Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial

*RESTART Collaboration**

Summary

Background Antiplatelet therapy reduces the risk of major vascular events for people with occlusive vascular disease, although it might increase the risk of intracranial haemorrhage. Patients surviving the commonest subtype of intracranial haemorrhage, intracerebral haemorrhage, are at risk of both haemorrhagic and occlusive vascular events, but whether antiplatelet therapy can be used safely is unclear. We aimed to estimate the relative and absolute effects of antiplatelet therapy on recurrent intracerebral haemorrhage and whether this risk might exceed any reduction of occlusive vascular events.

Methods The REstart or STop Antithrombotics Randomised Trial (RESTART) was a prospective, randomised, open-label, blinded endpoint, parallel-group trial at 122 hospitals in the UK. We recruited adults (≥18 years) who were taking antithrombotic (antiplatelet or anticoagulant) therapy for the prevention of occlusive vascular disease when they developed intracerebral haemorrhage, discontinued antithrombotic therapy, and survived for 24 h. Computerised randomisation incorporating minimisation allocated participants (1:1) to start or avoid antiplatelet therapy. We followed participants for the primary outcome (recurrent symptomatic intracerebral haemorrhage) for up to 5 years. We analysed data from all randomised participants using Cox proportional hazards regression, adjusted for minimisation covariates. This trial is registered with ISRCTN (number ISRCTN71907627).

Findings Between May 22, 2013, and May 31, 2018, 537 participants were recruited a median of 76 days (IQR 29–146) after intracerebral haemorrhage onset: 268 were assigned to start and 269 (one withdrew) to avoid antiplatelet therapy. Participants were followed for a median of 2·0 years (IQR [1·0– 3·0]; completeness 99·3%). 12 (4%) of 268 participants allocated to antiplatelet therapy had recurrence of intracerebral haemorrhage compared with 23 (9%) of 268 participants allocated to avoid antiplatelet therapy (adjusted hazard ratio 0·51 [95% CI 0·25–1·03]; p=0·060). 18 (7%) participants allocated to antiplatelet therapy experienced major haemorrhagic events compared with 25 (9%) participants allocated to avoid antiplatelet therapy (0·71 [0·39–1·30]; p=0·27), and 39 [15%] participants allocated to antiplatelet therapy had major occlusive vascular events compared with 38 [14%] allocated to avoid antiplatelet therapy (1·02 [0·65–1·60]; p=0·92).

Interpretation These results exclude all but a very modest increase in the risk of recurrent intracerebral haemorrhage with antiplatelet therapy for patients on antithrombotic therapy for the prevention of occlusive vascular disease when they developed intracerebral haemorrhage. The risk of recurrent intracerebral haemorrhage is probably too small to exceed the established benefits of antiplatelet therapy for secondary prevention.

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*Members listed at end of the paper

Correspondence to:
Prof Rustam Al-Shahi Salman, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh EH16 4SB, UK
rustam.al-shahi@ed.ac.uk

Introduction

Adults with stroke due to spontaneous intracerebral haemorrhage often have a history of occlusive vascular disease, such as myocardial infarction or ischaemic stroke.[1] Consequently, at least a third of adults in high-income countries are taking oral antithrombotic (antiplatelet or anticoagulant) drugs at the onset of intracerebral haemorrhage.[2] Generally, antithrombotic drugs are immediately discontinued because of the risk of early haematoma growth. Discontinuation of these drugs is often permanent because of the perceived risk of recurrent intracerebral haemorrhage. However, the risk of occlusive vascular events might be higher,[3] so resumption of antithrombotic therapy might be beneficial overall.

Results of randomised trials have found a favourable balance of the benefits and risks of antiplatelet and anticoagulant therapy for the secondary prevention of occlusive vascular disease for a variety of conditions, but these trials excluded people with a history of major bleeding.[4–6] Therefore, no published randomised trials are available on whether long-term antithrombotic therapy is safe or beneficial for survivors of intracerebral haemorrhage overall,[7] or in subgroups who are at higher risk of bleeding, such as people with lobar intracerebral haemorrhage.[1]

The use of antiplatelet therapy for about 2 days did not result in adverse effects for patients who had been enrolled in randomised trials of aspirin, without

Research in context

Evidence before this study

The Antithrombotic Trialists' Collaboration meta-analysis of randomised controlled trials found that aspirin use for the secondary prevention of occlusive vascular disease reduces risk of major vascular events, even though it might increase the risk of intracranial haemorrhage (a composite of intracerebral, subarachnoid, or subdural haemorrhages). However, these trials excluded patients with intracerebral haemorrhage, the commonest subtype of intracranial haemorrhage with the worst outcome. We searched the Cochrane Stroke Group Register, the Cochrane Central Register of Controlled Trials, Ovid MEDLINE (from 1948), Ovid Embase (from 1980), online registries of clinical trials, and bibliographies of relevant publications on Jan 28, 2019, (appendix) for randomised controlled trials of starting versus avoiding antiplatelet therapy after intracerebral haemorrhage, from database inception until Jan 28, 2019, without language restrictions. We found no completed randomised controlled trials. A meta-analysis of observational studies found no difference in the risk of haemorrhagic events and a lower risk of occlusive vascular events associated with antiplatelet therapy resumption after any type of intracranial haemorrhage.

Added value of this study

The REstart or STop Antithrombotics Randomised Trial (RESTART) is the first randomised controlled trial comparing the effects of starting versus avoiding antiplatelet therapy for patients with previous intracerebral haemorrhage that occurred while taking antithrombotic (antiplatelet or anticoagulant) therapy. Participants allocated to start antiplatelet therapy experienced proportionally (but not statistically) fewer recurrences of intracerebral haemorrhage (adjusted hazard ratio 0·51 [95% CI 0·25–1·03]; p=0·060), fewer major haemorrhagic events (0·71 [0·39–1·30]; p=0·27), and similar numbers of major occlusive vascular events (1·02 [0·65–1·60]; p=0·92), compared with participants allocated to avoid antiplatelet therapy. These results exclude all but a very modest increase in the risk of recurrent intracerebral haemorrhage with antiplatelet therapy. The risk of recurrent intracerebral haemorrhage is probably too small to exceed the established benefits of antiplatelet therapy for the secondary prevention of occlusive vascular disease.

Implications of all the available evidence

RESTART's findings provide reassurance about the safety of antiplatelet therapy after intracerebral haemorrhage that occurred while taking antithrombotic therapy. Replication of these findings and investigation of the possibility that antiplatelet therapy reduces the risk of recurrent intracerebral haemorrhage require further investigation in ongoing randomised trials (RESTART-Fr NCT02966119 and STATICH NCT03186729), a subsequent meta-analysis of RESTART, and an adequately powered definitive randomised controlled trial.

knowing their stroke was due to intracerebral haemorrhage.[8] In the longer term (months to years), findings from a systematic review and meta-analysis[9] of observational studies of patients with any type of intracranial haemorrhage (ie, intracerebral, subarachnoid, or subdural haemorrhage) showed lower risks of occlusive vascular events and no difference in haemorrhagic events associated with resumption compared with avoidance of antiplatelet therapy. Small, non-randomised observational studies of patients with intracerebral haemorrhage have reported similar associations with starting antiplatelet therapy compared with its avoidance.[10–14] Because of the paucity of evidence, no guidelines with strong recommendations about long-term antiplatelet therapy after intracerebral haemorrhage are available,[15,16] so variations in clinical practice occur.[3] Therefore, randomised controlled trials are needed to establish whether to use antiplatelet therapy after intracerebral haemorrhage.[7]

We initiated the REstart or STop Antithrombotics Randomised Trial (RESTART) with the aim of estimating the relative and absolute effects of starting versus avoiding antiplatelet therapy on recurrent symptomatic intracerebral haemorrhage and whether this risk might exceed any reduction of occlusive vascular events.[17].

For more on the **RUSH programme** see www.RUSH.ed.ac.uk

Methods

Study design

RESTART was an investigator-led, pragmatic, multicentre, prospective, randomised, open-label, blinded endpoint, parallel-group trial in 122 hospitals in the UK. The Scotland A Research Ethics Committee approved the trial protocol (Nov 2, 2012).[17] The trial co-sponsors were the University of Edinburgh and National Health Service Lothian Health Board. The patient reference group for the Research to Understand Stroke due to Haemorrhage (RUSH) programme reviewed the study materials and progress. The trial steering committee and co-sponsors approved the trial protocol and the statistical analysis plan.[17,18]

Participants

We included adults (≥18 years) who had survived at least 24 h after spontaneous intracerebral haemorrhage confirmed by brain imaging and were taking antithrombotic (antiplatelet or anticoagulant) therapy for the prevention of occlusive vascular disease at the onset of intracerebral haemorrhage, after which therapy was discontinued. Patients were ineligible if the intracerebral haemorrhage was attributable to preceding head injury, haemorrhagic transformation of an ischaemic stroke, or intracranial haemorrhage without intracerebral haemorrhage; if they were still taking antithrombotic therapy at

the time of consent (ie, after intracerebral haemorrhage); if they were pregnant, breastfeeding, or of childbearing age and not taking contraception; or if they or their carer was unable to understand spoken or written English. Patients, or their nearest relative or representative if the patient did not have mental capacity, provided written informed consent in inpatient or outpatient hospital settings. Participants could be enrolled if they or their nearest relative, and their physician in secondary care, were uncertain about whether to start or avoid antiplatelet therapy and had consented, in which case randomisation was done at least 24 h after stroke symptom onset.[17]

Randomisation and masking

Investigators supplied complete information about participants' demographics, comorbidities, functional status, previous antithrombotic therapy, intracerebral haemorrhage, and their preferred antiplatelet therapy into a database via a secure web interface with in-built validation to ensure complete baseline data before randomisation. A central computerised randomisation system incorporating a minimisation algorithm randomly assigned participants (1:1) to start or avoid antiplatelet therapy. The algorithm randomly allocated the first participant with a probability of 0·5 to one group of the trial. Thereafter, adaptive stratification (ie, minimisation) allocated each subsequent participant with a probability of 0·8 to the group that minimised differences between the two groups of the trial with respect to five baseline variables: qualifying intracerebral haemorrhage location (lobar *vs* non-lobar); time since symptom onset (1–6 days, 7–30 days, >30 days); antiplatelet therapy preferred by the patient's physician if allocated to start (aspirin alone *vs* other antiplatelet therapy); participant age at randomisation (<70 years *vs* ≥70 years); and predicted probability of being alive and independent at 6 months (<0·15 *vs* ≥0·15).[19] The five variables were weighted equally, and the weights were constant over the duration of recruitment. The web interface displayed each participant's unique study identification number and their allocation to either starting or avoiding antiplatelet therapy, which was also sent in an email to all investigators at the hospital site, having been concealed until that point. If the participant was allocated to start antiplatelet therapy, the system reminded investigators to prescribe the prespecified preferred antiplatelet therapy within 24 h.

Treatment allocation was open to participants, the clinicians caring for them in primary and secondary care, and local investigators. Staff following up the participants at the trial coordinating centre were masked to treatment allocation. Outcome event adjudicators were masked to participant identity, treatment allocation, and drug use.

Procedures

Participants who had not already been imaged with MRI but complied with the trial's MRI protocol, and who were able and willing to undergo brain MRI, provided informed consent and had a brain MRI scan before randomisation. After randomisation, anyone of a panel of consultant neuroradiologists (PMW, DPM, DM, PB, JCduP, or YJ), who was masked to treatment allocation, used the web-based Systematic Image Review System tool to review anonymised DICOM images of diagnostic brain CT or MRI to confirm or refute eligibility and to support the adjudication of cerebral outcome events.

The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant. The comparator was a policy of avoiding antiplatelet therapy (ie, no placebo group). Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation. We measured adherence after randomisation regardless of treatment allocation by recording antiplatelet therapy use before the first outcome event according to the preceding clinic or hospital discharge form or follow-up questionnaire. We collected information about blood-pressure lowering drugs and blood pressure control at discharge and during follow-up.

We followed up participants by sending a postal questionnaire to their primary care practitioners (who hold a comprehensive lifelong medical record for each patient registered with them), followed by a postal questionnaire to surviving participants (or carers) who had not withdrawn, to check vital status, medication use, modified Rankin scale score, and the occurrence of outcomes. We sent questionnaires at set intervals after randomisation (6 months or 1 year, 2 years, 3 years, 4 years, and 5 years). Participants who did not respond to the questionnaire were interviewed by phone.[20,21]

We recorded serious adverse events (that were neither an outcome event nor an expected complication of stroke) via investigators if they occurred before hospital discharge or via primary care practitioners' annual reports of hospital admissions. Investigators reported protocol deviations and violations to the trial coordinating centre and the sponsor.

Monitoring included central statistical monitoring of trial conduct, data quality, and participant safety, supplemented by triggered onsite monitoring visits if required and detailed source data verification at the trial coordinating centre. All baseline and outcome data underwent completeness, range, consistency, validation, and logic checks within the web-based case report forms.

Outcomes

The primary outcome was fatal or non-fatal radiographically or pathologically proven recurrent symptomatic intracerebral haemorrhage assessed in all participants (except one participant who withdrew before the first follow-up).[17]

The secondary outcomes were a composite of all major haemorrhagic events and a composite of all major occlusive vascular events.[17] Major haemorrhagic events included recurrent symptomatic intracerebral haemorrhage (primary outcome), other forms of symptomatic spontaneous or traumatic intracranial haemorrhage, and symptomatic major extracranial haemorrhage at any site (requiring transfusion or endoscopic treatment or surgery, or resulting in death within 30 days).[18] Major occlusive vascular events were ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; and carotid, coronary, or peripheral arterial revascularisation procedures.[18] The composite secondary outcome of all major haemorrhagic or occlusive vascular events combined these two composite outcomes.[18] In the protocol, we had specified a composite secondary outcome of all major vascular events defined by the Antithrombotic Trialists' Collaboration (non-fatal myocardial infarction, non-fatal stroke [ischaemic, haemorrhagic, or uncertain cause], or death from a vascular cause).[4,17]

See Online for appendix

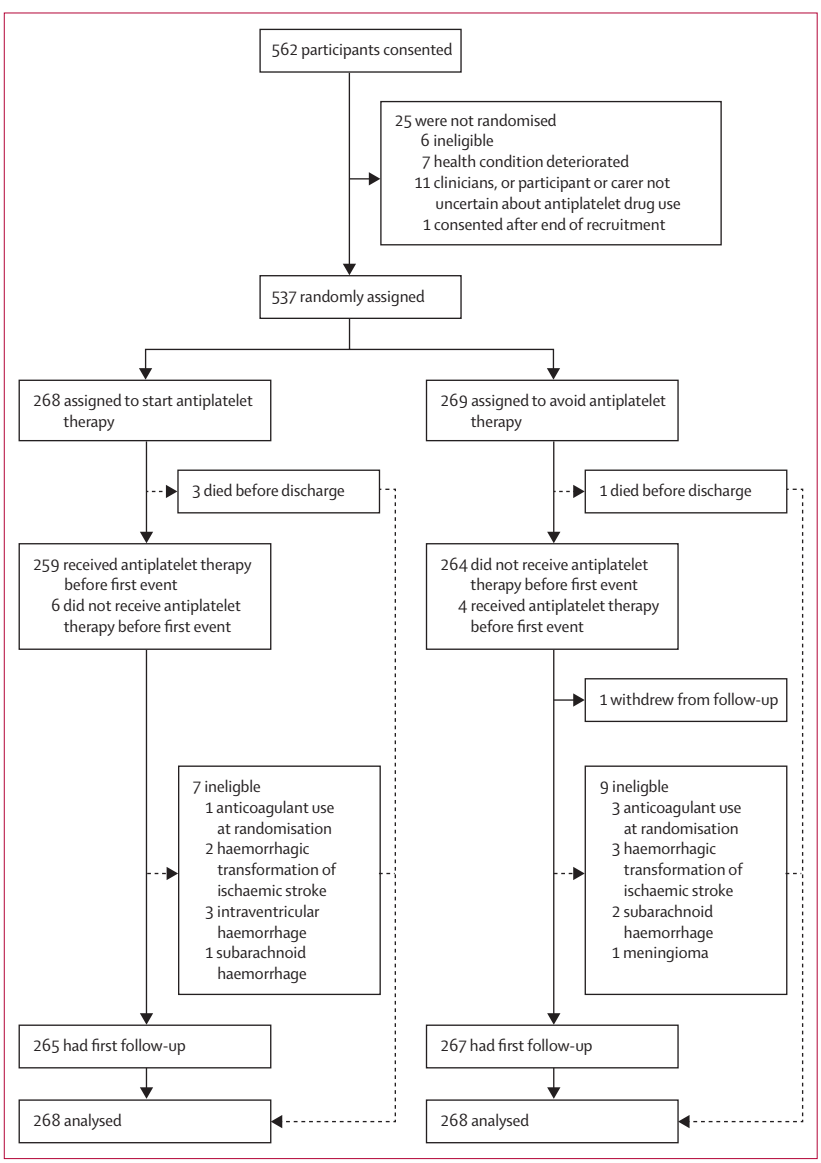

Figure 1: **Trial profile**

Two consultant neurologists (WNW and MRM) at the trial coordinating centre were internal assessors of reports of every outcome event, masked to treatment allocation and use of antithrombotic therapy, using all available source documentation including clinical records, death certificates, autopsy reports, imaging reports, outpatient clinic letters, and hospital discharge summaries. One consultant neurologist (TG) was an external assessor and reviewed the same information on a random sample of 25 internally assessed events. He agreed with the internal assessors for 24 (96%) events (appendix) and, therefore, the internal assessors' categorisations remained final. Standardised definitions guided the final categorisation of outcomes.[22,23]

Statistical analysis

We aimed to recruit 720 participants and follow them up for at least 2 years to cover several combinations of published estimates of the primary outcome event rate in cohort studies (1·8–7·4% per year)[1] and an up to four-times proportional increase in the absolute risk of the primary outcome with the use of antiplatelet therapy in observational studies.[10–12] For example, at the 5% significance level, the trial would have 90% power to detect a doubling of a primary outcome event rate of 4·5% per year, or 93% power to detect a four-times increase of a rate of 1% per year.[17]

Throughout the recruitment period, unmasked trial statisticians supplied the independent data monitoring committee with analyses of the accumulating baseline and follow-up data in strict confidence at least once every year, so that they could assess trial conduct, safety, and efficacy, and make recommendations to the trial steering committee. No formal fixed schedule of interim analyses was followed, but the data monitoring committee could advise the chairman of the trial steering committee if they thought the randomised comparisons provided proof beyond reasonable doubt that, for some patients, antiplatelet therapy was clearly indicated or contraindicated in clinical practice.

Without reference to data by randomised allocation or input from the unmasked trial statistician, the masked trial statistician (GDM) and chief investigator (RA-SS) prepared a statistical analysis plan that was approved by the trial steering committee before database lock, and then published.[18]

We estimated the survival function in each treatment group using a Kaplan-Meier survival analysis of time to first occurrence of a primary or secondary outcome event during all available follow-up after randomisation, censored at death unrelated to an outcome event or last available follow-up. We quantified completeness of follow-up as the proportion of participants with a complete follow-up questionnaire at each planned interval after

randomisation, and as the proportion of the planned duration of follow-up that was observed.[24] We quantified absolute differences in annual event rates. After assessing the proportional hazards assumption graphically and including a treatment by log(time) interaction, we compared the survival functions by allocated treatment using the log-rank test. We constructed an unadjusted Cox proportional hazards regression model and a second model adjusted for all five covariates included in the minimisation algorithm (which was the primary method of analysis) to calculate the hazard ratios (HRs). We prespecified a hierarchical testing of the primary outcome, key secondary outcomes, and other secondary outcomes, so we did not adjust the threshold of statistical significance for multiplicity.[18] We used the Mann–Whitney test to compare group summaries of modified Rankin scale scores by randomised group. We did sensitivity analyses by adding symptomatic stroke of uncertain subtype or deaths of undetermined cause to the primary outcome, and by calculating the cumulative incidence of all major haemorrhagic or occlusive vascular events.

We did prespecified exploratory subgroup analyses of the primary and secondary outcomes with statistical tests of interaction to estimate heterogeneity of treatment effect between the prespecified subgroups: the five covariates used by the minimisation algorithm, antithrombotic therapy before intracerebral haemorrhage, and history of atrial fibrillation.

The unmasked trial statistician (JS) did all statistical analyses with SAS version 9.4.

This trial is registered with ISRCTN (number ISRCTN71907627).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing and decision to publish this Article. The corresponding author had full access to all data in the trial and had final responsibility for the decision to submit for publication.

Results

Between May 22, 2013, and May 31, 2018, 562 participants consented to participate in the study, from 104 of 122 activated hospital sites (appendix, figure 1). 20 participants also enrolled in RESTART after they enrolled in the Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2) trial. Although the planned period of recruitment was extended by 1 year (until May 31, 2018), we did not achieve the planned sample size after a time-limited extension agreed by the funder, because only one in 12 eligible patients was recruited;[25] therefore, we increased the duration of follow-up by 1 year to accrue the planned numbers of person-years of follow-up and primary outcome events.

268 participants were randomly assigned to start antiplatelet therapy and 269 to avoid antiplatelet therapy (figure 1), of whom all but one participant in the avoidance group were included in the outcome analyses.

	Start antiplatelet therapy (n=268)	Avoid antiplatelet therapy (n=269)
Sex		
Male	173 (65%)	187 (70%)
Female	95 (35%)	82 (30%)
Age*		
Overall	77 (69–82)	76 (69–82)
<70 years	73 (27%)	73 (27%)
≥70 years	195 (73%)	196 (73%)
Ethnicity		
White	251 (94%)	242 (90%)
Asian	12 (4%)	18 (7%)
Black	4 (1%)	5 (2%)
Other	1 (<1%)	4 (1%)
Indication for antithrombotic therapy before intracerebral haemorrhage†		
At least one occlusive vascular disease		
With atrial fibrillation	42 (16%)	50 (19%)
Without atrial fibrillation	194 (72%)	189 (70%)
No occlusive vascular diseases		
With atrial fibrillation	19 (7%)	23 (9%)
Without atrial fibrillation	13 (5%)	7 (3%)
History of intracranial or extracranial haemorrhage†	22 (8%)	25 (9%)
Location of intracerebral haemorrhage*		
Lobar supratentorial	166 (62%)	166 (62%)
Non-lobar	102 (38%)	103 (38%)
Time since intracerebral haemorrhage symptom onset*		
Overall	80 (30–149)	71 (29–144)
1–6 days	10 (4%)	11 (4%)
7–30 days	59 (22%)	59 (22%)
>30 days	199 (74%)	199 (74%)
Probability of good 6-month outcome*[19]		
<0·15	48 (18%)	51 (19%)
≥0·15	220 (82%)	218 (81%)
Context of enrolment		
Hospital inpatient	87 (32%)	96 (36%)
Hospital outpatient	181 (68%)	173 (64%)
Participant consented	212 (79%)	213 (79%)
Proxy consented	56 (21%)	56 (21%)

Data are n (%) or median (IQR). *Variables used in the minimisation algorithm. †Complete list of comorbidities is in the appendix.

Table 1: **Baseline characteristics**

At baseline, participants in the two treatment groups were on average 76 years old, approximately two-thirds were male, and 92% were white (table 1). 62% of participants had lobar intracerebral haemorrhage, 88% had one or more previous occlusive vascular disease (mostly ischaemic heart disease, ischaemic stroke, or transient ischaemic attack), three-quarters had a history of high blood pressure, a quarter had diabetes, and a quarter had atrial fibrillation when they were randomised (appendix). Participants were randomly assigned to each

group a median of 76 days (IQR 29–146) after intracerebral haemorrhage onset. Half of the participants were taking aspirin, about a quarter clopidogrel, and approximately one-fifth oral anticoagulation at the onset of intracerebral haemorrhage (appendix). At baseline, participants' characteristics and use of antithrombotic therapy were well balanced for major prognostic factors and potential confounders (table 1). With the exception of 12 participants who were ineligible because their intracranial haemorrhage did not extend into the brain parenchyma or had intracerebral haemorrhages that were found to be secondary to a macrovascular cause (one cavernous malformation, one venous thrombosis, and one aneurysm) and four who were taking anticoagulants at randomisation, the remaining 522 (97%) participants had intracerebral haemorrhage without an underlying structural or macrovascular cause identified.

Follow-up ended on Nov 30, 2018. Four participants died (figure 1) before hospital discharge, and the remaining 533 participants were followed up at hospital or clinic discharge. Completeness of primary care practitioner questionnaires (79% by post, 16% by telephone, and 4% by both) was 100% at all follow-up timepoints (from 6 months to 4 years). Completeness of participant or carer questionnaires (60% by post, 38% by telephone, and 2% by both) was 99% at 6 months or at 1 year, 99% at 2 years, 98% at 3 years, and 94% at 4 years. We obtained 1064 of an intended 1071 person-years of follow-up (overall completeness 99·3%).

Immediate adherence to allocated treatment was good, with some decline over time: 99% at discharge, 93% after 6 months or 1 year, 89% after 2 years, 86% after 3 years, and 82% after 4 years (appendix). Few participants (≤10%) used anticoagulant therapy during follow-up (appendix). Most participants took at least one blood-pressure lowering drug during follow-up and achieved median systolic blood pressure 130 mm Hg, with good balance by treatment allocation (appendix).

The proportional hazards assumption was fulfilled for analyses of primary and secondary outcomes during follow-up.

For the primary outcome, 12 [4%] of 268 participants allocated to start antiplatelet therapy had recurrences of intracerebral haemorrhage compared with 23 [9%] of 268 participants who did not start therapy (adjusted HR 0·51 [95% CI 0·25–1·03]; p=0·060; tables 2, 3, figure 2, appendix). This proportional reduction in the primary outcome was similar in unadjusted and adjusted models, and in two sensitivity analyses involving the addition of symptomatic stroke of uncertain subtype (p=0·044) or death of undetermined cause (p=0·048) as possible occurrences of the primary outcome (table 3). 30-day case fatality after recurrent intracerebral haemorrhage was not different between participants starting antiplatelet therapy (5 [42%] of 12 participants) and those avoiding antiplatelet therapy (9 [39%] of 23 participants). No evidence was found of heterogeneity of the effects of antiplatelet therapy on the primary outcome in prespecified exploratory subgroup analyses (figure 3).

During follow-up (table 2), 104 (19%) participants died due to non-cardiovascular causes (n=57, 55%), primary or secondary outcome events (n=29, 28%), other cardiovascular deaths (n=16, 15%), or undetermined causes (n=2, 2%). 96 (18%) participants had at least one arterial major occlusive vascular event (including stroke of uncertain subtype), 46 (9%) had at least one major haemorrhagic event, 13 (2%) had at least one venous major occlusive vascular event, and 17 (3%) had a revascularisation procedure.

For the composite secondary outcomes,[18] 18 (7%) of 268 participants allocated to start antiplatelet therapy experienced major haemorrhagic events compared with 25 (9%) of 268 participants allocated to avoid antiplatelet therapy (adjusted HR 0·71 [95% CI 0·39–1·30]; p=0·27); 39 (15%) of 268 participants in the antiplatelet group had major occlusive vascular events compared with 38 (14%) of

	Start antiplatelet therapy (n=268)		Avoid antiplatelet therapy (n=268)	
	First event	All events	First event	All events
Primary outcome				
Recurrent symptomatic spontaneous intracerebral haemorrhage	12 (4%)	14	23 (9%)	27
Secondary outcomes				
Arterial events				
Major haemorrhagic events				
Spontaneous or traumatic intracranial extracerebral haemorrhage	4 (1%)	4	3 (1%)	3
Major extracranial haemorrhage	4 (1%)	4	0	0
Major occlusive vascular events				
Ischaemic stroke	19 (7%)	21	27 (10%)	28
Myocardial infarction	5 (2%)	5	8 (3%)	9
Peripheral arterial occlusion	5 (2%)	5	2 (1%)	2
Transient ischaemic attack	11 (4%)	12	18 (7%)	23
Retinal arterial occlusion	0	0	0	0
Mesenteric ischaemia	0	0	0	0
Stroke of uncertain subtype	0	0	1 (<1%)	1
Carotid, coronary, or peripheral arterial revascularisation procedures	12 (4%)	12	5 (2%)	5
Venous events				
Deep vein thrombosis	6 (2%)	6	2 (1%)	2
Pulmonary embolism	4 (1%)	4	1 (<1%)	1
Deaths				
Fatal outcome event	10 (4%)	10	19 (7%)	19
Other cardiovascular death	6 (2%)	6	8 (3%)	8
Sudden cardiac death	2 (1%)	2	0	0
Non-cardiovascular death	35 (13%)	35	22 (8%)	22
Undetermined cause	1 (<1%)	1	1 (<1%)	1

Data are n (%) or n.

Table 2: **Frequencies of the first occurrence and all primary and secondary outcome events during follow-up**

	Start antiplatelet therapy (n=268)	Avoid antiplatelet therapy (n=268)	Log-rank test p value	Unadjusted analysis		Adjusted analysis	
				HR (95% CI)	p value	HR (95% CI)	p value
Primary outcome							
Recurrent symptomatic spontaneous intracerebral haemorrhage	12	23	0·057	0·51 (0·26–1·03)	0·062	0·51 (0·25–1·03)	0·060
Sensitivity analyses of the primary outcome							
Recurrent symptomatic spontaneous intracerebral haemorrhage or symptomatic stroke of uncertain subtype	12	24	0·041	0·49 (0·25–0·99)	0·046	0·49 (0·24–0·98)	0·044
Recurrent symptomatic spontaneous intracerebral haemorrhage or death of undetermined cause	13	25	0·047	0·51 (0·26–1·00)	0·051	0·51 (0·26–0·99)	0·048
Secondary outcomes							
All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage)	18	25	0·27	0·71 (0·39–1·30)	0·27	0·71 (0·39–1·30)	0·27
All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial revascularisation procedures)	39	38	0·97	1·01 (0·65–1·58)	0·97	1·02 (0·65–1·60)	0·92
All major haemorrhagic or occlusive vascular events	54	61	0·42	0·86 (0·60–1·24)	0·42	0·86 (0·60–1·24)	0·43
Major occlusive vascular events*	45	52	0·39	0·84 (0·56–1·25)	0·39	0·84 (0·56–1·25)	0·39
Major vascular events (as defined by the Antithrombotic Trialists' Collaboration)	45	65	0·026	0·65 (0·45–0·95)	0·027	0·65 (0·44–0·95)	0·025

HR=hazard ratio. *As defined in the trial protocol.

Table 3: **Risks of first occurrence of primary and secondary outcome events during follow-up**

268 participants in the avoidance group (1·02 [0·65–1·60]; p=0·92); and 54 (20%) of 268 participants in the antiplatelet group had major haemorrhagic or occlusive vascular events compared with 61 (23%) of 268 participants in the avoidance group (0·86 [0·60–1·24]; p=0·43; table 3, appendix). In a sensitivity analysis, antiplatelet therapy did not reduce the cumulative incidence of all major haemorrhagic or occlusive vascular events (p=1·0). For the composite secondary outcome of all major vascular events specified in the trial protocol,[4,17] antiplatelet therapy seemed to reduce the risk of non-fatal myocardial infarction, non-fatal stroke (ischaemic, haemorrhagic, or uncertain cause), or death from a vascular cause (adjusted HR 0·65 [95% CI 0·44–0·95]; p=0·025; table 3, appendix). We found no evidence of heterogeneity of the effects of antiplatelet therapy on these secondary outcomes in prespecified exploratory subgroup analyses (appendix) or in the distribution of the modified Rankin scale score during follow-up (appendix). Few serious adverse events occurred (n=11), which were neither outcomes nor expected complications of stroke (appendix).

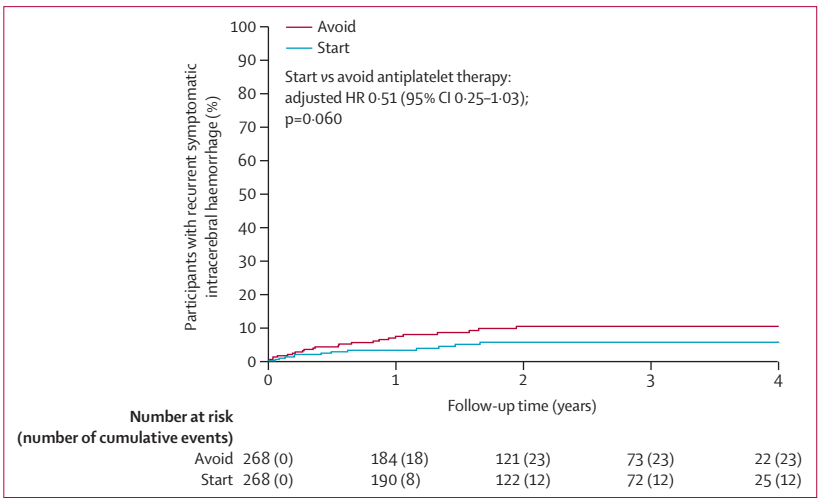

Figure 2: **Kaplan-Meier plot of the first occurrence of recurrent symptomatic intracerebral haemorrhage**
Numbers at risk refer to survivors under follow-up at the start of each year according to treatment allocation. Cumulative events indicate the participants in follow-up with a first event. HR=hazard ratio.

Discussion

In this randomised trial of 537 survivors of an intracerebral haemorrhage while on antithrombotic therapy, starting antiplatelet therapy might have reduced the risk of recurrent symptomatic intracerebral haemorrhage. The results exclude all but a very modest increase in the risk of recurrent intracerebral haemorrhage with antiplatelet therapy, which seems too small to exceed the established benefits of antiplatelet therapy for secondary prevention.[4] Therefore, starting antiplatelet therapy seems to be safe and might be beneficial in patients who survived a median of 76 days after intracerebral haemorrhage, most of whom had good functional ability at baseline and a higher probability of good functional outcome at 6-month follow up (table 1, appendix).[19] Our findings, alongside published observational studies,[9–14] provide reassurance about the use of long-term antiplatelet therapy in a range of patients after intracerebral haemorrhage associated with antithrombotic therapy.

RESTART is the first randomised trial comparing starting versus avoiding antiplatelet therapy after

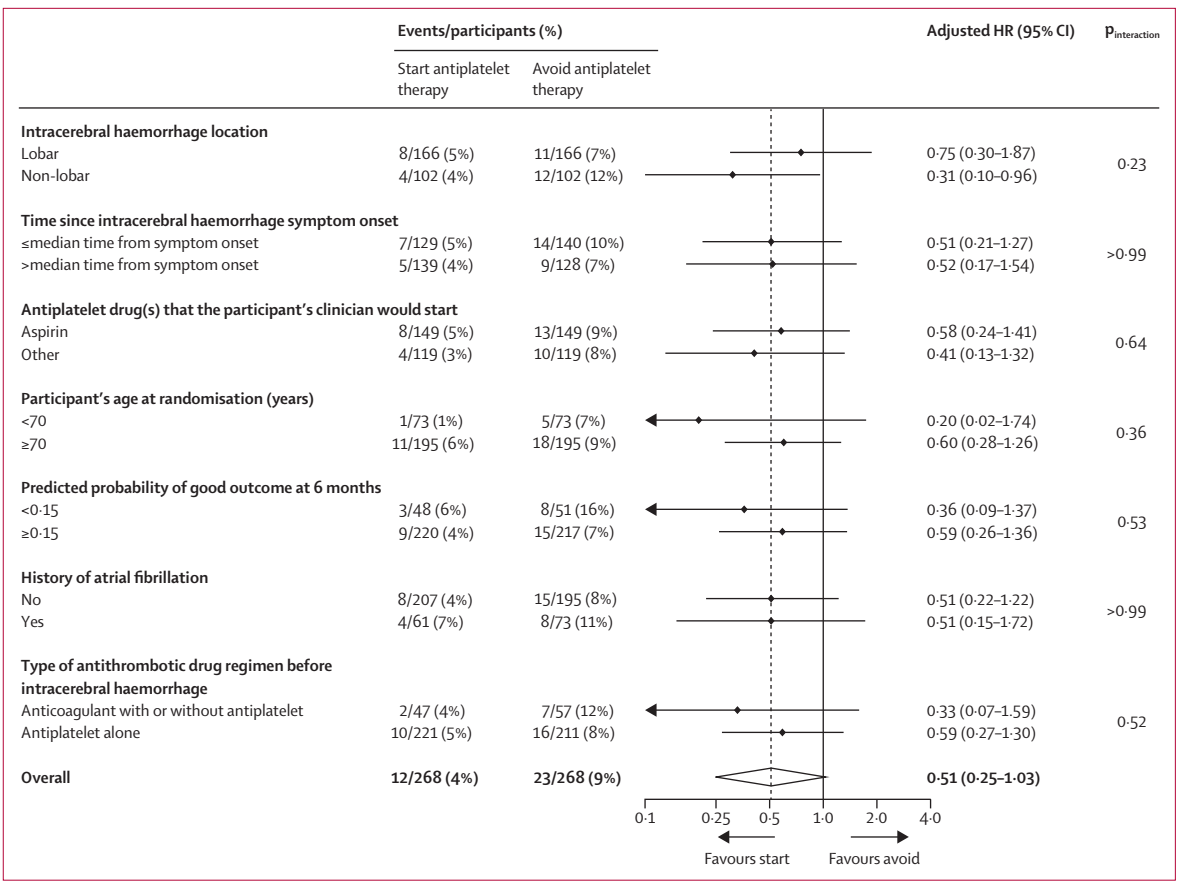

Figure 3: **Prespecified exploratory subgroup analyses of the risk of first recurrent symptomatic intracerebral haemorrhage**

intracerebral haemorrhage,[7] and provides more reliable estimates of the effects of antiplatelet therapy than previous observational studies.[9–14] We minimised selection bias by using central, computerised random sequence generation and concealing allocation on the web application until all baseline data were entered. The recruited participants were comparable to European hospital-based and population-based cohorts of survivors of intracerebral haemorrhage who had previously taken antithrombotic therapy.[3] Blood pressure was controlled for both groups throughout follow-up: half of the participants had a systolic blood pressure below the recommended target in the UK national stroke guideline and antihypertensive drug use was similar between groups. We minimised attrition bias by achieving 99·3% completeness of follow-up. The risk of recurrent intracerebral haemorrhage was at the lower end of the ranges reported in cohort studies,[1] but similar to the 0·61–1·20% annual rates observed with cilostazol or aspirin use in the recent PICASSO trial.[26] The risk of gastrointestinal haemorrhage was low (table 2), possibly due to the prevalence of proton pump inhibitor use in a contemporary population of older stroke survivors.[27] We masked outcome assessors to treatment allocation group and receipt of antithrombotic therapy, and used objective definitions of major outcomes and independent verification, to reduce misclassification of haemorrhagic and occlusive vascular events, and reduce bias that can arise in outcome assessment when treatment allocation is open.[28] We prespecified our outcomes and methods of analysis,[17] and report these according to our protocol and statistical analysis plan.[18] We also did prespecified exploratory analyses to investigate the effects of antiplatelet therapy according to brain imaging biomarkers that are often observed in clinical practice, which we report separately.[29]

RESTART has some limitations. We intended to recruit 720 participants and follow them up for 2 years, but we recruited only 537 people (75% of our target). Investigators managed to recruit only one in 12 eligible patients; the remainder were not randomised because 28% of patients were too unwell when approached, 26% of patients' physicians were certain about whether or not to use antiplatelet therapy, 9% of patients declined, 7% of patients were started on oral anticoagulation, and 30% were not recruited for other reasons.[25] Because of slow recruitment, we did a stepped wedge cluster randomised study within this trial at 72 of the sites to investigate whether stroke audit data extracts could boost recruitment; however, this strategy was not successful.[30]

As in many other randomised trials of intracerebral haemorrhage, most participants were male, which might be because of their propensity to be invited or consent rather than differences in incidence or outcome of intracerebral haemorrhage compared with women.[31,32] Although we did not mask the assigned treatment to participants and physicians, the outcomes were objective and adjudicated masked to treatment allocation, which minimises bias.[33] Antiplatelet regimens used were mostly monotherapy, so the effects of dual antiplatelet therapy remain uncertain. Adherence to the allocated treatment declined over time but was more than 80% even after 4 years of follow-up. Although the sample size was smaller than intended and multiple statistical comparisons were done, we prespecified our primary outcome and main hypothesis, and regarded analyses of secondary outcomes and effects in subgroups as exploratory.

Platelets are the dominant contributor to thrombus formation in the arterial circulation, so antiplatelet therapy predominantly prevents arterial thrombosis. We included venous occlusive events in our composite secondary outcome of all haemorrhagic or occlusive vascular events because randomised trials suggested that antiplatelet therapy might prevent venous occlusive events,[34] but this benefit was not evident in this trial. However, in this trial, antiplatelet therapy did reduce a composite of major vascular events used by the Antithrombotic Trialists' Collaboration (that did not include venous occlusive events), with a proportionate reduction similar to the effects of aspirin for secondary prevention in their meta-analysis.[4]

Our finding that antiplatelet therapy might have reduced the risk of recurrent intracerebral haemorrhage was unexpected. Although we cannot rule out a random effect, this observation might not be as counterintuitive as it first seems. First, arterial thrombosis can trigger haemorrhage.[35] Second, more spontaneous intracerebral haemorrhages than expected might be due to haemorrhagic transformation of ischaemic stroke. Finally, inflammation might be a key mechanism underlying intracerebral haemorrhage (as is thought to be the case for intracranial aneurysms). These potential mechanisms underlying RESTART's findings merit further investigation.

Our findings have several implications for future research. We will continue follow-up of the surviving participants in RESTART for another 2 years to improve precision of effect estimates, especially after 2 years of follow-up, and observe whether adherence changes after the trial result is known. Ongoing randomised trials, such as RESTART-Fr (NCT02966119, intended sample size 280) and STATICH (NCT03186729, intended sample size 250), might help to confirm or refute the effects of antiplatelet therapy seen in RESTART.[7] A prospectively planned individual patient data meta-analysis of RESTART and these trials, and in due course a larger randomised trial, could increase power to detect the overall effects of antiplatelet therapy in these patients and in subgroups of interest with further investigation at earlier times after intracerebral haemorrhage and of heterogeneity of treatment effect by imaging features.[29] RESTART's findings also support the conduct of randomised trials of oral anticoagulation for survivors of intracerebral haemorrhage with atrial fibrillation, for whom there is some justification for the use of antiplatelet therapy as a comparator.[36]

In summary, RESTART excluded all but a very modest increase in the risk of recurrent intracerebral haemorrhage with antiplatelet therapy, which seemed too small to exceed the established benefits of antiplatelet therapy for secondary prevention of major vascular events (video). Antiplatelet therapy might have reduced the recurrence of intracerebral haemorrhage. These findings provide reassurance about the use of antiplatelet therapy for similar patients in clinical practice. Ongoing randomised trials, their meta-analysis with RESTART, and an adequately powered definitive randomised trial should be done to strengthen the evidence.

For **Video** see https://www.youtube.com/embed/FnDqTXu3bnc

Contributors

RA-SS (chief investigator) and MSD conceived the idea for the study. RA-SS, MSD, GDM, DEN, PAGS, CLMS, PMW, WNW, and DJW obtained funding and developed the protocol. RA-SS and MSD designed and implemented the study, with input from the trial management group. GDM was the masked trial statistician. JS was the unmasked trial statistician who did the data analyses. JMW advised on brain imaging acquisition, collection, management, and assessment. RA-SS wrote the first draft of the manuscript. All members of the writing committee reviewed the analyses and drafts of this manuscript, and approved its final version.

The RESTART Collaboration*

Writing group: UK R Al-Shahi Salman, M S Dennis, P A G Sandercock, C L M Sudlow, J M Wardlaw, W N Whiteley, G D Murray, J Stephen, D E Newby (University of Edinburgh, Edinburgh); N Sprigg (University of Nottingham, Nottingham); D J Werring (University College London Queen Square Institute of Neurology, London); P M White (Newcastle University and Newcastle-upon-Tyne Hospitals, Newcastle-upon-Tyne).
Independent trial steering committee members: UK C Baigent (chairperson; University of Oxford, Oxford), D Lasserson (University of Birmingham, Birmingham), F Sullivan (University of St Andrews, St Andrews); J Carrie (patient–public representative; Edinburgh).
Other trial steering committee members: UK R Al-Shahi Salman, M S Dennis, G D Murray, D E Newby, P A G Sandercock, C L M Sudlow, W N Whiteley (University of Edinburgh, Edinburgh); N Sprigg (University of Nottingham, Nottingham); D J Werring (University College London, London); P M White (University of Newcastle-upon-Tyne, Newcastle-upon-Tyne).
Sponsor's representative: J Rojas (Edinburgh, UK).
Funder's representative: S Amoils (London, UK).
Data monitoring committee: UK J Bamford (chairperson; Leeds), J Armitage and J Emberson (University of Oxford, Oxford), G Rinkel (University Medical Centre Utrecht, Utrecht), G Lowe (University of Glasgow, Glasgow).
Trial management group: UK K Innes (senior trial manager, University of Edinburgh, Edinburgh); L Dinsmore (imaging manager, University of Edinburgh, Edinburgh); J Drever (data manager, University of Edinburgh, Edinburgh); C Williams (centre coordinator, University of Edinburgh, Edinburgh); D Perry, C McGill, D Buchanan, A Walker, A Hutchison, C Matthews (database programmers, University of Edinburgh, Edinburgh); R Fraser, A McGrath, A Deary, R Anderson, A Maxwell, P Walker (trial support officers, University of Edinburgh, Edinburgh); J Stephen, C Holm Hansen, R Parker, A Rodriguez (unmasked independent statisticians, University of Edinburgh, Edinburgh).
Outcome event internal adjudicators: UK W N Whiteley, M R Macleod (University of Edinburgh, Edinburgh).

For more on the **meta-analysis** see www.ed.ac.uk/clinical-brain-sciences/research/so-start/for-collaborators

Outcome event external adjudicator: Austria T Gattringer (Medical University of Graz, Graz).
Systematic Management, Archiving and Reviewing of Trial Images Service: UK J M Wardlaw (director, University of Edinburgh, Edinburgh); J Palmer (programmer, University of Edinburgh, Edinburgh); E Sakka and J Adil-Smith (imaging managers, University of Edinburgh, Edinburgh).
Brain imaging assessors: UK P M White, D P Minks, D Mitra, P Bhatnagar (Newcastle-upon-Tyne Hospitals NHS Trust, Newcastle-upon-Tyne); J C du Plessis (NHS Lothian, Edinburgh); Y Joshi (Addenbrooke's Hospital, Cambridge).
*Investigators at sites that recruited participants listed in the appendix.

Declaration of interests

RA-SS and GDM report a grant from the British Heart Foundation (SP/12/2/29422) paid to the University of Edinburgh for the conduct of RESTART. RA-SS reports grants from The Stroke Association, Chest Heart and Stroke Scotland, and GE Healthcare Limited, outside the submitted work. DEN reports grants and personal fees from AstraZeneca, Eli Lilly, Bristol Myers Squibb, and Jansen, during the conduct of the study. PAGS reports funding from Bayer outside the submitted work. NS reports a grant from National Institute for Health Research (NIHR) Health Technology Assessment for the TICH-2 trial, outside the submitted work. JMW reports grants from EU Framework 7, Medical Research Council, and the British Heart Foundation, outside the submitted work. DJW reports personal fees from Bayer and JFB consulting, outside the submitted work. PMW reports personal fees from Stryker Global Advisory Board on Haemorrhagic Stroke and MicroVention-Terumo, and a grant from MicroVention-Terumo outside the submitted work. WNW reports a Chief Scientist Office of the Scottish Government Health Department Senior Fellowship (SCAF_17_01) and a grant from the European Stroke Organisation, outside the submitted work. MSD, JS, and CLMS declare no competing interests.

Data sharing

A fully anonymised version of the dataset used for analysis with individual participant data and a data dictionary will be available for other researchers to apply for use 1 year after publication, via https://datashare.is.ed.ac.uk/handle/10283/3265. Written proposals will be assessed by members of the RESTART trial steering committee and a decision made about the appropriateness of the use of data. A data sharing agreement will be put in place before any data are shared.

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Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage: a randomised, open-label trial

Online appendix

Appendix of collaborators on delegation logs at hospital sites that recruited at least one participant to RESTART

Sites are listed in descending order of cumulative recruitment (quantified in square brackets), indicating which people took the role of principal investigator (PI).

Edinburgh Royal Infirmary, Edinburgh [39] (Prof. R Al-Shahi Salman (PI), Prof. G Mead, S Burgess, C Lerpiniere, R O'Brien, R Paulton, F Doubal, K McCormick, N Hunter, P Taylor, R Parakramawansha, J Perry, G Blair, A MacRaild); **Salford Royal Foundation Trust, Manchester [21]** (A Parry-Jones (PI), K Shaw, I Burger, A Ingham, T Marsden, J Morell, Z Naing, J Perez, A Hall, R Jarapa, E Wood, V O'Loughlin, S Marshall, L Harrison, M Punter, S Lee, M Johnes); **Northwick Park Hospital, Harrow [18]** (D Cohen (PI), S Davies, K Njoku, M Mpelembue, L Burgess, R Licenik, M Ngwako, N Nisar, R Niranchanan, T Roganova, R Bathula, J Devine, A David, A Oshodi, F Guo, M Abbdul-saheb, A Chandrakumar, A Chamberlain, R Ballantine, E Owoyele, V Sukdeo, P Poku); **Royal Hallamshire Hospital, Sheffield [13]** (K Harkness (PI), C Blank (PI), P Bayliss, E Richards, K Birchall, O Balitska, A Ali, F Kibutu, C Doyle, J Howe, C Kamara, K Stocks, Prof. A Majid, A Maatouk, L Barron, R Lindert, J Redgrave, K Dakin); **Torbay District General Hospital, Torquay [13]** (B Bhaskaran (PI), S Szabo, I Salih, D Kelly, D Tomlin, H Bearne, P Fitzell, J Buxton, G Ayres, H Bhakri, J Garfield-Smith, K Horan, A Saulat); **Southend University Hospital NHS Foundation Trust, Westcliff on Sea [12]** (P Guyler (PI), D Sinha (PI) T Loganathan, A Siddiqui, L Coward, S Tysoe, S Kunhunny, S Shah, K Ng, N Menon, R Orath Prabakaran, S Kelavkar, S Rashmi, D Ngo); **Monklands Hospital, Airdrie [11]** (M Barber (PI), D Esson, F Brodie); **Morriston Hospital, Swansea [11]** (T Anjum (PI), M Wani (PI), M Krishnan, L Quinn, J Spencer, S Chenna, S Storton, T Jones, H Thompson-Jones, L Dacey, S Thomas, T Beaty, S Treadwell, C Davies, L Connor, S Tucker, G Gainard, P Slade); **University Hospitals of North Midlands NHS Trust, Stoke-on-Trent [11]** (G Muddegowda (PI), R Sanyal (PI), S Stevens, A Butler, R Varquez, A Remegoso, N Abano, F Alipio, H Denic, R Carpio, C Causley, A Moores, S Lyjko, Prof. C Roffe, J Hiden, P Ferdinand, A Barry, H Maguire, J Grocott, K Finney); **Victoria Hospital, Kirkcaldy [11]** (V Cvoro (PI), M Couser, K Ullah, N Chapman, K McCormick, S Mcauley, S Pound); **City Hospital, Nottingham [10]** (S Raghunathan (PI), F Shelton, A Hedstrom, N Gilzeane, J Roffe, J Clarke, D Havard, A Buck, K Krishnan, M Godfrey, N Sprigg, S Sheikh, K Whittamore, R Keshvara, B Jackson, J Appleton, Z Law, O Matias, G Wilkes, C Jordan); **Hillingdon Hospital, Uxbridge [10]** (E Vasileiadis (PI), C Mason, A Parry, G Landers, M Holden, B Aweid); **Yeovil District Hospital, Yeovil [10]** (K Rashed (PI), L Balian, C Vickers, B Williams-Yesson, E Keeling, S Board, J Allison, C Buckley, J Board, D Wood, T Pitt-Kerby, A Tanate); **Doncaster Royal Infirmary, Doncaster [9]** (M Kini (PI), D Walstow, D Chadha, R Fong); **North Middlesex University Hospital, London [9]** (R Luder (PI), T Adesina, J Gallagher, M Bhargava, C van Someren, E Murali, H Bridger); **Royal Cornwall Hospital,**

Truro [9] (F Harrington (PI), A James, K Adie, A Mate, G Courtauld, C Schofield, K Bond, L Lucas, B Maund, S Ellis); **Royal Devon & Exeter Hospital, Exeter [9]** (P Mudd (PI), M James, S Keenan, A Bowring, J Cageao, D Strain, H Kingwell, C Roughan, A Hemsley, J Sword, K Miller, A Goff, K Gupwell, K Thorpe); **Royal Preston Hospital, Preston [9]** (H Emsley (PI), S Punekar (PI), A McLoughlin, S Sultan, B Gregory, S Raj, D Doyle); **Queen Elizabeth University Hospital, Glasgow [9]** (Prof. K Muir (PI), W Smith, N Day, A Welch, F Moreton, B Cheripelli, D Kalladka, X Huang, S El Tawil, S Ramachandran, C Crosbie, J Elliot); **Guys & St Thomas, London [8]** (Prof. T Rudd (PI), A Bhalla, J Birns, K Marks, S Kullane); **Southampton General Hospital, Southampton [8]** (N Weir (PI), C Allen, V Pressly, E Battersby-Wood, P Crawford, S Egerton, A Blades, G Howard, J Marigold, S Evans, A Walters, F Smith, I Gartrell, C Cox, R Creeden, S Smith, C Boxall); **Ystrad Mynach Hospital, Ystrad Mynach, Newport [8]** (J Hewitt (PI), C Nott, S Procter, S Buckle, J Whiteman, C Triscott, R Mardania, R Wallace, J Gray); **Calderdale Royal Hospital, Halifax [7]** (A Nair (PI), J Greig, P Rana, M Robinson, M Alam); **University College London Hospital, London [7]** (Prof D Werring (PI), I Jones, A Banaras, L Crook, C Watchurst, M Brezitski, K Patel, D Wilson, R Erande, C Hogan, N Oji, N Francia, A Ashton, S Feerick, I Hostettler, T Al-Mayhani, E Elliott); **Altnagelvin Hospital, Derry/Londonderry [6]** (M McCarron (PI), J McKee, M Doherty, F McVerry, C Blair); **Bristol Royal Infirmary, Bristol [6]** (C Holmes (PI), S Caine (PI), M Osborn, E Dodd, P Murphy, N Devitt, P Baker, A Steele, L Guthrie, S Clarke); **Gloucestershire Royal Hospital, Gloucester [6]** (D Dutta (PI), P Brown, D Ward, F Davis, J Turfrey, R Bakawala, C Hughes, K Collins, S O'Connell, J Glass); **James Cook University Hospital, Middlesbrough [6]** (D Broughton (PI), D Tryambake (PI), L Dixon, K Chapman, A Young, A Bergin, A Sigsworth); **Kings Mill Hospital, Mansfield [6]** (M Cooper (PI), M Nasar, I Wynter, A Rajapakse); **Leeds General Infirmary, Leeds [6]** (A Hassan (PI), M Kambafwile, L Makawa, D Waugh, E Veraque, M Randall, V Papavasileiou); **Royal Liverpool and Broadgreen University Hospital, Liverpool [6]** (A Manoj (PI), M Wilkinson, G Fletcher, P Lopez, P Cox, P Fitzsimmons, N Sharma); **Royal United Hospital, Bath [6]** (J Choulerton (PI), B Madigan, D Button, L Dow, L Gbadamoshi, J Avis, S McCann, L Shaw, D Howcroft, S Lucas, A Stone); **St Georges Healthcare NHS Trust, London [6]** (G Cluckie (PI), C Lovelock (PI), B Patel, B Clarke, N Chopra, K Kennedy, R Williams, L Kerin, N Jeyaraj, L Choy, N Clarke, F Watson, S Trippier, B Moynihan, U Khan, N Dayal, C Orefo, T Adedoyin, R Ghatala, A Blight, V Jones, J O'Reilly); **The Royal Bournemouth Hospital, Bournemouth [6]** (K Thavanesan (PI), D Tiwari (PI), C Cox, J Roberts, B Jupp, M Keltos, A Iqbal, C Bagnall, L Tucker, A Ljubez, O David, E Rogers, C Ovington, J Bell, B Longland, G Hann); **University Hospital Aintree, Liverpool [6]** (C Cullen (PI), H Thant, T Ingram, M Zoe, J Peters, V Sutton, R Durairaj, D Shackcloth, J Ewing, S Stevenson, M Harrison); **University Hospital of North Tees, Stockton [6]** (I Anwar (PI), B Kumar, H Skinner, T Nozedar, D McArdle, S Crawford, A Annamalai, A Ramshaw); **Western General Hospital, Edinburgh [6]** (Prof. M Dennis (PI), Prof. C Sudlow, W

Whiteley, C Lerpiniere, Prof. R Al-Shahi Salman, R Fraser); **Aberdeen Royal Infirmary, Aberdeen [5]** (M MacLeod (PI), J Irvine, A Joyson, H Gow, J Furnace, B Jagpal, S Ross, S Nelson, R Clarke, N Crouch, K Klaasen, B MacLennan, V Taylor); **Addenbrooke's Hospital, Cambridge [5]** (E O'Brien (PI), S Finlay, H Hayhoe, D Handley, S Kelly, J Francis, N Hannon, G Zachariah, J Mcgee, J Mitchell, E Amis, J Sesay, S Crisp); **Barnet Hospital, Barnet [5]** (D Epstein (PI), A Shukla, I Jones, V Krishnamurthy, P Nicholas, A Webber, S Qureshi, J Penge); **Bradford Royal Infirmary, Bradford [5]** (H Ramadan (PI), S Maguire, C Patterson, R Bellfield, B Hairsine, O Quinn, M Hooley, K Stewart); **John Radcliffe Hospital, Oxford [5]** (U Schulz (PI), R Teal, P Mathieson, I Reckless, J Kennedy, Prof. G Ford, G Lenti, G Harston); **Nevill Hall Hospital, Abergavenny [5]** (B Richard (PI), S Buckle, S Procter, S Moseley, C Nott, J Whiteman, C Triscott, R Wallace, M Edwards, H Lawson, M Tayler); **The Royal London Hospital, London [5]** (T Harrison (PI), K Saastamoinen (PI), A Salek-Haddadi, D Hove, L Howaniec, G Grimwood, O Redjep, F Humphries, S Amlani, L Cuenoud, E Erumere, G Auld, L Argandona); **University Hospital North Durham, Durham [5]** (Y Pai (PI), M Dhakal (PI), S Dima (PI), B Esisi (PI), G Smith, M Garside, D Bruce, R Hayman, S Clayton, E Brown, G Rogers, M Naeem, V Baliga); **University Hospital of Wales, Cardiff [5]** (T Hughes (PI), B Morse, S White, S Schwarz, E Tallantyre, A Osman, H De Berker, B Jelley); **Wythenshawe Hospital, Manchester [5]** (E Gamble (PI), B Charles, R Grue, A Chaudhry, S Blane, A Hague, C Lambert); **Ayr Hospital, Ayr [4]** (S Ghosh (PI), D Gilmour, E Barrie, M Henry); **Charing Cross Hospital, London [4]** (M Venter (PI), A Kar (PI), S Mashate, K Harvey, L Gardener, V Nguyen, B Hazel, O Geraghty, O Halse, P Wilding, V Tilley); **Derby Royal Hospital, Derby [4]** (Prof. T England (PI), A Hedstrom, M Maddula, Prof. R Donnelly); **Heartlands Hospital, Birmingham [4]** (R Yadava (PI), K Azhar (PI), M Sangombe, J Reddan, S Stafford); **New Cross Hospital, Wolverhampton [4]** (K Fotherby (PI), D Morgan, F Baig, K Jennings-Preece, D Butler, N Ahmad, B Rai, A Stevens, A Willberry); **Queen Alexandra Hospital, Portsmouth [4]** (P Siddegowda (PI), L Hyatt, A Saulat, J Tandy, P Howard, T Dobson, D Jarrett, S Ponnambath, S Valentine, C James, R Butler, Y Harrington-Davies, A Suttling); **Queen Elizabeth Hospital, Gateshead [4]** (B Esisi (PI), T Cassidy (PI), B McClelland, M Bokhari); **Raigmore Hospital, Inverness [4]** (P Findlay (PI), A Macaden, I Shread, C Barr); **Royal Infirmary, Glasgow [4]** (Prof. P Langhorne (PI), G Kerr, F Wright, R Graham, C McAlpine, L Humphreys, M Iqbal); **Royal Surrey County Hospital, Guildford [4]** (K Pasco (PI), O Balazikova, A Nasim, C Peixoto, S Shahmehri, L Gallagher); **William Harvey Hospital, Ashford [4]** (T Webb (PI), L Cowie, A Thomson, H Rudenko, A Verrion, E Beranova, T Cosier, S Walker, S McDonald, N Schumacher); **Derriford Hospital, Plymouth [3]** (A Mohd Nor (PI), C Eglinton, N Persad, C Brown, M Weinling, A Shah, J Baker, B Hyams); **Forth Valley Royal Hospital, Larbert [3]** (A Byrne (PI), C McGhee, A Smart, C Copeland); **Hull Royal Infirmary, Hull [3]** (R Rayessa (PI), L Wilson, C Naylor, A Rodgers, S Wilson, E Clarkson); **Pinderfields Hospital, Wakefield [3]** (M Carpenter (PI), M Walker, R Davey, A

Needle, R Fathima, G Bateman, A Stanners, P Datta, L Jackson, J Ball); **Royal Victoria Infirmary, Newcastle upon Tyne [3]** (M Davis (PI), H Guy, N Atkinson, M Fawcett, T Thompson, C Hays, S Woodward, V Hogg); **Salisbury District Hospital, Salisbury [3]** (T Black (PI), A Anthony, S Miriam, C Clarke, D Mead, M Tribbeck, J Cronin, R Fennelly); **St Mary's Hospital, Newport Isle of Wight [3]** (M Haque (PI), E Hakim (PI), S Symonds, M Maanoosi, J Herman); **St Richards Hospital, Chichester [3]** (S Ivatts (PI), Y Baird, M Sally, I Amey, L Clayton- Evans, S Newton, I Chadbourn); **Victoria Hospital, Blackpool [3]** (J McIlmoyle (PI), C Jeffs, C Dickinson, J Howard, S Anwar, S Dhar, K Jones, M Siddiq, C Clay); **Arrowe Park Hospital, Wirral [2]** (R Davies (PI), P Owings, G Sangster, V Gott, V Little, P Weir, S Cherian, D Jose, H Moroney, S Downham, A Dodd, L Codd, V Vettimootal Johnson, N Robinson); **Barnsley Hospital NHS Foundation Trust, Barnsley [2]** (A Ahmed (PI), M Albazzaz (PI), S Johnson, C Denniss, T Zahoor, M Cunningham); **Countess of Chester NHS Foundation Trust, Chester [2]** (T Webster (PI), K Chatterjee, A Nallasivan, S Haider, S Leason, C Perkins, S Seagrave); **Hereford County Hospital, Hereford [2]** (C Jenkins (PI), F Price, C Hughes, L Mercer); **Leicester Royal Infirmary, Leicester [2]** (D Eveson (PI), A Mistri, L Manning, C Patel, M Moqsith, S Khan, C Stephens, S Sattar, M Lam, K Musarrat); **Leighton Hospital, Crewe [2]** (L Kalathil (PI), R Miller, M Salehin, N Gautam, D Bailey, K Amor, J Meir); **Luton & Dunstable NHSFT University Hospital, Luton [2]** (L Sekaran (PI), F Justin, M Tate, K Bharaj, R Simon, N Mohammed, S Sethuraman, D Phiri, M Chauhan); **Musgrove Park Hospital, Taunton [2]** (M Hussain (PI), S Brown, M Harvey, R Whiting, M Khan, J Homan, L Foote, N Hunt, A Whitcher, C Pawley, E Foster, J Foot, H Durman, L Brotherton); **Norfolk & Norwich University Hospital, Norwich [2]** (K Metcalf (PI), J Jagger, S McDonald, K Waterfield, P Sutton, J Saada, A Wiltshire, R Perfitt, R Greenwood, N Shinh, A Anversha, G Ravenhill); **Pilgrim Hospital, Boston [2]** (D Mangion (PI), S Markova, A Hardwick, T Lawrence, J Fletcher, C Constantin, K Pettitt, I Thomas); **Queens Hospital, Romford [2]** (S Andole (PI), N Gadapa, K Dunne, M Krommyda, E Burssens, C Plewa, S King); **Royal Hampshire County Hospital, Winchester [2]** (N Smyth (PI), J Wilson, E Giallombardo, C Eglinton, L Sykes); **Royal Lancaster Infirmary, Lancaster [2]** (P Kumar (PI), P Thomas, l Dunn, C Culmsee, I Huggett, J Barker); **Royal Victoria Hospital, Belfast [2]** (I Wiggam (PI), A Wallace, E Kerr, A Fulton, A Hunter, S Tauro, S Cuddy); **Solihull Hospital, Solihull [2]** (K Elfandi (PI), U Khan, S Stafford, J Reddan); **Sunderland Royal Hospital, Sunderland [2]** (M Myint (PI), R O'Brien (PI), H Brew, N Majmudar, J OConnell, G Bunea, C Fox, D Gulliver, N Sattar, B Mokoena, A Smith, E Osborne, R Krishnamurthy); **Ulster Hospital, Belfast [2]** (D Wilson (PI), B Wroath, K Dynan, M Power, S Thompson, V Adell); **West Cumberland Hospital, Whitehaven [2]** (E Orugun (PI), U Poultney, H Crowther, R Glover, S Thornthwaite); **West Suffolk Hospital, Bury St Edmunds [2]** (A Nicolson (PI), L Wood, J Imam, J White); **Bedford Hospital, Bedford [1]** (H Ni (PI), C Graham, B Rahman, J Milligan, J Jose); **Chesterfield Royal Hospital, Chesterfield [1]** (M Sajid (PI), G Ghaly, M Ball, R Gascoyne); **Dorset County**

Hospital NHS Foundation Trust, Dorchester [1] (H Proeschel (PI), S Sharpe, S Horton, S Jones, E Beaves); **Epsom General Hospital, Epsom [1]** (J Putterill (PI), R Jha, R Gallifent, P Kakar); **Hairmyres Hospital, East Kilbride [1]** (B Yip (PI), M Bell, B MacInnes, L MacLiver, D Esson); **Lister Hospital, Stevenage [1]** (A Pusalkar (PI), K Chan, P Dangri, K Crabtree, H Beadle, A Cook); **Peterborough City Hospital, Peterborough [1]** (S Subramonian (PI), P Owusu-Agyei (PI), N Temple, N Butterworth-Cowin); **Poole Hospital, Poole [1]** (S Ragab (PI), K Knops, E Jinks, C Dickson, L Gleave, J Leggett, J Dube, T Garcia); **Prince Charles Hospital, Merthyr Tydfil [1]** (R Dewar (PI), K Thomas, J White); **Queen Elizabeth Hospital, Birmingham [1]** (D Sims (PI), J Hurley, M Willmot, C Sutton, E Littleton, S Maiden, J Cunningham, R Jones, C Green, M Bates); **Queen Elizabeth Hospital, Kings Lynn [1]** (R Shekhar (PI), R Crown, E Gilham, T Fuller, I Ahmed, K Waterfield); **Royal Blackburn Hospital, Blackburn [1]** (N Goorah (PI), A Bell, C Kelly, A Singh, J Walford, S Duberley, B Tomlinson, F Patel); **Royal Sussex County Hospital, Brighton [1]** (I Kane (PI), N Gainsborough, J Gaylard, J Breeds, Prof. C Rajkumar, S Hervey, A Pitt-Ford, L Latter, E Barbon, P Thompson); **Sandwell General Hospital, Birmingham [1]** (S Ispoglou (PI), R Evans, S Ankolekar, A Hayes); **South West Acute Hospital, Enniskillen [1]** (B Keegan (PI), M Doherty, J Kelly, C Blair); **Stepping Hill Hospital, Stockport [1]** (S Krishnamoorthy (PI), J Vassallo, D Walter, H Cochrane); **The Princess Royal Hospital, Telford [1]** (M Srinivasan (PI), F Hurford, D Donaldson, R Campbell, N Motherwell, I Mukherjee); **University Hospitals Coventry and Warwickshire, Coventry [1]** (A Kenton (PI), S Nyabadza, I Martin, B Hunt, H Hassan, B Dallol, S O'Toole).

Literature search strategies used to put the research in context

CENTRAL search strategy

#1 MESH DESCRIPTOR Basal Ganglia Hemorrhage EXPLODE ALL TREES

#2 MESH DESCRIPTOR Intracranial Hemorrhages

#3 MESH DESCRIPTOR Intracranial Hemorrhage, Hypertensive

#4 MESH DESCRIPTOR Cerebral Hemorrhage

#5 (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or putaminal or putamen or hemispher* or stroke or apoplex*):TI

#6 (basal and gangli*):TI

#7 (posterior and fossa):TI,AB,KY

#8 (haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed*):TI

#9 #5 or #6 or #7 and #8

#10 (ICH or ICHs):TI

#11 #1 or #2 or #3 or #4 or #9 or #10

#12 MESH DESCRIPTOR Anticoagulants EXPLODE ALL TREES

#13 MESH DESCRIPTOR Pipecolic Acids EXPLODE ALL TREES WITH QUALIFIERS AE,TU

#14 MESH DESCRIPTOR Vitamin K EXPLODE ALL TREES

#15 MESH DESCRIPTOR Thrombin EXPLODE ALL TREES WITH QUALIFIERS AI

#16 MESH DESCRIPTOR Factor Xa

#17 MESH DESCRIPTOR Blood Coagulation Factors EXPLODE ALL TREES WITH QUALIFIERS AI

#18 MESH DESCRIPTOR Blood Coagulation EXPLODE ALL TREES WITH QUALIFIERS DE

#19 MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES

#20 MESH DESCRIPTOR Hirudin Therapy EXPLODE ALL TREES

#21 (anticoagul* or antithromb*):TI,AB,KY

#22 (Vitamin next K next antagonist*):TI,AB,KY

#23 (VKA or VKAs):TI,AB,KY

#24 #22 or #23

#25 (direct* NEAR5 thrombin):TI,AB,KY

#26 "DTI":TI,AB,KY

#27 (factor next Xa NEAR5 inhib*):TI,AB,KY

#28 (factor next 10a NEAR5 inhib*):TI,AB,KY

#29 (fXa NEAR5 inhib*):TI,AB,KY

#30 (autoprothrombin NEAR5 inhib*):TI,AB,KY

#31 (thrombokinase NEAR5 inhib*):TI,AB,KY

#32 (acenocoumarol* or dicoumarol* or ethyl next biscoumacetate* or phenprocoumon* or warfarin* or ancrod* or citric next acid* or coumarin* or chromonar* or coumestro* or esculi* or ochratoxin* or umbelliferone* or dermatan next sulfate* or dextran* or edetic next acid* or enoxaparin* or gabexate* or heparin* or lmwh* or nadroparin* or pentosan next sulfuric next polyester* or phenindione* or protein next c or protein next s or tedelparin*):TI,AB,KY

#33 (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org next 10172 or mesoglycan or polysaccharide next sulphate* or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216):TI,AB,KY

#34 (Marevan or Fragmin* or Fraxiparin* or Klexane):TI,AB,KY

#35 (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin* or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil):TI,AB,KY

#36 (xabans or antistasin or apixaban or betrixaban or du next 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym next 150 or ym150 or LY517717):TI,AB,KY

#37 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36

#38 MESH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES WITH QUALIFIERS AI,DE

#39 MESH DESCRIPTOR Platelet Activation EXPLODE ALL TREES WITH QUALIFIERS DE

#40 MESH DESCRIPTOR Blood Platelets EXPLODE ALL TREES WITH QUALIFIERS DE

#41 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* or (platelet* NEAR5 inhibit*) or (thrombocyt* NEAR5 inhibit*)):TI,AB,KY #42 (alprostadil* or aspirin* or acetylsalicylic next acid or (acetyl ADJ salicylic and acid*) or (acetyl-salicylic and acid or epoprostenol* or ketanserin* or ketorolac next tromethamine* or milrinone* or mopidamol* or procainamide* or thiophen* or trapidil* or picotamide* or ligustrazine* or levamisol* or suloctidil* or ozagrel* or oky046 or oky-046 or defibrotide* or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151)):TI,AB,KY

#43 ((glycoprotein next iib* near/5 inhib*) or (glycoprotein next iib* near/5 antag*) or (gp next iib* near/5 inhib*) or (gp next iib* near/5 antag*) or GR144053 or GR-144053 or triflusal):TI,AB,KY

#44 (Argatroban or Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan next Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel):TI,AB,KY

#45 (Dispril or Albyl* or Ticlid* or Persantin* or Plavix or ReoPro or Integrilin* or Aggrastat):TI,AB,KY

#46 MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES

#47 #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46

#48 #37 or #47

#49 #48 and #11

MEDLINE search strategy

1. exp basal ganglia haemorrhage/ or intracranial hemorrhages/ or cerebral haemorrhage/ or intracranial haemorrhage, hypertensive/

2. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

3. ((h?emorrhag$ or bleed$) adj5 (stroke or apoplex$)).tw.

4. (ICH or ICHs).tw.

5. 1 or 2 or 3 or 4

6. exp anticoagulants/

7. exp Vitamin K/ai or thrombin/ai or factor Xa/ai or exp Blood coagulation factors/ai

8. exp antithrombins/ or hirudin therapy/

9. (anticoagul$ or antithromb$).tw.

10. (Vitamin K antagonist$ or VKA or VKAs).tw.

11. (direct$ adj3 thrombin adj3 inhib$).tw.

12. DTI$1.tw.

13. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj3 inhib$).tw.

14. (activated adj3 (factor X or factor 10) adj3 inhib$).tw.

15. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or

dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw,nm.

16. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw,nm.

17. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw,nm.

18. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw,nm.

19. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw,nm.

20. exp platelet aggregation inhibitors/ or exp platelet glycoprotein gpiib-iiia complex/ai

21. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj3 inhibit$) or (thrombocyt$ adj3 inhibit$)).tw.

22. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw,nm.

23. (Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel).tw,nm.

24. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw,nm.

25. or/6-24

26. Randomized Controlled Trials as Topic/

27. random allocation/

28. Controlled Clinical Trials as Topic/

29. control groups/

30. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

31. double-blind method/

32. single-blind method/

33. Placebos/

34. placebo effect/

35. randomised controlled trial.pt.

36. controlled clinical trial.pt.

37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

38. (random$ or RCT or RCTs).tw.

39. (controlled adj5 (trial$ or stud$)).tw.

40. (clinical$ adj5 trial$).tw.

41. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

42. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

43. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

44. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

45. (placebo$ or sham).tw.

46. trial.ti.

47. (assign$ or allocat$).tw.

48. or/26-47

49. 5 and 25 and 48

50. exp animals/ not humans/

51. 49 not 50

EMBASE (Ovid) search strategy

1. anticoagulant agent/ or antivitamin k/ or exp blood clotting inhibitor/ or exp coumarin anticoagulant/ or defibrotide/ or dextran sulfate/ or fluindione/ or glycosaminoglycan polysulfate/ or exp heparin derivative/ or lupus anticoagulant/ or phenindione/

2. (anticoagul$ or antithromb$).tw.

3. (Vitamin K antagonist$ or VKA or VKAs).tw.

4. (direct$ adj5 thrombin adj5 inhib$).tw.

5. DTI$1.tw.

6. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib$).tw.

7. (activated adj5 (factor X or factor 10) adj5 inhib$).tw.

8. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosane sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw.

9. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw.

10. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw.

11. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw.

12. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw.

13. or/1-12

14. exp antithrombocytic agent/

15. fibrinogen receptor/dt [Drug Therapy]

16. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw.

17. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw.

18. (Argatroban or Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel).tw.

19. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw.

20. or/14-19

21. 13 or 20

22. *basal ganglion hemorrhage/ or *brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/

23. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or stroke or apoplex$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).ti.

24. 22 or 23 or (ICH or ICHs).ti.

25. randomized controlled trial/ or "randomized controlled trial (topic)"/

26. Randomization/

27. Controlled Study/

28. control group/

29. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/

30. Double Blind Procedure/

31. Single Blind Procedure/ or triple blind procedure/

32. placebo/

33. drug comparison/ or drug dose comparison/

34. "types of study"/

35. random$.tw.

36. (controlled adj5 (trial$ or stud$)).tw.

37. (clinical$ adj5 trial$).tw.

38. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)).tw.

39. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

40. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

41. placebo$.tw.

42. controls.tw.

43. or/25-42

44. meta analysis/ or "meta analysis (topic)"/ or "systematic review"/ or "systematic review (topic)"/

45. meta analy$.tw.

46. metaanaly$.tw.

47. (systematic adj (review$1 or overview$1)).tw.

48. literature/

49. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or medline or pubmed).ab.

50. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search).ab.

51. (selection criteria or data extraction).ab.

52. review.pt. or literature/ or review/

53. 51 and 52

54. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 53

55. (letter or editorial).pt.

56. 54 not 55

57. 43 or 56

58. 21 and 24 and 57

59. limit 58 to human

Trials register search strategies

1. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

'Randomised' AND 'intracerebral haemorrhage'

2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch)

'Intracerebral haemorrhage' OR 'Intracerebral hemorrhage' OR 'ICH'

3. ISRCTN Registry (www.isrctn.com)

'Intracerebral haemorrhage' OR 'Intracerebral hemorrhage' OR 'ICH'

4. Stroke Trials Registry – the Internet Stroke Center (www.strokecenter.org/trials/)

'Intracerebral haemorrhage' OR 'Intracerebral hemorrhage' OR 'ICH'

External assessment of a random sample of internally assessed outcome events

RESTART's primary sources of outcome event ascertainment were: (1) participant/carer and general practitioner postal/telephone follow-up questionnaires, performed at six or 12 months after randomisation, and annually thereafter and (2) ad hoc reports of outcome events by local researchers at sites, general practitioners, and participants/carers. Reports of outcome events that were reported to the Trial Coordinating Centre are added to the trial database by trial staff. Trial staff reviewed these reports of outcome events, identified duplicate reports, and gathered information to support the characterisation of each event guided by the *RESTART reported event processing flowchart*): clinical records, death certificates, autopsy report (if performed), and brain imaging relating to any cerebral outcome events (local imaging report as well as the original imaging studies, which were independently reviewed by one of the consultant neuroradiologist members of the RESTART imaging panels). Trial staff redacted information that might identify participants or their antithrombotic drug use from these sources of information. These redacted documents were combined with a structured review form (*RESTART reported event processing checklist*) and given to a consultant neurologist medical assessor (Will Whiteley or Malcolm Macleod) for adjudication. A medical assessor classified the report of an outcome event as: (a) impossible to adjudicate (in which case trial staff obtained more information to enable subsequent adjudication), (b) an SAE/SUSAR, (c) a duplicate report of an outcome event, (d) not an outcome event, or (e) an outcome event (in which case they recorded an outcome event type and date of symptom onset). The outcome events that were confirmed after internal adjudication (e) were the only events that are used for analysis for reports for the Data Monitoring Committee and the final trial report. On 23 March 2018, the RESTART data manager (Jonathan Drever) exported all of the reported outcome events and internally adjudicated outcome events that had been categorised as the primary outcome in RESTART (recurrent intracerebral haemorrhage [ICH]). After removing duplicates and removing reports of outcome events that had not been internally adjudicated, he split the remaining events into three categories:

1. Reports of recurrent ICH that were not categorised as recurrent ICH after internal adjudication (n=10). We used all of these for external adjudication.
2. Reports of events that were not reported as recurrent ICH but were categorised as recurrent ICH after internal adjudication (n=5). We used all of these for external adjudication.
3. Reports of recurrent ICH that were categorised as recurrent ICH after internal adjudication (n=25). We took a random sample of ten of these events for external adjudication.

Dr Thomas Gattringer (consultant neurologist at Universitätsklinik für Neurologie, Medical University of Graz, Austria) was the independent external assessor during his visit to the Centre for Clinical Brain Sciences at the University of

Edinburgh in 2018. He reviewed the same information that had been provided to a medical assessor for internal adjudication, masked to the outcome of internal adjudication, and independently reviewed and categorised all 25 events (table overleaf). There was 96% agreement between the internal medical assessor and the external adjudicator on whether or not the 25 events were recurrent ICH.

Patient	Event	Reported event type	Classification by the internal adjudicator	Date of event	Classification by the external adjudicator	Agreement
87	213	Other Intracranial Haemorrhage	Recurrent ICH	24/06/2016	Recurrent ICH	yes
146	121	Other Intracranial Haemorrhage	Recurrent ICH	29/07/2016	Recurrent ICH	yes
12	45	Other Type of Stroke	Recurrent ICH	18/06/2015	Recurrent ICH	yes
153	168	Other Type of Stroke	Recurrent ICH	17/08/2015	Recurrent ICH	yes
156	112	Death	Recurrent ICH	01/02/2016	Death from frailty after index, not recurrent, ICH	no
56	32	Recurrent ICH	Ischaemic Stroke	18/08/2014	Ischaemic Stroke	yes
76	186	Recurrent ICH	Ischaemic Stroke	02/01/2017	Ischaemic Stroke	yes
89	42	Recurrent ICH	Not an Outcome Event	13/07/2015	Epileptic seizures	yes
89	41	Recurrent ICH	Not an Outcome Event	27/09/2015	Epileptic seizures	yes
96	188	Recurrent ICH	Not an Outcome Event	28/11/2017	Fall at home	yes
126	22	Recurrent ICH	Not an Outcome Event	02/02/2015	ICH before randomisation	yes
290	138	Recurrent ICH	Not an Outcome Event	18/04/2016	Death due to pre-randomisation ICH	yes
56	31	Recurrent ICH	Other Intracranial Haemorrhage	19/08/2014	Haemorrhagic transformation of ischaemic stroke	yes
370	171	Recurrent ICH	Other Intracranial Haemorrhage	27/01/2017	Convexity SAH	yes
452	192	Recurrent ICH	Other Intracranial Haemorrhage	31/10/2017	Convexity SAH	yes
26	11	Recurrent ICH	Recurrent ICH	16/01/2015	recurrent ICH	yes
79	149	Recurrent ICH	Recurrent ICH	22/09/2015	Recurrent ICH	yes
117	124	Recurrent ICH	Recurrent ICH	04/09/2015	Recurrent ICH	yes
124	76	Recurrent ICH	Recurrent ICH	28/03/2016	Recurrent ICH	yes
126	17	Recurrent ICH	Recurrent ICH	15/02/2015	Recurrent ICH	yes
126	51	Recurrent ICH	Recurrent ICH	17/04/2015	Recurrent ICH	yes
153	169	Recurrent ICH	Recurrent ICH	04/09/2015	Recurrent ICH	yes
189	67	Recurrent ICH	Recurrent ICH	31/12/2015	Recurrent ICH	yes
196	68	Recurrent ICH	Recurrent ICH	18/11/2015	Recurrent ICH	yes
336	177	Recurrent ICH	Recurrent ICH	14/11/2016	Recurrent ICH	yes

ICH = intracerebral haemorrhage; SAH = subarachnoid haemorrhage

Participant characteristics at randomisation by treatment allocation

	Start antiplatelet therapy (n=268)		Avoid antiplatelet therapy (n=269)	
Occlusive vascular diseases before intracerebral haemorrhage *				
Ischaemic heart disease	133	(50%)	110	(41%)
Ischaemic stroke	75	(28%)	88	(33%)
Transient ischaemic attack	57	(21%)	76	(28%)
Atrial fibrillation/flutter	42	(16%)	50	(19%)
Peripheral arterial disease	22	(8%)	14	(5%)
Valvular heart disease	11	(4%)	18	(7%)
Symptomatic venous thromboembolism	9	(3%)	10	(4%)
Stroke of uncertain pathological type	2	(<1%)	3	(1%)
Retinal artery occlusion	3	(<1%)	5	(2%)
Mesenteric ischaemia	1	(<1%)	1	(<1%)
Past history of haemorrhage before intracerebral haemorrhage				
Intracerebral haemorrhage	8	(3%)	11	(4%)
Gastrointestinal haemorrhage	7	(3%)	6	(2%)
Other type of intracranial haemorrhage	5	(2%)	6	(2%)
Other type of extracranial haemorrhage	3	(1%)	2	(1%)
Other relevant co-morbidities before intracerebral haemorrhage				
High blood pressure	194	(72%)	207	(77%)
Diabetes mellitus	57	(21%)	70	(26%)
Congestive cardiac failure	12	(5%)	8	(3%)
Renal failure on dialysis	3	(1%)	3	(1%)
Functional status[1]				
Able to lift both arms off the bed	242	(90%)	244	(91%)
Able to walk without the help of another person	199	(74%)	196	(73%)
Able to talk and not confused	234	(87%)	238	(89%)

Data are n (%). * Some participants had more than one co-morbidity.

Antithrombotic therapy before randomisation and during follow-up

	Start antiplatelet therapy (n=268)		Avoid antiplatelet therapy (n=269)	
Antithrombotic therapy used before intracerebral haemorrhage				
Antiplatelet therapy				
Aspirin monotherapy	132	(49%)	137	(51%)
Clopidogrel monotherapy	70	(26%)	63	(23%)
Aspirin and Clopidogrel	9	(3%)	5	(2%)
Aspirin and Dipyridamole	6	(2%)	5	(2%)
Other	4	(1%)	2	(1%)
Anticoagulant therapy				
Vitamin K antagonist	30	(11%)	41	(15%)
Non-vitamin K antagonist	8	(3%)	11	(4%)
Antiplatelet and anticoagulant therapy	9	(3%)	5	(2%)
Preferred antiplatelet therapy that would be prescribed if allocated to start antiplatelet therapy *				
Aspirin monotherapy	149	(56%)	150	(56%)
Clopidogrel monotherapy	117	(44%)	112	(42%)
Aspirin and Clopidogrel	1	(<1%)	5	(2%)
Dipyridamole monotherapy	1	(<1%)	1	(<1%)
Aspirin, Clopidogrel and Dipyridamole	0	(0%)	1	(<1%)
Adherence to allocated treatment strategy before the first outcome event after randomisation §				
Hospital/clinic discharge	259/265	(98%)	266/266	(99%)
First annual follow-up	193/218	(89%)	205/211	(97%)
Second annual follow-up	104/122	(85%)	105/113	(93%)
Third annual follow-up	59/71	(83%)	61/69	(88%)
Fourth annual follow-up	21/26	(81%)	20/24	(83%)

* Variable used in the minimisation algorithm. § Denominators indicate the number of participants surviving at each follow-up timepoint without a preceding outcome event

Anticoagulant therapy at discharge and during follow-up

	Start antiplatelet therapy (n=268)		Avoid antiplatelet therapy (n=269)	
Hospital/clinic discharge	1/268	(<1%)	1/269	(<1%)
First annual follow-up	8/265	(3%)	6/267	(2%)
Second annual follow-up	6/165	(4%)	5/161	(3%)
Third annual follow-up	9/103	(9%)	3/107	(3%)
Fourth annual follow-up	4/42	(10%)	1/39	(3%)

Denominators indicate the number of participants surviving at each follow-up timepoint

Blood pressure-lowering drug use at discharge and during follow-up, with average achieved blood pressures during follow-up, by treatment allocation

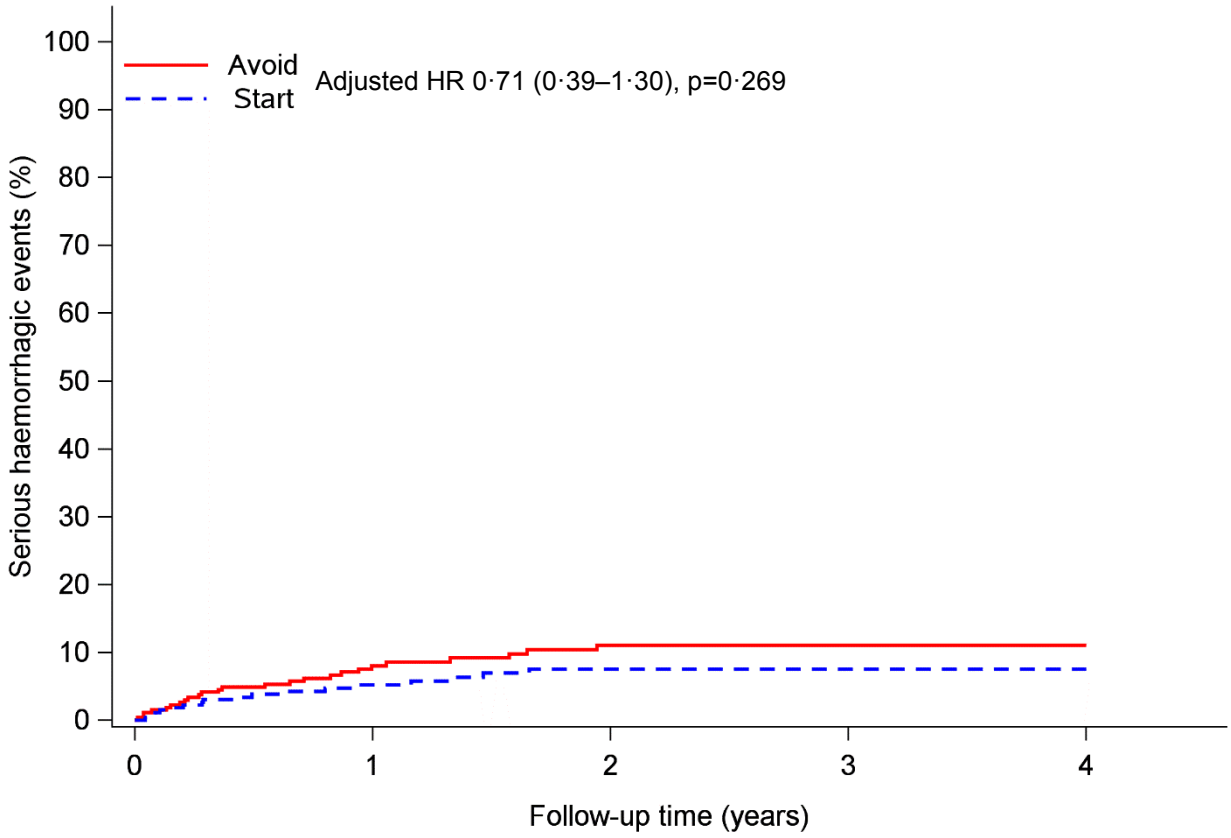
	Start antiplatelet therapy		Avoid antiplatelet therapy	
Hospital/clinic discharge	n=268		n=269	
None	53	(20%)	41	(15%)
One	82	(31%)	92	(34%)
Two	92	(34%)	84	(31%)
Three	30	(11%)	36	(13%)
Four or more	11	(4%)	16	(6%)
First annual follow-up	n=265		n=267	
Median systolic blood pressure, mmHg	132	(120-140)	130	(121-140)
Median diastolic blood pressure, mmHg	74	(70-80)	74	(69-80)
None	46	(17%)	34	(13%)
One	54	(20%)	78	(29%)
Two	85	(32%)	75	(28%)
Three	56	(21%)	50	(19%)
Four or more	24	(9%)	30	(11%)
Second annual follow-up	n=165		n=161	
Median systolic blood pressure, mmHg	129	(120-138)	130	(120-140)
Median diastolic blood pressure, mmHg	72	(66-80)	72	(67-80)
None	29	(18%)	27	(17%)
One	39	(24%)	34	(21%)
Two	41	(25%)	48	(30%)
Three	34	(21%)	33	(21%)
Four or more	10	(10%)	11	(10%)
Third annual follow-up	n=103		n=107	
Median systolic blood pressure, mmHg	133	(120-141)	131	(120-140)
Median diastolic blood pressure, mmHg	76	(70-82)	72	(68-80)
None	22	(21%)	21	(20%)
One	25	(24%)	19	(18%)
Two	23	(22%)	31	(29%)
Three	23	(22%)	25	(23%)
Four or more	10	(10%)	11	(10%)
Fourth annual follow-up	n=42		n=39	
Median systolic blood pressure, mmHg	132	(120-140)	129	(120-139)
Median diastolic blood pressure, mmHg	72	(62-80)	74	(63-80)
None	9	(21%)	3	(8%)
One	11	(26%)	11	(28%)
Two	15	(36%)	9	(23%)
Three	7	(17%)	12	(31%)
Four or more	0	(0%)	4	(10%)

Data are n (%) or median (inter-quartile range).

Cumulative absolute risks, and risk differences, of the primary outcome and key secondary outcomes, by treatment allocation and by year

	Start antiplatelet therapy (n=268)		Avoid antiplatelet therapy (n=268)		Risk difference	
Recurrent symptomatic spontaneous intracerebral haemorrhage						
Year 1	3·1	(1·6 to 6·2)	7·3	(4·6 to 11·4)	-4·2	(-8·1 to -0·3)
Year 2	5·5	(3·1 to 9·7)	10·3	(6·9 to 15·2)	-4·8	(-9·9 to 0·4)
Year 3	5·5	(3·1 to 9·7)	10·3	(6·9 to 15·2)	-4·8	(-9·9 to 0·4)
Year 4	5·5	(3·1 to 9·7)	10·3	(6·9 to 15·2)	-4·8	(-9·9 to 0·4)
All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage)						
Year 1	5·2	(3·0 to 8·8)	8·0	(5·3 to 12·2)	-2·9	(-7·2 to 1·5)
Year 2	7·6	(4·7 to 12·0)	11·0	(7·5 to 16·0)	-3·5	(-8·9 to 2·0)
Year 3	7·6	(4·7 to 12·0)	11·0	(7·5 to 16·0)	-3·5	(-8·9 to 2·0)
Year 4	7·6	(4·7 to 12·0)	11·0	(7·5 to 16·0)	-3·5	(-8·9 to 2·0)
All major occlusive vascular events (symptomatic ischaemic stroke, myocardial infarction, mesenteric ischaemia, peripheral arterial occlusion, deep vein thrombosis, pulmonary embolism, or carotid/coronary/peripheral arterial revascularisation procedures)						
Year 1	7·6	(4·9 to 11·8)	9·6	(6·6 to 14·1)	-2·0	(-7·1 to 3·0)
Year 2	14·2	(10·0 to 20·0)	14·0	(9·9 to 19·5)	0·2	(-6·6 to 7·1)
Year 3	19·0	(13·6 to 26·1)	19·2	(13·7 to 26·4)	-0·2	(-9·0 to 8·6)
Year 4	30·9	(21·3 to 43·4)	23·9	(16·4 to 33·9)	7·0	(-7·0 to 21·0)
All major haemorrhagic or occlusive vascular events						
Year 1	12·7	(9·1 to 17·6)	17·1	(12·9 to 22·4)	-4·4	(-10·7 to 1·9)
Year 2	21·4	(16·3 to 27·7)	23·7	(18·5 to 30·0)	-2·3	(-10·3 to 5·7)
Year 3	24·0	(18·5 to 30·9)	28·6	(22·4 to 36·0)	-4·6	(-13·7 to 4·6)
Year 4	33·1	(24·2 to 44·2)	33·3	(25·2 to 43·1)	-0·1	(-13·6 to 13·3)
All major occlusive vascular events (protocol-defined)						
Year 1	9·5	(6·4 to 14·0)	14·4	(10·6 to 19·6)	-4·9	(-10·8 to 0·9)
Year 2	18·6	(13·8 to 24·9)	20·6	(15·7 to 26·8)	-2·0	(-9·8 to 5·9)
Year 3	22·4	(16·8 to 29·7)	25·7	(19·7 to 33·3)	-3·3	(-12·7 to 6·0)
Year 4	29·9	(21·2 to 41·1)	30·5	(22·5 to 40·6)	-0·6	(-14·1 to 12·8)
All major vascular events (protocol-defined)						
Year 1	8·8	(5·9 to 13·1)	16·7	(12·6 to 22·0)	-7·9	(-13·7 to -2·1)
Year 2	16·2	(11·8 to 22·0)	25·6	(20·2 to 32·1)	-9·3	(-17·1 to -1·5)
Year 3	21·5	(16·0 to 28·6)	31·1	(24·7 to 38·7)	-9·6	(-19·0 to -0·2)
Year 4	30·2	(21·6 to 41·1)	35·5	(27·5 to 45·1)	-5·4	(-18·5 to 7·8)

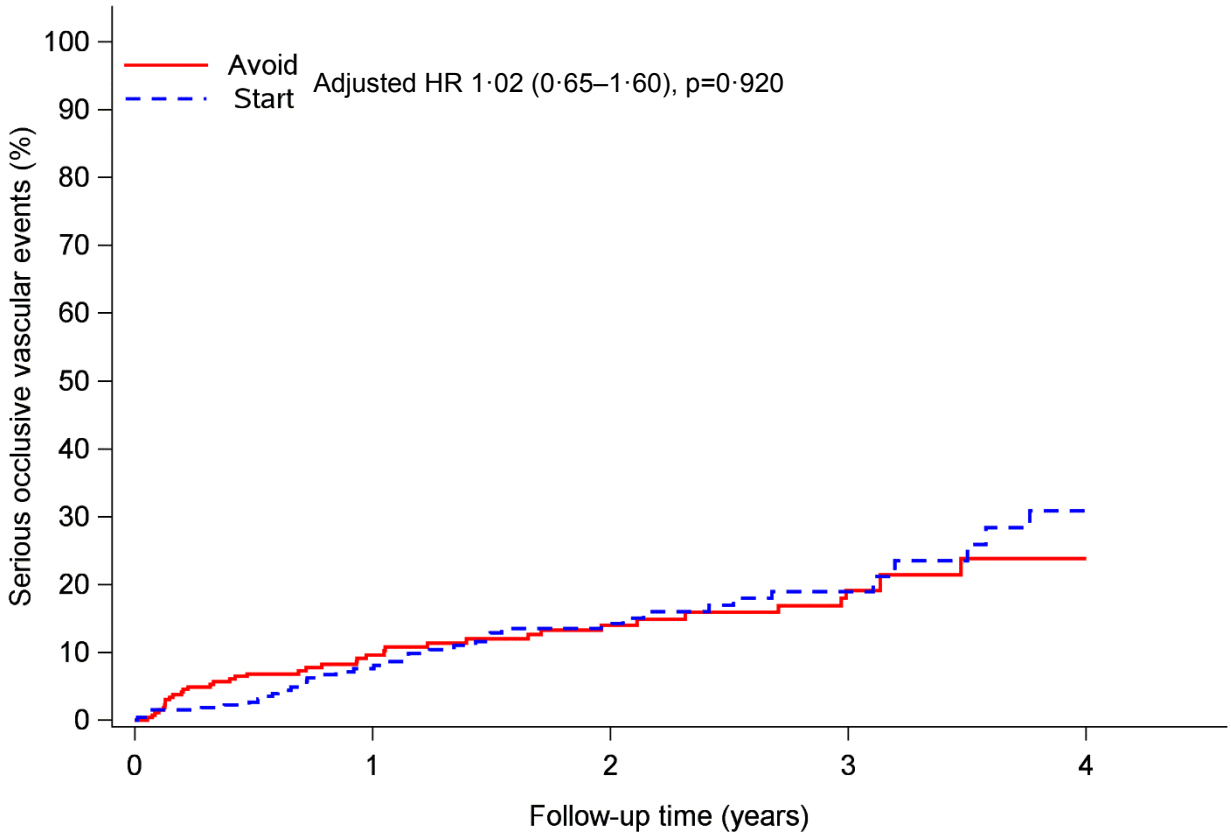
Kaplan-Meier plot showing the risk of the first occurrence of any major haemorrhagic event



Patients-at-Risk (No. Cumulative Events)					
Avoid	268 (0)	184 (20)	121 (25)	73 (25)	22 (25)
Start	268 (0)	188 (13)	120 (17)	70 (17)	24 (17)

Numbers below the x-axis indicate numbers of survivors under follow-up at the start of each year (and the cumulative number of participants with a first event in follow-up) according to treatment allocation

Kaplan-Meier plot showing the risk of the first occurrence of any major occlusive vascular event

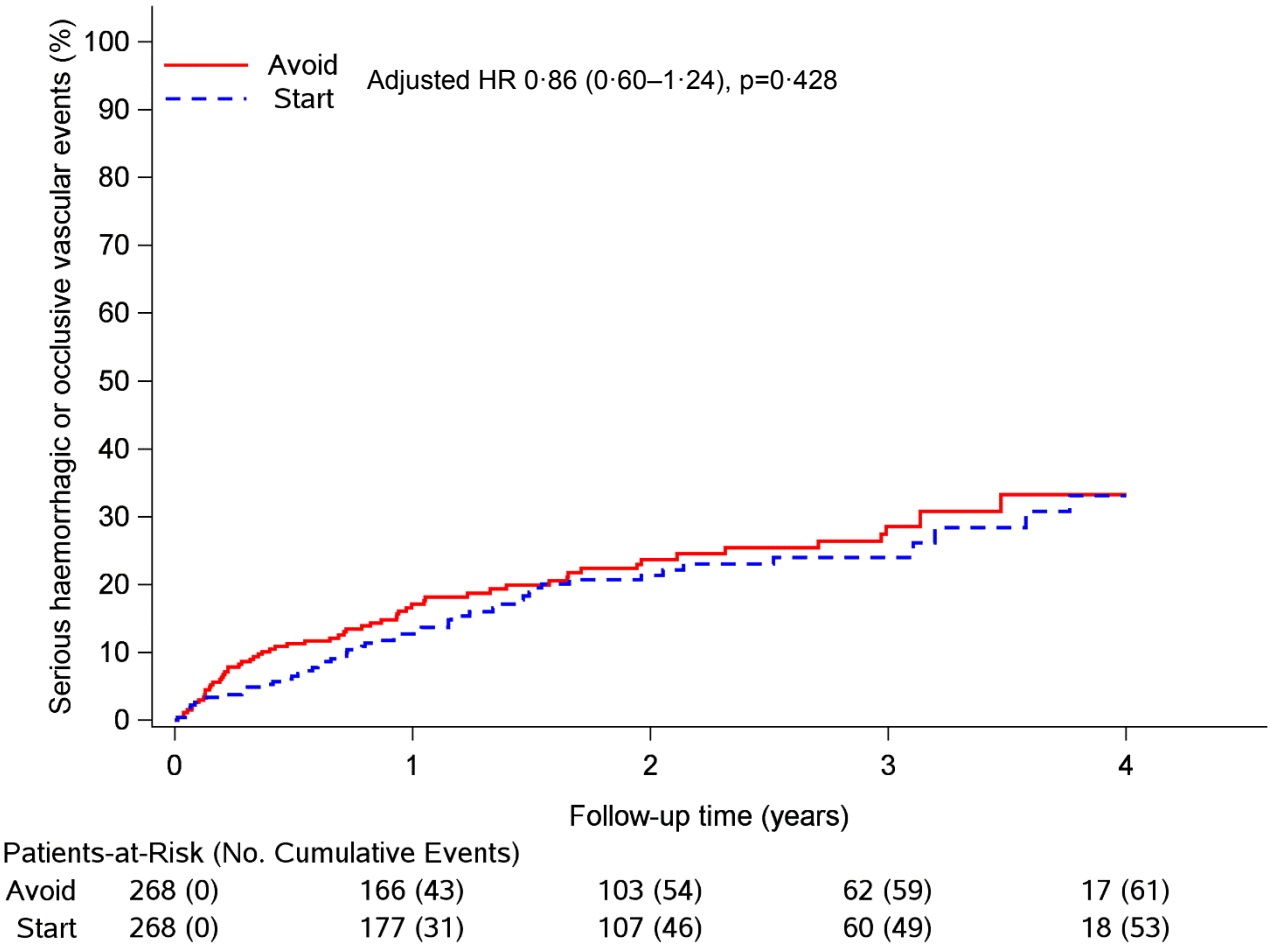


Patients-at-Risk (No. Cumulative Events)

Avoid	268 (0)	172 (24)	111 (31)	66 (36)	18 (38)
Start	268 (0)	181 (18)	111 (29)	62 (34)	18 (39)

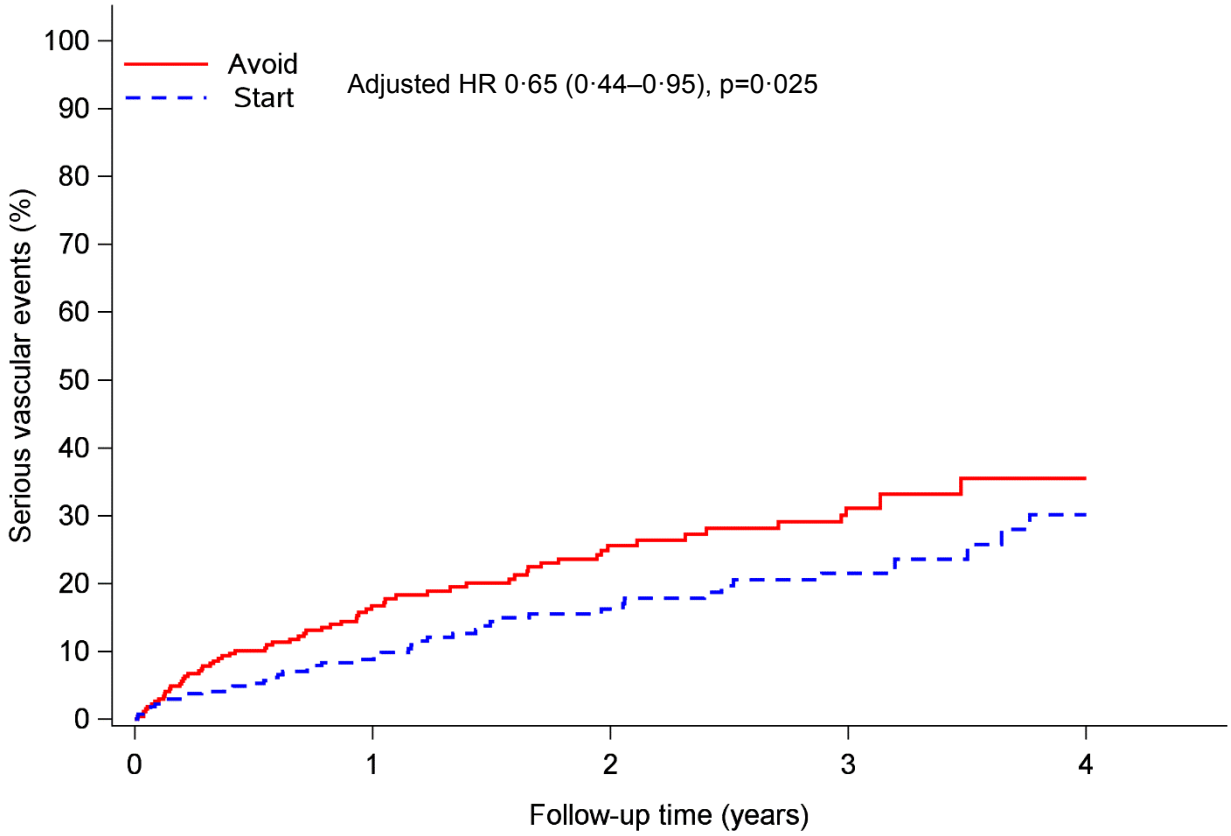
Numbers below the x-axis indicate numbers of survivors under follow-up at the start of each year (and the cumulative number of participants with a first event in follow-up) according to treatment allocation

Kaplan-Meier plot showing the risk of the first occurrence of any major haemorrhagic or occlusive vascular event



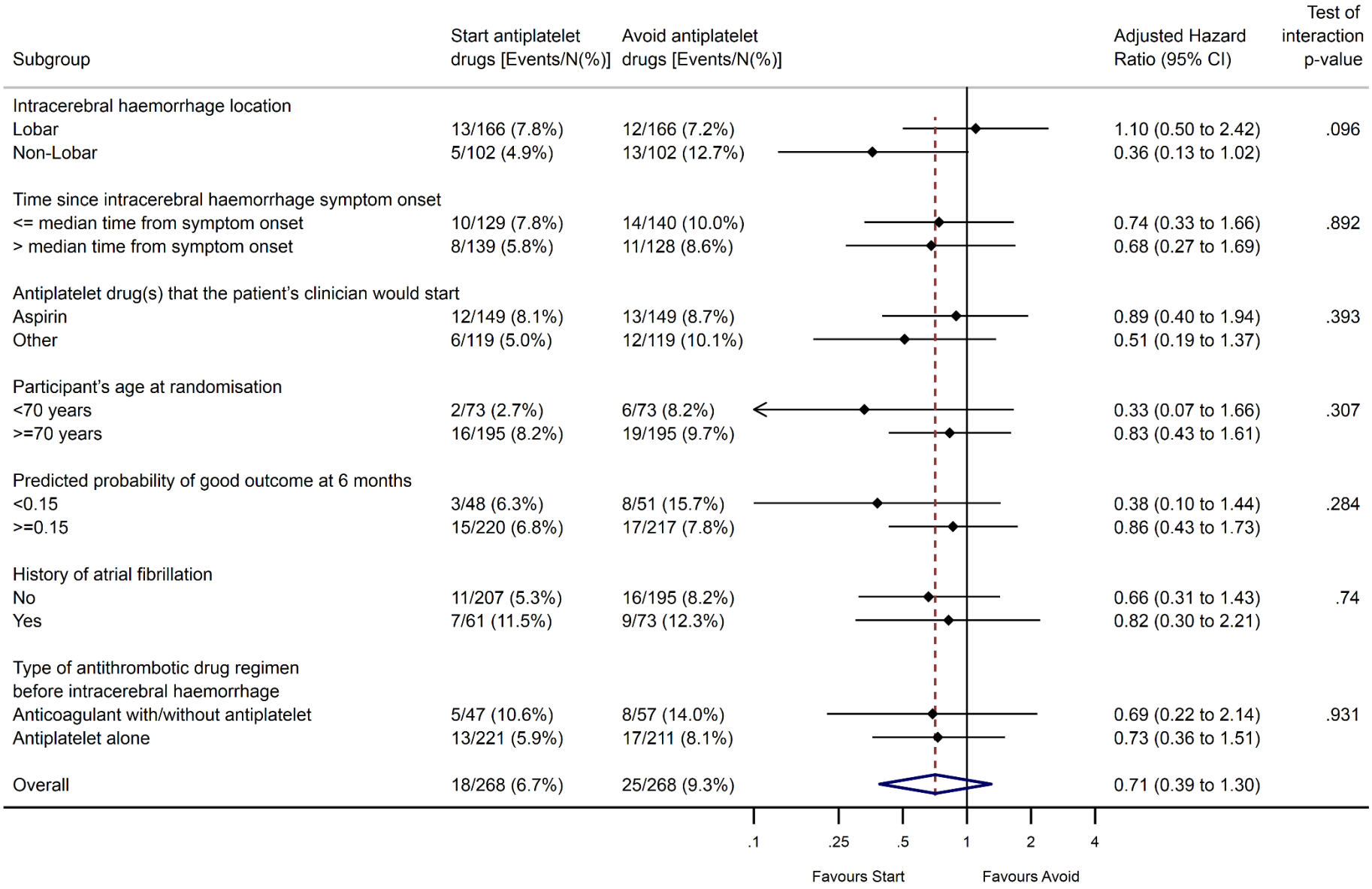
Numbers below the x-axis indicate numbers of survivors under follow-up at the start of each year (and the cumulative number of participants with a first event in follow-up) according to treatment allocation

Kaplan-Meier plot showing the risk of the first occurrence of the composite outcome of major vascular events, as proposed in the trial protocol



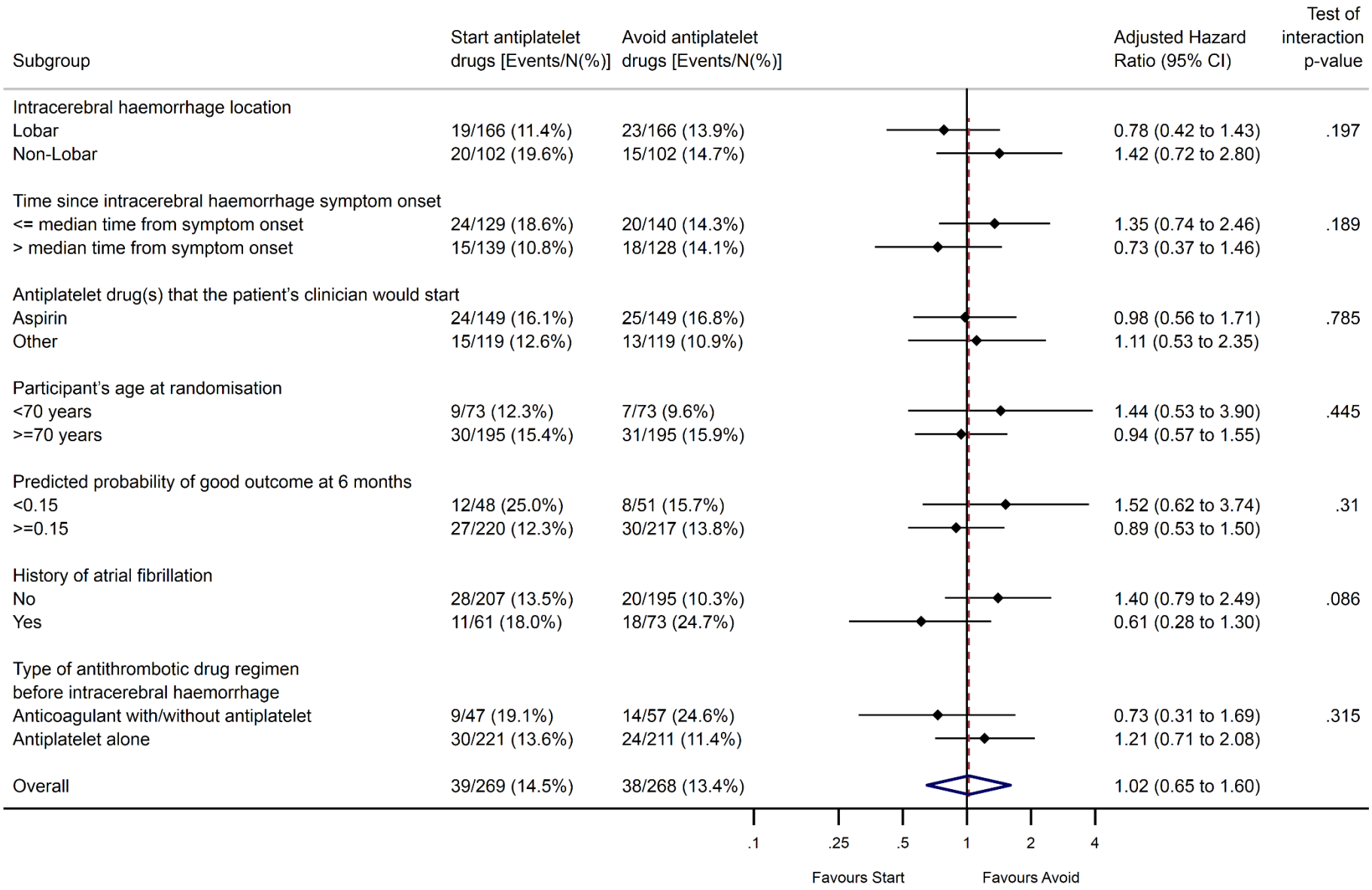
Numbers below the x-axis indicate numbers of survivors under follow-up at the start of each year (and the cumulative number of participants with a first event in follow-up) according to treatment allocation

Pre-specified exploratory sub-group analyses of all major haemorrhagic events

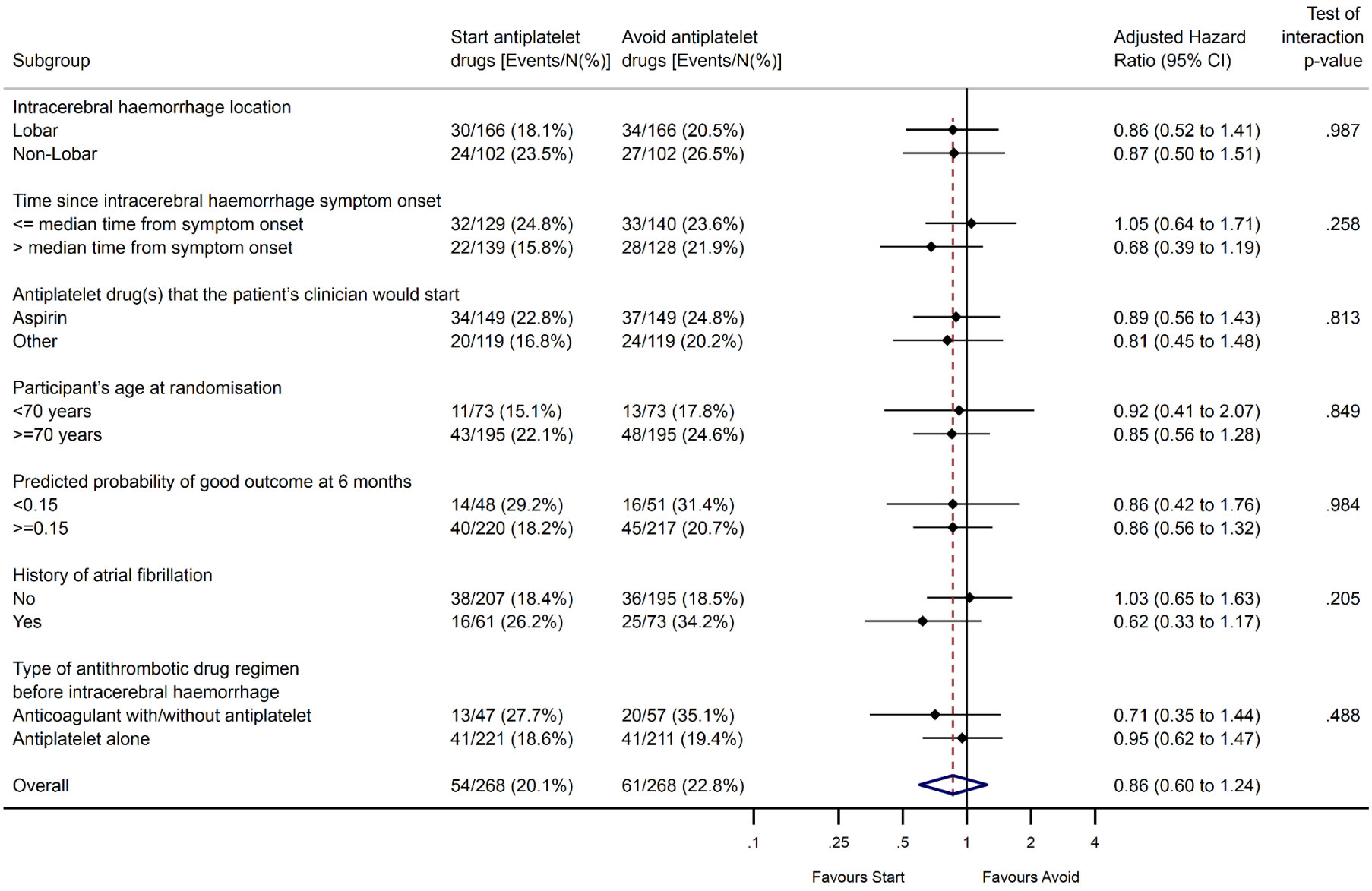


Pre-specified exploratory sub-group analyses of all major occlusive vascular events

Subgroup	Start antiplatelet drugs [Events/N(%)]	Avoid antiplatelet drugs [Events/N(%)]	Adjusted Hazard Ratio (95% CI)	Test of interaction p-value
Intracerebral haemorrhage location				
Lobar	19/166 (11.4%)	23/166 (13.9%)	0.78 (0.42 to 1.43)	.197
Non-Lobar	20/102 (19.6%)	15/102 (14.7%)	1.42 (0.72 to 2.80)	
Time since intracerebral haemorrhage symptom onset				
<= median time from symptom onset	24/129 (18.6%)	20/140 (14.3%)	1.35 (0.74 to 2.46)	.189
> median time from symptom onset	15/139 (10.8%)	18/128 (14.1%)	0.73 (0.37 to 1.46)	
Antiplatelet drug(s) that the patient's clinician would start				
Aspirin	24/149 (16.1%)	25/149 (16.8%)	0.98 (0.56 to 1.71)	.785
Other	15/119 (12.6%)	13/119 (10.9%)	1.11 (0.53 to 2.35)	
Participant's age at randomisation				
<70 years	9/73 (12.3%)	7/73 (9.6%)	1.44 (0.53 to 3.90)	.445
>=70 years	30/195 (15.4%)	31/195 (15.9%)	0.94 (0.57 to 1.55)	
Predicted probability of good outcome at 6 months				
<0.15	12/48 (25.0%)	8/51 (15.7%)	1.52 (0.62 to 3.74)	.31
>=0.15	27/220 (12.3%)	30/217 (13.8%)	0.89 (0.53 to 1.50)	
History of atrial fibrillation				
No	28/207 (13.5%)	20/195 (10.3%)	1.40 (0.79 to 2.49)	.086
Yes	11/61 (18.0%)	18/73 (24.7%)	0.61 (0.28 to 1.30)	
Type of antithrombotic drug regimen before intracerebral haemorrhage				
Anticoagulant with/without antiplatelet	9/47 (19.1%)	14/57 (24.6%)	0.73 (0.31 to 1.69)	.315
Antiplatelet alone	30/221 (13.6%)	24/211 (11.4%)	1.21 (0.71 to 2.08)	
Overall	39/269 (14.5%)	38/268 (13.4%)	1.02 (0.65 to 1.60)	



Pre-specified exploratory sub-group analyses of the composite outcome of all major haemorrhagic or occlusive vascular events



modified Rankin Scale (mRS) scores rated at randomisation by collaborators and during follow-up by participants/carers,[2-4] by treatment allocation

	Start antiplatelet therapy		Avoid antiplatelet therapy	
At randomisation	n=268		n=269	
0 (no symptoms)	31	(12%)	26	(10%)
1 (no significant disability)	66	(25%)	59	(22%)
2 (slight disability)	47	(17%)	62	(23%)
3 (moderate disability)	55	(21%)	53	(20%)
4 (moderately severe disability)	57	(21%)	50	(18%)
5 (severe disability)	12	(4%)	19	(7%)
First annual follow-up (p=0·920)	n=230		n=231	
0 (no symptoms)	34	(15%)	36	(16%)
1 (no significant disability)	41	(18%)	36	(16%)
2 (slight disability)	20	(9%)	28	(12%)
3 (moderate disability)	75	(33%)	72	(31%)
4 (moderately severe disability)	21	(9%)	13	(6%)
5 (severe disability)	16	(7%)	24	(10%)
6 (dead)	23	(10%)	22	(10%)
Second follow-up (p=0·408)	n=176		n=178	
0 (no symptoms)	19	(11%)	27	(15%)
1 (no significant disability)	21	(12%)	22	(12%)
2 (slight disability)	16	(9%)	20	(11%)
3 (moderate disability)	63	(36%)	52	(29%)
4 (moderately severe disability)	11	(6%)	8	(5%)
5 (severe disability)	15	(9%)	17	(10%)
6 (dead)	31	(18%)	32	(18%)
Third annual follow-up (p=0·328)	n=118		n=121	
0 (no symptoms)	13	(11%)	12	(10%)
1 (no significant disability)	7	(6%)	16	(13%)
2 (slight disability)	11	(9%)	17	(14%)
3 (moderate disability)	41	(35%)	31	(26%)
4 (moderately severe disability)	7	(6%)	6	(5%)
5 (severe disability)	8	(7%)	10	(8%)
6 (dead)	31	(26%)	29	(24%)
Fourth annual follow-up (p=0·783)	n=49		n=48	
0 (no symptoms)	4	(8%)	5	(10%)
1 (no significant disability)	4	(8%)	5	(10%)
2 (slight disability)	2	(4%)	4	(8%)
3 (moderate disability)	19	(38%)	13	(27%)
4 (moderately severe disability)	2	(4%)	1	(2%)
5 (severe disability)	4	(8%)	5	(10%)
6 (dead)	15	(30%)	15	(31%)

The analysis for each year is restricted to participants who were randomised at least the same number of years before the end of recruitment, to avoid including early deaths in the relevant follow-up year when the corresponding surviving recruits would not have had the potential to be assessed.

Serious adverse events, classified by organ system

MedDRA system organ class	Start antiplatelet therapy (n=268)	Avoid antiplatelet therapy (n=269)
Blood and lymphatic system disorders	n=0	n=0
Cardiac disorders	n=2	n=0
Congenital, familial and genetic disorders	n=0	n=0
Ear and labyrinth disorders	n=0	n=0
Endocrine disorders	n=0	n=0
Eye disorders	n=0	n=0
Gastrointestinal disorders	n=0	n=0
General disorders and administration site conditions	n=0	n=0
Hepatobiliary disorders	n=0	n=1
Immune system disorders	n=0	n=0
Infections and infestations	n=0	n=0
Injury, poisoning and procedural complications	n=1	n=1
Investigations	n=0	n=0
Metabolism and nutrition disorders	n=0	n=0
Musculoskeletal and connective tissue Disorders	n=1	n=1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	n=0	n=1
Nervous system disorders	n=1	n=1
Pregnancy, puerperium and perinatal Conditions	n=0	n=0
Psychiatric disorders	n=0	n=0
Renal and urinary disorders	n=0	n=0
Reproductive system and breast disorders	n=0	n=0
Respiratory, thoracic and mediastinal disorders	n=0	n=0
Skin and subcutaneous tissue disorders	n=0	n=0
Social circumstances	n=0	n=0
Surgical and medical procedures	n=1	n=0
Vascular disorders	n=0	n=0

References

1. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. *Stroke* 2002; **33**(4): 1041-7.
2. Bruno A, Akinwuntan AE, Lin C, et al. Simplified modified rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke* 2011; **42**(8): 2276-9.
3. Bruno A, Shah N, Lin C, et al. Improving modified Rankin Scale assessment with a simplified questionnaire. *Stroke* 2010; **41**(5): 1048-50.
4. Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal and telephone questionnaires. *Stroke* 2012; **43**(3): 851-3.