Stroke (Primary Outcome).
The inset shows the same data on an expanded y axis.

were consistent across prespecified subgroups (Figs. S6 and S7).

SAFETY

Serious adverse events occurred in 193 patients (23.2%) in the triple-pill group and 218 (26.0%) in the placebo group (Table 2 and Table S29). The incidence of adverse events of special interest in the first 6 weeks of follow-up was approximately 7% in both groups. Overall, early discontinuation of the trial regimen due to an adverse event occurred in 113 patients (13.6%) in the triple-pill group and 50 (6.0%) in the placebo group (Table S30). According to the protocol, patients were required to discontinue the trial regimen if their serum creatinine level rose by 20% or more, which occurred in 7.1% of the patients in the triple-pill group and in 2.5% of those in the placebo group. Discontinuation due to hypotension occurred in 3.0% in the triple-pill group and 0.6% in the placebo group, and discontinuation for other reasons occurred in 3.5% and 2.9%, respectively. A reduction in the estimated glomerular filtration rate occurred with initial use of the triple pill, but no evidence of increased progression of chronic kidney disease after week 6 or of an excess of severe kidney outcomes, such as an indication for dialysis, was observed (Table S31). Serum biochemical results and heart rate over time did not differ substantially between the groups (Figs. S9, S10, and S11 and Table S32).

DISCUSSION

Among patients with intracerebral hemorrhage, a combination of three low-dose antihypertensive agents in a single pill was associated with a lower incidence of recurrent stroke and major cardiovascular events than placebo, but not lower cardiovascular mortality, over a median follow-up of 2.5 years. The large treatment effect appeared to be driven by the prevention of recurrent intracerebral hemorrhage. Over the course of the trial, the patients assigned to receive the triple pill had better blood-pressure control than those assigned to receive placebo, with a mean systolic blood pressure in the triple-pill group of 127 mm Hg, approximately 9 mm Hg lower than that in the placebo group. This difference was achieved despite the use of background blood-pressure–lowering therapy in a high proportion of patients in both groups, according to standard care.

The triple pill achieved a large treatment effect: the number of patients who would need to be treated to prevent one stroke was 35 (95% CI, 24 to 53). This result is consistent with previous evidence suggestive of benefits from intensive blood-pressure lowering in patients with intracerebral hemorrhage. Among the 660 patients with previous intracerebral hemorrhage who participated in PROGRESS, which compared active treatment (perindopril with or without indapamide) with placebo over a mean of 4 years, a reduction in blood pressure of 11/4 mm Hg was associated with a reduction in the risk of stroke of 49% (95% CI, 18 to 66).[18,19] Open-label trials of more intensive blood-pressure lowering as compared with less intensive lowering showed large reductions in the risk of recurrent intracerebral hemorrhage with more intensive lowering among participants with previous ischemic stroke or intracerebral hemorrhage.[17,23,24] Finally, cohort and mendelian randomization studies show particularly strong associations between blood pressure and intracerebral hemorrhage, with each reduction of 10 mm Hg in systolic blood pressure associated with a reduction of approxi-

mately 40% in the risk of intracerebral hemorrhage.[25,26]

The trial had some limitations. The majority of the patients were from Sri Lanka, which may limit the generalizability of the results. However, the blood-pressure reductions with the triple pill were consistent among patients from different participating countries and different demographic groups. The age, sex, and disease profile of the trial population were similar to those of patients with intracerebral hemorrhage worldwide.[27,28] The placebo group in this trial had a mean systolic blood pressure of approximately 140 mm Hg, which was similar to that among patients who underwent follow-up at a large tertiary care center in the United States after intracerebral hemorrhage.[9] The only treatment for stroke prevention after intracerebral hemorrhage is lowering blood pressure, so the likelihood of income-dependent disparities in the care received by the patients in the trial is small.

The active run-in phase was designed to provide efficiency gains in a long-term prevention trial. This approach means that the findings apply only to patients who were able to adhere to an initial 2 weeks of therapy without adverse effects. We were required by a regulatory agency to change the protocol to exclude patients who

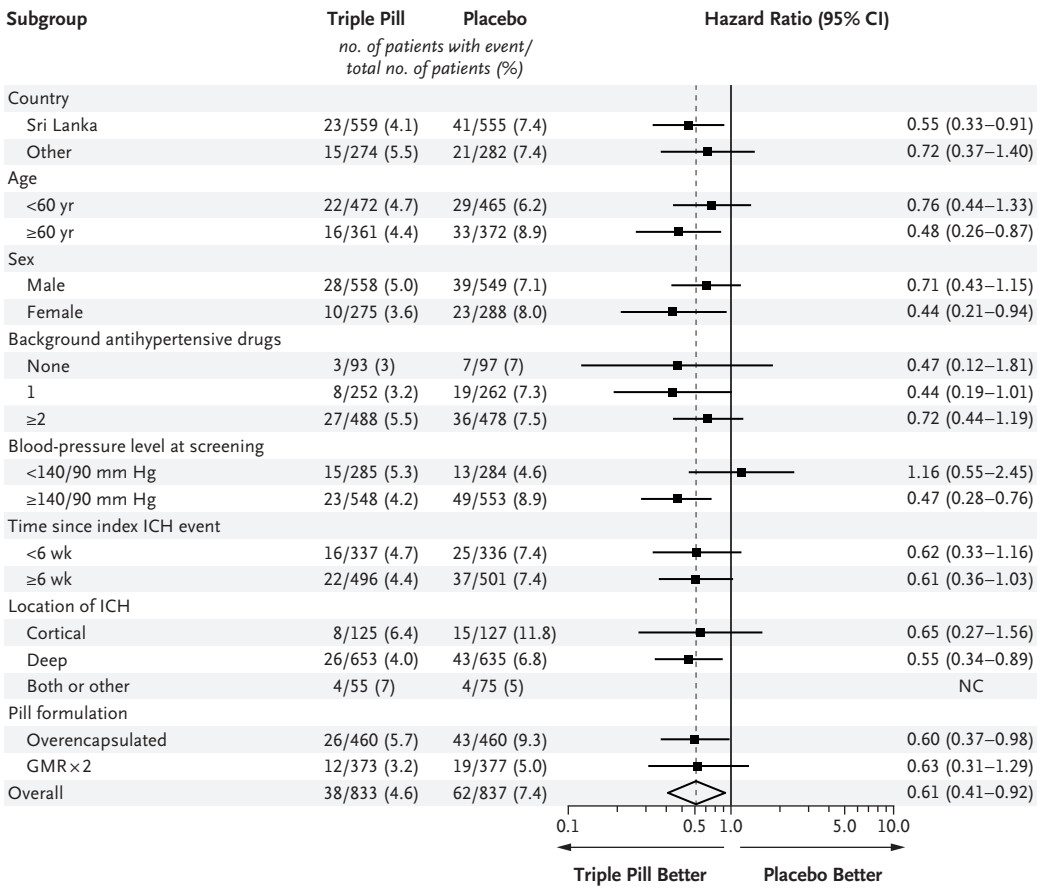


Figure 3. Primary Outcome According to Prespecified Subgroups.

Subgroups were stratified according to characteristics recorded at the start of the active run-in phase. A hazard ratio was not calculated (NC) for the subgroup with both or other as the location of intracerebral hemorrhage because of the small numbers of patients. GMRx2 indicates a bespoke triple pill and matching placebo manufactured for the trial. ICH denotes intracerebral hemorrhage.

had an increase in serum creatinine levels of 20% or more during the run-in phase and follow-up. However, evidence now suggests that such changes in serum creatinine levels are predominantly the result of a hemodynamic response and are not necessarily associated with long-term progression of kidney disease, and that an increase of at least 30% in the serum creatinine level is a more reasonable threshold to trigger clinical evaluation and consideration of dose reduction or cessation.[29,30] The triple pill was associated with only a small excess of discontinuation due to symptomatic adverse effects. The number of recurrent strokes in the first year after randomization was not large enough to determine definitively when the event curves for the two groups separated; however, the manifestation of clear benefits of the triple pill after 1 year is consistent with the results of a recent open-label trial of long-term intensive blood-pressure control in patients with a history of stroke in China.[24]

Among patients with intracerebral hemorrhage, treatment with a combination of three low-dose antihypertensive agents in a single pill for a median of 2.5 years was associated with a lower incidence of recurrent stroke than placebo owing to improved blood-pressure control, as well as a lower incidence of major cardiovascular events.

These results were presented at the 17th World Stroke Congress in Barcelona, October 22 to 24, 2025.

Supported by project grants (APP1149987, APP1103886, APP1159055, GNT1081356, GNT1175861, GNT2033176, and GNT2033235) from the National Health and Medical Research Council of Australia and by a grant (NUP 25000.169363/2023-94) from the Brazilian Ministry of Health Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde, Hospital Moinhos de Vento. George Medicines provided the GMRx2 formulation of the triple pill and matching placebo.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the patients and the clinical and research teams, and Prof. Kazunori Toyoda and Prof. Masatoshi Koga at the National Cerebral and Cardiovascular Center, Osaka, Japan, for their early efforts in trying to set up the trial in Japan.

AUTHOR INFORMATION

Craig S. Anderson, M.B., B.S., Ph.D.,[1-3] Clara K. Chow, M.B., B.S., Ph.D.,[4] H. Asita de Silva, M.B., B.S., D.Phil.,[5] Bimsara Senanayake, M.D.,[6] Kolawole Wahab, M.B., B.S., M.D.,[7] Rustam Al-Shahi Salman, Ph.D., F.Med.Sci.,[8] Catharina J.M. Klijn, M.D., Ph.D.,[9] Sheila Ouriques Martins, M.D., Ph.D.,[10,11] Natalie Espinosa, M.Sc.,[2] Lauren Kuhles, B.N.,[2] Laurent Billot, M.Res.,[2,12] Hisatomi Arima, M.D., Ph.D.,[13] Cheryl Carcel, M.D., Ph.D.,[2] Xia Wang, Ph.D.,[2] Qiang Li, M.Biostat.,[2] Sana Shan, M.Biostat.,[2] Mathangi Shanthakumar, M.Sc.,[2] Huy Thang Nguyen, M.D.,[14] Dilum Palliyaguruge, M.D.,[15] Janaka Peiris, M.D.,[16] Udaya K. Ranawaka, M.D.,[17] Senaka Bandusena, M.D.,[18] Thambipillai Rajendiran, M.D.,[18] Darshana Wijegunasinghe, M.D.,[17] Harsha Gunasekera, M.D.,[19] Indunil Wijeweera, M.D.,[16] Athula Dissanayake, M.D.,[20] Ajantha Keshavaraj, M.D.,[21] Reginald O. Obiako, M.D., Ph.D.,[22] Rufus Akinyemi, M.D., Ph.D.,[23] Luiz Nasi, M.D., Ph.D.,[24] Rodrigo Bazan, M.D., Ph.D.,[25] Carla Heloisa Cabral Moro, M.D.,[26] Mariana Battaglini, M.D.,[27] Viviane Zétola, M.D., Ph.D.,[28] Wan Chung Law, M.D.,[29] Yuen Kang Chia, M.D.,[30] Dennis Cordato, M.B., B.S., Ph.D.,[31,32] Rohan Grimley, M.B., B.S., Ph.D.,[33,34] Anuradha Dahanayaka, M.Sc.,[35] Sonali Liyanagamage, M.Sc.,[35] Nilukshi Fernando, M.D.,[36] Nihara Abdul Rasheed, M.D.,[37] Nodar Kakabadze, M.D.,[38] Maia Beridze, M.D., Ph.D.,[39] Mythily Aravinthan, M.D.,[6] Vithoosan Sahathevan, M.D.,[6] Devasmitha Wijesundara, M.D.,[6] Pramith Ruwanpathirana, M.D.,[6] Wan Asyraf Wan Zaidi, M.Med.,[40] Tinatin Kherkheulidze, M.D.,[38] Urs Fischer, M.D.,[41] Ana Cláudia de Souza, M.D., Ph.D.,[11] Tsong-Hai Lee, M.D., Ph.D.,[42,43] Christopher Chen, M.D.,[44] Octavio Pontes-Neto, M.D., Ph.D.,[45] Thompson Robinson, M.B., Ch.B.,[46,47] Jiguang Wang, M.D., Ph.D.,[48] Sharon L. Naismith, D.Psych.,[49,50] Michael Barnett, M.B., B.S., Ph.D.,[3,49] Carlos Delfino, M.D.,[2,51] Shoujiang You, M.D., Ph.D.,[52] Feifeng Liu, M.D., Ph.D.,[53] Candice Delcourt, M.D., Ph.D.,[2,54] Tom J. Moullaali, M.B., B.S., Ph.D.,[8] Tim Wilkinson, M.B., Ch.B., Ph.D.,[8] Neil Watson, M.B., Ch.B., M.D.,[8] Karla Santo, M.D., Ph.D.,[55] Qiao Han, M.D., Ph.D.,[2] Mariana Almudi Souza, M.D.,[24] Wilmar M.T. Jolink, M.D., Ph.D.,[56] Anderson Berni Cristofari, M.D.,[57] Zien Zhou, M.D., Ph.D.,[2] Floris H. Schreuder, M.D., Ph.D.,[9] Richard I. Lindley, M.B., B.S., M.D.,[2,4] Manuela Armenis,[2] Mark Woodward, Ph.D.,[2,58] Ruth Freed, M.Sc.,[2] Lili Song, M.D., Ph.D.,[1,2] John Chalmers, M.B., B.S., Ph.D.,[2] and Anthony Rodgers, M.B., Ch.B., Ph.D.[2,58]

[1] Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai; [2] George Institute for Global Health, University of New South Wales, Sydney; [3] Neurology Department, Royal Prince Alfred Hospital, Sydney; [4] Westmead Applied Research Centre, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead, NSW, Australia; [5] Clinical Trials Unit, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka; [6] Institute of Neurology, National Hospital of Sri Lanka, Colombo, Sri Lanka; [7] Department of Medicine, University of Ilorin, Ilorin, Nigeria; [8] Institute for Neuroscience and Cardiovascular Research, University of Edinburgh, Edinburgh; [9] Department of Neurology, Donders Institute for Brain, Cognition, and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands; [10] Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [11] Neurology Service Hospital Moinhos de Vento, Porto Alegre, Brazil; [12] School of Public Health, University of Bordeaux, Bordeaux, France; [13] Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan; [14] Stroke Unit, 115 Hospital, Ho Chi Minh City, Vietnam; [15] Neurology Department, Teaching Hospital Kurunegala, Kurunegala, Sri Lanka; [16] Neurology Department, National Hospital, Kandy, Sri Lanka; [17] Department of Medicine, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka; [18] Neurology Department, Kalubowila (Colombo South) Teaching Hospital, Dehiwala, Sri Lanka; [19] Neurology Department, Sri Jayewardenepura General Hospital, Nugegoda, Sri Lanka; [20] Neurology Department, Karapitiya Teaching Hospital, Galle, Sri Lanka; [21] Neurology Department, Jaffna Teaching Hospital, Jaffna, Sri Lanka; [22] Department of Medicine, Ahmadu Bello

University Teaching Hospital, Zaria, Nigeria; [23] Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria; [24] Neurology Department, Hospital Moinhos de Vento, Porto Alegre, Brazil; [25] Department of Neuroscience and Mental Health, Botucatu School of Medicine, Universidade Estadual Paulista, Botucatu, Brazil; [26] Neurology Department, Clinica Neurológica e Neurocirurgica de Joinville, Joinville, Brazil; [27] Neurology Department, Hospital de Base São José do Rio Preto, São José do Rio Preto, Brazil; [28] Federal University of Parana, Curitiba, Brazil; [29] Neurology Department, Sarawak General Hospital, Jalan Hospital, Kuching, Malaysia; [30] Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia; [31] Neurology Department, Liverpool Hospital, Liverpool, NSW, Australia; [32] Faculty of Medicine, University of New South Wales, Sydney; [33] Department of Neurology, Sunshine Coast University Hospital, Sunshine Coast, QLD, Australia; [34] School of Medicine and Dentistry, Griffith University, Birtinya, QLD, Australia; [35] RemediumOne Contract Research Organization, Colombo, Sri Lanka; [36] Peradeniya Teaching Hospital, Kandy, Sri Lanka; [37] Neurology Department, Gampaha District General Hospital, Gampaha, Sri Lanka; [38] Urgent Neurological Clinic "Neurology," Tbilisi State Medical University, Tbilisi, Georgia; [39] First University Clinic, Tbilisi State Medical University, Tbilisi, Georgia; [40] Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [41] Department of Neurology, University Hospital Bern and University of Bern, Bern, Switzerland; [42] Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [43] College of Medicine, Chang Gung University, Taoyuan, Taiwan; [44] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [45] Department of Neurosciences and Behavioral Sciences, Ribeirao Preto School of Medicine, University of São Paulo, Ribeirao Preto, Brazil; [46] College of Life Sciences, University of Leicester, Leicester, United Kingdom; [47] National Institute for Health and Care Research Biomedical Research Centre, University of Leicester, Leicester, United Kingdom; [48] Center for Epidemiological Studies and Clinical Trials, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai; [49] Brain and Mind Centre, University of Sydney, Camperdown, NSW, Australia; [50] Charles Perkins Centre, University of Sydney, Sydney; [51] Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile; [52] Department of Neurology and Clinical Research Center of Neurologic Disease, Second Affiliated Hospital of Soochow University, Suzhou, China; [53] Department of Neurology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai; [54] Department of Clinical Medicine, Faculty of Medicine, Health, and Human Sciences, Macquarie University, Sydney; [55] Academic Research Organization, Hospital Israelita Albert Einstein, São Paulo; [56] Department of Neurology, Isala Hospital, Zwolle, the Netherlands; [57] Universidade de Lisboa, Lisbon, Portugal; [58] George Institute for Global Health, School of Public Health, Imperial College London, London.

REFERENCES

1. GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol 2024;23:973-1003.
2. Steiner T, Purrucker JC, Aguiar de Sousa D, et al. European Stroke Organisation (ESO) and European Association of Neurosurgical Societies (EANS) guideline on stroke due to spontaneous intracerebral haemorrhage. Eur Stroke J 2025;10:1007-86.
3. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke 2022;53(7):e282-e361.
4. Writing Committee Members, Jones DW, Ferdinand KC, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2025;152(11):e114-e218.
5. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. Eur Heart J 2024;45:3912-4018.
6. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021;398:957-80.
7. Zhang M, Shi Y, Zhou B, et al. Prevalence, awareness, treatment, and control of hypertension in China, 2004-18: findings from six rounds of a national survey. BMJ 2023;380:e071952.
8. McGurgan IJ, Kelly PJ, Turan TN, Rothwell PM. Long-term secondary prevention: management of blood pressure after a transient ischemic attack or stroke. Stroke 2022;53:1085-103.
9. Biffi A, Anderson CD, Battey TW, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. JAMA 2015;314:904-12.
10. Bonello K, Nelson APK, Moullaali TJ, Al-Shahi Salman R. Prescription of blood pressure lowering treatment after intracerebral haemorrhage: prospective, population-based cohort study. Eur Stroke J 2021;6:44-52.
11. Zahuranec DB, Wing JJ, Edwards DF, et al. Poor long-term blood pressure control after intracerebral hemorrhage. Stroke 2012;43:2580-5.
12. Rodgers A, Salam A, Schutte AE, et al. Efficacy and safety of a novel low-dose triple single-pill combination compared with placebo for initial treatment of hypertension. J Am Coll Cardiol 2024;84:2393-403.
13. Chow CK, Atkins ER, Hillis GS, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. Lancet 2021;398:1043-52.
14. Wang N, Rueter P, Salam A, et al. Low-dose combinations with 3 or 4 blood pressure-lowering medications for the treatment of hypertension. JACC Adv 2025;4:101883.
15. Anderson CS, Rodgers A, de Silva HA, et al. Triple therapy prevention of recurrent intracerebral disease events trial: rationale, design and progress. Int J Stroke 2022;17:1156-62.
16. Billot L, Shan S, Rodgers A, Anderson C, Bliss R. Triple therapy prevention of recurrent intracerebral disease events trial (TRIDENT). August 25, 2025 (https://www.medrxiv.org/content/10.1101/2025.08.24.25334319v1). preprint.
17. Kitagawa K, Yamamoto Y, Arima H, et al. Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: a randomized clinical trial and meta-analysis. JAMA Neurol 2019;76:1309-18.
18. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41.

19. Arima H, Chalmers J, Woodward M, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens 2006;24:1201-8.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509 (https://www.jstor.org/stable/2670170).
21. Chung S-C, Pujades-Rodriguez M, Duyx B, et al. Time spent at blood pressure target and the risk of death and cardiovascular diseases. PLoS One 2018;13(9):e0202359.
22. Abdi H. Holm's sequential Bonferroni procedure. In: Salkind NJ, ed. Encyclopedia of research design. Thousand Oaks, CA: Sage, 2010:1-8.
23. The SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet 2013;382:507-15.
24. Li J, Lei L, Li Y, et al. Effect of intensive blood pressure control on stroke: a prespecified secondary analysis of the ESPRIT trial. J Am Coll Cardiol 2025;86:1405-17.
25. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 2003;21:707-16.
26. Clarke R, Wright N, Walters R, et al. Genetically predicted differences in systolic blood pressure and risk of cardiovascular and noncardiovascular diseases: a Mendelian randomization study in Chinese adults. Hypertension 2023;80:566-76.
27. Ma L, Hu X, Song L, et al. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. Lancet 2023;402:27-40.
28. Kittner SJ, Sekar P, Comeau ME, et al. Ethnic and racial variation in intracerebral hemorrhage risk factors and risk factor burden. JAMA Netw Open 2021;4(8):e2121921.
29. Malhotra R, Craven T, Ambrosius WT, et al. Effects of intensive blood pressure lowering on kidney tubule injury in CKD: a longitudinal subgroup analysis in SPRINT. Am J Kidney Dis 2019;73:21-30.
30. Neuen BL, Tighiouart H, Heerspink HJL, et al. Acute treatment effects on GFR in randomized clinical trials of kidney disease progression. J Am Soc Nephrol 2022;33:291-303.