



Intensive blood pressure lowering after spontaneous intracerebral haemorrhage for secondary stroke prevention (RECAP-ICH): a systematic review and individual participant data meta-analysis

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Summary

Background Blood pressure-lowering treatment prevents stroke after spontaneous intracerebral haemorrhage. However, there is uncertainty over the consistency of the effects across clinically relevant subgroups as well as the time course over which benefits accrue. We aimed to pool individual-level data across diverse settings and treatment strategies to quantify the size, heterogeneity, and timing of the effects of blood pressure-lowering treatment for the secondary prevention of major cardiovascular endpoints in patients with a history of intracerebral haemorrhage.

Methods We did a systematic review and meta-analysis of identified randomised controlled trials evaluating long-term blood pressure-lowering for secondary prevention in adults with a history of spontaneous intracerebral haemorrhage. We searched Embase and Ovid MEDLINE, from database inception to Jan 25, 2026, with two authors (YG and MJV) independently screening titles, abstracts, and full-text articles for eligibility. Trials were eligible if they enrolled adults (aged 18 years or older) with previous spontaneous intracerebral haemorrhage, randomly assigned participants to fixed-dose antihypertensive therapy or an intensive, titrated target-based blood pressure-lowering strategy versus placebo or standard blood pressure management, and reported clinical outcomes. Stroke trials had available individual participant data for subgroups of at least 100 participants with acute intracerebral haemorrhage. Methodological quality was assessed using the Cochrane Risk of Bias 2 tool. The primary outcome was first recurrent stroke of any type. We pooled individual participant data with a one-stage intention-to-treat meta-analysis using Cox proportional hazards models, incorporating a random effect for trial and adjustment for prespecified covariates. Prespecified subgroup analyses included demographic variables and baseline blood pressure, with formal tests for treatment-by-subgroup interaction. We estimated the time to benefit for a clinically meaningful absolute risk reduction, defined as 1% risk difference. The protocol is registered with PROSPERO (CRD420251274994).

Findings Of 236 records screened, 37 trials were retrieved, 24 were assessed for eligibility after duplicates were removed, and four eligible trials provided individual participant data for analysis. 2944 participants were included in the meta-analysis. The mean age was 59.6 years (SD 10.6), 972 (33.0%) were female, 1972 (67.0%) were male, 2218 (75.3%) were Asian, and the median follow-up was 42.0 months (IQR 24.0–66.0). The mean systolic blood pressure difference between blood pressure-lowering treatment and control over follow-up was 11.2 mm Hg (95% CI 10.7–11.7). Intensive blood pressure-lowering reduced the hazard of first recurrent stroke of any type compared with control (96 [6.5%] of 1487 participants versus 152 [10.4%] of 1457 participants; adjusted hazard ratio [HR] 0.62, 95% CI 0.48–0.80; $p=0.0002$). This finding was driven by fewer recurrent intracerebral haemorrhage events (33 [2.2%] of 1487 participants on blood pressure lowering-treatment versus 81 [5.6%] of 1457 control participants; adjusted HR 0.39, 95% CI 0.26–0.59; $p<0.0001$). Serious adverse events occurred in 429 (28.9%) of 1487 patients in the intensive group and 481 (33.0%) of 1457 patients in the control group. Treatment effects were consistent across prespecified subgroups (eg, age, sex, region, background blood pressure-lowering treatment, baseline blood pressure, and time since index event). The time to achieve a 1% absolute benefit was estimated to be 6.1 months (95% CI 3.5–14.8).

Interpretation Intensive blood pressure-lowering treatment after spontaneous intracerebral haemorrhage reduces recurrent stroke, mainly by preventing recurrent haemorrhage, without evidence of excess serious adverse events. Effects were consistent across patient characteristics, including time since the index event and baseline level of blood pressure. The early accrual and durability of benefit after treatment initiation strengthens the case for sustained long-term blood pressure control as the cornerstone of secondary prevention after intracerebral haemorrhage.

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Research in context

Evidence before this study

We searched Embase and Ovid MEDLINE from database inception to Jan 25, 2026, without language restriction to identify randomised controlled trials and systematic review or meta-analysis of randomised controlled trials of blood pressure lowering for secondary prevention in adults with intracerebral haemorrhage. The search strategy used the following keywords: intracerebral haemorrhage, blood pressure lowering interventions, secondary prevention, and randomised controlled trials. We also screened reference lists of relevant reviews and potentially eligible studies. TRIDENT was the only trial conducted exclusively in patients with a history of intracerebral haemorrhage. We also identified four large secondary prevention blood pressure-lowering trials (ESPRIT, PROGRESS, RESPECT, and PATS) that reported outcomes in an intracerebral haemorrhage subgroup that included at least 100 patients. Individual randomised controlled trials have shown a linear relationship between blood pressure reduction and risk of recurrent stroke, with the benefits being greater for intracerebral haemorrhage than ischaemic stroke. In the PROGRESS trial, for the 660 participants whose baseline event was intracerebral haemorrhage, the relative risk reduction for recurrent stroke of any type was 49% (95% CI 18–68) compared with 26% (12–38) in the 4262 participants with previous ischaemic stroke, despite similar reductions in systolic blood pressure of 9 mm Hg. In RESPECT, recurrent intracerebral haemorrhage differed substantially between intensive (<120 mm Hg; one event) and standard (<140 mm Hg; 11 events) systolic blood pressure targets in the subgroup of 189 participants with previous intracerebral haemorrhage over a mean follow-up of 3.9 years. However, these trials were not powered to analyse intracerebral haemorrhage subgroup outcomes, limiting the precision of the estimates and the assessment of heterogeneity. Previous meta-analyses established the benefits of blood-pressure lowering treatment

after stroke, but intracerebral haemorrhage-specific evidence remained limited. Only the Cochrane review reported an analysis among participants with intracerebral haemorrhage as the qualifying event, and this estimate was derived entirely from the PROGRESS trial rather than from a pooled analysis of multiple trials.

Added value of this study

This meta-analysis pooled harmonised individual participant data from four randomised controlled trials with 2944 patients with spontaneous intracerebral haemorrhage, providing more precise estimates of the benefits and harms of intensive blood pressure-lowering for secondary prevention after an intracerebral haemorrhage than is possible from any single trial. Intensive blood pressure-lowering reduced recurrent stroke of any type and major cardiovascular events, with the greatest reduction being in recurrent intracerebral haemorrhage. There was no evidence of any increase in serious adverse events. Treatment effects were broadly consistent across prespecified subgroups of age, sex, ethnicity, history of hypertension, baseline blood pressure, and time since intracerebral haemorrhage. Furthermore, time-to-benefit modelling showed that a clinically meaningful absolute reduction in stroke events emerged within the first year and continued to accumulate over time.

Implications of all the available evidence

The available evidence supports sustained, effective long-term blood pressure control after spontaneous intracerebral haemorrhage as the foundation of secondary prevention, with clinically meaningful reductions in recurrent stroke achievable over a short time horizon. These data do not establish preferential use of a particular drug combination or a universal systolic target less than 120 mm Hg. Future research is required to refine implementation pathways (including early post-discharge titration) and evaluate long-term tolerability in frail and disadvantaged patient subgroups.

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Introduction

Patients who survive an acute spontaneous, non-traumatic intracerebral haemorrhage are at high risk of recurrent stroke (haemorrhagic or ischaemic) and other serious cardiovascular events (non-fatal myocardial infarction or vascular death), with an estimated annual risk of 7–19%.^{1–4} Effective control of blood pressure is central to preventing recurrent stroke. This recommendation was first indicated by the results of a subgroup of participants in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) with acute intracerebral haemorrhage at baseline,⁵ in whom a 11 mm Hg decrease in systolic blood pressure conferred a 49% (95% CI 18–68) reduction in recurrent stroke.^{6,7} Most recently, the Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT),^{8,9} undertaken specifically in patients with a history of acute intracerebral haemorrhage, showed that the recommended treatment target could be readily

reached with a single, triple low-dose antihypertensive combination pill, which in turn effectively reduced the risk of recurrent stroke. Guidelines recommend a long-term blood pressure control target of less than 130/80 mm Hg in such a high-risk group.¹⁰ However, in practice, published cohort data suggest that long-term hypertension control after intracerebral haemorrhage remains suboptimal even in high-resource settings. In routine care, adherence barriers frequently prevent patients from reaching or sustaining the recommended target blood pressure.^{11,12} TRIDENT also showed that the risk of recurrent stroke remained high in control participants despite receipt of antihypertensive therapy, including multiple agents in a substantial proportion of patients.⁹ Although TRIDENT provides important randomised evidence to guide clinical practice, uncertainties remain, including whether the effects of intensive blood pressure-lowering treatment vary by age,

sex, race, and presence of several key comorbid conditions. The time course over which the benefit of blood pressure control accrues is also unclear. To address these gaps, we conducted an individual participant data meta-analysis of randomised controlled trials, identified from a systematic review, to investigate intensive long-term blood pressure-lowering for secondary prevention of major cardiovascular endpoints after intracerebral haemorrhage.

Methods

Search strategy and selection criteria

For this meta-analysis, we conducted a systematic review according to a prespecified protocol¹³ to identify randomised controlled trials evaluating long-term blood pressure-lowering treatment for secondary prevention in adults with a history of spontaneous intracerebral haemorrhage. We searched Embase and Ovid MEDLINE, from data inception to Jan 25, 2026. Searches were restricted to human studies and combined terms for intracerebral haemorrhage, blood pressure lowering interventions, secondary prevention, and randomised controlled trials, with no language restrictions. Precise search terms are in the appendix (pp 3–4). We also screened reference lists of relevant reviews and potentially eligible studies. Grey literatures were identified from the reference list of ESPRIT, PROGRESS, RESPECT, TRIDENT, PATS, and Individual Data Analysis of Antihypertensive Intervention Trials (INDANA). We also searched of ClinicalTrials.gov for unpublished studies. The protocol is registered with PROSPERO (CRD420251274994).

Eligible trials enrolled adults (aged 18 years or older) with a history of spontaneous intracerebral haemorrhage, randomly assigned participants to fixed-dose antihypertensive therapy or an intensive, titrated target-based blood pressure-lowering strategy (eg, intensive systolic blood pressure-lowering to <120 mm Hg) versus placebo or contemporaneous guideline-based blood pressure management, and reported clinical outcomes. Stroke trials were eligible if individual participant data were available for subgroups with at least 100 patients with acute intracerebral haemorrhage. For trials including patients other than those with intracerebral haemorrhage, we only included patients with previous intracerebral haemorrhage. Patients with secondary intracerebral haemorrhage (eg, due to trauma, tumour, or vascular malformation) were excluded.

Two authors (YG and MJV) independently screened titles and abstracts and assessed full-text articles for eligibility. A third author (XW) was consulted if there were any conflicts. The protocol and a letter of invitation were sent to investigators of eligible studies, inviting them to join the RECAP-ICH Collaboration and share individual participant data. To ensure transparency, collaborators sharing data with RECAP-ICH were asked to sign a data transfer agreement for the predefined and appropriate use of their data according to our protocol.

The authors of each trial performed the individual participant data extraction, and the pooling and analysis was undertaken at The George Institute for Global Health. Three authors (XW, YG, and MJV) compared the individual participant data with published results to confirm completeness and accuracy, resolving queries with trial investigators. They also harmonised the trial datasets and outcome definitions using agreed nomenclature before analysis.

Data analysis

The primary outcome was first recurrent stroke of any type (ischaemic, haemorrhagic, or unknown type). Secondary outcomes were major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death), intracerebral haemorrhage, ischaemic stroke, stroke of unknown type, non-fatal stroke, non-fatal myocardial infarction, cardiovascular death, non-cardiovascular death, and death of any cause. Safety was assessed with the incidence of any serious adverse event.

Primary analyses were performed using the intention-to-treat dataset from each trial, with a one-stage approach to individual participant data meta-analysis.¹⁴ We excluded patients without the minimum dataset for prespecified covariable adjustment (ie, age, sex, history of hypertension, and history of diabetes). Descriptive statistics were presented as mean (SD) or median (IQR) for continuous data, or frequency (percentage) for categorical data, and Kruskal-Wallis or χ^2 tests were used to make comparisons between treatment groups.

The effects of blood pressure-lowering treatment on the primary, secondary, and safety outcomes were estimated as hazard ratio (HR) and 95% CI in a Cox proportional hazards model. Age, sex, history of hypertension and diabetes, and trial-by-treatment interaction in the event of heterogeneity of treatment effect across trials were included as fixed covariates, and clustering by trial was used as a random effect. Heterogeneity was assessed using an I^2 estimate. We first assessed the significance of the regression coefficient for the trial-by-treatment interaction effects and, if not significant, a reduced model was run without the interaction term. We assessed the proportionality assumption using the Schoenfeld residual test and the time interaction variable in the model if violated. Sensitivity analyses included a Fine and Gray competing risk model,¹⁵ an unadjusted one-stage model, and an adjusted two-stage random effect model to test the robustness of our findings. No multiplicity adjustment was applied to the secondary endpoints, which need to be considered exploratory.

Heterogeneity of the treatment effect on the primary outcome was assessed across predefined subgroups: age, sex, race, country of recruitment, number of antihypertensive drugs, history of hypertension, time since the index intracerebral haemorrhage event, baseline systolic blood pressure, baseline diastolic blood pressure,

See Online for appendix

and trial. Subgroup-specific HRs and 95% CIs were estimated and presented descriptively. For participant-level subgroup variables, formal tests for treatment-by-subgroup interaction were performed using Cox proportional hazards models stratified by trial. To separate within-trial from across-trial information and reduce aggregation bias, subgroup covariates were centred around their trial-specific means before fitting the interaction models. For binary subgroup variables, 0 and 1 indicators were centred within trial. For categorical subgroup variables with more than two levels, $k-1$ trial-specific centred indicator variables were created, with the reference category omitted. Interaction p values were obtained from likelihood ratio tests comparing models with and without the treatment-by-centred-subgroup interaction terms. For categorical subgroup variables with more than two levels, the likelihood ratio test provided an overall p value for interaction across all centred indicator variables.^{16,17}

Time-to-benefit data from all trials were analysed using a Weibull survival model to estimate pooled survival curves for the treatment and control groups, converting these to cumulative risks and for an estimation of the absolute risk reduction at time t as the between-group difference in cumulative risk.¹⁸ Time to benefit was defined as the earliest time at which the absolute risk reduction exceeded prespecified thresholds (0.001, 0.005, 0.01, 0.02, and 0.03), with 95% CI derived from 5000 bootstrap resamples.

We assessed all eligible studies for bias using the Cochrane Collaboration tool and used the robvis risk of bias tool to generate visual summaries.¹⁹ Two-sided p values are reported, with a value less than 0.05 considered statistically significant. R, version 4.5.1, was used in all analyses.

Role of the funding source

There was no funding source for this study.

Results

Of 236 records screened, 37 trials were retrieved and 24 were assessed for eligibility after duplicates were removed. Five trials were eligible but only four supplied individual participant data and thus were retained for analysis (figure 1). No unpublished studies were identified. TRIDENT⁸ was the only trial conducted exclusively in patients with spontaneous intracerebral haemorrhage. We also identified only four other large secondary prevention blood pressure-lowering trials: Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events (ESPRIT),^{20,21} PROGRESS,⁵ Recurrent Stroke Prevention Clinical Outcome Study (RESPECT),²² and Post-Stroke Antihypertensive Study (PATS),²² which all reported outcomes in an intracerebral haemorrhage subgroup of at least 100 participants. PATS could not contribute individual participant data to this study. ESPRIT

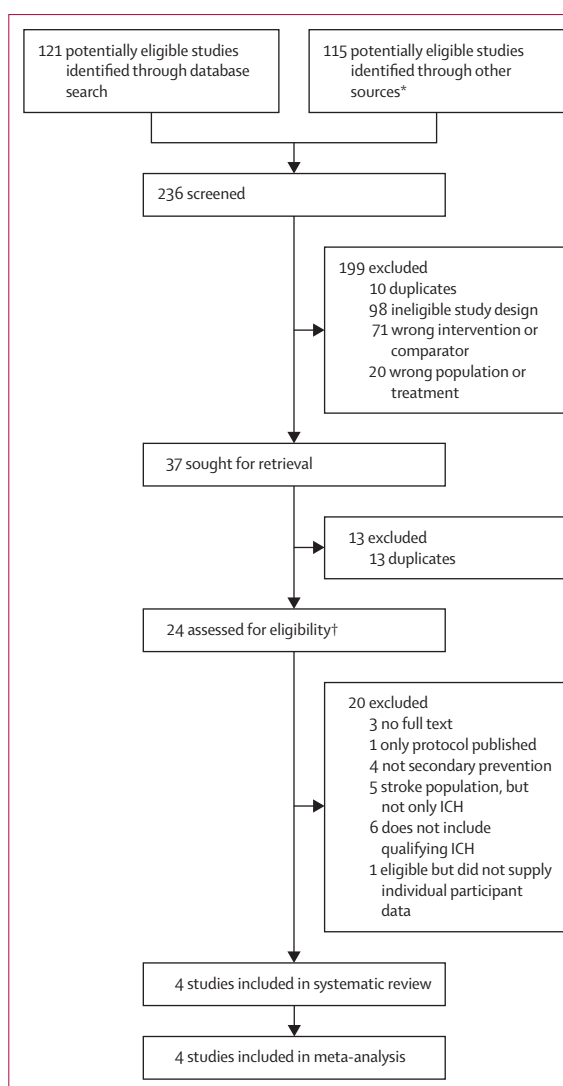


Figure 1: Literature search and selection process

ICH=intracerebral haemorrhage. *Grey literatures were identified from the reference list of ESPRIT, PROGRESS, RESPECT, and TRIDENT. †Subgroup analyses and substudies were included. However, if there were multiple publications of the same trial, all outputs were attributed to the main trial paper.

compared a systolic blood pressure target of less than 120 mm Hg with less than 140 mm Hg; RESPECT compared stepwise antihypertensive treatment targeting systolic blood pressure less than 120 mm Hg versus less than 140 mm Hg; PROGRESS evaluated perindopril, with or without indapamide, versus placebo on top of standard therapy; and TRIDENT evaluated a fixed low-dose combination of telmisartan, amlodipine, and indapamide versus placebo on top of standard care. The included evidence comprised two target-based intensive blood pressure-lowering strategies and two fixed-dose antihypertensive drug regimens; two trials were open-label with masked endpoint assessment and two were double-blinded and placebo-controlled (appendix pp 5–14). All the included trials had low overall risk of

For the Cochrane Collaboration tool see <https://methods.cochrane.org/bias/>

	Overall (n=2944)	Blood pressure lowering-treatment (n=1487)	Control (n=1457)
Age, years	59.6 (10.6)	59.3 (10.4)	59.9 (10.7)
Sex			
Female	972 (33.0%)	474 (31.9%)	498 (34.2%)
Male	1972 (67.0%)	1013 (68.1%)	959 (65.8%)
Race			
Asian	2218 (75.3%)	1130 (76.0%)	1088 (74.7%)
Black	198 (6.7%)	96 (6.5%)	102 (7.0%)
White	469 (15.9%)	231 (15.5%)	238 (16.3%)
Other*	59 (2.0%)	30 (2.0%)	29 (2.0%)
Country or region			
Australia or Europe	433 (14.7%)	212 (14.3%)	221 (15.2%)
East Asia†	1040 (35.3%)	539 (36.2%)	501 (34.4%)
Sri Lanka	1114 (37.8%)	559 (37.6%)	555 (38.1%)
Other‡	357 (12.1%)	177 (11.9%)	180 (12.4%)
Systolic blood pressure, mm Hg	144 (13)	144 (13)	144 (13)
Diastolic blood pressure, mm Hg	88 (10)	88 (10)	88 (10)
eGFR, mL/min per 1.73m ² §			
<60	281/2930 (9.6%)	149/1482 (10.1%)	132/1448 (9.1%)
60 to <90	1177/2930 (40.2%)	588/1482 (39.7%)	589/1448 (40.7%)
≥90	1472/2930 (50.2%)	745/1482 (50.3%)	727/1448 (50.2%)
Medical history			
Hypertension	2270/2943 (77.1%)	1130 (76.0%)	1140/1456 (78.3%)
Previous intracerebral haemorrhage¶	1386/2943 (47.1%)	710 (47.7%)	676/1456 (46.4%)
Previous ischaemic or undifferentiated stroke	276/2580 (10.7%)	143/1295 (11.0%)	133/1285 (10.4%)
Atrial fibrillation	56/2943 (1.9%)	30 (2.0%)	26/1456 (1.8%)
Ischaemic heart disease	212/2943 (7.2%)	100 (6.7%)	112/1456 (7.7%)
Diabetes	534/2943 (18.1%)	260 (17.5%)	274/1456 (18.8%)
Current alcohol consumption	445/2755 (16.2%)	227/1386 (16.4%)	218/1369 (15.9%)
Current smoker	262/2433 (10.8%)	137/1233 (11.1%)	125/1200 (10.4%)
Concomitant medications			
Antihypertensive drugs	2508 (85.2%)	1275 (85.7%)	1233 (84.6%)
Number of antihypertensive drugs			
Nil	436 (14.8%)	212 (14.3%)	224 (15.4%)
Single	1110 (37.7%)	565 (38.0%)	545 (37.4%)
Multiple	1398 (47.5%)	710 (47.7%)	688 (47.2%)
Anticoagulation	103 (3.5%)	51 (3.4%)	52 (3.6%)
Antiplatelet agents	496 (16.8%)	261 (17.6%)	235 (16.1%)
Statin	834 (28.3%)	429 (28.9%)	405 (27.8%)
Haematoma location (TRIDENT only)			
Deep	1408/1669 (84.4%)	704/833 (84.5%)	704/836 (84.2%)
Lobar	252/1669 (15.1%)	125/833 (15.0%)	127/836 (15.2%)
Mixed	9/1669 (0.5%)	4/833 (0.5%)	5/836 (0.6%)
Days since index intracerebral haemorrhage			
<80 days	81 (34–256)	80 (33–254)	82 (35–257)
<80 days	1155/2330 (49.6%)	579/1165 (49.7%)	576/1165 (49.4%)

Data are mean (SD), n (%), n/N (%), or median (IQR). Sample size is shown where this differs from the overall sample size. eGFR=estimated glomerular filtration rate. *Other includes Australian Aboriginal, Hispanic or Latino, Indigenous Brazilian, Middle Eastern, Pacific Islander, mixed, or other. †East Asia includes China, Japan, or Taiwan. ‡Other includes Brazil, Malaysia, Nigeria, or Singapore. §eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration 2021. ¶Index or qualifying.

Table 1: Baseline characteristics by randomised treatment

bias (appendix p 21). The I^2 p value was 0.75 across the four trials.

Overall, the four trials contributed 2944 patients with intracerebral haemorrhage to this analysis. The median duration of follow-up was 42.0 months (IQR 24.0–66.0; appendix pp 5–14). 1487 patients were allocated to intensive blood pressure-lowering treatment and 1457 to control (less intensive or placebo). Baseline characteristics were well balanced between the two groups (table 1). In 2944 overall patients, the mean age was 59.6 years (SD 10.6), 972 (33.0%) were female, 1972 (67.0%) were male, and 2218 (75.3%) were Asian. Most patients had a history of hypertension (2270 [77.1%]); other comorbidities included ischaemic stroke or undifferentiated stroke (276 [10.7%]), ischaemic heart disease (212 [7.2%]), and diabetes (534 [18.1%]). At study entry, most patients were receiving antihypertensive therapy (2508 [85.2%]), with 1398 (47.5%) receiving two or more blood pressure lowering drugs; anticoagulants were used in 103 (3.5%) patients and concomitant antiplatelets were used in 496 (16.8%) patients. Among trials with available data, the median time from the index intracerebral haemorrhage event to randomisation was 81 days (IQR 34–256). Baseline characteristics by randomised treatment group in each trial are presented in the appendix (appendix pp 7–14).

Blood pressure during follow-up is shown in the appendix (pp 15–17, 22–27). In PROGRESS, mean systolic blood pressure was 138 mm Hg (SD 20) at commencement of the run-in phase and 138 mm Hg (20) at baseline. In TRIDENT, mean systolic blood pressure was 143 mm Hg (10) at commencement of the run-in phase and 127 mm Hg (17) at baseline. Mean systolic blood pressure was 144 mm Hg (13) in RESPECT and 147 mm Hg (11) in ESPIRIT at randomisation. During follow-up, mean systolic blood pressure was 127 mm Hg in the treatment group and 138 mm Hg in the control group; between-group mean systolic blood pressure difference was 11.2 mm Hg (95% CI 10.7–11.7; appendix pp 15–17, 22–27). Mean diastolic blood pressure difference was 5.2 mm Hg (95% CI 4.9–5.5) over follow-up ($p<0.0001$).

As no significant trial-by-treatment interaction was observed, a reduced model without the interaction term was fitted. The proportional hazards assumptions were met for all the outcomes (appendix p 28). During follow-up of up to 6 years, recurrent stroke of any type occurred in 96 (6.5%) of 1487 patients assigned intensive blood pressure-lowering treatment and 152 (10.4%) of 1457 patients assigned control treatment (adjusted HR 0.62, 95% CI 0.48 to 0.80; $p=0.00021$; figure 2; table 2). The treatment effect was homogeneous across the trials ($p_{\text{interaction}}=0.52$; figure 3; appendix pp 29, 31). Results remain consistent after adding PATS (appendix p 30). Patients who entered the trials with a blood pressure of 130/80 mm Hg or lower had high rates of recurrent stroke, but these rates were improved

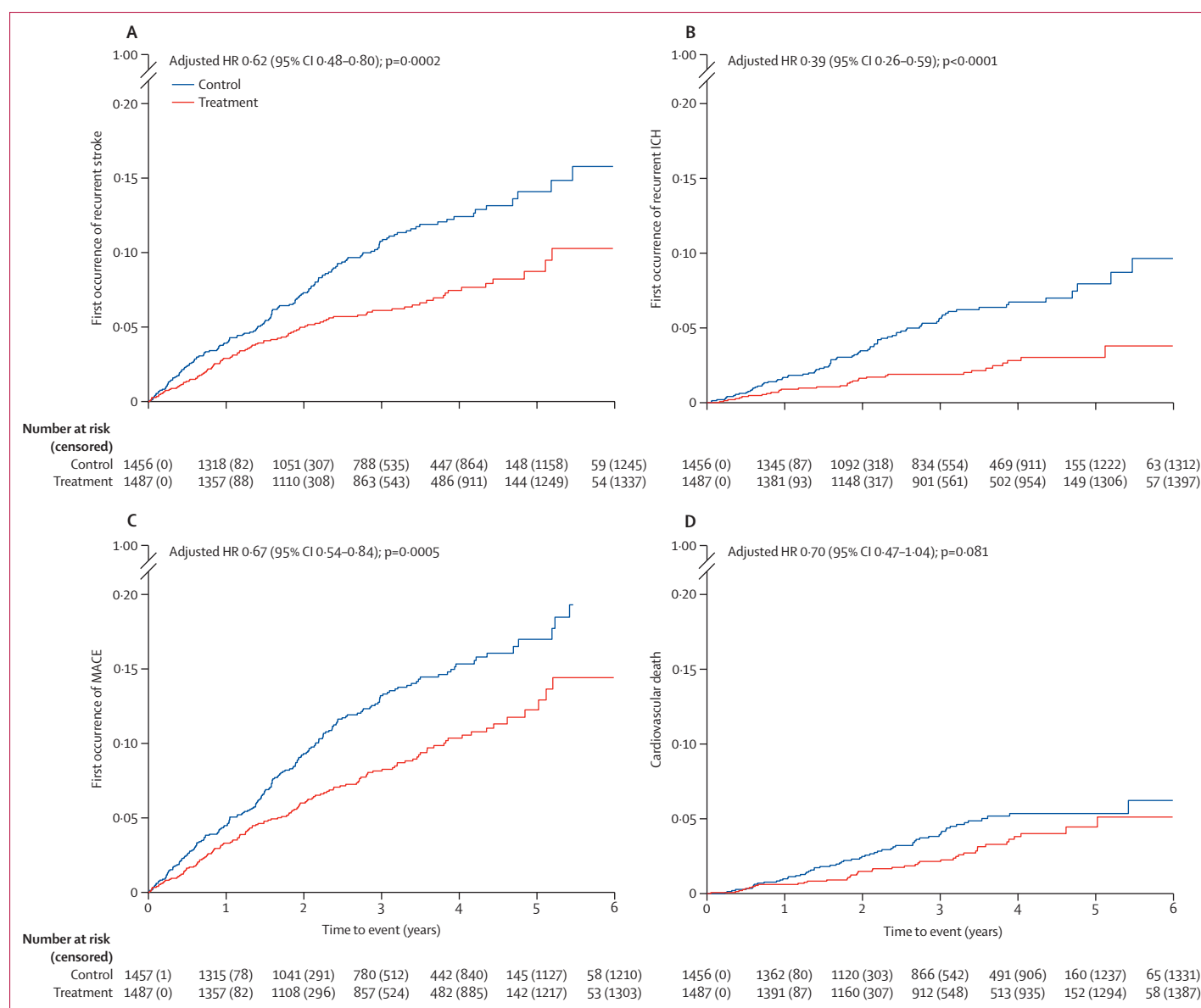


Figure 2: Kaplan-Meier event curves

(A) Recurrent stroke of any type. (B) Intracerebral haemorrhage. (C) Any major adverse cardiovascular event (death from cardiovascular causes, recurrent myocardial infarction, or stroke). (D) Death from cardiovascular causes. Models were adjusted for age, sex, history of hypertension, and history of diabetes, with a random effect for trial. HR=hazards ratio. ICH=intracerebral haemorrhage. MACE=major adverse cardiovascular event

with intensive treatment (for systolic ≤ 130 : 13.9% in the control group vs 5.1% in the intervention group; for diastolic ≤ 80 : 12.3% vs 6.2%).

In sensitivity analysis, the result was unchanged when death was treated as a competing risk (appendix p 30), in an unadjusted model (appendix p 18), and in a two-stage analysis (appendix p 29). Treatment effects were consistent across all prespecified subgroups (figure 3), including time since index intracerebral haemorrhage event ($p_{\text{interaction}}=0.89$), baseline systolic blood pressure ($p_{\text{interaction}}=0.66$), and baseline diastolic blood pressure ($p_{\text{interaction}}=0.59$). Similar proportional

effects were observed among those randomised within 1 month of the index intracerebral haemorrhage event compared with those randomised after 1 month (eg, >12 months).

Intensive blood pressure-lowering treatment reduced major adverse cardiovascular events (adjusted HR 0.67, 95% CI 0.54–0.84; $p=0.0005$). The reduction in recurrent stroke of any type was primarily driven by fewer recurrent intracerebral haemorrhage events (0.39, 0.26–0.59; $p<0.0001$). However, there was no evidence of a reduced risk of ischaemic stroke (0.92, 0.66–1.30; $p=0.64$). There were no statistically

	Blood pressure lowering-treatment (n=1487)	Control (n=1457)	Adjusted hazard ratio (95% CI)*	p value
Primary outcome				
Recurrent stroke of any type	96 (6.5%)	152 (10.4%)	0.62 (0.48–0.80)	0.0002
Secondary outcomes				
Major adverse cardiovascular event†	131 (8.8%)	190 (13.0%)	0.67 (0.54–0.84)	0.0005
Cardiovascular death	42 (2.8%)	60 (4.1%)	0.70 (0.47–1.04)	0.081
Intracerebral haemorrhage	33 (2.2%)	81 (5.6%)	0.39 (0.26–0.59)	<0.0001
Ischaemic stroke	64 (4.3%)	69 (4.7%)	0.92 (0.66–1.30)	0.64
Stroke of unknown type	6 (0.4%)	15 (1.0%)	0.40 (0.15–1.03)	0.057
Non-fatal stroke	82/1386‡ (5.9%)	120/1369‡ (8.8%)	0.67 (0.51–0.89)	0.0051
Non-fatal myocardial infarction	12 (0.8%)	19 (1.3%)	0.62 (0.30–1.28)	0.20
Non-vascular death	57 (3.8%)	65 (4.5%)	0.91 (0.63–1.30)	0.59
Death of any cause	99 (6.7%)	125 (8.6%)	0.81 (0.62–1.05)	0.11
Safety				
Patients with serious adverse event§	429 (28.9%)	481 (33.0%)	0.82 (0.70–0.96)	0.015

Data are n (%) or n/N (%), unless otherwise stated. *Adjusted for age, sex, history of hypertension, and history of diabetes, with trial included as a random effect. †Non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death. ‡ESPIRIT did not have non-fatal stroke as an outcome. §Serious adverse events were prespecified to include events that might or might not be considered to be related to the treatment and that were life-threatening or resulted in hospitalisation or prolongation of existing hospitalisation, 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. Data are shown for number of people with one or more event; in total 822 events were observed in the treatment groups and 954 events were observed in the control groups.

Table 2: Primary and secondary outcomes and safety in the intention-to-treat population

significant differences in the rates of cardiovascular death (0.70, 0.47–1.04; $p=0.081$), non-vascular death (0.91, 0.63–1.30; $p=0.59$), or all-cause death (0.81, 0.62–1.05; $p=0.11$; table 2; figure 2; appendix pp 32–35). These results were unchanged in the unadjusted models (appendix p 18).

Safety outcomes are summarised in table 2. At least one serious adverse event during follow-up occurred in 429 (28.9%) of 1487 patients in the intensive group and 481 (33.0%) of 1457 patients in the control group (adjusted HR 0.82, 95% CI 0.70–0.96; $p=0.015$). The number of patients with major adverse kidney events, including sustained 40% decline or higher in estimated glomerular filtration rate, end-stage kidney disease, ongoing dialysis, kidney transplantation, or renal death, was similar between the two groups, although available variables differed across trials (appendix p 19).

Time-to-benefit modelling showed an early emergence of benefit after treatment starts (appendix p 20; figure 4). The modelled times to achieve absolute risk reductions in stroke of 1%, 2%, and 3% were 6.1 months (95% CI 3.5–14.8), 14.3 months (8.1–34.8), and 24.0 months (13.4–54.0), respectively. Consistent with these estimates, intensive blood pressure-lowering treatment prevented approximately 16 recurrent strokes per 1000 patients within 1 year, with absolute reductions increasing with longer follow-up (figure 4; appendix p 20; around 20% by 2 years and widening thereafter).

Discussion

In this individual participant data meta-analysis of 2944 patients with previous spontaneous intracerebral haemorrhage from four randomised controlled trials, intensive long-term blood pressure-lowering treatment reduced the risks of recurrent stroke of any type and major adverse cardiovascular events, with the benefit largely driven by the prevention of recurrent intracerebral haemorrhage. We found no clear effect on ischaemic stroke or death, no excess in serious adverse events, and no clinically important heterogeneity of the effect across prespecified subgroups. The modelled time to achieve a 1% absolute benefit was 6.1 months (95% CI 3.5–14.8), with absolute reductions increasing with longer follow-up.

These findings strengthen and extend the evidence supporting long-term blood pressure-lowering treatment as the cornerstone of secondary prevention after intracerebral haemorrhage. Meta-analyses indicate that a 10 mm Hg reduction in systolic blood pressure (or 5 mm Hg in diastolic blood pressure) is associated with an approximately 40% reduction in recurrent stroke risk,^{23,24} with proportionally larger reductions for intracerebral haemorrhage than ischaemic stroke.^{5–7,20–22,25} TRIDENT showed that a fixed triple low-dose combination antihypertensive pill can achieve durable blood pressure control and reduce recurrent stroke after intracerebral haemorrhage, predominantly by preventing recurrent intracerebral haemorrhage.⁸ By pooling harmonised participant-level data across trials with differing designs, populations, and health-care settings, our analysis provides precise and generalisable estimates of benefit and harm, confirms consistency across key subgroups, and quantifies the early time course of benefit.

Our subgroup findings provide additional insight into the optimal intensity of long-term control of blood pressure. Although guidelines typically recommend a target of less than 130/80 mm Hg after intracerebral haemorrhage,¹⁰ our data showed that patients who entered the trials with a blood pressure of 130/80 mm Hg or lower remained at substantial risk of recurrent stroke (13.9% in the control group for systolic blood pressure ≤ 130 mm Hg and 12.3% in the control group for diastolic blood pressure ≤ 80 mm Hg) and derived significant benefit from intensive treatment (5.1% in the intervention group for systolic ≤ 130 and 6.2% in the intervention group for diastolic ≤ 80). Many patients in routine care cannot reach or maintain these targets, and inadequate blood pressure control after intracerebral haemorrhage has been associated with increased recurrence risk.¹² Consistent with randomised evidence derived from the Blood Pressure Lowering Treatment Trialists Collaboration,²⁶ these data provides support for sustained blood pressure control across different blood pressures at study entry, rather than proving that all patients with previous intracerebral haemorrhage should be treated to a universal systolic target less than

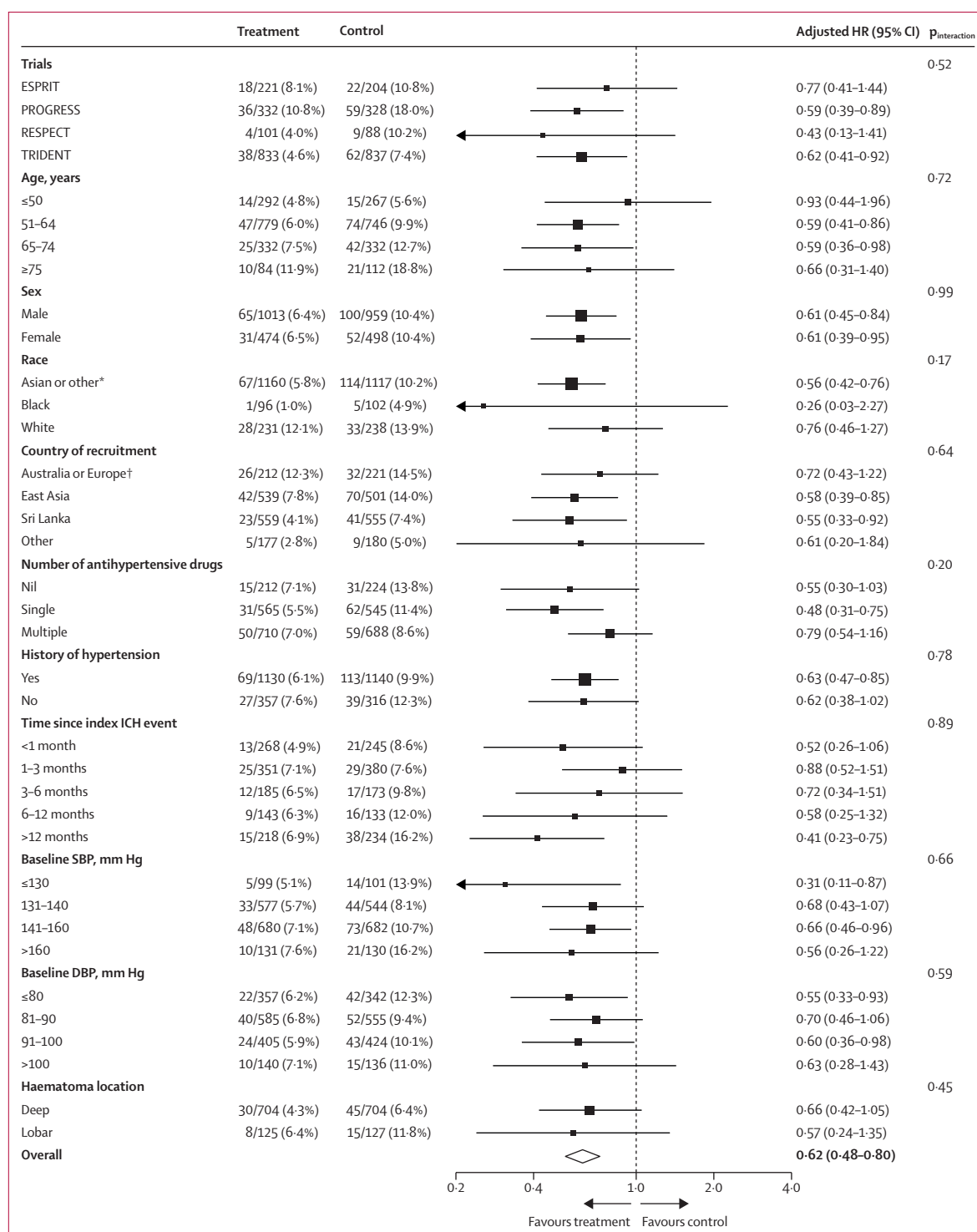


Figure 3: Within-study and prespecified subgroup analyses of the treatment effect of blood-pressure lowering on the time to first recurrent stroke

Subgroup-specific HRs were estimated using Cox models adjusted for age, sex, history of hypertension, and history of diabetes, with trial included as a random effect. Comparing these HRs directly could introduce aggregation bias. Formal p values for interaction were estimated separately using trial-stratified Cox models with trial-specific centred subgroup variables. DBP=diastolic blood pressure. HR=hazards ratio. SBP=systolic blood pressure. ICH=intracerebral haemorrhage.

*Other includes Australian Aboriginal, Hispanic or Latino, Indigenous Brazilian, Middle Eastern, Pacific Islander, mixed, or other backgrounds. †Europe includes France, Georgia, Italy, the Netherlands, Sweden, and the UK.

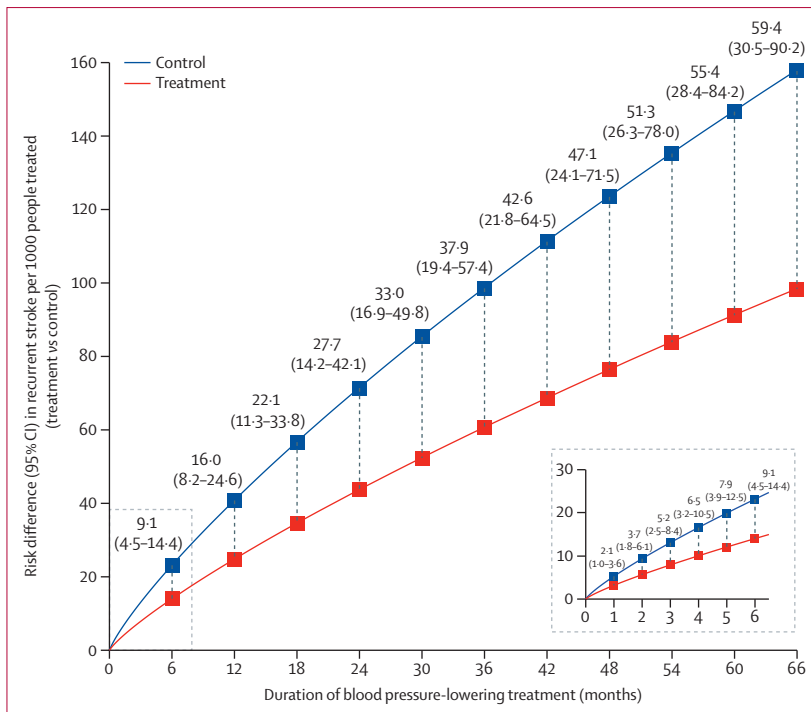


Figure 4: Time to benefit of intensive blood-pressure lowering for recurrent stroke prevention after intracerebral haemorrhage

Dotted lines are the number of recurrent strokes prevented per 1000 people treated with intensive blood pressure lowering (absolute risk reduction), compared with control. The figure inset shows the risk difference across the first 6 months of treatment.

120 mm Hg or with any specific antihypertensive drug combination.

We found that the proportional treatment effect was consistent across time intervals since the index intracerebral haemorrhage event. However, only 34 patients were randomly assigned within 30 days of the index event, and the median time to randomisation was 81 days. Therefore, our findings primarily inform intensive blood pressure-lowering initiated in the subacute (ie, several weeks) and chronic (ie, several months) phases after intracerebral haemorrhage, and the optimal timing of initiation in the earliest post-intracerebral haemorrhage period is uncertain. Time-to-benefit analysis indicates that, once treatment is started, benefit begins to accrue within months and increases with long-term blood pressure control. These findings have practical implications. First, blood pressure-lowering treatment should be optimised and maintained during follow-up after intracerebral haemorrhage as part of long-term secondary prevention. Second, strategies that reliably achieve and maintain blood pressure control—in particular structured titration protocols and simplified fixed-dose combination regimens—are likely to be required to overcome therapeutic inertia and adherence barriers.^{11,27–29} Third, the absence of an excess of serious adverse events provides reassurance that intensive blood

pressure-lowering can be implemented safely within structured care pathways.

Strengths of this work include the acquisition of individual participant data from all included trials, enabling consistent outcome definitions, prespecified covariate adjustment, harmonised time-to-event modelling with appropriate clustering by trial, and prespecified subgroup analyses. Inclusion of patients from diverse health-care settings and both target-based and fixed-dose strategies strengthens the external validity.

This individual participant data meta-analysis also has limitations. The cohort was predominantly Asian and young. Although we did not observe statistically significant heterogeneity by race or region, the small number of non-Asian participants limits power to exclude modest ethnic differences in treatment response. This limitation is relevant because previous hypertension studies suggest that antihypertensive drug response can vary by ethnicity;³⁰ therefore, the generalisability of our findings to other ethnic populations should be interpreted with caution. Trial participation criteria and run-in phases could also limit the applicability of the findings to older, frail, and socially disadvantaged groups. Furthermore, some datasets were from older trials; however, they are still relevant because there have been limited advances in the treatment of acute intracerebral haemorrhage since then.

Our findings confirm the substantial benefits of long-term intensive blood pressure-lowering after intracerebral haemorrhage. Future trials should focus on strategies to enhance the uptake of intensive blood pressure-lowering treatment. As TRIDENT assessed the effectiveness of the triple-pill as an add-on therapy to patients already controlled according to guideline recommendations, new studies should examine use of the triple-pill as initial treatment with additional blood pressure-lowering treatment towards lower systolic pressures compared with use of the triple-pill alone. Identifying which patients might benefit from or be harmed by intensive blood pressure-lowering treatment is crucial. Further research should focus on patients with chronic renal disease, cerebral small vessel disease, and frailty.

Overall, intensive long-term blood pressure-lowering treatment after spontaneous intracerebral haemorrhage reduces recurrent stroke of any type—predominantly recurrent intracerebral haemorrhage—without an apparent safety trade-off. The early accrual and durability of benefit after treatment initiation support for sustained long-term blood pressure control as the core secondary prevention strategy after intracerebral haemorrhage.

Contributors

XW, CSA, and AR conceived the study, supervised the planned analyses, data interpretation, and writing of the report. XW wrote the first draft of the manuscript. YG and MJV did the statistical analysis. XW, YG, and KH directly accessed and verified the underlying data. All authors

revised the draft and contributed to data collection, analysis, interpretation, and report writing. All authors had full access to all data in the study, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

CSA has received grants from the Australian National Health and Medical Research Council (NHMRC) and the UK Medical Research Foundation, and honoraria for advisory board activities for Auzone Biotechnology, Shanghai, AstraZeneca, Bayer, and Merck. He is President-elect of the World Stroke Organization and Editor-in-Chief of Cerebrovascular Diseases. XW holds an investigator grant, from the NHMRC (APP1195237). CSA holds an NHMRC Senior Investigator Fellowship. All other authors declare no competing interests.

Data sharing

Individual, de-identified participant data used in these analyses can be shared by request from any qualified investigator following approval of a protocol and signed data access agreement via the Research Office of The George Institute for Global Health, Australia.

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