TITLE

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

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SUMMARY

Background Oral anticoagulation reduces the rate of systemic embolism for patients with atrial fibrillation by two-thirds, but its benefits for patients with prior intracranial haemorrhage are uncertain. For survivors of intracranial haemorrhage with atrial fibrillation, we aimed to determine whether starting is non-inferior to avoiding oral anticoagulation.

Methods The Start or STop Anticoagulants Randomised Trial (SoSTART) was a prospective, randomised, open-label, assessor-blinded, parallel-group pilot phase trial at 67 hospitals in the UK. We recruited adults (≥18 years) who had symptomatic spontaneous intracranial haemorrhage, survived 24 h, and had atrial fibrillation and CHA_2DS_2-VASc score ≥2. Web-based computerised randomisation incorporating minimisation allocated participants (1:1) to start or avoid long-term (≥1y) full treatment dose open-label oral anticoagulation. We followed participants for ≥1y for the primary outcome (recurrent symptomatic spontaneous intracranial haemorrhage), which was adjudicated blinded to treatment allocation. We performed intention-to-treat analyses of time to first outcome event for all randomised participants using Cox proportional hazards regression, adjusted for minimisation covariates. We planned a sample size of 190 participants (1-sided p=0·025, power 90%, allowing for non-adherence) based on a non-inferiority margin of 12% (or adjusted hazard ratio of 3·2). This trial is registered with ClinicalTrials.gov (NCT03153150) but recruitment and follow-up have stopped.

Findings Between March 28, 2018 and February 27, 2020, consent was obtained at 61sites for 218 people to participate, of whom 203 (93%) were randomised a median of 115 days (IQR 49–265) after intracranial haemorrhage onset: 101 were assigned to start (one withdrew) and 102 to avoid oral anticoagulation. Participants were followed for median 1·2 years (IQR 0·97–1·95) (completeness 97·2%). Starting oral anticoagulation was not non-inferior to avoiding oral anticoagulation (8/101

[8%] *vs* 4/102 [4%] had intracranial haemorrhage recurrences; adjusted hazard ratio [HR] 2·42, 95% CI 0·72–8·09; $p_{non\text{-}inferiority}$=0·152).

Interpretation Starting oral anticoagulation was not non-inferior to avoiding it for people with atrial fibrillation after intracranial haemorrhage, although rates of recurrent intracranial haemorrhage were lower than expected. In light of 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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RESEARCH IN CONTEXT

Evidence before this study

Randomised controlled trials have shown that oral anticoagulation reduces the large risk of systemic embolism by almost two-thirds for patients with atrial fibrillation despite doubling their small 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 11 June 2021 (appendix). We found one completed randomised feasibility study involving 30 patients (NASPAF-ICH, NCT02998905) and one completed randomised phase II 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 lower 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 experienced more intracranial haemorrhage recurrences, but our pre-specified margin for declaring non-inferiority was not met ($p_{\text{non-inferiority}}$=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 dilemma in their clinical practice so that these trials and a planned individual participant data meta-analysis (from the Collaboration Of Controlled Randomised trials of Oral Antithrombotic agents after intraCranial Haemorrhage [COCROACH]; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021246133) are adequately powered to provide definitive evidence.

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 (~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 ~64% relative reduction in the risk of stroke in atrial fibrillation compared to control/placebo, despite a small increase in the risk of major bleeding.[10] Treatment with a direct (non-vitamin K antagonist) oral anticoagulant (DOAC) reduces the risk of stroke, intracranial haemorrhage, and death compared to warfarin for patients with atrial fibrillation.[11] However, the randomised controlled trials that confirmed these effects did not include survivors of intracranial haemorrhage with 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 involving 30 patients and the Apixaban After Anticoagulation-associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation (APACHE-AF) phase II randomised trial involving 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 to 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 Antitcoagulants Randomised Trial (SoSTART) for survivors of spontaneous intracranial haemorrhage with atrial fibrillation to determine 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-blinded, parallel-group, pilot phase non-inferiority trial at 67 hospitals in the UK. The Scotland A Research Ethics Committee approved the trial protocol (version 3.0, September 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 (www.RUSH.ed.ac.uk) co-designed the study materials and reviewed progress. The trial steering committee and sponsor approved the trial protocol (final version 6.0, January 23, 2020, published before the close of recruitment at

http://dx.doi.org/10.17504/protocols.io.bcw4ixgw) and the statistical analysis plan (final version 2.0 finalised 26 April 2021 before data lock and analysis).

This pilot phase trial had an internal feasibility phase that lasted until 60 participants were randomised, which involved investigators keeping screening logs of patients considered for inclusion to record whether they were eligible or approached, whether they provided consent, and whether they were randomised.[25] The feasibility phase aimed to determine 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. The aim of the entire pilot phase trial was to determine whether the risk of the primary outcome of recurrent symptomatic spontaneous intracranial haemorrhage was sufficiently low (non-inferior) to justify a definitive trial.

Participants

We recruited adults (≥18 years) who had survived ≥24 h after symptomatic spontaneous intracranial haemorrhage (i.e. intracerebral haemorrhage, non-aneurysmal subarachnoid haemorrhage, intraventricular haemorrhage, or subdural haemorrhage) that was not known to be due to an underlying macrovascular cause (e.g. intracranial aneurysm, arteriovenous malformation, cerebral cavernous malformation, dural arteriovenous fistula, 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 CHA_2DS_2-VASc score ≥2 (a score for predicting the risk of stroke or thromboembolism in atrial fibrillation based on Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65-74 years, and Sex category).[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 <1 year; antiplatelet therapy would also be prescribed if allocated to start oral anticoagulation; they or their doctor was certain about whether 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 one year; or they had already been randomised in SoSTART. Patients, or their nearest relative or representative if the patient lacked mental capacity, provided written informed consent. 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.

Randomisation and blinding

Investigators supplied complete information about participants' demographics, comorbidities, functional status, previous antithrombotic therapy, intracranial haemorrhage, their preferred oral anticoagulant (if the patient should be allocated to start oral anticoagulation), and their 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 start or avoid full treatment dose oral anticoagulation (with dose adjustment if required according to renal function, age, body weight, 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 (i.e. minimisation) allocated each subsequent participant with a probability of 0·8 to the group that minimised differences between the two arms of the trial 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 pre-specified preferred oral anticoagulant within 24 h.

Treatment allocation was open to participants, clinicians caring for them in primary and secondary care, and local investigators. The outcome event adjudicator was blinded 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 blinded to treatment allocation, used the web-based Systematic Image Review System

tool (SIRS, https://sirs2.ccbs.ed.ac.uk) to review anonymised DICOM 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).

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), 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 drugs, and blood pressure control at discharge and during follow-up.

We followed 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 three 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, approached, declined, consented, and randomised.

The primary clinical outcome was recurrent symptomatic spontaneous intracranial haemorrhage, which has been the most frequent major bleeding outcome that has been used to determine the safety of oral anticoagulation for atrial fibrillation in prior randomised trials.[28] The secondary clinical outcomes in the pilot phase were: symptomatic serious 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, stroke of uncertain sub-type); 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, 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, blinded 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 on 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 analyses

We based the sample size calculation on the annual rates of ischaemic stroke (5·8-14·9%) and recurrent symptomatic spontaneous intracranial haemorrhage (4·2-8·6%) 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,[32-34] and the relative risk reduction in ischaemic stroke with oral anticoagulation compared to no antithrombotic therapy (0·36).[10] If the annual rate of recurrent symptomatic spontaneous intracranial haemorrhage with oral anticoagulation increased from ~6% to ~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 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 hazard ratio for the effect of starting oral anticoagulation on recurrent symptomatic spontaneous intracranial haemorrhage is less than 3·2. SL used nQuery Advisor v7.0 to determine that these assumptions would require a sample size of 83 per group (166 in total) with 1-sided p=0·025 and power 90%, based on a difference in proportions. Allowing for non-adherence, we aimed to recruit at least 190 participants in a pilot phase and follow them for at least one year.

Throughout the recruitment period, the unblinded 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 pre-specified statistical analysis plan without reference to data by randomised allocation or input from the only statistician who had been unblinded during the conduct of the trial (JS); the trial steering committee approved the statistical analysis plan before database lock.

The primary analysis (performed by CK) used the intention-to-treat population, defined as all randomised participants, irrespective of whether they adhered to the allocated treatment, in the group to which they were allocated. We estimated the survival function in each treatment group using a Kaplan-Meier survival analysis of time to the 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 all planned follow-up that was observed.[35]

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 hazard ratio with its corresponding 95% confidence interval (CI) and p-value. If adjustment for all minimisation variables was impossible, we pre-specified that 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 pre-specified 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 [i.e. not within 30 days of an outcome event]; death of an unknown cause); any stroke (ischaemic stroke, or symptomatic spontaneous intracerebral or subarachnoid haemorrhage); 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 [i.e. not within 30 days of an outcome event]; death of an unknown cause). We also pre-specified 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 sub-groups (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 sub-groups in the MRI sub-study (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 sub-group 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.

An unblinded trial statistician did all statistical analyses (JS or CK) with SAS version 9.4.

The trial is registered with ClinicalTrials.gov (number NCT03153150).

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 and statisticians (SL, CK, JR and JS) had full access to all data in the trial and had final responsibility for the decision to submit for publication.

RESULTS

In the internal feasibility phase between March 28, 2018 and December 27, 2018, 908 patients were screened (appendix), 204 (22%) were eligible and alive, and 109 (53%) of them were approached. Of the 109 patients approached, 46 (42%) declined, 63 (58%) provided consent and 60 (55%) were recruited and randomised. By the time the target recruitment of the feasibility phase was reached, 20 sites had been active for ≥6 months and their median recruitment rate was 0·25 (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 28, 2018 and February 27, 2020, 61 of the 67 active sites (appendix) obtained consent for 218 patients to participate, of whom 15 were not randomised, leaving 203 (93%) to be randomly assigned ahead of target (appendix, figure 1): 101 were randomly assigned to start oral anticoagulation (one withdrew after 36 days) and 102 to avoid oral anticoagulation (figure 1), all of whom were included in the outcome analyses.

At baseline, participants were on average 79 years old, almost two-thirds were male, and most were white (table 1). Most participants had intracerebral haemorrhage, one-third of which were reported to be in lobar locations. Participants were randomised a median of 115 days (IQR 49–265) after intracranial haemorrhage onset. Three-quarters of participants had persistent or permanent atrial fibrillation, which was detected before intracranial haemorrhage in most participants. More than three-quarters of participants had systemic arterial hypertension, more than one-third had a history of transient ischaemic attack or ischaemic stroke, almost one-quarter had a history of ischaemic heart

disease, almost one-quarter had diabetes mellitus, and more than a tenth had congestive cardiac failure (appendix). Median CHA_2DS_2-VASc score was 4 and median HAS-BLED score was 2. Before the qualifying intracranial haemorrhage, more than four-fifths had used a DOAC or a vitamin K antagonist, and one-sixth had used an antiplatelet agent (appendix). 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 infarct. Brain CT review confirmed that the majority of participants had intracerebral haemorrhage (one-third lobar), median volume ~5 mL, 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).[36] Review of brain MRI performed for 112 participants in the MRI sub-study confirmed similar findings, as well as the presence of ≥2 cerebral microbleeds in over half, one-fifth of which were in strictly lobar locations, and one-fifth had focal or disseminated superficial siderosis, such that very few had probable cerebral amyloid angiopathy according to the modified Boston criteria.[37] At baseline, participants' characteristics and use of antithrombotic therapy were quite 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 died (figure 1) before hospital discharge, and the remaining 201 were followed-up at hospital or clinic discharge. We obtained 202/203 (99·5%) of primary care practitioner questionnaires at one year (one participant withdrew after discharge; table 1) and 71/79 (89·9%) at two years. We obtained 177/180 (98·3%) of questionnaires sent to surviving participants at one year, and 59/61 (96·7%) at two years. Using both methods of follow-up, participants were followed for a median of 1·2 years (IQR 0·97–1·95), and we obtained 251 of an intended 259 person-years for the trial cohort (overall completeness 97·2%).

Adherence to allocated treatment until the first outcome event or last follow-up was excellent: 199/203 (98·0%) at discharge after randomisation, 154/161 (95·7%) after one year, and 45/47 (95·7%) after two years (appendix). Investigators intended to start a DOAC in 198/203 (96%), and 120/203 (59%) pre-specified Apixaban if a participant would be allocated to start oral anticoagulation. Investigators intended to start an antiplatelet agent in 56/203 (28%), and 33/56 (59%) pre-specified Clopidogrel if a participant would be allocated to avoid oral anticoagulation. These preferences were implemented reliably after randomisation (table 1, appendix). Only one participant in the avoid arm underwent left atrial appendage occlusion during follow-up. Most participants took at least one blood pressure-lowering drug during follow-up, and achieved median systolic blood pressure ~130mmHg, 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 clinical outcome, 8 (8%) of 101 participants allocated to start oral anticoagulation had recurrent symptomatic spontaneous intracranial haemorrhage compared with 4 (4%) of 102 participants who did not start oral anticoagulation (adjusted HR 2·42 [95% CI 0·72–8·09]; table 2, figure 2, figure 3), which did not provide evidence of non-inferiority ($p_{\text{non-inferiority}}$=0·152). After allocation to start oral anticoagulation, 7/8 (88%) of primary outcomes were fatal (when all participants were taking an oral anticoagulant), whereas after allocation to avoid oral anticoagulation none of the four primary outcomes were fatal (when two participants were taking an oral anticoagulant) (figure 2, appendix). Primary outcomes occurred in almost all of the pre-specified sub-groups in both arms of the main trial and the MRI sub-study (appendix).

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, two deaths from another vascular cause [congestive cardiac failure], 23 deaths of non-vascular causes, and no deaths of unknown cause; figure 2). 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 pre-specified composite secondary outcomes) in a participant allocated to start oral anticoagulation. For the pre-specified composite secondary outcomes, we found weak evidence that starting might be superior to avoiding oral anticoagulation for preventing any symptomatic major vascular event and findings were similar but less statistically significant for the composite outcomes of any stroke, and any stroke or vascular death (table 2, figure 4). Survival times are summarised descriptively for ischaemic stroke in the appendix.

The distributions of the modified Rankin Scale scores appeared similar at randomisation and largely reflect the deaths during follow-up after starting (n=22) or avoiding (n=11) oral anticoagulation (appendix). Quality of life appeared similar at randomisation and during follow-up (appendix). There were few serious adverse events, which were neither outcomes nor expected complications of stroke, by MedDRA preferred term and treatment allocation group (appendix).

DISCUSSION

In this randomised trial of survivors of intracranial haemorrhage with atrial fibrillation, we found that it would be feasible for a six-year definitive main phase trial at 60 sites to recruit 800 participants and follow them for one 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.

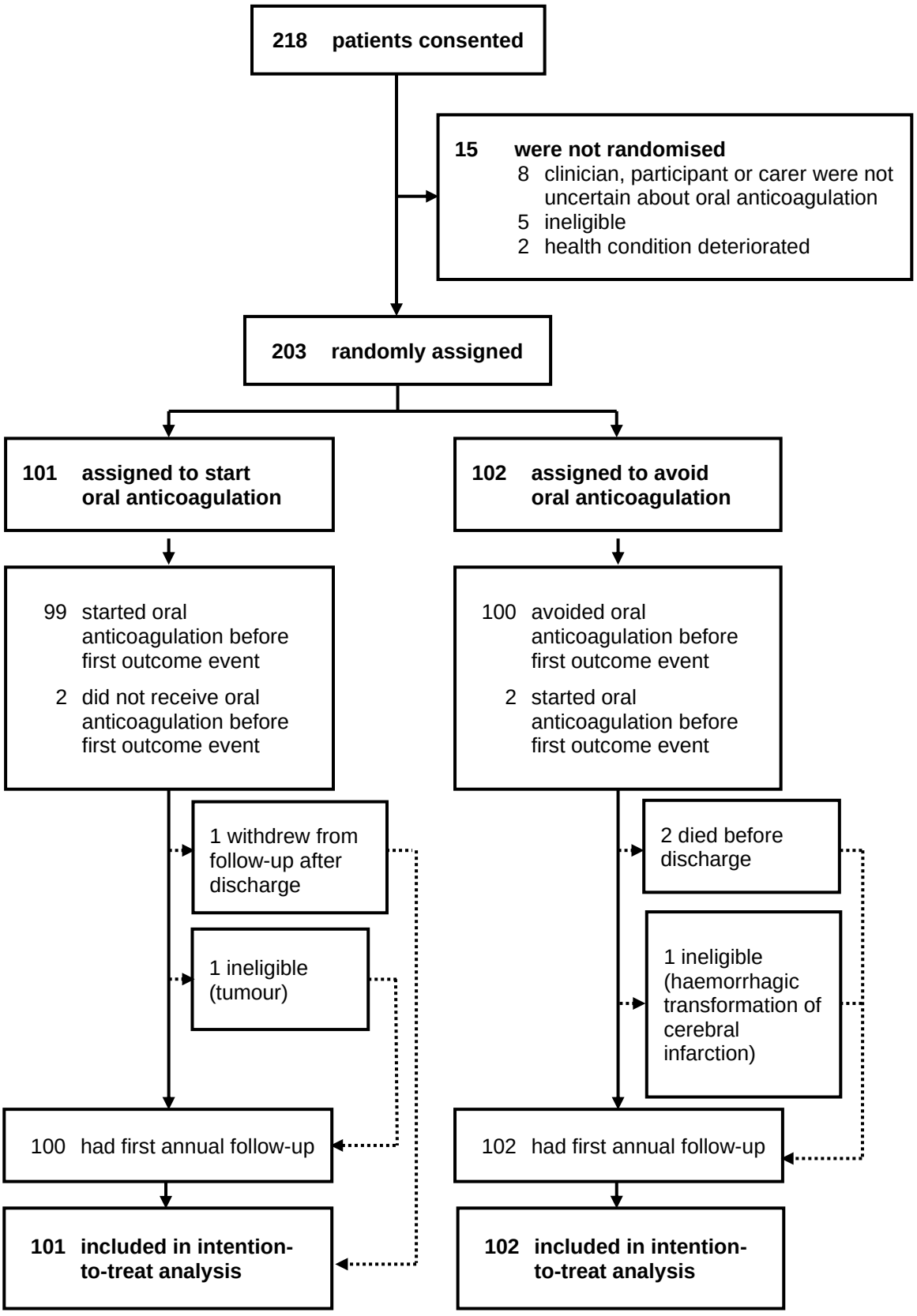
This trial exceeded its recruitment target and is, to our knowledge the largest published randomised trial of oral anticoagulation for atrial fibrillation after intracranial haemorrhage to date.[14-16] We minimised selection bias by using central, computerised random sequence generation and concealing 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.[17,18,33] The oral anticoagulant agents used were similar to a recent international survey of this scenario.[38] The use of antiplatelet therapy in some participants allocated to avoiding oral anticoagulation could be justified by participants' comorbidities (appendix), and the effects of antiplatelet therapy on major vascular events for patients with atrial fibrillation[10] and intracerebral haemorrhage survivors.[39] Adherence to randomly allocated treatment was good, only one patient had left atrial appendage occlusion, blood pressure was controlled for both groups throughout, and antihypertensive drug use was similar between groups. We minimised attrition bias by achieving 97·2% completeness with centralised postal/telephone follow-up, although any added benefits of in-person assessment remain uncertain.[40] We blinded outcome assessors 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.[41] 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]

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 (figure 2); this competing risk 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 much smaller feasibility study,[14] but may be more accurate given the larger sample size of this study. 42% of patients approached declined, which seems higher than we found in RESTART,[39,42] 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.[43] 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.[38] Although we did not blind the assigned treatment to participants and physicians, the outcomes were objective and adjudicated blinded to treatment allocation, which minimises bias.[44] Only 29% (60/204) of eligible patients was recruited in the internal feasibility phase, the majority of recruited participants were white, and participants were recruited from similar state-funded healthcare services in four countries of the United Kingdom, 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 (figure 2). Ultimately, a meta-analysis will maximise the precision of estimates of effect both overall as well as in important demographic, clinical, and imaging sub-groups as part of a planned collaborative individual participant data meta-analysis (www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021246133).

Figure 1. Trial profile



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

	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%)
Supratentorial deep	44		44	
Cerebellar	10		12	
Brainstem	4			
Other	8	(8%)	8	(8%)
Intraventricular	4		0	
Subarachnoid	3		3	
Acute subdural	2		5	
Chronic subdural	1		1	
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	(74%)
Type of atrial arrhythmia §				
Persistent atrial fibrillation	28	(28%)	24	(24%)
Permanent atrial fibrillation	51	(51%)	51	(51%)
Paroxysmal atrial fibrillation	22	(22%)	26	(26%)
Atrial flutter	0	(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	(26%)
5	21	(21%)	15	(15%)

	Start oral anticoagulation (n=101)		Avoid oral anticoagulation (n=102)	
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 ¥ [45]				
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

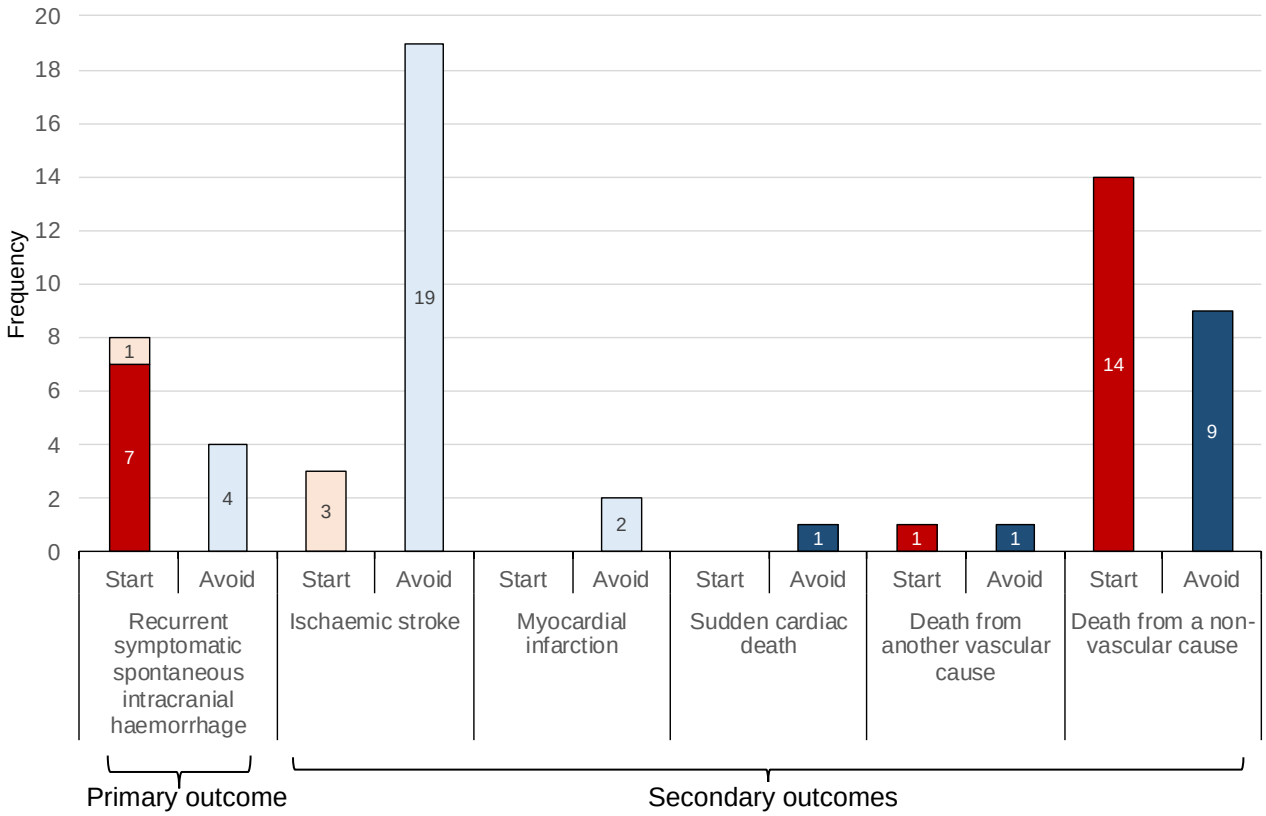
[ʃ] Haemorrhage could affect multiple locations in one participant

[§] Complete list of co-morbidities is in the appendix

[†] The CHA_2DS_2-VASc score to predict the risk of ischaemic stroke or systemic embolism for patients with atrial fibrillation ranges from 0-9 and is based on the sum of individual scores for: congestive heart failure or left ventricular dysfunction (1); systemic arterial hypertension (1); age ≥75 years (2); diabetes mellitus (1); stroke or transient ischaemic attack or other thromboembolism (2); vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) (1); age 65-74 years (1); female sex (1).

[¥] The HAS-BLED score to predict the risk of major bleeding for patients with atrial fibrillation ranges from 0-9 and is based on the sum of the individual scores for: hypertension (1); abnormal renal and liver function (1 point each); stroke (1); bleeding history or disposition (1), labile international normalised ratio (1); elderly i.e. age >65 years (1); drugs or alcohol concomitantly (1 point each).

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



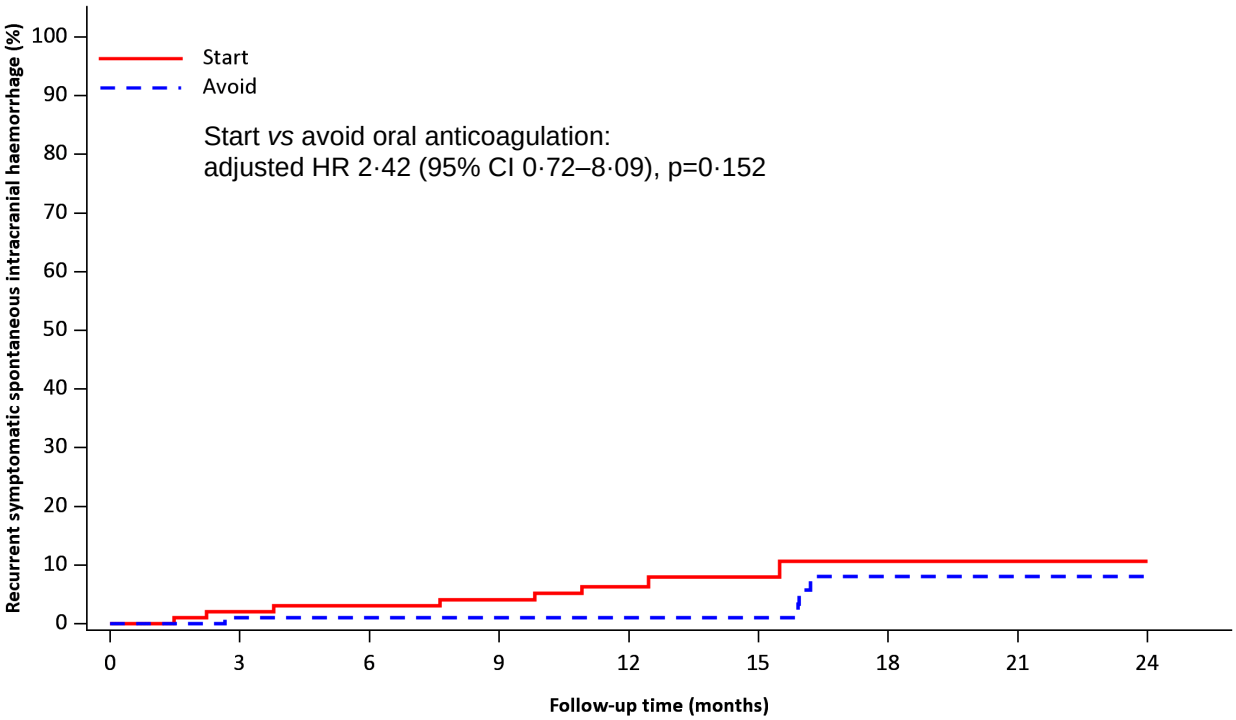
Clustered stacked bar chart of natural frequencies of outcome events after starting (fatal = dark red, non-fatal = light red) or avoiding (fatal = dark blue, non-fatal = light blue) oral anticoagulation.

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

	Start oral anticoagulation (n=101)	Avoid oral anticoagulation (n=102)	Unadjusted analysis HR (95% CI)	p-value	Adjusted* analysis aHR (95% CI)	p-value
Primary outcome						
Recurrent symptomatic spontaneous intracranial haemorrhage	8	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	24	0·51 (0·26–1·03)	p=0·061	0·51 (0·26–1·03)	p=0·060
Any stroke‡	11	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	23	0·55 (0·27–1·10)	p=0·092	0·55 (0·27–1·10)	p=0·090

HR = hazard ratio. aHR = adjusted 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. † 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 (i.e. not within 30 days of an outcome event); death of an unknown cause. ‡ Ischaemic stroke, or symptomatic spontaneous intracerebral or subarachnoid haemorrhage. § 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 (i.e. not within 30 days of an outcome event); death of an unknown cause.

Figure 3. Kaplan-Meier plot of the first recurrent symptomatic spontaneous intracranial haemorrhage

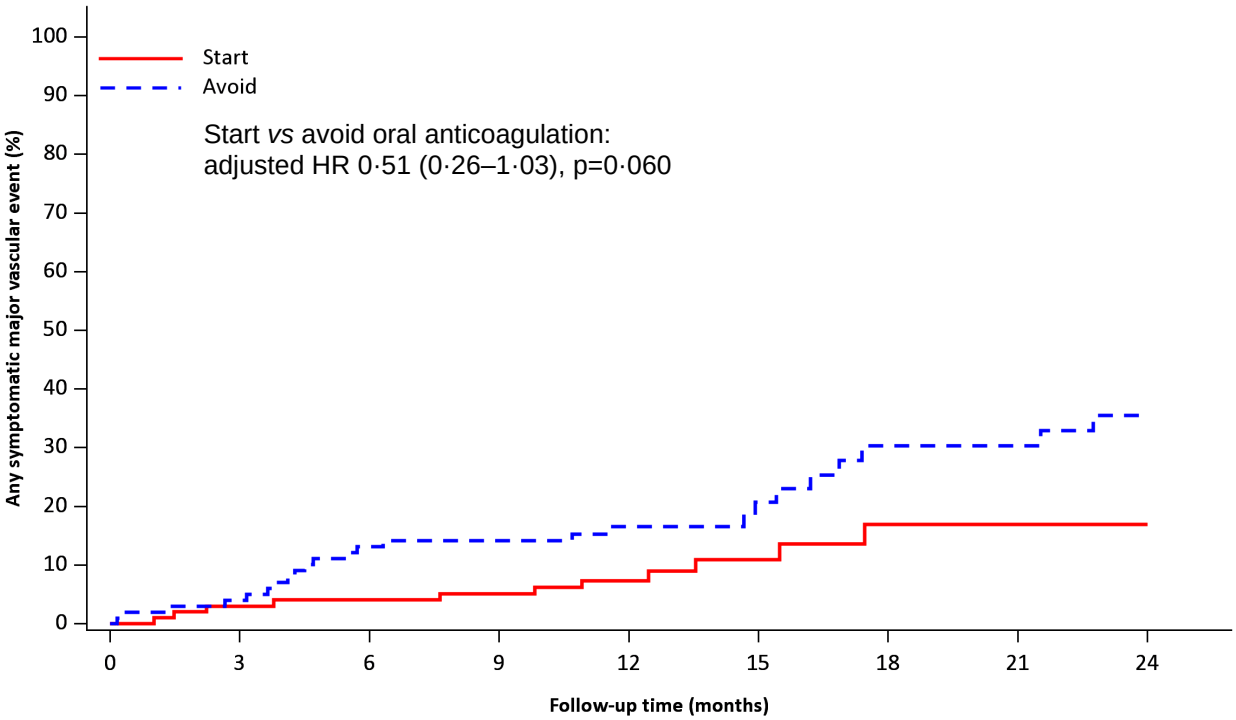


Patients-at-Risk (No. Cumulative Events)									
Start	101 (0)	95 (2)	90 (3)	88 (4)	65 (6)	35 (7)	26 (8)	25 (8)	14 (8)
Avoid	102 (0)	97 (1)	96 (1)	96 (1)	69 (1)	45 (1)	35 (4)	34 (4)	19 (4)
Number censored (cumulative)									
Start	1	4	8	9	30	59	67	68	79
Avoid	0	4	5	5	32	56	63	64	79

Cumulative event rate, % (95% CI)	**12 months**	**24 months**
Start	6·3 (2·9–13·6)	10·7 (5·1–21·4)
Avoid	1·0 (0·1–6·9)	8·1 (3·0–20·9)

Numbers at risk refer to 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 estimated from Kaplan Meier analyses. HR=hazard ratio.

Figure 4. Kaplan-Meier plot of the first occurrence of any symptomatic major vascular event (top), any stroke (middle), and any stroke or vascular death (bottom)



Patients-at-Risk (No. Cumulative Events)

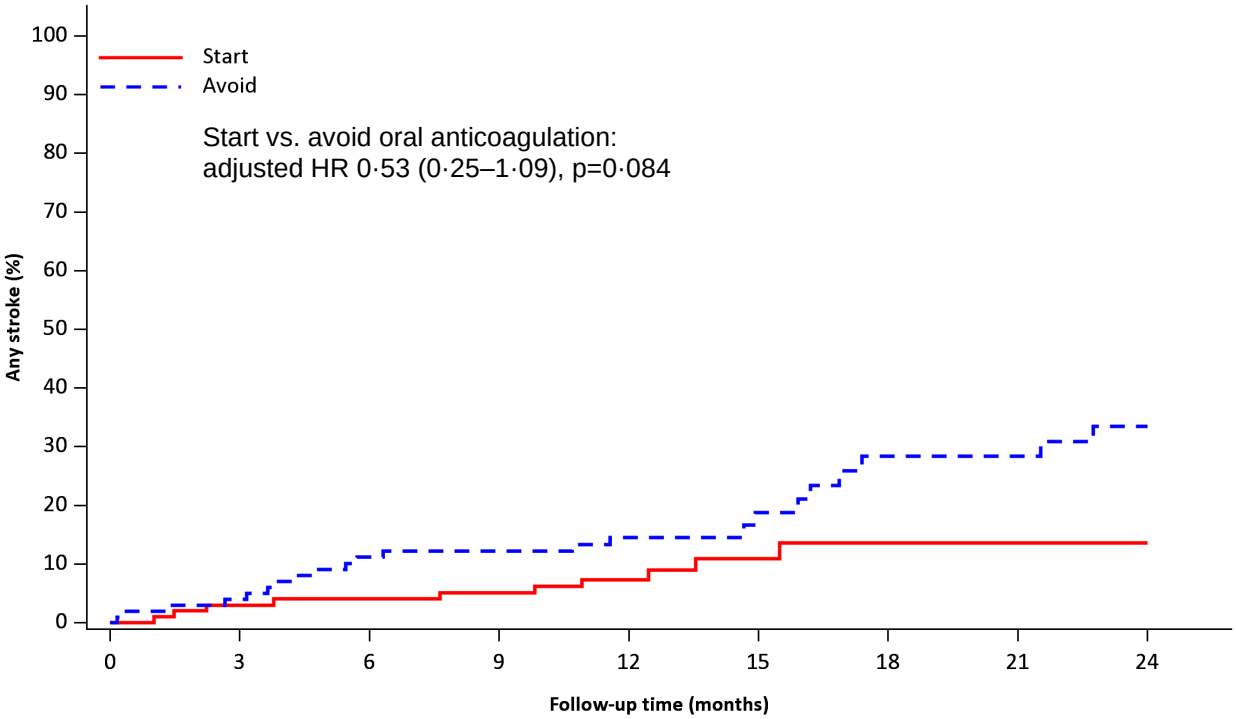
Start	101 (0)	94 (3)	89 (4)	87 (5)	65 (7)	34 (9)	25 (11)	24 (11)	14 (11)
Avoid	102 (0)	94 (4)	85 (13)	84 (14)	59 (16)	36 (18)	27 (22)	27 (22)	16 (24)

Number censored (cumulative)

Start	1	4	8	9	29	58	65	66	76
Avoid	0	4	4	4	27	48	53	53	62

Cumulative event rate, % (95% CI)	**12 months**	**24 months**
Start	7·3 (3·6–14·8)	16·9 (9·0–30·6)
Avoid	16·5 (10·5–25·6)	35·5 (24·2–50·0)

45



Patients-at-Risk (No. Cumulative Events)									
Start	101 (0)	94 (3)	89 (4)	87 (5)	65 (7)	34 (9)	25 (10)	24 (10)	14 (10)
Avoid	102 (0)	94 (4)	86 (11)	85 (12)	60 (14)	37 (16)	28 (20)	28 (20)	16 (22)
Number censored (cumulative)									
Start	1	4	8	9	29	58	66	67	77
Avoid	0	4	5	5	28	49	54	54	64

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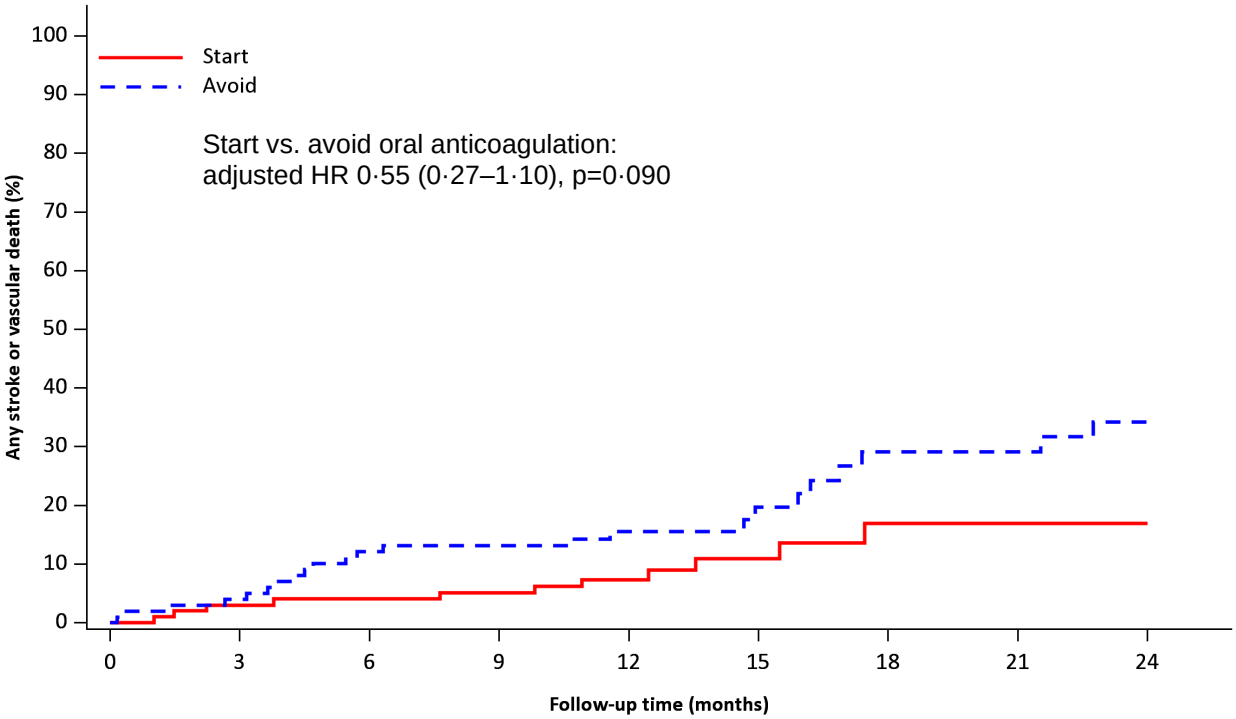
Cumulative event rate, % (95% CI)	12 months	24 months
Start	7·3 (3·6–14·8)	13·6 (7·2–25·1)
Avoid	14·6 (8·9–23·4)	33·5 (22·4–48·1)

47



Patients-at-Risk (No. Cumulative Events)

Start	101 (0)	94 (3)	89 (4)	87 (5)	65 (7)	34 (9)	25 (11)	24 (11)	14 (11)
Avoid	102 (0)	94 (4)	86 (12)	85 (13)	60 (15)	37 (17)	28 (21)	28 (21)	16 (23)

Number censored (cumulative)

Start	1	4	8	9	29	58	65	66	76
Avoid	0	4	4	4	27	48	53	53	63

Cumulative event rate, % (95% CI)	**12 months**	**24 months**
Start	7·3 (3·6–14·8)	16·9 (9·0–30·6)
Avoid	15·5 (9·6–24·4)	34·2 (23·1–48·7)

Numbers at risk refer to 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 estimated from Kaplan Meier analyses. HR=hazard ratio

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 blinded trial statistician. JS and CK were the unblinded 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. 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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DECLARATION OF INTERESTS

RASS, DEN, CK, MSD, SL and JS have nothing to disclose. 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

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DATA SHARING

A de-identified 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 for other researchers to apply for use 1 year after publication, via https://datashare.ed.ac.uk/handle/10283/3967. 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.

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