Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial

*SoSTART Collaboration**

Summary

Background Oral anticoagulation reduces the rate of systemic embolism for patients with atrial fibrillation by two-thirds, but its benefits for patients with previous intracranial haemorrhage are uncertain. In the Start or STop Anticoagulants Randomised Trial (SoSTART), we aimed to establish whether starting is non-inferior to avoiding oral anticoagulation for survivors of intracranial haemorrhage who have atrial fibrillation.

Methods SoSTART was a prospective, randomised, open-label, assessor-masked, parallel-group, pilot phase trial done at 67 hospitals in the UK. We recruited adults (aged ≥18 years) who had survived at least 24 h after symptomatic spontaneous intracranial haemorrhage, had atrial fibrillation, and had a CHA_2DS_2-VASc score of at least 2. Web-based computerised randomisation incorporating a minimisation algorithm allocated participants (1:1) to start or avoid long-term (≥1 year) full treatment dose open-label oral anticoagulation. The participants assigned to start oral anticoagulation received either a direct oral anticoagulant or vitamin K antagonist, and the group assigned to avoid oral anticoagulation received standard clinical practice (antiplatelet agent or no antithrombotic agent). The primary outcome was recurrent symptomatic spontaneous intracranial haemorrhage, and was adjudicated by an individual masked to treatment allocation. All outcomes were ascertained for at least 1 year after randomisation and assessed in the intention-to-treat population of all randomly assigned participants, using Cox proportional hazards regression adjusted for minimisation covariates. We planned a sample size of 190 participants (one-sided p=0·025, power 90%, allowing for non-adherence) based on a non-inferiority margin of 12% (or adjusted hazard ratio [HR] of 3·2). This trial is registered with ClinicalTrials.gov (NCT03153150) and is complete.

Findings Between March 29, 2018, and Feb 27, 2020, consent was obtained at 61 sites for 218 participants, of whom 203 were randomly assigned at a median of 115 days (IQR 49–265) after intracranial haemorrhage onset. 101 were assigned to start and 102 to avoid oral anticoagulation. Participants were followed up for median of 1·2 years (IQR 0·97–1·95; completeness 97·2%). Starting oral anticoagulation was not non-inferior to avoiding oral anticoagulation: eight (8%) of 101 in the start group versus four (4%) of 102 in the avoid group had intracranial haemorrhage recurrences (adjusted HR 2·42 [95% CI 0·72–8·09]; p=0·152). Serious adverse events occurred in 17 (17%) participants in the start group and 15 (15%) in the avoid group. 22 (22%) patients in the start group and 11 (11%) patients in the avoid group died during the study.

Interpretation Whether starting oral anticoagulation was non-inferior to avoiding it for people with atrial fibrillation after intracranial haemorrhage was inconclusive, although rates of recurrent intracranial haemorrhage were lower than expected. In view of weak evidence from analyses of three composite secondary outcomes, the possibility that oral anticoagulation might be superior for preventing symptomatic major vascular events should be investigated in adequately powered randomised trials.

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Introduction

Compared with the general population, survivors of spontaneous (non-traumatic) intracerebral haemorrhage are at higher risk of ischaemic stroke and myocardial infarction, and their risk of all major vascular events is higher still (about 8% per year overall).[1–3] Atrial fibrillation is present in 14–42% of patients with any type of intracranial haemorrhage,[4–9] and more than doubles the risk of major vascular events.[3]

The oral vitamin K antagonist warfarin provides about a 64% relative reduction in the risk of stroke in atrial fibrillation compared with control or placebo, despite a small increase in the risk of major bleeding.[10] Treatment with a direct (ie, non-vitamin K antagonist) oral anticoagulant (DOAC) reduces the risk of stroke, intracranial haemorrhage, and death compared with warfarin for patients with atrial fibrillation.[11] However, the randomised controlled trials that confirmed these effects

Research in context

Evidence before this study

Randomised controlled trials have shown that oral anticoagulation reduces the high risk of systemic embolism by almost two-thirds for patients with atrial fibrillation despite doubling their low risk of major bleeding. However, these trials excluded patients with intracranial haemorrhage. We searched the Cochrane Central Register of Controlled Trials, MEDLINE Ovid (from 1946), Embase Ovid (from 1974), online registers of clinical trials, and bibliographies of relevant publications on June 11, 2021, with no language restrictions (for search terms see appendix pp 3–5). We found one completed randomised feasibility study involving 30 patients (NASPAF-ICH, NCT02998905) and one completed randomised phase 2 trial involving 101 patients (APACHE-AF, NCT02565693) that compared the effects of oral anticoagulation versus antiplatelet therapy for participants with atrial fibrillation after intracerebral haemorrhage; these trials were inconclusive about clinical outcomes. Meta-analyses of observational studies of patients with atrial fibrillation and intracranial haemorrhage mostly found associations between oral anticoagulation and reduced risks of major ischaemic vascular events, but no significant change in the risk of recurrent major haemorrhagic vascular events.

Added value of this study

The Start or STop Anticoagulants Randomised Trial (SoSTART) is, to our knowledge, the largest randomised controlled trial to date to compare the effects of starting versus avoiding oral anticoagulation for atrial fibrillation after intracranial haemorrhage. Participants allocated to start oral anticoagulation had more intracranial haemorrhage recurrences, but our prespecified margin for declaring non-inferiority was not met (p=0·152). However, non-significant results for our three composite secondary outcomes suggest that starting oral anticoagulation might be superior to avoiding oral anticoagulation for preventing any symptomatic major vascular event.

Implications of all the available evidence

Further randomised trials are justified to investigate the non-inferiority of the effects of oral anticoagulation on major bleeding for patients with atrial fibrillation after intracranial haemorrhage or whether oral anticoagulation might be superior for preventing symptomatic major vascular events (especially those that are fatal or disabling). Clinicians should embed ongoing randomised controlled trials that are addressing this problem in their clinical practice so that these trials and the COCROACH planned individual participant data meta-analysis are adequately powered to provide definitive evidence.

did not include survivors of intracranial haemorrhage who had atrial fibrillation. These patients are at higher risk of intracranial haemorrhage than the general population[3,12] and intracranial haemorrhages are more likely to be fatal when associated with oral anticoagulant use,[13] leaving uncertainty about the effects of oral anticoagulation for these patients.

The NOACs for Stroke Prevention in Patients With Atrial Fibrillation and Previous ICH (NASPAF-ICH) randomised feasibility study in 30 patients and the Apixaban After Anticoagulation-associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation (APACHE-AF) phase 2 randomised trial in 101 patients have compared the effects of starting oral anticoagulation versus antiplatelet therapy or no antithrombotic therapy for participants with atrial fibrillation after intracerebral haemorrhage, but were inconclusive about safety and efficacy.[14–16] Cohort studies of patients with spontaneous intracranial haemorrhage and atrial fibrillation comparing oral anticoagulation with either antiplatelet agents or no antithrombotic therapy have mostly found associations between oral anticoagulation and lower risks of major ischaemic vascular events, but no significant change in the risk of recurrent major haemorrhagic vascular events, although these studies are susceptible to selection bias.[17,18] Consequently, recent guidelines throughout the world have been unable to make strong recommendations about oral anticoagulation for atrial fibrillation after intracranial haemorrhage, although they tend to recommend a DOAC over a vitamin K antagonist if used, and avoidance of antiplatelet agents.[19–24]

We initiated the Start or STop Anticoagulants Randomised Trial (SoSTART) for survivors of spontaneous intracranial haemorrhage who have atrial fibrillation to establish the feasibility of performing a definitive randomised trial in an acceptable timescale and to estimate whether the risk of recurrent symptomatic spontaneous intracranial haemorrhage after oral anticoagulation is sufficiently low (non-inferior) to justify a definitive randomised trial.

Methods

Study design

SoSTART was a prospective, randomised, open-label, assessor-masked, parallel-group, pilot-phase, non-inferiority trial done at 67 hospitals in the UK. The Scotland A Research Ethics Committee approved the trial protocol (version 3.0, Sept 11, 2017). The trial co-sponsors were the University of Edinburgh and NHS Lothian Health Board. The patient reference group for the Research to Understand Stroke due to Haemorrhage (RUSH) programme co-designed the study materials and reviewed progress. The trial steering committee and

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

sponsor approved the trial protocol (final version 6.0, Jan 23, 2020, available online, published before the close of recruitment) and the statistical analysis plan (final version 2.0, finalised April 26, 2021, before data lock and analysis). Patients, or their nearest relative or representative if the patient was not considered capable of deciding themselves, provided written informed consent before randomisation.

This pilot-phase trial had an internal feasibility phase that lasted until 60 participants were randomly assigned, which involved investigators keeping screening logs of patients considered for inclusion to record whether they were eligible and approached, whether they provided consent, and whether they were enrolled and randomly assigned.[25] The feasibility phase aimed to establish the acceptability and feasibility of recruiting the target sample size in a definitive trial in an acceptable timescale, measured by a primary outcome of the rate of participant recruitment per site.

Participants

We recruited adults (≥18 years) who had survived for at least 24 h after symptomatic spontaneous intracranial haemorrhage (ie, intracerebral haemorrhage, non-aneurysmal subarachnoid haemorrhage, intraventricular haemorrhage, or subdural haemorrhage) that was not known to be due to an underlying macrovascular cause (eg, intracranial aneurysm, arteriovenous malformation, cerebral cavernous malformation, dural arteriovenous fistula, or intracranial venous thrombosis), head injury, or haemorrhagic transformation of cerebral infarction. Participants were required to have atrial fibrillation (persistent or paroxysmal) or atrial flutter and a CHA_2DS_2-VASc score of at least 2 (a score for predicting the risk of stroke or thromboembolism in atrial fibrillation, based on congestive heart failure [1 point]; hypertension [1 point]; age ≥75 years [2 points]; diabetes [1 point]; previous stroke, transient ischaemic attack, or thromboembolism [2 points]; vascular disease [1 point]; age 65–74 years [1 point]; and sex category [1 point for female]).[26] Adults were ineligible if they had a prosthetic mechanical heart valve or severe (haemodynamically significant) native valve disease; left atrial appendage occlusion had been performed or was planned; oral or parenteral anticoagulation was going to be prescribed; the allocated treatment strategy would be implemented for less than 1 year; antiplatelet therapy would also be prescribed if allocated to start oral anticoagulation; they or their doctor was certain about whether or not to start oral anticoagulation; brain imaging that first diagnosed the intracranial haemorrhage was not available; they were not registered with a primary care practitioner; they were pregnant, breastfeeding, or of childbearing age and not taking contraception; they and their carer were unable to understand spoken or written English; they were intolerant of lactose; they had a contraindication to any of the permitted oral anticoagulants other than recent intracranial haemorrhage; they had a life expectancy less than 1 year; or they had already been randomly assigned in SoSTART. Participants could be enrolled if they or their nearest relative and their physician in secondary care were uncertain about whether to start or avoid oral anticoagulation and had consented, in which case randomisation was done at least 24 h after stroke symptom onset.

For the **study protocol** see https://www.protocols.io/view/start-or-stop-anticoagulants-randomised-trial-sost-bcw4ixgw

Randomisation and masking

Investigators supplied complete information about participants' demographics, comorbidities, functional status, previous antithrombotic therapy, and previous intracranial haemorrhage, the physician's preferred oral anticoagulant (if the patient should be allocated to start oral anticoagulation), and the physician's preferred comparator (an antiplatelet agent or no antithrombotic agents) via a secure web interface with in-built validation to ensure complete baseline data entry into the trial database before randomisation. A central, web-based, computerised randomisation system incorporating a minimisation algorithm randomly assigned participants (1:1) to either start or avoid full treatment dose oral anticoagulation (with dose adjustment if required according to renal function, age, bodyweight, or concomitant medications). The algorithm randomly allocated the first participant with a probability of 0·5 to one group in 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 trial groups with respect to six baseline variables: qualifying intracranial haemorrhage location (lobar intracerebral haemorrhage vs non-lobar intracerebral haemorrhage vs other), time since qualifying intracranial haemorrhage onset (<10 weeks *vs* ≥10 weeks), use of oral anticoagulation before qualifying intracranial haemorrhage (yes *vs* no), oral anticoagulant preferred by the patient's physician if allocated to start oral anticoagulation (DOAC *vs* other), comparator preferred by the patient's physician if allocated to avoid oral anticoagulation (antiplatelet agent vs no antithrombotic agent), and predicted probability of being alive and independent at 6 months (<0·15 *vs* ≥0·15).[27] These six 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 starting or avoiding oral anticoagulation, 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 oral anticoagulation, the system reminded investigators to prescribe the prespecified preferred oral anticoagulant within 24 h.

Treatment allocation was known to participants, clinicians caring for them in primary and secondary care, and local investigators. The outcome event adjudicator was masked to participant identity, treatment allocation,

and drug use by redaction of this information from source documents.

Procedures

Participants who were able and willing to undergo brain MRI provided informed consent and had a brain MRI scan before randomisation. After randomisation, a consultant neuroradiologist (PMW or JP), who was masked to treatment allocation, used the web-based Systematic Image Review System tool to review anonymised Digital Imaging and Communications in Medicine images of diagnostic brain CT or MRI to confirm or refute eligibility and collect imaging features of intracranial haemorrhage and cerebral small vessel disease, and to support the adjudication of cerebral outcome events using standardised evaluation tools (appendix p 25).

For more on the **Systematic Image Review System tool** see https://sirs2.ccbs.ed.ac.uk

See **Online** for appendix

The intervention of starting oral anticoagulation for atrial fibrillation was restricted to the use of either a DOAC (factor Xa inhibitor [apixaban, rivaroxaban, or edoxaban] or direct thrombin inhibitor [dabigatran etexilate]) or vitamin K antagonist (warfarin sodium, acenocoumarol, or phenindione) at full treatment dose (with adjustment if required by renal function, age, bodyweight, or concomitant medications), initiated within 24 h of randomisation. The comparator was standard clinical practice without oral anticoagulation (either an antiplatelet agent or no antithrombotic agents). Participants were permitted to start or discontinue anticoagulant or antiplatelet agents if clinically indicated by outcome events during follow-up, regardless of treatment allocation. We measured adherence after randomisation regardless of treatment allocation by the use of antithrombotic agents (recorded by the preceding clinic or hospital discharge form or follow-up questionnaire) before the first outcome event. We collected information about use of antithrombotic agents, left atrial appendage occlusion, blood pressure lowering agents, 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 who had not withdrawn, to check vital status, medication use, and the occurrence of outcomes. We intended to follow up participants annually by sending questionnaires every year after randomisation for up to 3 years until the end of the trial. We interviewed participants or their carers by telephone if there was no response to the questionnaire or their response was incomplete or required clarification.

Because the side-effects of oral anticoagulants are well known, we recorded serious adverse events (that were not an outcome event, expected complication of stroke, or known adverse reaction to oral anticoagulation) 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

In the internal feasibility phase, the primary feasibility outcome was the rate of participant recruitment per site, and the secondary feasibility outcomes were the proportions of eligible patients who were unsuitable to be approached to participate, who were approached, who declined, who consented, and who were randomised.

The primary clinical outcome of this pilot-phase trial was recurrent symptomatic spontaneous intracranial haemorrhage, which has been the most frequent major bleeding outcome that has been used to establish the safety of oral anticoagulation for atrial fibrillation in previous randomised trials.[28] The secondary clinical outcomes in the pilot phase were: symptomatic major vascular events (recurrent symptomatic spontaneous intracranial haemorrhage, ischaemic stroke, myocardial infarction, sudden cardiac death, death from another vascular cause, or death of an unknown cause); individual symptomatic vascular events (major haemorrhagic events, symptomatic ischaemic events, revascularisation procedures, or stroke of uncertain subtype); individual types of fatal events (vascular deaths [within 30 days of outcome events or from another vascular cause], sudden cardiac deaths, deaths of an unknown cause, or deaths from a non-vascular cause); and annual ratings of participant dependence and quality of life.

One medically trained clinical research fellow (TJM) at the trial coordinating centre was the internal assessor of reports of every outcome event, masked to treatment allocation and use of antithrombotic agents, using all available source documentation including clinical records, death certificates, autopsy reports, imaging reports, outpatient clinic letters, and hospital discharge summaries.

Investigators rated dependence with the modified Rankin Scale and quality of life using the EQ-5D-5L before randomisation, whereas participants or their carers rated dependence using the simplified modified Rankin Scale questionnaire and quality of life on the EQ-5D-5L at each annual follow-up.[29–31]

Statistical analysis

We based the sample size calculation on the annual rates of ischaemic stroke (5·8–14·9%)[32,33] and recurrent symptomatic spontaneous intracranial haemorrhage (4·2–8·6%)[33,34] for people with atrial fibrillation who did

not take antithrombotic agents after intracranial haemorrhage in cohort studies published at the time of planning this trial, and the relative risk reduction in ischaemic stroke with oral anticoagulation compared with no antithrombotic therapy (0·36).[10] If the annual rate of recurrent symptomatic spontaneous intracranial haemorrhage with oral anticoagulation increased from about 6% to about 18%, then this harm would be likely to exceed any reduction in ischaemic stroke, so the non-inferiority margin was set at 12%. This non-inferiority margin equates to a hazard ratio (HR) of 3·2 ($\log_e$[1–0·18]/$\log_e$[1–0·06]), so non-inferiority would be confirmed if the upper limit of the 95% CI of the adjusted HR for the effect of starting oral anticoagulation on recurrent symptomatic spontaneous intracranial haemorrhage is less than 3·2. SL used nQuery Advisor, version 7.0, to establish that these assumptions would require a sample size of 83 per group (166 in total) with one-sided p value of 0·025 and power of 90%, based on a 12% difference in proportions. Allowing for non-adherence, we aimed to recruit at least 190 participants in the pilot phase and follow them up for at least 1 year.

Throughout the recruitment period, the unmasked trial statistician 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. There was no formal fixed schedule of interim analyses, 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 at least some patients, oral anticoagulation was clearly indicated or contraindicated in clinical practice.

Two statisticians (CK and SL) and the chief investigator (RA-SS) prepared a prespecified statistical analysis plan without reference to data by randomised allocation or input from the only statistician who had been unmasked during the conduct of the trial (JS); the trial steering committee approved the statistical analysis plan before database lock.

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 all planned follow-up that was observed.[35] 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 time after randomisation, censored at death unrelated to an outcome event or last available follow-up.

The primary analysis first involved an assessment of the proportional hazards assumption, both graphically as well as by including a non-proportional treatment effect in the model. If the assumption held, the survival functions were compared by allocated treatment in a Cox proportional hazards model, including terms for treatment group (start *vs* avoid oral anticoagulation) and, providing there were sufficient outcome events, adjusting for the covariates included in the minimisation algorithm to give an adjusted HR with its corresponding 95% CI and p value. If adjustment for all minimisation variables was impossible, we prespecified that the time since qualifying intracranial haemorrhage onset would take precedence as the most important adjustment, followed by type of qualifying intracranial haemorrhage. We performed unadjusted Cox regression models for comparison with the findings of the primary analyses.

We prespecified that we would use the primary analysis method for three composites of secondary outcomes: any symptomatic major vascular event (myocardial infarction; symptomatic spontaneous intracerebral, subarachnoid, intraventricular, or subdural haemorrhage; ischaemic stroke; death within 30 days of recurrent symptomatic spontaneous intracranial haemorrhage, ischaemic stroke, myocardial infarction, or symptomatic deep vein thrombosis; sudden cardiac death; death from another vascular cause [ie, not within 30 days of an outcome event]; or

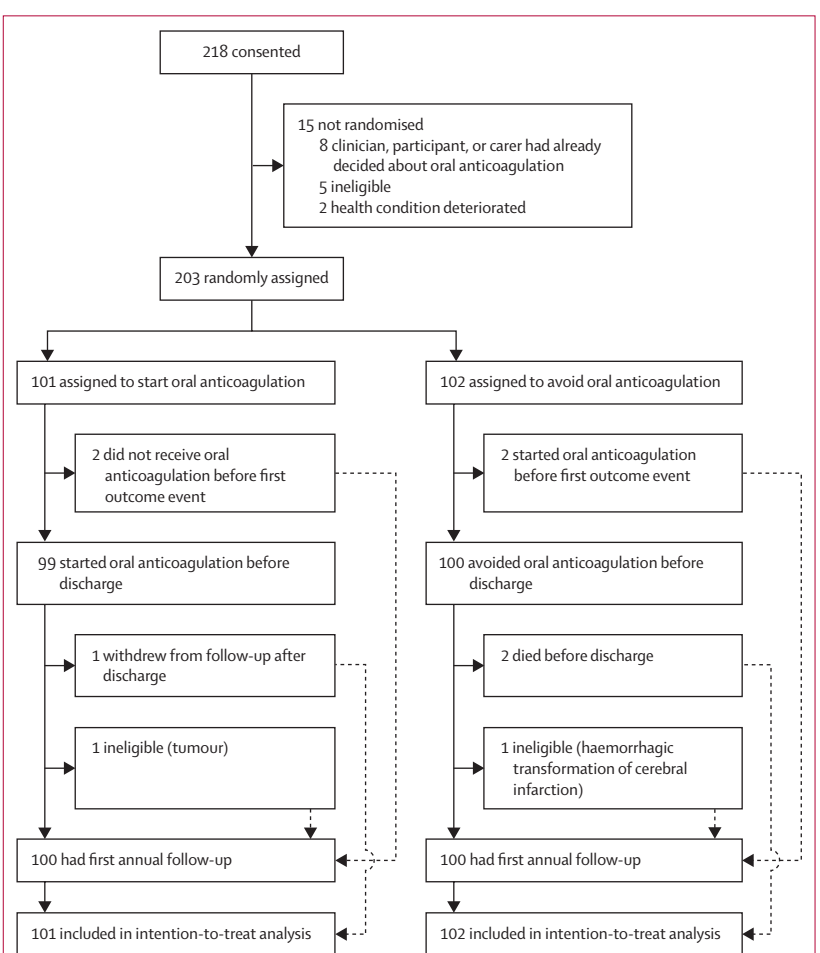


Figure 1: **Trial profile**

	Start oral anticoagulation (n=101)	Avoid oral anticoagulation (n=102)
Median age, years	79 (74–85)	79 (74–84)
Sex		
Male	62 (61%)	65 (64%)
Female	39 (39%)	37 (36%)
Ethnicity		
White	92 (91%)	96 (94%)
Asian	7 (7%)	4 (4%)
Black	1 (1%)	1 (1%)
Mixed	0 (0%)	1 (1%)
Other	1 (1%)	0 (0%)
Type of qualifying spontaneous intracranial haemorrhage*†		
Lobar intracerebral haemorrhage	35 (35%)	38 (37%)
Non-lobar intracerebral haemorrhage	58 (57%)	56 (55%)
Other	8 (8%)	8 (8%)
Time since qualifying intracranial haemorrhage symptom onset*		
Median, days	104 (44–244)	115 (51–288)
<10 weeks	37 (37%)	38 (37%)
≥10 weeks	64 (63%)	64 (63%)
Probability of good 6-month outcome*[27]		
<0·15	21 (21%)	22 (22%)
≥0·15	80 (79%)	80 (78%)
Type of atrial arrhythmia‡		
Persistent atrial fibrillation	28 (28%)	24 (24%)
Permanent atrial fibrillation	51 (50%)	51 (50%)
Paroxysmal atrial fibrillation	22 (22%)	26 (25%)
Atrial flutter	0	1 (1%)
Detection of atrial arrhythmia		
Before intracranial haemorrhage	92 (91%)	95 (93%)
After intracranial haemorrhage	9 (9%)	7 (7%)
CHA_2DS_2-VASc score[26]		
2	14 (14%)	18 (18%)
3	22 (22%)	20 (20%)
4	32 (32%)	26 (25%)
5	21 (21%)	15 (15%)
6	9 (9%)	17 (17%)
7	3 (3%)	6 (6%)
Use of oral anticoagulation before qualifying intracranial haemorrhage*		
Yes	84 (83%)	86 (84%)
No	17 (17%)	16 (16%)
HAS-BLED score[36]		
0	3 (3%)	0 (0%)
1	48 (48%)	46 (45%)
2	34 (34%)	31 (30%)
3	12 (12%)	20 (20%)
4	4 (4%)	5 (5%)
Intended type of oral anticoagulation (if allocated to start)*		
Direct oral anticoagulant	97 (96%)	101 (99%)
Other	4 (4%)	1 (1%)
Intended comparator (if allocated to avoid)*		
No antithrombotic agents	77 (76%)	70 (69%)
Antiplatelet agent	24 (24%)	32 (31%)

Data are n (%) or median (IQR). *Variables used in the minimisation algorithm. †Haemorrhage could affect multiple locations in one participant. ‡Complete list of co-morbidities is in the appendix (p 8).

Table 1: **Baseline characteristics of the intention-to-treat population**

death of an unknown cause); any stroke (ischaemic stroke or symptomatic spontaneous intracerebral or subarachnoid haemorrhage); and any stroke or vascular death (ischaemic stroke or symptomatic spontaneous intracerebral or subarachnoid haemorrhage; death within 30 days of recurrent symptomatic spontaneous intracranial haemorrhage, ischaemic stroke, myocardial infarction, or symptomatic deep vein thrombosis; sudden cardiac death; death from another vascular cause [ie, not within 30 days of an outcome event]; or death of an unknown cause). We also prespecified that we would describe survival times for ischaemic stroke and major haemorrhagic events and annual ratings of dependence and quality of life by treatment allocation group, but that we would not undertake formal statistical testing.

We planned analyses of the primary outcome of the pilot phase in three clinical subgroups (time since qualifying intracranial haemorrhage onset [<10 weeks *vs* ≥10 weeks], CHA_2DS_2-VASc score [dichotomised], and HAS-BLED score [dichotomised]) and two imaging biomarker subgroups in the MRI substudy (cerebral microbleed number [0–1 *vs* ≥2] and location [strictly lobar *vs* other]). However, we decided that we would not undertake formal statistical analysis of subgroup interactions because of the low incidence of primary outcome events, instead presenting summaries of the frequency of primary outcome events for each of the subgroups, split by treatment group.

The primary analysis (performed by CK) used the intention-to-treat population, defined as all randomly assigned participants, irrespective of whether they adhered to the allocated treatment, in the group to which they were allocated. An unmasked trial statistician did all statistical analyses (JS or CK) with SAS, version 9.4. The trial is registered with ClinicalTrials.gov (NCT03153150) and is complete.

Role of the funding source

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

	Start oral anticoagulation (n=101)	Avoid oral anticoagulation (n=102)	Unadjusted HR (95% CI), p value	Adjusted* HR (95% CI), p value
Primary outcome				
Recurrent symptomatic spontaneous intracranial haemorrhage	8 (8%)	4 (4%)	2·31 (0·69–7·68), p=0·173	2·42 (0·72–8·09), p=0·152
Composite secondary outcomes				
Any symptomatic major vascular event	12 (12%)	24 (24%)	0·51 (0·26–1·03), p=0·061	0·51 (0·26–1·03), p=0·060
Any stroke	11 (11%)	22 (22%)	0·53 (0·25–1·09), p=0·082	0·53 (0·25–1·09), p=0·084
Any stroke or vascular death	12 (12%)	23 (23%)	0·55 (0·27–1·10), p=0·092	0·55 (0·27–1·10), p=0·090

HR=hazard ratio. *Cox proportional hazards models were adjusted for two of the six minimisation variables: time since intracranial haemorrhage symptom onset (<10 weeks [reference] *vs* ≥10 weeks) and type of qualifying intracranial haemorrhage (lobar intracerebral haemorrhage *vs* non-lobar intracerebral haemorrhage and lobar intracerebral haemorrhage *vs* other); model non-convergence due to the low number of events prevented the inclusion of any more minimisation variables.

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

Results

In the internal feasibility phase, between March 29, 2018, and Dec 27, 2018, 908 patients were screened (appendix p 6), 204 were eligible, and 109 of them were invited to participate. 46 declined, 63 provided consent, and 60 were enrolled. By the time the target recruitment of the feasibility phase was reached, 20 sites had been active for 6 months or longer and their median recruitment rate was 0·25 participants (IQR 0·12–0·47) per site per month; we used this recruitment rate, the trial's rate of opening new sites, and the observed frequency of changes of principal investigator that led to interruption of recruitment, to estimate that it would take 5·0 years to recruit 800 participants in a definitive randomised trial involving 60 sites.

In the entire pilot phase trial, between March 29, 2018, and Feb 27, 2020, 61 of the 67 active sites (appendix p 2) obtained consent for 218 patients to participate, of whom 15 were not randomised. The remaining 203, exceeding the target sample size, were randomly assigned before the target end date of recruitment (appendix p 7, figure 1): 101 were randomly assigned to start oral anticoagulation (one withdrew after 36 days) and 102 to avoid oral anticoagulation, all of whom were included in the intention-to-treat population.

At baseline, the 203 participants had a median age of 79 years (IQR 74–85), 127 (63%) were men, and 188 (93%) were White (table 1). 187 (92%) participants had intracerebral haemorrhage, and 73 (36%) of these were reported to be in lobar locations. Participants were randomly assigned a median of 115 days (IQR 49–265) after intracranial haemorrhage onset. 154 (96%) participants had persistent or permanent atrial fibrillation, which was detected before intracranial haemorrhage in most participants. 161 (79%) participants had systemic arterial hypertension, 73 (36%) had a history of transient ischaemic attack or ischaemic stroke, 48 (24%) had a history of ischaemic heart disease, 46 (23%) had diabetes, and 23 (11%) had congestive cardiac failure (appendix p 8). Median CHA_2DS_2-VASc score was 4 (IQR 3–5) and median HAS-BLED score was 2 (1–2). Before the qualifying intracranial haemorrhage, 170 (84%) participants had used a DOAC or a vitamin K antagonist, and 32 (16%) had used an antiplatelet agent (appendix p 13). Independent review of brain imaging deemed 201 (99%) eligible, except for one participant found to have a brain tumour and another found to have haemorrhagic transformation of a cerebral infarction. Brain CT review confirmed that most participants (178 [92%] of 194) had intracerebral haemorrhage (63 [35%] of 178 lobar), median volume 5·4 mL (IQR 1·4–12·2), and frequent biomarkers of cerebral small vessel disease, and very few had a high probability of cerebral amyloid angiopathy according to the simplified Edinburgh criteria (appendix p 10).[37] Review of brain MRI performed for 112 participants in the MRI substudy confirmed similar findings, as well as the presence of at least two cerebral microbleeds in 62 participants (55%; 13 [21%] of which were in strictly lobar locations), and 23 (21%) had focal or disseminated superficial siderosis,

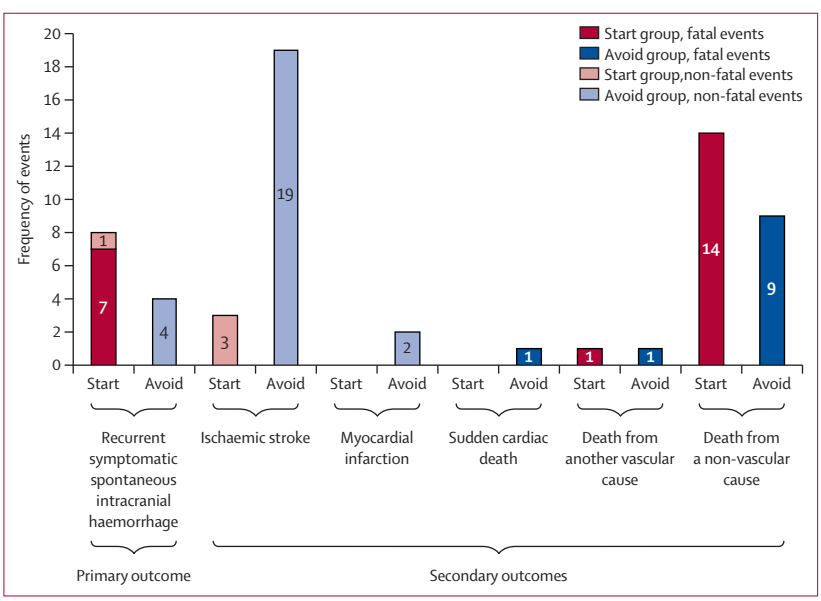
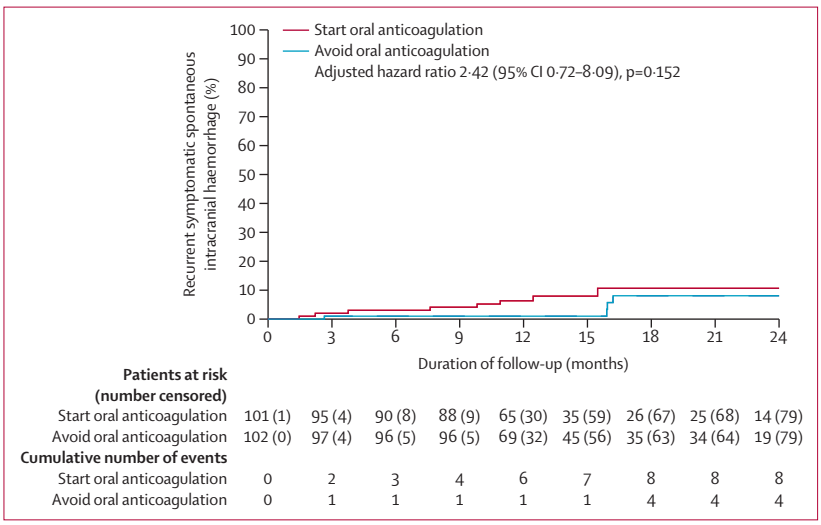


Figure 2: **Frequencies of the first occurrence of all primary and secondary outcome events that occurred during follow-up**



Patients at risk (number censored)									
Start oral anticoagulation	101 (1)	95 (4)	90 (8)	88 (9)	65 (30)	35 (59)	26 (67)	25 (68)	14 (79)
Avoid oral anticoagulation	102 (0)	97 (4)	96 (5)	96 (5)	69 (32)	45 (56)	35 (63)	34 (64)	19 (79)
Cumulative number of events									
Start oral anticoagulation	0	2	3	4	6	7	8	8	8
Avoid oral anticoagulation	0	1	1	1	1	1	4	4	4

Figure 3: **Kaplan-Meier plot of the first recurrent symptomatic spontaneous intracranial haemorrhage**
Numbers at risk are survivors under follow-up at the start of each 3-month period according to treatment allocation. Plot censored at 24 months (the Cox proportional hazards models used all available follow-up). Cumulative events indicate the participants in follow-up with a first event. Event rates at 12 months and 24 months were estimated from Kaplan-Meier analyses. Cumulative event rates were 6·3% (95% CI 2·9–13·6) in the start oral anticoagulation group versus 1·0% (0·1–6·9) in the avoid oral anticoagulation group at 12 months and 10·7% (5·1–21·4) versus 8·1% (3·0–20·9) at 24 months.

such that 36 (32%) of 112 had possible or probable cerebral amyloid angiopathy according to the modified Boston criteria (appendix pp 11–12).[38] At baseline, participants' characteristics and use of antithrombotic therapy were well balanced for major prognostic factors and potential confounders, especially those used in the minimisation algorithm (table 1).

Follow-up and outcome adjudication ended on March 26, 2021. Two participants in the avoid group died before hospital discharge (figure 1), and the remaining 201 were followed up at hospital or clinic discharge. We obtained 202 (>99%) of 203 of primary care practitioner questionnaires at 1-year follow-up (one participant withdrew after discharge; figure 1) and 71 (90%) of 79 at 2-year follow-up. We obtained 177 (98%) of 180 questionnaires sent to surviving participants at 1-year follow-up, and 59 (97%) of 61 at 2-year follow-up. Using both methods of follow-up, participants were followed up for a median of 1·2 years (IQR 0·97–1·95), and we obtained 251·25 of an intended 258·53 person-years for the trial cohort (overall completeness 97·2%).

Adherence to allocated treatment until the first outcome event or last follow-up was high: 199 (98%) of 203 at discharge after randomisation, 154 (96%) of 161 after 1 year, and 45 (96%) of 47 after 2 years (appendix p 14). Investigators intended to start a DOAC in 198 (96%) of 203, and 120 (59%) of 203 prespecified apixaban if a participant would be allocated to start oral anticoagulation. Investigators intended to start an antiplatelet agent in 56 (28%) of 203 participants, and 33 (59%) of 56 prespecified clopidogrel if a participant were allocated to avoid oral anticoagulation (appendix p 13). These preferences were implemented reliably after randomisation (table 1; appendix pp 13–14). One participant in the avoid group had left atrial appendage occlusion during follow-up. Most participants took at least one blood pressure-lowering agent during follow-up, and achieved median systolic blood pressure of about 130 mm Hg, with good balance by treatment allocation (appendix p 15). The proportional hazards assumption was fulfilled for analyses of primary and secondary outcomes during follow-up.

For the primary clinical outcome, eight (8%) of 101 participants allocated to start oral anticoagulation had recurrent symptomatic spontaneous intracranial haemorrhage compared with four (4%) of 102 participants who did not start oral anticoagulation (adjusted HR 2·42 [95% CI 0·72–8·09]; table 2, figures 2, 3), which did not provide evidence of non-inferiority (p=0·152). After allocation to start oral anticoagulation, seven (88%) of eight of the primary outcome events were fatal (all participants were taking an oral anticoagulant), whereas after allocation to avoid oral anticoagulation, none of the four primary outcomes were fatal (two participants were taking an oral anticoagulant; figure 2; appendix pp 16–19). Primary outcomes occurred in almost all of the prespecified subgroups in both groups of the main trial and the MRI substudy (appendix p 20).

For the secondary outcomes, none of the ischaemic strokes and myocardial infarctions were fatal, but all of the remaining events were fatal (one sudden cardiac death in the avoid group, two deaths from another vascular cause [congestive cardiac failure; one in each group], and 23 deaths of non-vascular causes [14 in the start group and nine in the avoid group]; figure 2). There were no deaths of unknown cause and no other secondary outcomes occurred, apart from one non-fatal symptomatic deep vein thrombosis (that did not meet the inclusion criteria for any of our prespecified composite secondary outcomes) in a participant allocated to start oral anticoagulation. For the prespecified composite secondary outcomes, we found weak evidence that starting might be superior to avoiding oral anticoagulation for preventing any symptomatic major vascular event, any stroke, and any stroke or vascular death (table 2, figure 4). Survival times are summarised descriptively for ischaemic stroke in the appendix (p 21).

The distributions of the modified Rankin Scale scores appeared similar between the treatment groups at randomisation and largely reflect the deaths during follow-up after starting (22 deaths) or avoiding (11 deaths) oral anticoagulation (appendix p 22). Quality of life appeared similar between the groups at randomisation and during follow-up (appendix p 23). 17 (17%) participants assigned to start and 15 (15%) assigned to avoid oral anticoagulation had serious adverse events (25 events in each group), all of which were neither outcomes nor expected complications of stroke, by MedDRA preferred term and treatment allocation group (appendix p 24). The most common serious adverse

events were hospital admissions for aortic stenosis (three [3%]), fall (two [2%]), and atrial fibrillation (two [2%]) in the 101 participants in the start oral anticoagulation group, and urinary tract infection, atrial fibrillation, and gastroenteritis (two each [2%]) in the 102 participants in the avoid oral anticoagulation group.

Discussion

In this randomised trial of survivors of intracranial haemorrhage who had atrial fibrillation, we established that it would be feasible for a 6-year definitive main phase trial at 60 sites to recruit 800 participants and follow them for 1 year. We did not find evidence that starting oral anticoagulation was non-inferior to avoiding oral anticoagulation with respect to intracranial haemorrhage. In analyses of three composite secondary outcomes, we found weak evidence that starting oral anticoagulation might be superior to avoiding oral anticoagulation for preventing any symptomatic major ischaemic or haemorrhagic vascular event.

This trial exceeded its recruitment target and is, to our knowledge, the largest published randomised trial of oral anticoagulation for atrial fibrillation after intracranial haemorrhage to date.[14–16] 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 age, sex, and CHA_2DS_2-VASc scores of the participants were similar to cohort studies, but time to initiation of oral anticoagulation after intracranial haemorrhage was longer.[17,18,34] The oral anticoagulant agents used were similar to a recent international survey of this scenario.[39] The use of antiplatelet therapy in some participants allocated to avoiding oral anticoagulation could be justified by participants' comorbidities (appendix p 8), and the effects of antiplatelet therapy on major vascular events for patients with atrial fibrillation[10] and intracerebral haemorrhage survivors.[40] Adherence to randomly allocated treatment was good. Only one patient had left atrial appendage occlusion, blood pressure was controlled for both groups throughout, and anti-hypertensive agent use was similar between groups. We minimised attrition bias by achieving 97·2% complete-

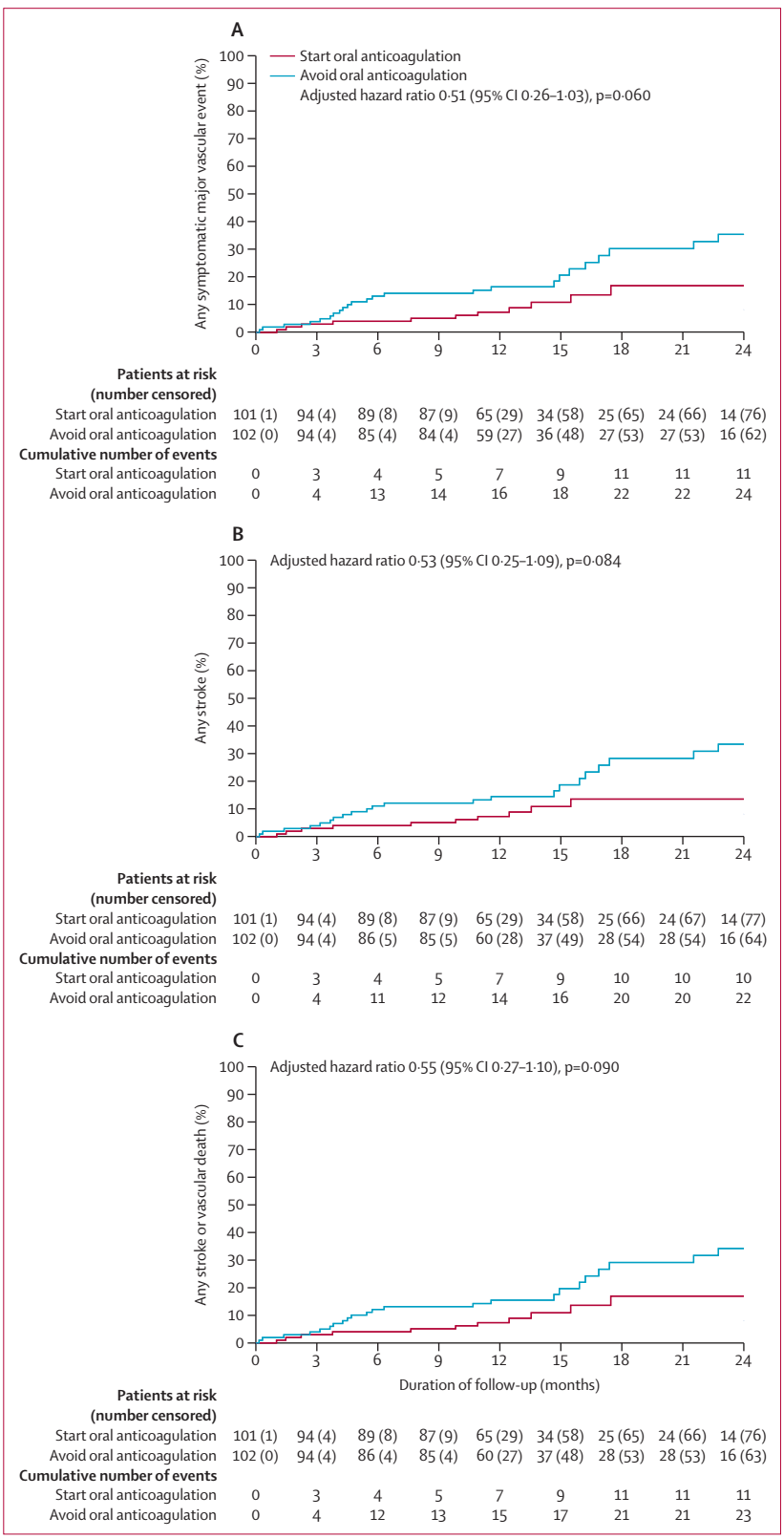


Figure 4: **Kaplan-Meier plots of the first occurrence of any symptomatic major vascular event (A), any stroke (B), and any stroke or vascular death (C)**
Numbers at risk are survivors under follow-up at the start of each year according to treatment allocation. Plot censored at 24 months (the Cox proportional hazards models used all available follow-up). Cumulative events indicate the participants in follow-up with a first event. Event rates at 12 months and 24 months are estimated from Kaplan Meier analyses. (A) Cumulative event rates for any symptomatic major vascular event were 7·3% (95% CI 3·6–14·8) in the start oral anticoagulation group versus 16·5% (10·5–25·6) in the avoid oral anticoagulation group at 12 months and 16·9% (9·0–30·6) versus 35·5% (24·2–50·0) at 24 months. (B) Cumulative event rates for any stroke were 7·3% (3·6–14·8) versus 14·6% (8·9–23·4) at 12 months and 13·6% (7·2–25·1) versus 33·5% (22·4–48·1) at 24 months. (C) Cumulative event rates for any stroke or vascular death were 7·3% (3·6–14·8) versus 15·5% (9·6–24·4) at 12 months and 16·9% (9·0–30·6) versus 34·2% (23·1–48·7) at 24 months.

ness with centralised postal or telephone follow-up, although any added benefits of in-person assessment remain uncertain.[41] We masked the outcome assessor to treatment allocation 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 label.[42] We prespecified our outcomes and methods of analysis, and report these according to our protocol and statistical analysis plan. The relative effects of oral anticoagulation in this trial were consistent with the effects observed in patients without intracranial haemorrhage.[10]

For more on the **PROSPERO study** see www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021246133

This trial has limitations. The primary outcome event rates observed were lower than assumed in the sample size calculation, so the estimate of effect on the primary outcome is less precise than expected. There were more non-cardiovascular deaths in the group assigned to start oral anticoagulation, which is a competing risk that might have reduced the observed risk of recurrent symptomatic spontaneous intracranial haemorrhage in this group. The recruitment rate in the feasibility phase was lower than in a smaller feasibility study,[14] but might be more accurate given the larger sample size of this study. 42% of patients approached declined, which seems higher than we found in RESTART,[40,43] and this should be investigated and addressed in future trials. Women were under-represented in this trial, as they have been in other trials after stroke, and the reasons for this should be found and addressed.[44] Although a variety of oral anticoagulants were used in the intervention group and the comparator could include the use of antiplatelet agents or no antithrombotic, these patterns were representative of contemporaneous clinical practice.[39] 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.[45] Only 60 (29%) of 204 eligible patients were recruited in the internal feasibility phase, most recruited participants were White, and participants were recruited from similar state-funded health-care services in four countries of the UK, so the generalisability of our findings to all patients, ethnic groups, and countries is uncertain.

The directions of the effects and the severities of the outcomes that we have observed can inform discussions with patients and carers in clinical practice, mainly to counsel them about the need for their participation in ongoing randomised trials to resolve this therapeutic dilemma (STATICH [NCT03186729], A3ICH [NCT03243175], ASPIRE [NCT03907046], ENRICH-AF [NCT03950076], and PRESTIGE-AF [NCT03996772]). Definitive randomised trials appear feasible, justified, and are ongoing, to investigate the effects of oral anticoagulation on major bleeding, any stroke, or any symptomatic major vascular event. Safety monitoring and analysis of ongoing trials should consider the varying severities and frequencies of the outcome events that we observed. Ultimately, a meta-analysis will maximise the precision of estimates of effect both overall as well as in important demographic, clinical, and imaging subgroups as part of a planned collaborative individual participant data meta-analysis, COCROACH (PROSPERO CRD42021246133).

Contributors

RA-SS (chief investigator) conceived the idea. RA-SS, MSD, DEN, JMW, and JN obtained funding. RA-SS designed and implemented the study, with input from the trial steering committee (including DEN, MSD, GYHL, AP-J, and PMW) and the trial management group. JMW and PMW advised on brain imaging acquisition, collection, management, and assessment. SL was the masked trial statistician. JS and CK were the unmasked trial statisticians who performed the analyses. RA-SS, CK, JR, and JS have accessed and verified the underlying data, which could have been accessed by anyone in the writing group if they wished. The corresponding author and statisticians (SL, CK, JR, and JS) also had full access to all data in the trial and had final responsibility for the decision to submit for publication. 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.

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*Investigators at sites that randomised participants are listed in the appendix (p 2).

Declaration of interests

JMW reports grants from EU Horizon 2020, Medical Research Council, Fondation Leducq, The Stroke Association, Alzheimer's Society, and the

British Heart Foundation, outside the submitted work. PMW reports personal fees from Stryker Global Advisory Board on Haemorrhagic Stroke and MicroVention-Terumo, and institutional grants from MicroVention-Terumo, Penumbra, Stryker, and Medtronic, outside the submitted work. GYHL reports consultancy and speaker fees (not received personally) from Bristol Myers Squibb/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo, outside the submitted work. A-PJ declares personal fees from Alexion Pharmaceuticals, outside the submitted work. All other writing group members declare no competing interests.

Data sharing

A deidentified version of the dataset used for analysis with individual participant data (excluding participants who opted out of data sharing) and a data dictionary, the study protocol, the statistical analysis plan, and the informed consent form will be available online for other researchers to apply for use 1 year after publication. Written proposals will be assessed by members of the SoSTART 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.

For more on **SoSTART data sharing** see https://datashare.ed.ac.uk/handle/10283/3967

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