Effects of oral anticoagulation in people with atrial fibrillation after spontaneous intracranial haemorrhage (COCROACH): prospective, individual participant data meta-analysis of randomised trials

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Summary

Background The safety and efficacy of oral anticoagulation for prevention of major adverse cardiovascular events in people with atrial fibrillation and spontaneous intracranial haemorrhage are uncertain. We planned to estimate the effects of starting versus avoiding oral anticoagulation in people with spontaneous intracranial haemorrhage and atrial fibrillation.

Methods In this prospective meta-analysis, we searched bibliographic databases and trial registries using the strategies of a Cochrane systematic review (CD012144) on June 23, 2023. We included clinical trials if they were registered, randomised, and included participants with spontaneous intracranial haemorrhage and atrial fibrillation who were assigned to either start long-term use of any oral anticoagulant agent or avoid oral anticoagulation (ie, placebo, open control, another antithrombotic agent, or another intervention for the prevention of major adverse cardiovascular events). We assessed eligible trials using the Cochrane Risk of Bias tool. We sought data for individual participants who had not opted out of data sharing from chief investigators of completed trials, pending completion of ongoing trials in 2028. The primary outcome was any stroke or cardiovascular death. We used individual participant data to construct a Cox regression model of the time to the first occurrence of outcome events during follow-up in the intention-to-treat dataset supplied by each trial, followed by meta-analysis using a fixed-effect inverse-variance model to generate a pooled estimate of the hazard ratio (HR) with 95% CI. This study is registered with PROSPERO, CRD42021246133.

Findings We identified four eligible trials; three were restricted to participants with atrial fibrillation and intracranial haemorrhage (SoSTART [NCT03153150], with 203 participants) or intracerebral haemorrhage (APACHE-AF [NCT02565693], with 101 participants, and NASPAF-ICH [NCT02998905], with 30 participants), and one included a subgroup of participants with previous intracranial haemorrhage (ELDERCARE-AF [NCT02801669], with 80 participants). After excluding two participants who opted out of data sharing, we included 412 participants (310 [75%] aged 75 years or older, 249 [60%] with CHA_2DS_2-VASc score ≤4, and 163 [40%] with CHA_2DS_2-VASc score >4). The intervention was a direct oral anticoagulant in 209 (99%) of 212 participants who were assigned to start oral anticoagulation, and the comparator was antiplatelet monotherapy in 67 (33%) of 200 participants assigned to avoid oral anticoagulation. The primary outcome of any stroke or cardiovascular death occurred in 29 (14%) of 212 participants who started oral anticoagulation versus 43 (22%) of 200 who avoided oral anticoagulation (pooled HR 0·68 [95% CI 0·42–1·10]; I^2=0%). Oral anticoagulation reduced the risk of ischaemic major adverse cardiovascular events (nine [4%] of 212 *vs* 38 [19%] of 200; pooled HR 0·27 [95% CI 0·13–0·56]; I^2=0%). There was no significant increase in haemorrhagic major adverse cardiovascular events (15 [7%] of 212 *vs* nine [5%] of 200; pooled HR 1·80 [95% CI 0·77–4·21]; I^2=0%), death from any cause (38 [18%] of 212 *vs* 29 [15%] of 200; 1·29 [0·78–2·11]; I^2=50%), or death or dependence after 1 year (78 [53%] of 147 *vs* 74 [51%] of 145; pooled odds ratio 1·12 [95% CI 0·70–1·79]; I^2=0%).

Interpretation For people with atrial fibrillation and intracranial haemorrhage, oral anticoagulation had uncertain effects on the risk of any stroke or cardiovascular death (both overall and in subgroups), haemorrhagic major adverse cardiovascular events, and functional outcome. Oral anticoagulation reduced the risk of ischaemic major adverse cardiovascular events, which can inform clinical practice. These findings should encourage recruitment to, and completion of, ongoing trials.

Funding British Heart Foundation.

Lancet Neurol 2023

Published Online October 12, 2023 https://doi.org/10.1016/S1474-4422(23)00315-0

See Online/Comment https://doi.org/10.1016/S1474-4422(23)00331-9

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See Online for appendix

Research in context

Evidence before this study

Initial searches of 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 March 24, 2017 (appendix pp 3–5), found four randomised trials (SoSTART [NCT03153150], APACHE-AF [NCT02565693], NASPAF-ICH [NCT02998905], and ELDERCARE-AF [NCT02801669]) comparing the effects of starting versus avoiding oral anticoagulation for atrial fibrillation in participants, all or some of whom had spontaneous intracranial haemorrhage. We updated searches on June 23, 2023, and identified five ongoing trials that will complete by 2028. None of the four completed trials individually reported evidence of superiority, inferiority, or non-inferiority of starting oral anticoagulation, but they showed feasibility of recruitment and provided preliminary estimates of effects. Previous meta-analyses addressing this therapeutic dilemma are unreliable, because they combined randomised trials with observational cohort studies or used aggregate estimates of treatment effects instead of individual participant data.

Added value of this study

This individual participant data meta-analysis includes 412 participants with intracranial haemorrhage and atrial fibrillation (99·5% of available data) from four completed trials that compared starting oral anticoagulation (99% direct oral anticoagulant and 1% vitamin K antagonist) with avoiding oral anticoagulation (67% no antithrombotic therapy and 33% antiplatelet monotherapy). Treatment allocation was open in three of the four trials, conferring a risk of performance bias. By analysing individual participant data from the four completed trials, we found weak evidence for a benefit of starting oral anticoagulation (numerically fewer stroke and cardiovascular events). We also found that starting oral anticoagulation reduced time to first ischaemic major adverse cardiovascular event, a finding that was not reported by any of the individual trials.

Implications of all the available evidence

Although oral anticoagulation reduces the risk of ischaemic major adverse cardiovascular events, uncertainties remain for survivors of intracranial haemorrhage with atrial fibrillation with respect to the hazards and net effects of oral anticoagulation overall and in subgroups, whether assessed by ischaemic and haemorrhagic outcomes, or by functional outcome. Completion of the five ongoing trials, which might add about 2000 participants to this meta-analysis in the next 5 years, could resolve these uncertainties.

Introduction

Adults with spontaneous (non-traumatic) intracranial haemorrhage due to intracerebral haemorrhage, intraventricular haemorrhage, subarachnoid haemorrhage, or subdural haemorrhage are at substantial risk of major adverse cardiovascular events.[1–3] Intracranial haemorrhage survivors with atrial fibrillation are at the highest risk of all major adverse cardiovascular events,[4] and the risk seems higher than predicted by the CHA_2DS_2-VASc score for people with atrial fibrillation without previous intracranial haemorrhage.[5,6] Oral anticoagulation reduces the risk of stroke by almost two-thirds for people with atrial fibrillation compared with control despite increasing the risk of bleeding,[7,8] as does antiplatelet therapy to a lesser extent.[9] However, people with previous intracranial haemorrhage were excluded from the randomised controlled trials that identified these benefits.

Cohort studies of intracranial haemorrhage survivors with atrial fibrillation have found associations between the use of oral anticoagulation and mostly lower risks of ischaemic major adverse cardiovascular events,[10,11] as well as better functional outcome regardless of intracerebral haemorrhage location,[12] but these observational studies are likely to be subject to selection bias and confounding by indication. The effects of oral anticoagulation for atrial fibrillation after intracranial haemorrhage remain uncertain after the completion of three pilot-phase trials that estimated treatment effects[13–15] but could not individually provide evidence of superiority, inferiority, or non-inferiority. A systematic review and study-level meta-analysis of these three completed trials found moderate-certainty evidence that oral anticoagulation probably reduces major adverse cardiovascular events,[16] but it did not include people with intracranial haemorrhage from a relevant completed trial[17] and was unable to estimate whether treatment effects varied across subgroups. Other recent study-level and network meta-analyses addressing this dilemma might not be valid because they have combined trials with cohort studies.[18–20]

Therefore, we planned a prospective meta-analysis of individual participant data from all trials that included survivors of intracranial haemorrhage with atrial fibrillation and compared starting versus avoiding long-term oral anticoagulation. Prospective individual participant data meta-analysis has methodological advantages over study-level meta-analysis of aggregate data,[21] by avoiding potential selection and publication biases, standardising outcomes, standardising methods of analysis, conducting time-to-event analyses,[22] and allowing statistically appropriate investigation of treatment effect modifiers in subgroups.[23] We set out to estimate the effects of oral anticoagulation in people with atrial fibrillation after intracranial haemorrhage overall and in subgroups of interest (age, sex, higher risk of ischaemic events [higher CHA_2DS_2-VASc score], and higher risk of recurrent intracranial haemorrhage [earlier initiation of oral anticoagulation and lobar intracerebral haemorrhage or non-aneurysmal subarachnoid haemorrhage location]).

We performed the first iteration of this meta-analysis because four eligible trials reported results in 2020–21, five ongoing eligible trials will not be complete until 2028, and evidence synthesis now should inform clinical practice and ongoing trials in the interim. Furthermore, variation in the effects of oral anticoagulation by intracranial haemorrhage location is of contemporary interest given recent advice from the Data Monitoring Committee of the ongoing ENRICH-AF trial (NCT03950076) to stop oral anticoagulation among 174 participants enrolled after lobar intracerebral haemorrhage and to cease enrolment of people with lobar intracerebral haemorrhage, based on data as of June 1, 2023, and to stop oral anticoagulation among 34 participants enrolled with convexity subarachnoid haemorrhage and to cease enrolment of people with convexity subarachnoid haemorrhage, based on data as of Aug 2, 2023.[24]

Methods

Search strategy and selection criteria

The Collaboration of Controlled Randomised Trials of Long-Term Oral Antithrombotic Agents After Spontaneous Intracranial Haemorrhage (COCROACH) planned at the European Stroke Organisation Conference on May 17, 2017, before the results of any relevant trials were known, to do an individual participant data meta-analysis. Trials were eligible for inclusion if they were registered with a trial registry and included participants with spontaneous intracranial haemorrhage who were randomly assigned to start long-term use of any oral anticoagulant or to avoid oral anticoagulation (which could include placebo, open control, standard care, another antithrombotic agent, or another intervention for the prevention of major adverse cardiovascular events). If a trial included a broader group of participants, the subgroup of eligible participants with spontaneous intracranial haemorrhage could be included. Trials were eligible regardless of setting, epoch, sample size, length of follow-up, publication, and language of publication. There were no exclusion criteria.

We used the literature search strategies of the related Cochrane review,[16] which was first published on April 8, 2016 (appendix pp 3–5),[25] to search 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 23, 2023. The related Cochrane review shares the same eligibility criteria and determines the eligibility of trials for inclusion. In the event that we could not locate the full text of a randomised controlled trial, or required a specific data extract, we contacted the researchers or the relevant data sharing platform.

Two reviewers (who resolved disagreements in discussion or by arbitration by a third reviewer[16]) determined the overall risk of bias of individual trials using the Cochrane Risk of Bias tool,[26] which involves assigning a judgment of high, low, or unclear risk of material bias for six domains of bias: selection, performance, detection, attrition, reporting, and other. Risk of bias did not affect data synthesis.

RA-SS requested de-identified individual participant data from the chief investigator of each included trial after the completion of a collaboration and data sharing agreement. The participant-level data requested were confirmation of eligibility; medical history; demographic, clinical, and brain imaging characteristics determined by investigators at baseline; concomitant medications; date of randomisation; treatment assigned by randomisation; treatment received; and time-to event and censoring data on outcome events required to reproduce the result of each trial and perform the main and subgroup analyses specified in the COCROACH protocol and Statistical Analysis Plan. Available individual participant data could be included if the terms of informed consent did not preclude data sharing or a research ethics committee approved data sharing, and participants had not opted out of data sharing.

The individual participant data meta-analysis follows a prespecified protocol (published in PROSPERO on March 31, 2021; appendix pp 24–49) and a prespecified Statistical Analysis Plan (approved by the principal investigators of the included trials, published in PROSPERO on Dec 2, 2021; appendix pp 50–61). When the protocol was agreed, the results of eligible trials were unknown, except for one randomised feasibility study involving 30 participants,[15] which is included in this meta-analysis.

Data analysis

Collaborators transferred deidentified participant-level data to the University of Edinburgh (Edinburgh, UK) using DataSync, which is a secure, encrypted file-hosting service. If trial data could not leave a trusted research environment, our statistician (JS) obtained secure access to analyse individual participant data within that environment and extracted only aggregate data and effect measures to incorporate into two-step meta-analysis. The statistician checked the range, completeness, internal consistency, and validity of the shared data by confirming that they could reproduce the frequencies of key participant characteristics and outcomes, and effect estimates on at least the primary outcome (and any other outcomes that are included in our analyses) that appeared in the report of the completed trial. The statistician harmonised any baseline covariates if their categorisation differed between trials. The statistician and RA-SS clarified definitions of outcome events using published reports, or with the chief investigator of a trial if required, to ensure consistency of definitions.

For more on **DataSync** see www.ed.ac.uk/is/datasync

The Statistical Analysis Plan (appendix pp 50–61) predefined the primary outcome of major adverse cardiovascular events as any non-fatal symptomatic stroke (defined as alive 30 days after onset of

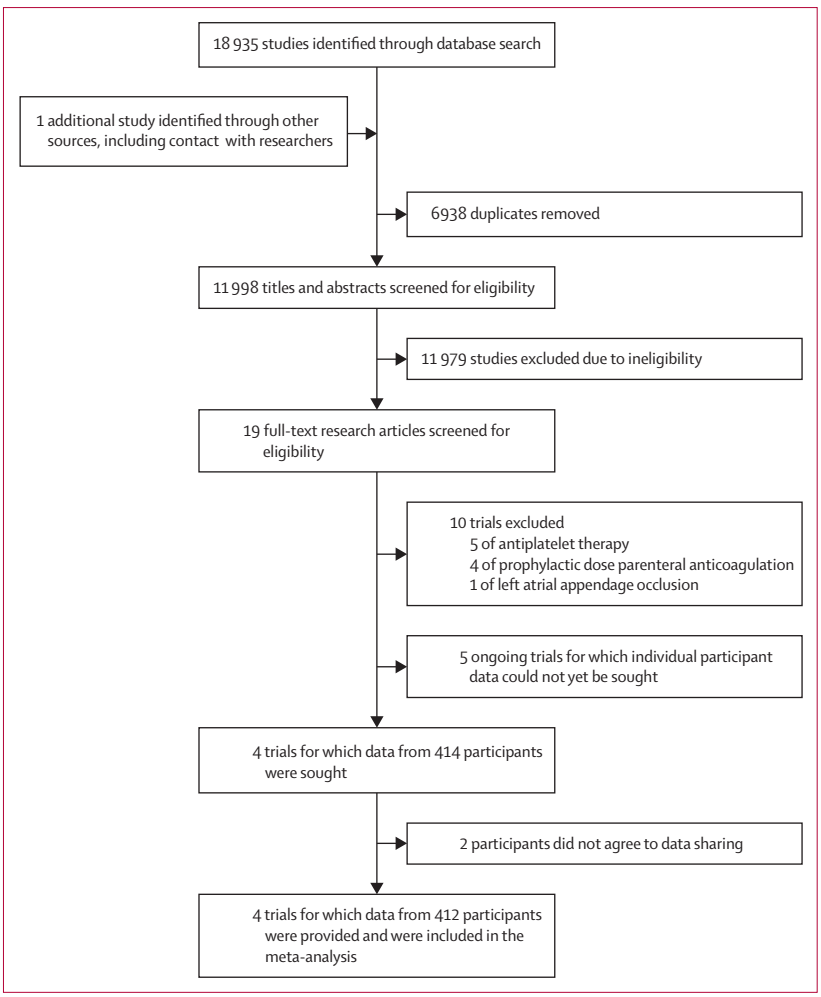

Figure 1: **Study selection**

ischaemic stroke, haemorrhagic stroke [ie, intracerebral haemorrhage, intraventricular haemorrhage, or subarachnoid haemorrhage], or stroke of unknown pathological subtype) or cardiovascular death (defined as death within 30 days of symptomatic stroke or other intracranial haemorrhage, extracranial haemorrhage, myocardial infarction, or systemic embolism [arterial or pulmonary embolism]; sudden cardiac death; death from another vascular cause and not within 30 days of an outcome event; or death of an unknown cause). The secondary outcomes were ischaemic major adverse cardiovascular events (ischaemic stroke [not including transient ischaemic attack], systemic arterial embolism, pulmonary embolism, or myocardial infarction), haemorrhagic major adverse cardiovascular events (spontaneous intracranial haemorrhage [intracerebral haemorrhage, intraventricular haemorrhage, subdural haemorrhage, or subarachnoid haemorrhage] or major extracranial haemorrhage [gastrointestinal or other]), death from any cause, and death or dependence (score 3–6 on the modified Rankin Scale [mRS]). All included trials organised independent adjudication of these outcomes blinded to assigned treatment.

For time-to-event outcomes (ie, all, except the mRS score), survival times were the time to first outcome event during follow-up from randomisation. Follow-up was censored at death (unrelated to an outcome event) or last available follow-up. The hazard ratio (HR) with a 95% CI was the principal measure of effect for these outcomes. For the analysis of the mRS score, we intended to use a proportional odds model for this ordinal measure, but because there were zero cell counts in several categories in two of the trials, we used a conventional dichotomy of score 3–6 (dead or dependent) *vs* 0–2 (independent).[27]

Less than 10% of participants had missing baseline variables, so we used complete case analysis. We constructed a Cox regression model for each time-to-event primary outcome in each trial. We used Firth's method if no outcomes occurred in one of the treatment groups in a trial.[28] We summarised survival times descriptively for each treatment group in each trial using Kaplan-Meier curves, displaying the maximum overall follow-up. We used a two-stage meta-analysis approach to generate estimates separately for each trial and then pooled them to estimate treatment effects and investigate heterogeneity. We prespecified a fixed-effect inverse variance model for the primary analysis, with a sensitivity analysis using a random-effects inverse variance model.[29] We judged statistical heterogeneity by comparing the effect estimates and 95% CIs of the trials, and quantified heterogeneity using the I^2 statistic with p values from Cochran's Q test.

We prespecified that we would explore the effects of oral anticoagulation in stratified analyses, examining statistical interactions between subgroups and the overall effect within each trial and then pooling these interactions across the trials (referred to as the deft approach).[23] We prespecified exploration of heterogeneity of treatment effect on the primary outcome in the following subgroups: age (<75 years *vs* ≥75 years), sex (male *vs* female), intracranial haemorrhage location (exclusively lobar intracerebral haemorrhage or non-aneurysmal subarachnoid haemorrhage [due to the likelihood of underlying cerebral amyloid angiopathy][2,30] *vs* other intracranial haemorrhage [non-lobar intracerebral haemorrhage, intraventricular haemorrhage, or subdural haemorrhage], time between intracranial haemorrhage onset and randomisation (<8 weeks *vs* ≥8 weeks), and CHA_2DS_2-VASc score (≤4 *vs* >4). We performed post-hoc sensitivity analyses of effects after the exclusion of ELDERCARE-AF; in participants with confirmed intracerebral haemorrhage; on fatal outcomes; on the mRS score after adjusting for mRS at baseline; and on the secondary outcome of intracranial haemorrhage in subgroups. We assessed risk of bias of the accumulated body of evidence qualitatively by visual inspection of funnel plots and with Egger's test. All statistical analyses were done with SAS (version 9.4) or STATA (version 16.0).

This study is registered with PROSPERO, CRD42021246133.

Role of the funding source

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

Results

We screened 11 998 publications that were identified by the literature search (figure 1). We assessed the full text of 19 trials for eligibility. We excluded ten trials because the intervention was either antiplatelet therapy (five studies) or a prophylactic dose of parenteral anticoagulation (four studies), or the comparator was left atrial appendage occlusion (one study, in which the number of participants with intracranial haemorrhage was unclear and not provided). Five trials were eligible but recruitment or follow-up was ongoing (STATICH [NCT03186729], A3-ICH [NCT03243175], ASPIRE [NCT03907046], ENRICH-AF [NCT03950076], and [PRESTIGE-AF] NCT03996772). These ongoing trials are not due to complete until 2024–28. Thus, individual participant data were sought for four trials (SoSTART [NCT03153150] with 203 participants; APACHE-AF [NCT02565693] with 101 participants; NASPAF-ICH [NCT02998905] with 30 participants; and ELDERCARE-AF [NCT02801669] with 80 participants). Of the 414 participants in these four trials, data could only be obtained for 412, because two of the 203 participants in SoSTART had opted out of data sharing. In SoSTART, 100 participants were assigned to start oral anticoagulation and 101 to avoid oral anticoagulation; respective numbers in APACHE-AF were 50 to start and 51 to avoid, in ELDERCARE-AF were 41 to start and 39 to avoid, and in NASPAF-ICH were 21 to start and nine to avoid.

The included trials recruited participants from Europe (SoSTART and APACHE-AF), Canada (NASPAF-ICH), and Japan (ELDERCARE-AF; appendix pp 6–7). Three trials (SoSTART, APACHE-AF, and NASPAF-ICH) recruited adults with one or more subtype of intracranial haemorrhage and atrial fibrillation, whereas the fourth trial (ELDERCARE-AF) recruited people aged 80 years or older with atrial fibrillation and one or more reasons for concern about therapeutic dose oral anticoagulation (which included previous intracranial haemorrhage). Among the 212 participants assigned to start oral anticoagulation, the intervention was a direct oral anticoagulant in 209 (99%) in all four trials (130 were assigned apixaban, 61 edoxaban, 12 dabigatran, and six rivaroxaban); the oral vitamin K antagonist warfarin was given to three (1%) participants in SoSTART. Except for ELDERARE-AF, in which low-dose (15 mg once daily) edoxaban was used, the other three trials encouraged use of full-dose oral anticoagulation. Among the 200 participants assigned to avoid oral anticoagulation, the comparator was no antithrombotic drug in 133 (67%) participants in all four trials; an antiplatelet agent was given to 67 (34%) participants in three trials (SoSTART, APACHE-AF, and NASPAF-ICH). ELDERCARE-AF was placebo controlled whereas the other three trials were open label. Three trials

	Start oral anticoagulation	Avoid oral anticoagulation
Participants in all included trials		
Number of participants	212	200
Age group, years		
<75	46 (22%)	56 (28%)
75–85	109 (51%)	87 (44%)
>85	57 (27%)	57 (29%)
CHA_2DS_2-VASc score*		
≤4	131 (62%)	118 (59%)
>4	81 (38%)	82 (41%)
Participants in SoSTART, APACHE-AF, and NASPAF-ICH†		
Number of participants	171	161
Age, years	78·2 (74·0–84·7)	78·7 (73·4–83·6)
Sex		
Male	101 (59%)	97 (60%)
Female	70 (41%)	64 (40%)
Ethnicity		
White	161 (94%)	154 (96%)
All other ethnic groups	10 (6%)	7 (4%)
Lobar intracerebral haemorrhage‡	55 (32%)	51 (32%)
Non-lobar intracerebral haemorrhage§	107 (63%)	101 (63%)
Supratentorial deep origin	81/107 (76%)	76/101 (75%)
Cerebellar origin	20/107 (19%)	21/101 (21%)
Brainstem origin	6/107 (6%)	4/101 (4%)
Other	9 (5%)	9 (6%)
Intraventricular	5/9 (56%)	1/9 (11%)
Subarachnoid	2/9 (22%)	3/9 (33%)
Subdural	2/9 (22%)	5/9 (56%)
Time from qualifying intracranial haemorrhage symptom onset to randomisation, days	77 (34–169)	75 (36–179)
CHA_2DS_2-VASc score*		
1	2 (1%)	1 (1%)
2	31 (18%)	26 (16%)
3	35 (20%)	31 (19%)
4	49 (29%)	46 (29%)
5	33 (19%)	25 (16%)
6	14 (8%)	22 (14%)
7	6 (4%)	9 (6%)
8	1 (1%)	1 (1%)

Data are n, n (%), median (IQR), or n/N (%). *The CHA_2DS_2-VASc score to predict the risk of ischaemic stroke or systemic embolism for patients with atrial fibrillation ranges from 0 to 9 (no patient had scores 0 and 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 or older (2); diabetes (1); stroke or transient ischaemic attack or other thromboembolism (2); vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque; 1); age 65–74 years (1); and female sex (1). †Baseline covariates for the ELDERCARE-AF trial were not available in the anonymised dataset provided via the data sharing platform. ‡Confined to the supratentorial lobes of the brain. §Includes intracerebral haemorrhage in mixed locations.

Table 1: **Baseline characteristics**

	Start oral anticoagulation (n=212)	Avoid oral anticoagulation (n=200)
Primary outcome		
Any stroke or cardiovascular death	29 (14%)	43 (22%)
Secondary outcomes		
Ischaemic major adverse cardiovascular events	9 (4%)	38 (19%)
Ischaemic stroke	9 (4%)	31 (16%)
Systemic arterial embolism	0	0
Pulmonary embolism	0	4 (2%)
Myocardial infarction	0	4 (2%)
Haemorrhagic major adverse cardiovascular events	15 (7%)	9 (5%)
Intracranial haemorrhage	12 (6%)	5 (3%)
Major extracranial haemorrhage	3 (1%)	4 (2%)
Death from any cause	38 (18%)	29 (15%)
Cardiovascular death	17 (8%)	12 (6%)
Death from any other cause	21 (10%)	17 (9%)
Death or dependence (modified Rankin Scale score 3–6) after 1 year*	78 (53%)	74 (51%)

Data are n (%). *Data were available for 147 participants who started oral anticoagulation and 145 participants who avoided oral anticoagulation in APACHE-AF, NASPAF-ICH, and SoSTART (appendix p16).

Table 2: **Frequencies of the first occurrence of outcome events during follow-up in all included trials**

(APACHE-AF, SoSTART, and ELDERCARE-AF) assigned participants in a 1:1 ratio, whereas NASPAF-ICH assigned participants to start or avoid oral anticoagulation in a 2:1 ratio. All trials sought and recorded major adverse cardiovascular events between 2–6 years of maximum follow-up (appendix pp 6–7, 9–13).

No issues with the integrity of individual participant data were identified. The risk of bias was generally low for every domain within each trial, with the exception of performance bias due to no blinding in three trials (appendix p 8). There was no evidence of bias across trials by visual inspection of funnel plots and with Egger's test (appendix p 17). There was no evidence of violation of the proportional hazards assumption in each trial.

Baseline characteristics were well balanced between treatment groups (table 1). 310 (75%) of the 412 participants were aged 75 years or older. 163 (40%) had a CHA_2DS_2-VASc score higher than 4. Some baseline covariates for the ELDERCARE-AF trial were not available in the anonymised dataset provided via the data-sharing platform. However, assuming that the participants in ELDERCARE-AF were Asian (because they were recruited in Japan), about 76% of participants were White. Of the 332 participants with available data, 134 (40%) were female. 106 (32%) of 332 participants had exclusively lobar intracerebral haemorrhage. Random assignments happened about 76 days after onset of symptoms of intracranial haemorrhage.

The primary outcome of any stroke or cardiovascular death occurred in 29 (14%) of 212 participants who started oral anticoagulation versus 43 (22%) of 200 who avoided oral anticoagulation (pooled HR 0·68 [95% CI 0·42–1·10]; I^2=0%; table 2; figure 2). Oral anticoagulation was associated with a significant decrease in ischaemic major adverse cardiovascular events compared with no oral anticoagulation (nine [4%] of 212 *vs* 38 [19%] of 200; pooled HR 0·27 [95% CI 0·13–0·56]; I^2=0%; table 2; figure 2). The most frequent ischaemic major adverse cardiovascular event was ischaemic stroke, which was less frequent after starting oral anticoagulation compared with no oral anticoagulation (nine [4%] of 212 *vs* 31 [16%] of 200 (table 2); pooled HR 0·37 [95% CI 0·17–0·83]; I^2=0%; appendix p 14). No evidence was found that oral anticoagulation was associated with a significant increase in haemorrhagic major adverse cardiovascular events (15 [7%] of 212 *vs* nine [5%] of 200; pooled HR 1·80 [95% CI 0·77–4·21]; I^2=0%), or death from any cause (38 [18%] *vs* 29 [15%]; 1·29 [0·78–2·11]; I^2=50%; table 2; figure 2). The analyses using fixed-effect models were very similar in prespecified sensitivity analyses using random-effects models (appendix p 15). Oral anticoagulation did not affect death or dependence in participants who died or survived to 1 year and who were scored on the mRS at 1 year (78 [53%] of 147 *vs* 74 [51%] of 145; pooled odds ratio [OR] 1·12 [95% CI 0·70–1·79]; table 2; I^2=0%; this estimate was similar in a post-hoc sensitivity analysis after adjusting for mRS score at baseline; appendix p 16).

The frequency and distribution of the primary outcome could be analysed according to subgroups in prespecified, exploratory, pooled analyses of treatment effect modification for two trials (SoSTART and APACHE-AF), involving 302 participants with similar baseline characteristics and primary outcome event frequencies to the whole dataset (appendix pp 18–19). No evidence was found that the effect of oral anticoagulation on the primary outcome varied across subgroups by age, sex, time since intracranial haemorrhage onset, and CHA_2DS_2-VASc score (figure 3). In particular, no evidence was found for treatment effect modification by intracranial haemorrhage location (pooled $p_{interaction}$=0·98).

Post-hoc sensitivity analyses found similar effects on the primary outcome in 332 participants after the exclusion of ELDERCARE-AF data (pooled HR 0·72 [95% CI 0·43–1·20]; I^2=8%; appendix p 20), in 314 participants with confirmed intracerebral haemorrhage (0·78 [0·45–1·33]; I^2=%; appendix p 21), and a qualitatively different direction of effect when restricted to fatal outcomes (1·32 [0·60–2·90]; I^2=44%; appendix p 22). A post-hoc analysis of the effects of oral anticoagulation on the secondary outcome of intracranial haemorrhage in subgroups found imprecise estimates of effect due to a paucity of outcomes (appendix p 23).

Discussion

In this prospective individual participant data meta-analysis of 412 participants with intracranial haemorrhage and atrial fibrillation from four completed randomised trials, we found only weak evidence that starting oral anticoagulation might reduce the primary outcome of stroke or cardiovascular death. There was some evidence of a

reduction in ischaemic major adverse cardiovascular events with oral anticoagulation (99% used direct oral anticoagulants) compared with control (33% used antiplatelet monotherapy) that had not been identified by any of the reports of the individual trials in the meta-analysis, including the largest completed trial.[13]

These findings suggest that oral anticoagulation is associated with a decrease in ischaemic major adverse cardiovascular events in survivors of intracranial haemorrhage with atrial fibrillation, similar to the effects of the vitamin K antagonist warfarin in people with atrial fibrillation but no previous intracranial haemorrhage.[7] However, there is likely to be a trade-off with an increase in haemorrhagic major adverse cardiovascular events. The absolute risk reduction in ischaemic major adverse cardiovascular events seems greater than the potential absolute increase in risk of haemorrhagic major adverse cardiovascular events, but a net benefit of oral anticoagulation remains to be determined. Furthermore, haemorrhagic events are more likely to result in death or disability than ischaemic events, but it is unclear whether any net absolute risk reduction in all major adverse cardiovascular events also results in a net risk reduction in death or dependence.

The strengths of this analysis are that we took a methodologically rigorous approach to pool individual participant data from four similar trials and adhered to a prespecified protocol and Statistical Analysis Plan. The participants were recruited from seven countries in three continents, and their overall characteristics are similar to patients in everyday clinical practice.[10,11] There was good balance of participant characteristics between treatment groups overall and in the two largest trials contributing to the subgroup analyses. We found no evidence of heterogeneity between estimates of treatment effect in the trials on any of the outcomes other than moderate heterogeneity in effects on death of any cause. Our results were consistent in fixed-effect and random-effects models. We took the recommended deft approach to investigating heterogeneity of treatment effect in subgroups. Although we did not find any significant subgroup interactions due to the limited sample sizes of the complete trials, the possibility of greater benefit in women compared with men (in data from SoSTART and APACHE-AF) seems to tally with some sex differences in trials of direct oral anticoagulants.[31]

This meta-analysis has some limitations. We were unable to obtain some baseline covariates for the ELDERCARE-AF trial because they were not available in the anonymised dataset provided via the data-sharing platform (eg, the deidentification policy mandated removal of sex and ethnicity data).[17] Two participants opted out of data sharing in the SoSTART trial.[13] Treatment allocation was open label in three of the four trials, conferring a risk of performance bias (such as under-reporting of mild outcomes). However, most outcomes require hospitalisation, are objective, and were adjudicated blind to treatment assignment by the included trials, which minimises the risk of bias.[32] There were some differences in the intervention (largely the specific type of direct oral anticoagulant used, the dose, and the timing of initiation in relation to intracranial haemorrhage) and the comparator between the included trials. Incomplete adherence to oral anticoagulation in the trials with open treatment assignment and the use of an antiplatelet agent as a comparator in a third of the participants[9] might have attenuated effect sizes. We did not perform as-treated or per-protocol analyses because they were not specified in our Statistical Analysis Plan. We extrapolated, after assuming most participants in ELDERCARE-AF would be Asian, that the overall proportion of White participants was about 76%, but Black and other ethnic groups were under-represented. The sample sizes of the included trials were small, and they were insufficient both individually and when pooled to adequately power assessments of heterogeneity of treatment effects in subgroups, but they provide priors to inform the conduct and interpretation of ongoing trials.

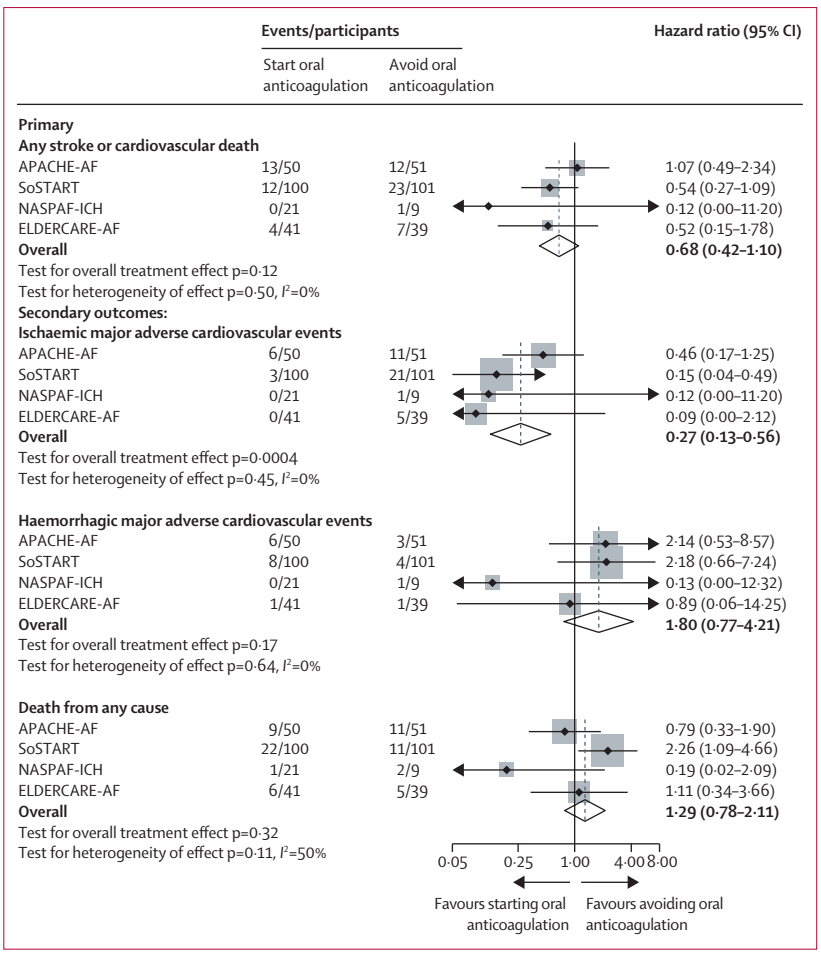

Figure 2: **Effect of starting versus avoiding oral anticoagulation for atrial fibrillation after intracranial haemorrhage on primary and secondary outcomes, using individual participant data from four trials**

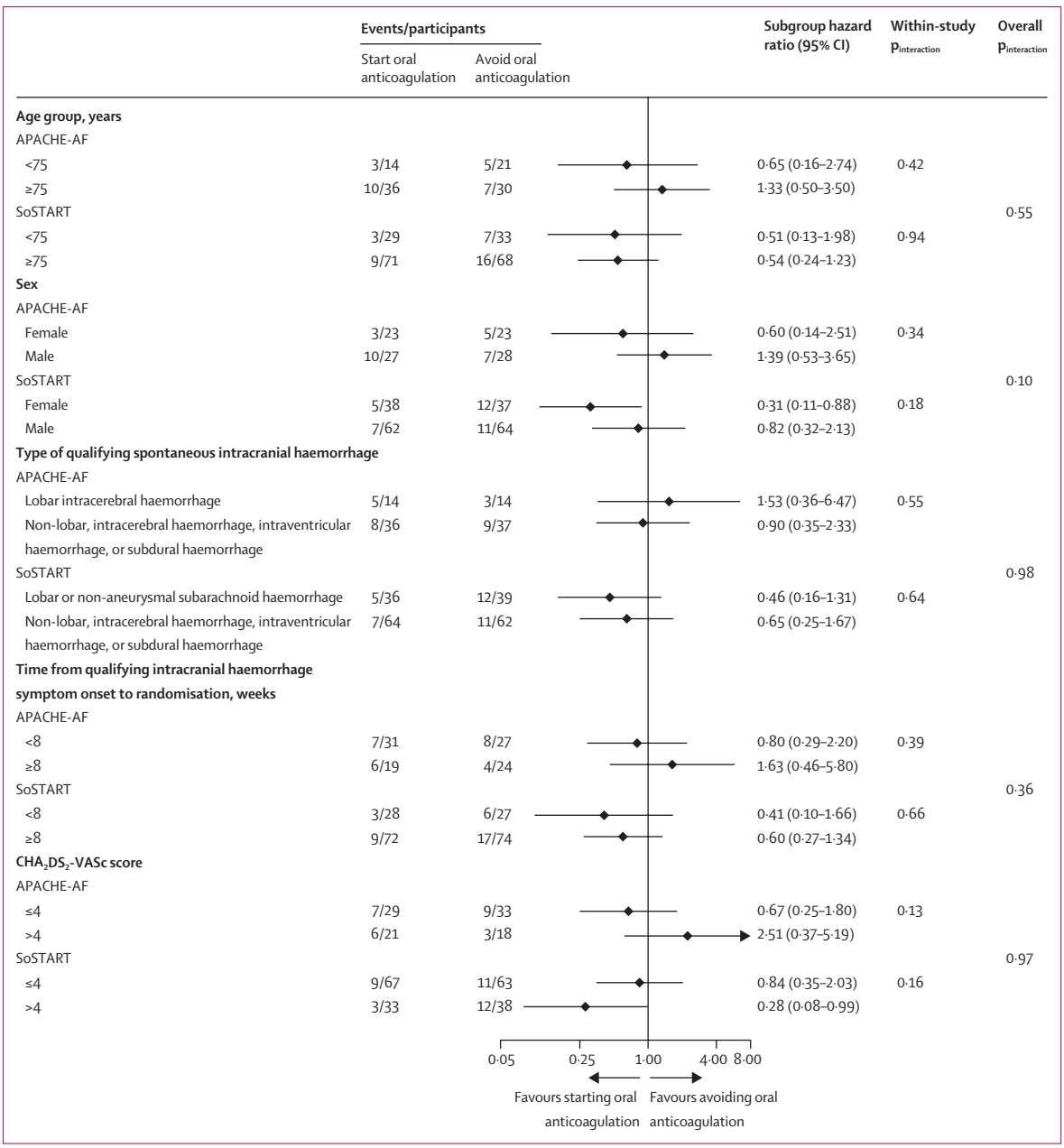

Figure 3: **Subgroup analysis of the effect of starting versus avoiding oral anticoagulation for atrial fibrillation after intracranial haemorrhage on any stroke or cardiovascular death, using individual participant data from SoSTART and APACHE-AF**

The main implication of our findings for clinical practice is that patients with spontaneous intracranial haemorrhage and atrial fibrillation can be informed that oral anticoagulation was associated with a decrease in major ischaemic cardiovascular events, and ischaemic stroke specifically, to the same extent seen for people with atrial fibrillation but no history of intracranial haemorrhage. However, patients should know that there is uncertainty and concern about the effect of oral anticoagulation on haemorrhagic major cardiovascular events overall and especially in some subgroups (such as lobar intracerebral haemorrhage and subarachnoid haemorrhage).

The Data Monitoring Committee of the ENRICH-AF trial (NCT03950076) recommended that participants with lobar intracerebral haemorrhage should have study drug terminated as soon as possible and that no more patients with lobar intracerebral haemorrhage be enrolled after analysis of data from 174 participants with lobar intracerebral haemorrhage on June 1, 2023.[24] This urgent safety measure was due to an observation of an unacceptably high risk of recurrent haemorrhagic stroke among patients with lobar intracerebral haemorrhage

assigned to the edoxaban group.[24] These data from ENRICH-AF are unpublished, but they suggest that oral anticoagulation might not result in net benefit for people with convexity subarachnoid haemorrhage or lobar intracerebral haemorrhage[33] who have higher risks of recurrent intracerebral haemorrhage[4] and underlying cerebral amyloid angiopathy than their counterparts.[30] However, our meta-analysis including 103 participants with lobar intracerebral haemorrhage or non-aneurysmal convexity subarachnoid haemorrhage (which also has a high prevalence of underlying cerebral amyloid angiopathy[2]) did not find any suggestion of an interaction between intracranial haemorrhage location and the net effects of oral anticoagulation. The contrast between our findings and the urgent safety measure in ENRICH-AF leaves some uncertainty about differences in effect by intracranial haemorrhage location, which mandates further investigation in ongoing trials and an update of this meta-analysis when their recruitment and follow-up are complete.

The implications of our findings for further research are that the ongoing trials investigating oral anticoagulation for this indication (STATICH, A3-ICH, ASPIRE, ENRICH-AF, and PRESTIGE-AF) should complete recruitment as quickly as possible. There are already 1349 participants in these ongoing trials, which could reach a maximum target sample size of 2265 (unpublished). Completion of these trials is likely to resolve the uncertainties about effects on stroke or cardiovascular death, haemorrhagic major adverse cardiovascular events, and functional outcome (death or dependence) for this group of patients at high risk of stroke or cardiovascular death. These results will inform whether left atrial appendage occlusion is appropriate as an alternative to oral anticoagulation in some or all patients, which is already under investigation in two trials (NCT02830152 and NCT03243175). In due course, an update of this individual participant data meta-analysis could provide precise and definitive evidence of effects of oral anticoagulation overall, when compared with antiplatelet therapy or no antithrombotic therapy, and whether effects vary according to intracranial haemorrhage location as well as other subgroups (such as ethnicity, atrial fibrillation subtype, dose of oral anticoagulant, or by imaging biomarkers of cerebral small vessel disease).

Contributors

RA-SS had the idea for, initiated, and leads COCROACH, and obtained funding for analyses. RA-SS wrote the protocol, with input from AS, HBvdW, JT, and CJMK, and with the approval of the chief investigators of eligible trials (AS, RGH, CC, KNS, HK, RV, KTL, HBvdW, and CJMK). SCL and RA-SS wrote the Statistical Analysis Plan. JS performed statistical analyses with oversight from SCL, JFT, and RA-SS. JS and SCL accessed and verified the underlying data that were shared with the University of Edinburgh (SoSTART, APACHE-AF, and NASPAF-ICH) or accessed via the Vivli data sharing platform (ELDERCARE-AF). RA-SS wrote the first draft of the manuscript. All co-authors reviewed the analyses and drafts of this manuscript and approved the final version. The corresponding author and statisticians had full access to all data and had final responsibility for the decision to submit for publication.

Declaration of interests

SJC reports institutional funding from Daiichi Sankyo. CC reports funding from the French Ministry of Health, Novartis (advisory board), and Biogen, Bayer and Bristol Myers Squibb (BMS; steering committees). HK reports funding from the US National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS; U01NS095869, R01HL144541, R01NS123576, and U01NS106513); funding from BMS-Pfizer Alliance; funding from Roche Diagnostics; being Deputy Editor for *JAMA Neurology*; participation on clinical trial steering or executive committees for Medtronic, Janssen, and Javelin Medical; participation on endpoint adjudication committees for AstraZeneca, Novo Nordisk, and Boehringer Ingelheim; and household ownership interests in TETMedical, Spectrum Plastics Group, and Burke Porter Group. CJMK and FHBMS report institutional funding from the Dutch Heart Foundation Clinical Established Investigator grant (2012T077) for APACHE-AF. DEN reports institutional funding from BMS and provision of a PET tracer from Life Molecular Imaging. APJ reports personal consulting fees and speaker fees from AstraZeneca. RA-SS reports institutional funding from the British Heart Foundation (CS/18/2/33719) for this work, institutional funding from the UK National Institute for Health and Care Research and The Stroke Association outside the submitted work, being Data Monitoring Committee chair for ELAN (NCT03148457), and consulting fees paid to the University of Edinburgh from Recursion Pharmaceuticals, Bioxodes, and Population Health Research Institute at McMaster University (Hamilton, ON, Canada). KS reports institutional funding from NIH NINDS (U01NS106513, U24NS129500, R01MD016178, R01EB31114, U24NS107215, R01NR018335, R01NS110721), American Heart Association, Hyperfine, Biogen, and Bard, and consulting fees from Astrocyte, Zoll and Sense (Data Safety and Monitoring Board), and CSL Behring. AS reports institutional funding from Heart and Stroke Foundation of Canada, Canadian Institutes of Health Research, NIH, Bayer, Daiichi Sankyo, and Servier Canada; consulting fees from Bayer, Daiichi Sankyo, Servier Canada, AstraZeneca, and Bioxodes; speaker fees from Bayer, Daiichi Sankyo, Servier Canada, and AstraZeneca; payment for expert testimony from Canadian Medical Protective Agency, support for meetings from Bayer, and Data Monitoring Committee membership for Bayer. HBvdW reports institutional funding from Stryker, Dutch Heart Foundation, and the EU, consulting fees from Bayer and TargED, and membership of the Executive Committee of the European Stroke Organisation. RV reports institutional funding from Bayer, BMS, Pfizer, Daiichi Sankyo, Boehringer, and Medtronic; consulting fees from AstraZeneca; speaker fees from BMS-Pfizer, Data Monitoring Committee participation for Bayer and Portola; stock options in Bayer and Novartis; materials from Medtronic; and chair of the World Stroke Organisation research committee. CV reports personal support from NIH NINDS (UO1NS106513). PMW reports institutional funding from Stryker, Medtronic, and Penumbra, and Data Monitoring Committee membership for PROTECT-U, TENSION, and MR CLEAN NO IV. All other authors declare no competing interests.

Data sharing

Contributing trials shared data on condition that the data recipient (University of Edinburgh) shall not sub-license, transfer, disclose, or otherwise make available the data in whole or part to any third party except with specific previous written consent from the data provider. Written proposals will be assessed by representatives of the contributing trials and a decision made about the appropriateness of re-use of data. A data-sharing agreement will be put in place before any data are shared. Individual trial datasets can be shared according to the terms described by each trial. Please contact the corresponding author about data access.

Acknowledgments

This iteration of the COCROACH individual participant data meta-analysis was funded by the British Heart Foundation (CS/18/2/33719). APACHE-AF was funded by the Dutch Heart Foundation (2012T077). NASPAF-ICH was funded by the Heart and Stroke Foundation of Canada, Canadian Stroke Prevention Intervention Network and the Population Health Research Institute. SoSTART was funded by the Medical Research Council (G10026051), Chest Heart & Stroke Scotland (Res 16 A166), and the British Heart Foundation (CS/18/2/33719) via the University of Edinburgh. JFT was funded by the UK Medical Research

Council (MC_UU_00004/06). RV is the chief investigator of PRESTIGE-AF, which has received funding from the EU's Horizon 2020 research and innovation programme under grant agreement number 754517. This publication is based on research using data from data contributors Daiichi Sankyo that has been made available through Vivli. Vivli has not contributed to nor approved, and is not in any way responsible for, the contents of this publication.

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