Safety and efficacy of early versus delayed acetylsalicylic acid after surgery for spontaneous intracerebral haemorrhage in China (E-start): a prospective, multicentre, open-label, blinded-endpoint, randomised trial

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Summary

Background Patients with non-traumatic intracerebral haemorrhage have a substantial risk of major adverse cardiovascular and cerebrovascular events, including ischaemic stroke, after surgery. The optimal timing of antiplatelet therapy after surgery for spontaneous intracerebral haemorrhage in patients at high risk of postoperative ischaemic events has not been characterised. We aimed to investigate the safety and efficacy of early versus late initiation of antiplatelet therapy after surgery for spontaneous intracerebral haemorrhage.

Methods This prospective, open-label, blinded-endpoint, randomised trial was done at eight stroke centres in China. Eligible patients were aged 18–70 years, undergoing surgery for the evacuation of spontaneous intracerebral haemorrhage, and had a high risk of postoperative ischaemic events. Using the minimisation method in an online randomisation system, patients were randomly assigned (1:1) to receive 100 mg acetylsalicylic acid once per day in either the early-start group (starting on the third day after surgery until the 90th day after surgery) or the late-start group (starting on the 30th day after surgery until the 90th day after surgery). Medication was taken orally or delivered via a feeding tube. The primary efficacy outcome was a composite of new major ischaemic cardiovascular, cerebrovascular, or peripheral vascular events within 90 days and the primary safety outcome was any intracranial bleeding within 90 days, both measured in the intention-to-treat population. The trial is registered at ClinicalTrials.gov, NCT04820972, and is complete.

Findings From May 1, 2021, to May 1, 2023, 7323 patients were screened, of whom 269 (4%) were enrolled and randomly assigned: 134 to the early-start group and 135 to the late-start group. 195 (72%) patients were male, 74 (28%) were female, and the median age was 60·2 years (IQR 52·0–66·5). Haematomas were supratentorial and deep in most (170 [63%] of 269) patients. Ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events occurred within 90 days after surgery in 27 (20%) of 134 patients in the early-start group and 42 (31%) of 135 patients in the late-start group (odds ratio 0·56 [95% CI 0·32–0·98]; p=0·041). Intracranial bleeding occurred in one (1%) of 134 patients in the early-start group and four (3%) of 135 patients in the late-start group. Non-bleeding serious adverse events occurred in 57 (42%) of 134 patients in the early-start group and 57 (42%) of 135 patients in the late-start group.

Interpretation Starting acetylsalicylic acid on the third day after surgery for spontaneous intracerebral haemorrhage in Chinese patients at high risk of postoperative ischaemic events resulted in fewer postoperative ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events than starting acetylsalicylic acid therapy at 30 days, with no increased risk of intracranial bleeding. Whether early initiation of acetylsalicylic acid therapy is safe and improves clinical outcomes for broader populations of patients with spontaneous intracerebral haemorrhage requires further research.

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Introduction

Patients with spontaneous intracerebral haemorrhage who undergo neurosurgery are at increased risk of major cardiovascular, cerebrovascular, and deep vein thrombosis events, some of which can be fatal.[1,2] Although antiplatelet therapy is an effective way to prevent ischaemic cardiovascular and cerebrovascular events and peripheral vascular events (including deep vein thrombosis and

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See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE, the Cochrane Library, and ClinicalTrials.gov, using the search terms "randomized controlled trial", "intracranial hemorrhage", "intracerebral hemorrhage", "antiplatelet treatments" and "aspirin", without any language restrictions, from database inception to Sept 30, 2024. We found two randomised controlled trials evaluating the efficacy of antithrombotic medications in preventing post-haemorrhage ischaemic events in patients with intracerebral haemorrhage: one completed trial involving 23 patients (RESTART-Fr, NCT02966119) and one ongoing trial involving 500 patients (STATICH, NCT03186729). However, the clinical outcomes of these trials are not currently reported. In our cohort study (SAP-ICH, ChiCTR1900024406), in 794 patients with spontaneous intracerebral haemorrhage, the incidence of ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events within 90 days of surgery was 30·3% and such events were a major cause of death (Liu Q et al, unpublished). Another randomised trial (RESTART, ISRCTN71907627) found that antiplatelet resumption neither increased the risk of recurrent intracerebral haemorrhage nor reduced the incidence of ischaemic events among patients with intracerebral haemorrhage who received antithrombotic therapy before their haemorrhage. A retrospective study of patients with spontaneous intracerebral haemorrhage found a similar risk of rebleeding between those with early and delayed resumption of antiplatelet therapy. In a meta-analysis, post-haemorrhage antiplatelet therapy was not found to contribute to increased all-cause mortality or deterioration of neurological function.

Added value of this study

To the best of our knowledge, E-start is the first randomised controlled trial of postoperative, early-start antiplatelet therapy in patients with spontaneous intracerebral haemorrhage and a high risk of ischaemic events. Starting antiplatelet therapy early was associated with a reduction of ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events within 90 days after surgery compared with a later start, without any increase in the risk of bleeding.

Implications of all the available evidence

There are no current guidelines or consensus for the postoperative use and timing of antiplatelet therapy in patients undergoing neurosurgery for spontaneous intracerebral haemorrhage. Our trial highlights the possibility of reducing the occurrence of postoperative ischaemic cardiovascular, cerebrovascular, or peripheral vascular events through the early initiation of antiplatelet therapy. However, whether early initiation is safe and effective for other groups of patients with spontaneous intracerebral haemorrhage requires further research.

pulmonary embolism),[3] particularly in patients at high risk, concerns about postoperative bleeding and the absence of guidelines or consensus on postoperative antiplatelet therapy often delay its initiation. The optimal timing for the initiation of antiplatelet therapy to prevent these events is therefore unclear.

Several studies have reported the high risk of major cardiovascular, cerebrovascular, and peripheral vascular events in patients with spontaneous intracerebral haemorrhage[4–6] and in patients undergoing non-cardiac surgery.[7] The Perioperative Ischemic Evaluation-2 (POISE-2) trial showed that acetylsalicylic acid had no effect on major cardiovascular events throughout the early postsurgical period after non-cardiac surgical procedures; however, patients with spontaneous intracerebral haemorrhage were excluded from the trial.[8] Our previous prospective cohort study found no increased risk of postoperative intracranial bleeding in patients with spontaneous intracerebral haemorrhage after acetylsalicylic acid administration.[9] Other studies have suggested that the early initiation of antiplatelet therapy after surgery in patients with spontaneous intracerebral haemorrhage did not lead to an increased risk of bleeding,[10] although its efficacy in lowering the risk of ischaemic events remains unclear.[11] The Restart or Stop Antithrombotics Randomized Trial (RESTART) showed that restarting antiplatelet therapy did not increase the risk of rebleeding after spontaneous intracerebral haemorrhage, but the rate of ischaemic events did not differ.[11,12] However, the time from the occurrence of haemorrhage to the resumption of antiplatelet therapy was variable (29–146 days) and patients receiving neurosurgery for spontaneous intracerebral haemorrhage were excluded.

The Early Acetylsalicylic Acid After Surgical Treatment in Patients with Spontaneous Intracerebral Haemorrhage (E-start) trial aimed to test whether early initiation of antiplatelet therapy after surgery for spontaneous intracerebral haemorrhage could reduce the occurrence of major cardiovascular, cerebrovascular, and peripheral vascular events without increasing the risk of bleeding.

Methods

Study design

This prospective, open-label, blinded-endpoint, randomised trial (E-start) was conducted at eight comprehensive stroke centres in China. Trial centres, investigators, and committee members are listed in the appendix (pp 2–4, 6). Details of the trial rationale, design, and methods have been previously described[13] and are provided in the protocol (appendix pp 23–130). The trial was approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2021-053-02) and at each participating site. The steering committee (appendix p 2) was responsible for the design and conduct of the trial and regularly assessed safety outcomes. The trial is registered at ClinicalTrials.gov, NCT04820972, and is complete.

Participants

Participants were recruited by their neurologist at one of the eight participating stroke centres. Eligible patients were those who met the following criteria: age 18–70 years; presented with non-traumatic, spontaneous intracerebral haemorrhage; underwent a neurosurgical procedure for haematoma evacuation (craniotomy, craniectomy, or minimally invasive surgery [endoscopic or stereotactic aspiration]); were at high risk of ischaemic events (those who had a history of cerebral infarction, transient ischaemic attack, coronary heart disease, or myocardial infarction, or had a score of at least 10% on the 10-year atherosclerotic cardiovascular disease risk estimator,[14] or both); had no history of allergy to salicylic acid preparations; and had a postoperative Caprini risk score of greater than 2.[15] The Caprini risk score is widely used to evaluate the risk of venous thrombus embolism in hospitalised patients against 40 factors (eg, age, BMI, and comorbidities), with 1–2 indicating low-to-medium risk and greater than 2 indicating high risk. For patients with a Caprini risk score of greater than 2, anticoagulation treatment and active physiotherapy are recommended to prevent venous thromboembolism.[16]

Patients were excluded for any of the following reasons: major cardiovascular, cerebrovascular, or peripheral vascular events occurring after spontaneous intracerebral haemorrhage and before randomisation; rebleeding of intracerebral haemorrhage after neurosurgery but before randomisation; an underlying cerebrovascular lesion (eg, intracranial aneurysm or arteriovenous malformation) or intracranial neoplasm suspected to be related to spontaneous intracerebral haemorrhage; haemorrhagic conversion of ischaemic stroke; cerebral venous thrombosis; treatment with oral antithrombotic therapy before spontaneous intracerebral haemorrhage; history of coagulopathy; a history of atrial fibrillation; spontaneous intracerebral haemorrhage probably due to cerebral amyloid angiopathy (according to the modified Boston criteria[17]); or a new spontaneous intracerebral haemorrhage on postoperative imaging before randomisation. Patients or their representatives were informed of the purpose, procedures, potential risks, and potential benefits of the study, and provided written informed consent for participation.

Randomisation and masking

The investigators at each trial site obtained a randomisation code from the 24-h central online network randomisation system (an applet within WeChat) and eligible participants were randomly assigned (1:1) to either the early-start group or the late-start group. The online randomisation system displayed each participant's unique study identification number and their group allocation, which were also sent in a WeChat message and an email to all investigators at the hospital site except for those responsible for follow-up and outcome assessment. The minimisation randomisation method was used to balance trial-group assignments in terms of age (≥60 years or <60 years), sex, haematoma location (supratentorial or infratentorial), haematoma volume (≥50 mL or <50 mL, as established by the ABC/2 method),[18] and surgical method (craniotomy [with or without craniectomy] or minimally invasive surgery [endoscopic or stereotactic aspiration]).

Participants, the clinicians caring for them in primary and secondary care, and local investigators were aware of treatment allocation. Investigators responsible for follow-up were masked to treatment allocation. Outcome event adjudicators were masked to participant identification number, treatment allocation, and medicine administration.

Procedures

Surgeries were done by senior vascular neurosurgeons (with more than 10 years of experience) after agreement between the patients' legal representatives and the neurosurgeons. According to preliminary data from the Surgical Treatment for Antiplatelet Intracerebral Hemorrhage (SAP-ICH) cohort study, major cardiovascular, cerebrovascular, and peripheral vascular events commonly occurred within 2 weeks after surgical treatment, and almost all postoperative intracranial bleeding events occurred within 72 h (Liu Q et al, unpublished). In general, craniotomy or minimal invasive surgery were recommended for supratentorial haematoma and craniotomy was recommended for infratentorial haematoma.

Patients in the early-start group started receiving 100 mg of acetylsalicylic acid on the third postoperative day and continued receiving the same dose daily until the 90th postoperative day. Patients in the late-start group started receiving 100 mg of acetylsalicylic acid daily on the 30th postoperative day and continued receiving the same dose until the 90th postoperative day. For patients with feeding tubes, acetylsalicylic acid tablets were crushed and delivered via the feeding tube with water; for patients without feeding tubes, tablets were administrated orally. To ensure medication adherence, acetylsalicylic acid tablets were counted and given to patients by health-care providers while they were in hospital and were counted and given by health-care providers or the patients' guardians after discharge. Medication adherence during follow-up was assessed using the Morisky medication adherence scale[19] (with scores ranging from 0 to 8; 0–5 indicating poor adherence and 6–8 indicating good adherence) by asking health-care providers or patients' guardians. Both groups were medically managed according to the guidelines of the American Stroke Association.[20] All patients received intensive blood pressure management, which required lowering of systolic blood pressure to less than 140 mm Hg within 1 h after admission. Postoperatively, patients did physical activities assisted by health-care providers and had standard pneumatic

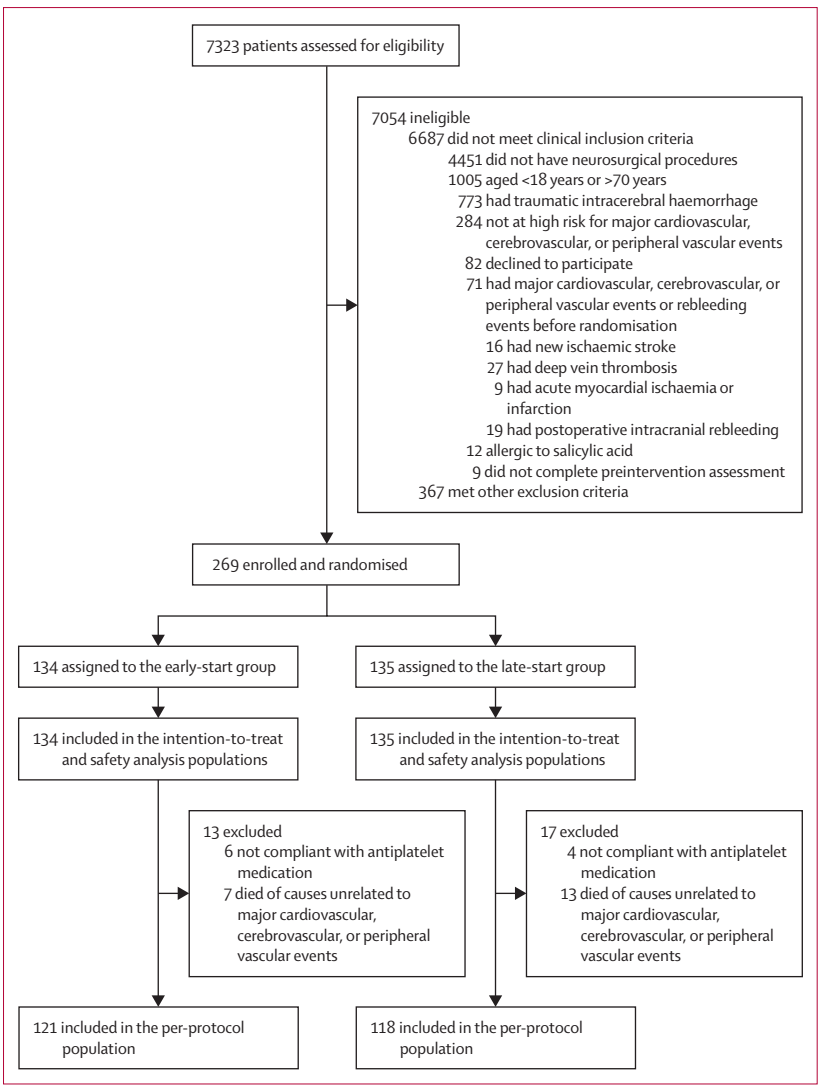


Figure 1: **Trial profile**

compression therapy to prevent deep venous thrombosis. All patients had a non-contrast CT scan within 6 h after surgery and additional examinations (non-contrast CT scan, venous ultrasonography of lower extremities, and measurement of myocardial enzyme concentrations) before randomisation to ensure that they had no new or enlarging intracranial bleeding and no new major cardiovascular, cerebrovascular, or peripheral vascular events. Follow-up non-contrast CT scans, venous ultrasonograms of legs, and myocardial enzyme concentrations were obtained at postoperative day 10 (range 6–14) and day 90 (83–97). Functional outcome scores at 90 days after surgery were assessed through telephone interviews or outpatient visits, with recording for quality control. All adverse events were confirmed by a clinical-event adjudication committee, the members of which were masked to the trial-group assignments.

Outcomes

The primary efficacy outcome, which was assessed centrally, was new major cardiovascular, cerebrovascular, and peripheral vascular events (including ischaemic major cardiovascular and cerebrovascular events, and peripheral deep venous thrombosis and pulmonary embolism) within 90 days after surgery for spontaneous intracerebral haemorrhage. Ischaemic major cardiovascular and cerebrovascular events comprised a new cerebral infarction outside the surgical area or enlargement of the original cerebral infarction (assessed by comparing the follow-up non-contrast CT scan with the last postoperative non-contrast CT scan before randomisation, and subsequently identified by MRI), a new myocardial infarction (identified by increasing concentrations of myocardial enzymes, electrocardiography, or symptoms of myocardial infarction), and treatment of the original myocardial infarction with reperfusion therapy. Deep venous thrombosis was identified from the follow-up venous ultrasonogram of lower extremities. Pulmonary embolism was identified by symptoms (eg, cough, chest pain, and dyspnoea) and examinations (CT pulmonary angiography). Secondary outcomes were death within 90 days after surgery, in-hospital death, and 90-day functional outcomes: modified Rankin Scale (mRS) score 0–3 on day 90 after surgery (0–3 represents no disability to moderate disability and 4–6 represents moderately severe disability to death[21]) and Glasgow Outcome Scale (GOS) score 3–5 on day 90 after surgery (3–5 represents severe disability to good recovery).[22]

The primary safety outcome was any new intracranial bleeding (either rehaemorrhage in the operated regions or new-onset intracranial bleeding events after administration of acetylsalicylic acid, identified by comparing the follow-up non-contrast CT scan and the last postoperative non-contrast CT scan before randomisation) within 90 days after surgery. Secondary safety outcomes were any new symptomatic intracranial bleeding or any new moderate or severe bleeding (defined by the standards of the Bleeding Academic Research Consortium [BARC] as bleeding requiring internal or surgical or transfusion treatment [2–3 type] and fatal bleeding [5 type]),[23] both within 90 days after surgery.

Statistical analysis

The staff of the Statistical and Data Management Center of the China National Clinical Research Center for Neurological Diseases (Beijing, China) did the statistical analyses. The statistical plan is described in the study protocol (appendix pp 23–130). We estimated that 250 patients with spontaneous intracerebral haemorrhage receiving surgical treatment would provide 80% power to detect a 50% relative risk reduction in the primary outcome (new major cardiovascular, cerebrovascular, and peripheral vascular events) in the early-start group compared with the late-start group. On the basis of the SAP-ICH study, we assumed an incidence of such events

of 30·3% among patients with spontaneous intracerebral haemorrhage after surgery (Liu Q et al, unpublished), anticipating an overall dropout rate of 5%.

An interim analysis of the primary efficacy outcomes was planned when half of the patients enrolled had completed a 90-day follow-up. A two-sided p value of 0·05 was adjusted to 0·048 to account for the interim analysis using an O'Brien–Fleming spending function. In the interim analysis, the trial would have been stopped early either for efficacy if a prespecified treatment effect (p<0·005) had been met or for futility if the results showed that a conclusion could not be made on the treatment effect with the current sample size. An independent data safety monitoring committee reviewed the overall incidence of trial outcomes and recommended continuation of the trial without unmasking. Therefore, the efficacy and safety outcomes were not compared between the two treatment groups in the interim analysis, no alpha was considered to have been expended, and the type I error level of the statistical significance was set at a two-sided p value of 0·05 in the final analysis.

Efficacy and safety analyses were conducted in the intention-to-treat population (all patients in the groups to which they were randomly assigned) and, as a sensitivity analysis, in the per-protocol population (all those who completed the allocated treatment). The differences in the incidence of new major cardiovascular, cerebrovascular, and peripheral vascular events between trial groups during the 90-day follow-up period were assessed using a logistic-regression model, with trial centres set as the random effect. Treatment effects, in the form of odds ratio (OR) and 95% CI, were calculated to detect the difference in the risk of such events between the two groups. The same approaches were used for the comparison of safety outcomes and secondary outcomes. We also analysed the primary outcome in prespecified subgroups (by age [≥65 years or <65 years], sex [male or female], BMI [≥25 kg/m² or <25 kg/m²], current smoking [yes or no], previous antiplatelet therapy [yes or no], diabetes [yes or no], chronic kidney disease [yes or no], history of ischaemic cardiovascular and cerebrovascular diseases [yes or no], haematoma volume [≥50 mL or <50 mL], and surgical methods [craniotomy, craniotomy plus craniectomy, or minimally invasive surgery]). Because the statistical analysis plan did not include a provision for correcting the widths of CIs for multiple comparisons when logistic-regression analyses were conducted on secondary outcomes, no definite conclusions could be drawn regarding these outcomes. A post-hoc mixed effect model that included trial site as a random effect was used to assess site effects. We conducted a post-hoc comparison between the two groups of the incidence of major cardiovascular, cerebrovascular, or peripheral vascular events within 14 days after surgery, using a logistic-regression model and a post-hoc logistic-regression model for primary efficacy outcome adjusted by age, sex, haematoma location and volume, and surgical method. We also did post-hoc analyses comparing the incidence of component events from the composite primary outcome. Statistical analyses were done using SAS software, version 9.4.

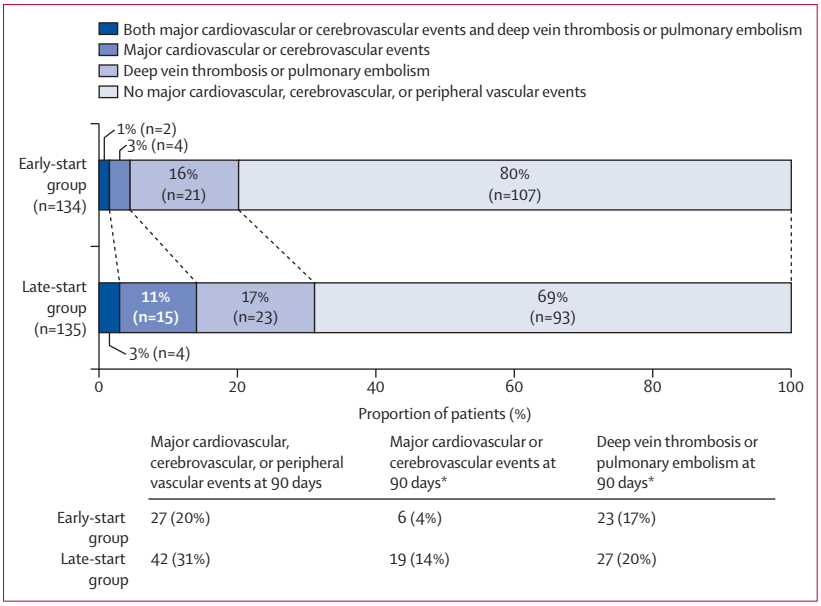
	Early-start group (N=134)	Late-start group (N=135)
Age, years	60 (50–66)	60 (52–66)
Sex		
Male	96 (72%)	99 (73%)
Female	38 (28%)	36 (27%)
Ethnicity*		
Han Chinese	131 (98%)	131 (97%)
Other	3 (2%)	4 (3%)
BMI, kg/m²	25·6 (24·1–27·3)	25·8 (23·9–27·5)
Medical history before haemorrhage		
Hypertension	119 (89%)	124 (92%)
Diabetes	20 (15%)	28 (21%)
Dyslipidaemia	15 (11%)	13 (10%)
Previous ischaemic stroke	28 (21%)	28 (21%)
Previous transient ischaemic attack	87 (65%)	91 (67%)
Previous haemorrhagic stroke	7 (5%)	8 (6%)
Coronary heart disease	14 (10%)	12 (9%)
Chronic kidney disease	14 (10%)	19 (14%)
Current smoker	35 (26%)	41 (30%)
Previous antiplatelet therapy before haemorrhage	30 (22%)	31 (23%)
Previous lipid-lowering therapy before haemorrhage	32 (24%)	31 (23%)
Modified Rankin Scale score before surgery†	4 (4–4)	4 (4–5)
Glasgow Coma Scale score before surgery‡	11 (8–12)	11 (8–12)
Haematoma location		
Supratentorial lobar	35 (26%)	37 (27%)
Supratentorial deep	86 (64%)	84 (62%)
Infratentorial	13 (10%)	14 (10%)
Haematoma volume before surgery, mL	53·1 (35·5–70·5)	53·1 (35·1–70·7)
Intraventricular haemorrhage before surgery	65 (49%)	64 (47%)
Time from symptom onset to surgery, h	7·2 (6·0–24·1)	8·4 (5·8–25·3)
Time from end of surgery to randomisation, h	71·5 (71·3–71·9)	71·4 (71·1–71·8)
Systolic blood pressure, mm Hg		
At admission	172 (148–196)	170 (141–190)
After standard medical therapy§	131 (127–136)	135 (125–139)
At randomisation	132 (128–139)	133 (127–136)
Surgical procedure		
Craniotomy	32 (24%)	33 (24%)
Craniectomy	19 (14%)	21 (16%)
Minimally invasive surgery	83 (62%)	81 (60%)

Data are n (%) or median (IQR). *Ethnicity was reported by the patient and verified by an identification card. The term other comprises Chinese ethnicities other than Han people (in this study, Manchu, Mongol, and Korean Chinese people). †The modified Rankin scale score assesses neurological function, with scores ranging from 0 to 6, with 0–3 indicating no disability to moderate disability and 4–6 indicating moderately severe disability to death. ‡Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating poorer consciousness. §Measured before anaesthesia.

Table 1: **Demographic and clinical characteristics of patients at baseline**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.



	Major cardiovascular, cerebrovascular, or peripheral vascular events at 90 days	Major cardiovascular or cerebrovascular events at 90 days*	Deep vein thrombosis or pulmonary embolism at 90 days*
Early-start group	27 (20%)	6 (4%)	23 (17%)
Late-start group	42 (31%)	19 (14%)	27 (20%)

Figure 2: **Distribution of major cardiovascular, cerebrovascular, or peripheral vascular events within 90 days after surgery in the intention-to-treat population**
*Includes participants who had both major cardiovascular or cerebrovascular events and deep vein thrombosis or pulmonary embolism.

	Early-start group (N=134)	Late-start group (N=135)	Odds ratio* (95% CI)	p value
Primary outcome				
Major cardiovascular, cerebrovascular, or peripheral vascular events within 90 days after surgery	27 (20%)	42 (31%)	0·56 (0·32–0·98)	0·041
Secondary outcomes				
Death within 90 days after surgery	10 (7%)	21 (16%)	0·44 (0·20–0·97)	0·042
In-hospital death	4 (3%)	4 (3%)	1·01 (0·25–4·12)	0·99
Modified Rankin Scale score of 0–3 at 90 days after surgery†	110 (82%)	104 (77%)	1·37 (0·75–2·48)	0·31
Glasgow Outcome Scale score of 3–5 at 90 days after surgery‡	117 (87%)	111 (82%)	1·49 (0·76–2·92)	0·25
Safety outcomes				
Any intracranial bleeding within 90 days after surgery	1 (1%)	4 (3%)	0·25 (0·03–2·23)	0·21
Any symptomatic intracranial bleeding within 90 days after surgery	1 (1%)	2 (1%)	0·50 (0·05–5·58)	0·57
Any moderate or severe bleeding events within 90 days after surgery	4 (3%)	6 (4%)	0·66 (0·18–2·40)	0·53

Data are n (%) unless otherwise indicated. *For all efficacy outcomes, treatment effect is reported as odds ratio; for safety outcomes, relative risk is reported as odds ratio. †Modified Rankin Scale scores range from 0 to 6, with 0–3 indicating no disability to moderate disability and 4–6 indicating moderately severe disability to death. ‡Glasgow Outcome Scale scores range from 1 to 5, with 3–5 representing severe disability to good recovery and 1–2 representing persistent vegetative state or death.

Table 2: **Primary, secondary, and safety outcomes**

Results

From May 1, 2021, to May 1, 2023, 7323 patients with spontaneous intracerebral haemorrhage were screened at eight medical centres in China. 269 (3·7%) patients were enrolled and randomly assigned: 134 to the early-start group and 135 to the late-start group (figure 1; appendix p 11). 7054 (96·3%) patients were excluded: 4451 patients with spontaneous intracerebral haemorrhage did not undergo neurosurgical treatment; 773 patients had traumatic intracerebral haemorrhage; 284 patients were not at high risk of major cardiovascular, cerebrovascular, or peripheral vascular events; and 1475 patients were excluded for other reasons; 71 patients were subsequently excluded owing to new postoperative spontaneous intracerebral haemorrhage or new major cardiovascular, cerebrovascular, or peripheral vascular events before randomisation (figure 1, appendix p 13). All 269 randomly assigned patients completed the 90-day follow-up and were included in the intention-to-treat population, and no primary outcome data were missing for these patients. 30 patients were excluded from the per-protocol analysis either because of poor medication adherence (six in the early-start group and four in the late-start group) or because they died of causes other than major cardiovascular, cerebrovascular, or peripheral vascular events (seven in the early-start group and 13 in the late-start group). Concomitant treatments within 90 days after surgery and details of neurosurgical procedures are reported in the appendix (pp 14–15).

The baseline demographic and clinical characteristics of the patients were similar in the two groups (table 1). The median age was 60·2 years (IQR 52·0–66·5); 195 (72%) of 269 patients were male and 74 (28%) were female. Haematomas were primarily supratentorial in location: supratentorial and deep in 170 (63%) of 269 patients, supratentorial and lobar in 72 (27%) patients, and infratentorial in 27 (10%) patients. The median haematoma volume was 53·1 mL (IQR 35·4–70·7). 129 (48%) of 269 patients had intraventricular haemorrhage. The median time from symptom onset to surgery was 8·2 h (IQR 6·0–24·4). 65 (24%) of 269 patients had a craniotomy, 40 (15%) had a craniectomy, and 164 (61%) had minimally invasive surgery. Local thrombolytics (urokinase) to disperse the intracerebral haemorrhage were administered in 118 (44%) of 269 patients: 57 (43%) of 134 patients in the early-start group and 61 (45%) of 135 patients in the late-start group. 61 (23%) of 269 patients did not receive antihypertensive therapy before spontaneous intracerebral haemorrhage and 254 (94%) of 269 patients received postoperative antihypertensive therapy.

Major cardiovascular, cerebrovascular, or peripheral vascular events occurred within 90 days after surgery in 27 (20%) of 134 patients in the early-start group (four patients had ischaemic major cardiovascular or cerebrovascular events, 21 had deep venous thrombosis or pulmonary embolism, and two had both a cardiovascular or cerebrovascular event and a deep vein thrombosis or pulmonary embolism) and 42 (31%) of 135 patients in the late-start group (15 patients had ischaemic major cardiovascular or cerebrovascular events, 23 had deep venous thrombosis or pulmonary

	Number of patients	Early-start group (N=134)	Late-start group (N=135)	Odds ratio (95% CI)	p_{trend}	$p_{interaction}$
Overall	**269**	**27 (20%)**	**42 (31%)**	**0·56 (0·32–0·98)**	**0·041**	
Age						0·28
≥65 years	90	9 (19%)	16 (38%)	0·38 (0·14–0·98)	0·044	
<65 years	179	18 (21%)	26 (28%)	0·68 (0·34–1·36)	0·28	
Sex						0·63
Male	195	19 (20%)	32 (32%)	0·52 (0·27–1·00)	0·048	
Female	74	8 (21%)	10 (28%)	0·69 (0·24–2·02)	0·50	
BMI						0·48
≥25 kg/m²	159	13 (17%)	26 (31%)	0·45 (0·21–0·96)	0·040	
<25 kg/m²	110	14 (24%)	16 (31%)	0·72 (0·31–1·66)	0·44	
Current smoker						0·39
Yes	76	9 (26%)	12 (29%)	0·84 (0·30–2·31)	0·73	
No	193	18 (18%)	30 (32%)	0·47 (0·24–0·93)	0·029	
Previous antiplatelet therapy						0·80
Yes	61	12 (40%)	15 (48%)	0·71 (0·26–1·96)	0·51	
No	208	15 (14%)	27 (26%)	0·48 (0·24–0·97)	0·041	
Diabetes						0·76
Yes	48	5 (25%)	9 (32%)	0·70 (0·20–2·55)	0·59	
No	221	22 (19%)	33 (31%)	0·54 (0·29–1·00)	0·049	
Previous ischaemic cardiovascular and cerebrovascular diseases						0·31
Yes	219	26 (24%)	41 (37%)	0·53 (0·29–0·95)	0·032	
No	50	1 (4%)	1 (4%)	1·00 (0·06–16·93)	1·00	
Chronic kidney disease						0·18
Yes	33	10 (71%)	12 (63%)	1·46 (0·33–6·46)	0·62	
No	223	12 (11%)	24 (22%)	0·43 (0·20–0·90)	0·026	
Haematoma volume						0·49
≥50 mL	148	12 (16%)	22 (30%)	0·44 (0·20–0·98)	0·044	
<50 mL	121	15 (25%)	20 (32%)	0·72 (0·32–1·58)	0·41	
Surgical method						0·46
Craniotomy	65	7 (22%)	17 (52%)	0·26 (0·09–0·78)	0·016	
Craniectomy	40	10 (53%)	5 (24%)	3·56 (0·92–13·70)	0·065	
Minimally invasive surgery	164	10 (12%)	20 (25%)	0·42 (0·18–0·96)	0·040	

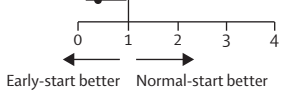


Figure 3: **Subgroup analyses of the incidence of major cardiovascular, cerebrovascular, or peripheral vascular events within 90 days**
Data for the early-start and late-start groups are number of patients with event (%). The trial was not powered to draw conclusions based on the results of the subgroup analyses.

embolism, and four had both a cardiovascular or cerebrovascular event and a deep vein thrombosis or pulmonary embolism; OR 0·56 [95% CI 0·32–0·98]; p=0·041; figure 2, table 2, appendix p 16). Of 69 new ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events, 41 (59%) occurred within 14 days after surgery. In a post-hoc analysis, a lower incidence of such events was found in the early-start group (13 [10%] of 134 patients) than in the late-start group (28 [21%] of 135 patients) within 14 days after surgery (p=0·012, appendix p 16). This result of risk analysis for 90-day ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events between the two groups remained consistent after adjustment for age, sex, haematoma location and volume, and surgical method (appendix p 17). The post hoc mixed-effect model analysis indicated that the trial-site effects were insignificant (appendix p 18). The results of our post-hoc analyses of individual parts of the primary outcome are reported in the appendix (p 16).

In secondary outcome analysis, the 90-day mortality rate was 7% (ten of 134 patients) in the early-start group and 16% (21 of 135 patients) in the late-start group (OR 0·44 [95% CI 0·20–0·97]; p=0·042). In-hospital mortality, mRS scores of 0–3, and GOS scores of 3–5 did not differ between groups at 90 days (table 2).

For the primary outcome, the efficacy of early-start antiplatelet therapy was similar among some predefined subgroups, including patients with ischaemic cardiovascular and cerebrovascular diseases, patients without chronic kidney disease, patients who had a craniotomy, and patients who had minimally invasive surgery (figure 3)—although the trial was underpowered for these analyses. The results of the per-protocol sensitivity analysis for the primary outcome were similar to those obtained for the intention-to-treat population (appendix pp 12, 19).

	Early-start group (N=134)	Late-start group (N=135)	p value
Serious adverse events other than bleeding events			
Overall	57 (43%)	57 (42%)	0·96*
Blood and lymphatic disorders	1 (1%)	0	0·50†
Hepatobiliary disorders	4 (3%)	5 (4%)	>0·99†
Infections and infestations	0	1 (1%)	>0·99†
Nervous system disorders	7 (5%)	8 (6%)	0·80*
Renal and urinary disorders	3 (2%)	2 (1%)	0·68†
Respiratory, thoracic, and mediastinal disorders	42 (31%)	41 (30%)	0·86*
Pneumonia	41 (31%)	39 (29%)	0·76*
Adverse events‡			
Overall	19 (14%)	16 (12%)	0·96*
Cardiac disorders	2 (1%)	5 (4%)	0·25†
Gastrointestinal disorders	5 (4%)	4 (3%)	0·73†
Skin and subcutaneous tissue disorders	5 (4%)	0	0·023†
Respiratory, thoracic, and mediastinal disorders	7 (5%)	7 (5%)	0·99†

Data are n (%). Patients with multiple events of one type were counted once. *Calculated by χ^2 test. †Calculated by Fisher's exact test. ‡Adverse events did not include serious adverse events.

Table 3: **Serious adverse events other than bleeding events and adverse events up to 90 days**

The primary safety outcome (new intracranial bleeding within 90 days after surgery) occurred in one (1%) of 134 patients in the early-start group and four (3%) of 135 patients in the late-start group (OR 0·25 [95% CI 0·03–2·23]; p=0·21; table 2, appendix p 20). The incidence of symptomatic intracranial bleeding or of any moderate or severe bleeding (as defined by BARC criteria) within 90 days after surgery did not differ between groups (table 2). Other (non-bleeding) serious adverse events occurred in 57 (43%) of 134 patients in the early-start group and 57 (42%) of 135 patients in the late-start group (table 3; appendix p 21). Adverse events occurred in 19 (14%) of 134 patients in the early-start group and 16 (12%) of 135 patients in the late-start group (table 3; appendix p 22).

Discussion

We found that early initiation of antiplatelet therapy—on the third postoperative day—was safe and associated with lower risk of major cardiovascular, cerebrovascular, or peripheral vascular events in patients who were undergoing surgery for spontaneous intracerebral haemorrhage and at high risk of such postoperative ischaemic events. No significant difference was observed in the rate of new intracranial bleeding or moderate or severe extracranial bleeding between patients in the early-start and late-start groups. Our findings favour early initiation of antiplatelet therapy in patients with intracerebral haemorrhage at high risk of postoperative ischaemic events.

Previous studies have attempted to establish the safety and efficacy of antiplatelet therapy after spontaneous intracerebral haemorrhage; however, results were mixed and patients undergoing neurosurgery were not included. A large retrospective study reported no difference in new ischaemic or haemorrhagic events when antiplatelet therapy was initiated within 30 days or 31–365 days after spontaneous intracerebral haemorrhage, although subgroup analysis suggested potential benefit for neurological outcome.[10] The RESTART trial found that restarting antiplatelet therapy after spontaneous intracerebral haemorrhage was safe but did not prevent new ischaemic events.[11] The POISE-2 trial showed that administration of acetylsalicylic acid early in the postsurgical period did not lead to fewer postoperative major cardiovascular events in patients undergoing non-cardiac surgery.[8] By contrast, our trial found that, among patients at high risk of ischaemic events who underwent surgery for spontaneous intracerebral haemorrhage, starting antiplatelet therapy on the third postoperative day decreased the risk of ischaemic events compared with starting on the 30th postoperative day. More than half of the primary outcome events occurred within 14 days after surgery. These findings are of interest because previous studies excluded patients undergoing neurosurgery for spontaneous intracerebral haemorrhage and, compared with our study, had longer delays and greater variation in the initiation of antiplatelet therapy within the early-start groups. According to our subgroup analyses, this decreased risk applied mainly to patients who had craniotomy or minimal invasive surgery; no significant protective effect of an early start to acetylsalicylic acid therapy was observed in patients who had craniectomy after spontaneous intracerebral haemorrhage. However, this analysis was underpowered owing to the small number of patients. Notably, in this study, many patients who had ischaemic cerebrovascular and cardiovascular diseases (eg, transient ischaemic attack) before spontaneous intracerebral haemorrhage had not previously received appropriate treatment, owing to insufficient compliance with stroke guidelines.[24] Given that most of these patients are aged at least 60 years and are at high risk of ischaemic diseases, the use and timing of antithrombotic therapy in this population requires attention.

Acetylsalicylic acid can inhibit platelet function and protect patients against ischaemic events. Our post-hoc analyses suggest that, for patients with spontaneous intracerebral haemorrhage, starting acetylsalicylic acid therapy early after surgery can reduce the incidence of postoperative major cardiovascular and cerebrovascular events (ie, the primary outcome excluding peripheral events; appendix p 16). Deep vein thrombosis is mainly caused by venous hypercoagulability and abnormal haemodynamic conditions. Antiplatelet therapy has also shown potential for postoperative thromboprophylaxis.[3,25,26] Although the incidence of deep vein thrombosis and pulmonary embolism in our study was not significantly different between the early-start and late-start groups, we did observe a numerical reduction in such events in the early-start group. However, additional trials with larger sample sizes are needed to investigate whether antiplatelet

therapy could prevent postoperative deep vein thrombosis events in patients with spontaneous intracerebral haemorrhage after neurosurgery.

Previous trials found that postoperative intracranial rebleeding events occurred in 3–9% of patients with spontaneous intracerebral haemorrhage.[27,28] In our trial, which enrolled patients without intracranial rebleeding within 72 h after surgery, intracranial bleeding events occurred in less than 1% of patients in the early-start group and the risk of any intracranial bleeding event was not significantly different between the two groups. Our data also showed no significant difference between the groups in secondary safety outcomes, including moderate or severe bleeding and symptomatic intracranial bleeding, although these results cannot be considered definitive owing to the low incidence of these events. These findings suggest that the early initiation of antiplatelet therapy is safe after surgery for spontaneous intracerebral haemorrhage, similar to the results of the RESTART trial and other studies.[10,11,29] Notably, patients had neurological examinations and postoperative neuroimaging before the initiation of antiplatelet therapy, which ensured that antiplatelet therapy was not administered in people who had new spontaneous intracerebral haemorrhage. Other randomised controlled trials—eg, the ongoing ASPIRING trial (NCT04522102) of acetylsalicylic acid, which involves a greater number of patients with spontaneous intracerebral haemorrhage than E-start—could help to establish whether our results can be generalised to patients with spontaneous intracerebral haemorrhage who do not undergo neurosurgery.

Previous studies have shown that ischaemic events are a major cause of death and poor outcome during long-term follow-up after spontaneous intracerebral haemorrhage.[4,29] We observed a reduction in 90-day mortality in patients in the early-start group. The ENRICH,[27] SWITCH,[30] and MISICH[31] trials have shown that surgical treatment can reduce poor outcomes in patients with spontaneous intracerebral haemorrhage. The 2022 guideline for the management of patients with spontaneous intracerebral haemorrhage from the American Heart Association and the American Stroke Association[32] recommended surgical treatment for patients with spontaneous intracerebral haemorrhage with broader surgical indications than those in the current study: those with a supratentorial haematoma of volume greater than 20 mL to 30 mL; Glasgow Coma Scale scores in the moderate range (5–12); or a cerebellar haematoma volume of 15 mL or more. Such recommendations could mean that more patients with severe spontaneous intracerebral haemorrhage receive surgical treatment in the future than those in the current study (who were managed according to the 2015 version of the guideline). Our data showed that more than 10% of screened patients were at high risk of postoperative ischaemic events. An early start to acetylsalicylic acid therapy could protect patients with spontaneous intracerebral haemorrhage against major cardiovascular, cerebrovascular, and peripheral vascular events and reduce mortality. However, we found no significant difference in functional outcomes between the early-start and the late-start groups, although our trial was not powered for this specific analysis. Further trials are needed to establish the effect of early antiplatelet therapy on functional outcomes.

Our trial has several limitations. First, 97% of the participants were Han Chinese and our results might not be generalisable to patients of other ethnicities. Second, this trial included only patients at a high risk of postoperative ischaemic events. Patients at a low or medium risk of such events might not benefit from antiplatelet therapy. Third, this study included only patients with spontaneous intracerebral haemorrhage who were receiving surgical treatment, the maximum age was 70 years, and haematomas were mainly supratentorial and deep; our results might therefore not be generalisable to other patient groups. Fourth, patients were screened for cerebral amyloid angiopathy on the basis of the non-contrast CT scan according to the 2018 modified Boston criteria. The percentage of spontaneous intracerebral haemorrhage due to cerebral amyloid angiopathy might be underestimated in this trial. Fifth, because anticoagulant therapy was not administered, deep vein thrombosis was the most common event in this trial. Given that anticoagulant therapy can lead to postoperative bleeding events, further studies are needed to ascertain an appropriate treatment protocol. Sixth, this trial considered only bleeding events as the safety outcome. Acetylsalicylic acid could also cause other severe adverse events, such as hypersensitivity reactions. Incomplete safety data could limit our conclusion, and we might have missed such events. Finally, the short follow-up interval (90 days) also limits our conclusions and would not capture any late ischaemic or haemorrhagic events that might occur during extended follow-up.[1]

Starting acetylsalicylic acid therapy early after surgery for spontaneous intracerebral haemorrhage in patients at high risk of postoperative ischaemic events resulted in fewer postoperative major cardiovascular, cerebrovascular, and peripheral vascular events than delaying acetylsalicylic acid therapy, with no increased risk of bleeding. Whether the early initiation of acetylsalicylic acid therapy is safe and improves clinical outcomes for all patients with spontaneous intracerebral haemorrhage requires further research.

Contributors

SW, YC, JZhao, QL, and JW participated in study design. SM, XT, and KW developed the protocol. SM, XT, KW, XuC, SC, SG, XLi, ML, LP, XS, JS, JP, KZ, JZhang, YL, YY, ZW, XN, YF, CL, HT, NW, JL, ZM, XLu, BN, BZ, DK, XiC, and YanZ enrolled patients. YW and YananZ were members of the independent monitoring committee. AW did the statistical analysis. QL, SM, and KW contributed to data collation and the generation of tables and figures. QL and SM wrote the first draft of the manuscript with help from CZ, YA, KUd, SY, KUc, TM, HY, DH, RD,

and MRL. The manuscript was revised by all authors. SW and AW directly accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SW declares support for the present manuscript, paid to their institution, from the National Key Research and Development Program of China. All other authors declare no competing interests.

Data sharing

The study protocol, statistical analysis plan, informed consent forms, and study data—including de-identified participant data and a data dictionary defining each field in the set—will be made available, with no date restrictions, to qualified researchers on formal request and receipt of a signed material transfer agreement. Requests should be made, with a study proposal, to the study steering committee via the corresponding author. Data will be shared only with the approval of the steering committee and the institutional review board of Beijing Tiantan Hospital, Capital Medical University.

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