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Direct oral anticoagulants versus no anticoagulation for the prevention of stroke in survivors of intracerebral haemorrhage with atrial fibrillation (PRESTIGE-AF): a multicentre, open-label, randomised, phase 3 trial.

Direct oral anticoagulants versus no anticoagulation for the prevention of stroke in survivors of intracerebral haemorrhage with atrial fibrillation (PRESTIGE-AF): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background Direct oral anticoagulants (DOACs) reduce the rate of thromboembolism in patients with atrial fibrillation but the benefits and risks in survivors of intracerebral haemorrhage are uncertain. We aimed to determine whether DOACs reduce the risk of ischaemic stroke without substantially increasing the risk of recurrent intracerebral haemorrhage.

Methods PRESTIGE-AF is a multicentre, open-label, randomised, phase 3 trial conducted at 75 hospitals in six European countries. Eligible patients were aged 18 years or older with spontaneous intracerebral haemorrhage, atrial fibrillation, an indication for anticoagulation, and a score of 4 or less on the modified Rankin Scale. Patients were randomly assigned (1:1) to a DOAC or no anticoagulation, stratified by intracerebral haemorrhage location and sex. Only the events adjudication committee was masked to treatment allocation. The coprimary endpoints were first ischaemic stroke and first recurrent intracerebral haemorrhage. Hierarchical testing for superiority and non-inferiority, respectively, was performed in the intention-to-treat population. The margin to establish non-inferiority regarding intracerebral haemorrhage was less than 1·735. The safety analysis was done in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, NCT03996772, and is complete.

Findings Between May 31, 2019, and Nov 30, 2023, 319 participants were enrolled and 158 were randomly assigned to the DOAC group and 161 to the no anticoagulant group. Patients' median age was 79 years (IQR 73–83). 113 (35%) of 319 patients were female and 206 (65%) were male. Median follow-up was 1·4 years (IQR 0·7–2·3). First ischaemic stroke occurred less frequently in the DOAC group than in the no anticoagulant group (hazard ratio [HR] 0·05 [95% CI 0·01–0·36]; log-rank p<0·0001). The rate of all ischaemic stroke events was 0·83 (95% CI 0·14–2·57) per 100 patient-years in the DOAC group versus 8·60 (5·43–12·80) per 100 patient-years in the no anticoagulant group. For first recurrent intracerebral haemorrhage, the DOAC group did not meet the prespecified HR for the non-inferiority margin of less than 1·735 (HR 10·89 [90% CI 1·95–60·72]; p=0·96). The event rate of all intracerebral haemorrhage was 5·00 (95% CI 2·68–8·39) per 100 patient-years in the DOAC group versus 0·82 (0·14–2·53) per 100 patient years in the no anticoagulant group. Serious adverse events occurred in 70 (44%) of 158 patients in the DOAC group and 89 (55%) of 161 patients in the no anticoagulant group. 16 (10%) patients in the DOAC group and 21 (13%) patients in the no anticoagulant group died.

Interpretation DOACs effectively prevent ischaemic strokes in survivors of intracerebral haemorrhage with atrial fibrillation but a part of this benefit is offset by a substantially increased risk of recurrent intracerebral haemorrhage. To optimise stroke prevention in these vulnerable patients, further evidence from ongoing trials and a meta-analysis of randomised data is needed, as well as the evaluation of safer medical or mechanical alternatives for selected patients.

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*Members of the PRESTIGE-AF Consortium are listed in the appendix (p 2)

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Introduction

Intracerebral haemorrhage is a devastating type of stroke. An estimated 25% of survivors of intracerebral haemorrhage have atrial fibrillation, most of whom are anticoagulated at the time of the event.[1,2] Survivors of intracerebral haemorrhage with atrial fibrillation are at an especially high risk of ischaemic stroke and cardiovascular events.[3,4] Although there is strong evidence that oral

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Research in context

Evidence before this study

Direct oral anticoagulants (DOACs) reduce the rate of thromboembolism in patients with atrial fibrillation but their benefits and risks in survivors of intracerebral haemorrhage are uncertain. In meta-analyses of observational studies, anticoagulation reduced the risk of ischaemic stroke without increasing the risk of recurrent intracerebral haemorrhage; however, these data were prone to selection bias and confounding by indication. We searched MEDLINE, Embase, Cochrane library, EudraCT, and ClinicalTrials.gov from database inception to January, 2025, for randomised controlled trials comparing anticoagulation with no anticoagulation using the key search terms "intracerebral haemorrhage", "atrial fibrillation", and "oral anticoagulation", with no language restrictions. We found an individual patient data meta-analysis on survivors of intracerebral haemorrhage with atrial fibrillation and data from the ELDERCARE-AF trial (NCT02801669). The meta-analysis reported uncertain effects of oral anticoagulation on the risk of any stroke, cardiovascular mortality, and haemorrhagic major adverse events but suggested ischaemic adverse cardiovascular events were reduced and data from larger randomised trials were needed to resolve the remaining uncertainty.

Added value of this study

The PRESTIGE-AF trial is the first completed phase 3 trial of antithrombotic stroke prevention in survivors of intracerebral haemorrhage with atrial fibrillation that compared the effects of DOACs versus no anticoagulation. Participants assigned to DOACs had significantly fewer ischaemic strokes than those assigned to no anticoagulation. This benefit was partly offset by a significantly increased risk of recurrent intracerebral haemorrhage and other major bleedings. Nevertheless, trends in favour of DOAC were observed for the prespecified secondary endpoint of all stroke and systemic embolism as well as for cardiovascular and all-cause mortality consistent with previous observations in pilot-phase trials.

Implications of all the available evidence

Anticoagulation with DOACs substantially reduces the risk of ischaemic stroke and other major ischaemic adverse outcomes in survivors of intracerebral haemorrhage with atrial fibrillation. However, a part of this benefit is offset by an increased risk of recurrent intracerebral haemorrhage and other major haemorrhagic complications. To optimise stroke prevention in these vulnerable patients, further evidence from ongoing trials and a meta-analysis of randomised data is needed. Potentially safer medical or mechanical alternatives are also being investigated in ongoing research including randomised trials.

anticoagulation prevents ischaemic strokes in patients with atrial fibrillation with no previous intracerebral haemorrhage,[5,6] the optimal preventive management of stroke among survivors of intracerebral haemorrhage with atrial fibrillation is uncertain because patients with intracerebral haemorrhage have been excluded from trials.

In 2017, systematic reviews and meta-analyses of observational studies suggested a benefit of oral anticoagulants (mostly vitamin K antagonists) for the prevention of ischaemic stroke in survivors of intracerebral haemorrhage,[7,8] and one large national register-based study showed a 45% reduction in mortality in patients receiving anticoagulants.[9] Anticoagulation was not associated with a significant increase in recurrent intracranial haemorrhage in these studies.[7] Subsequent pilot-phase, randomised controlled trials[10,11] using direct oral anticoagulants (DOACs), which confer about half the risk of intracranial haemorrhages compared with vitamin K antagonists, and an individual patient data meta-analysis of randomised controlled data[12] reported inconclusive effects of oral anticoagulation on the risk of any stroke, cardiovascular mortality, and haemorrhagic adverse events, but suggested a reduction of ischaemic adverse cardiovascular events. Hence, additional evidence from larger trials was needed to identify the best preventive management in survivors of intracerebral haemorrhage with atrial fibrillation.[12] We aimed to assess the efficacy and safety of DOACs compared with no anticoagulation in survivors of intracerebral haemorrhage with atrial fibrillation.

Methods

Study design

The PRESTIGE-AF trial was a multicentre, open-label, randomised, phase 3 trial done at 75 hospitals with stroke units in six countries in Europe (UK, Germany, Austria, Spain, Italy, and France). Details of the trial design have been published previously.[13] The trial followed the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Research ethics committees and authorities in each participating country approved the trial protocol (version 3; Oct 5, 2018, lead ethics approval in the UK 18/LO/1186) and subsequent amendments (appendix pp 6–7). The trial steering committee and sponsor approved the final version of the trial protocol (version 7; May 4, 2023; appendix) and the statistical analysis plan (final version 1.5; April 18, 2024, before database lock and analysis; appendix). This trial is registered with ClinicalTrials.gov, NCT03996772, and is complete.

Participants

Eligible patients were aged 18 years or older with a spontaneous intracerebral haemorrhage, atrial

fibrillation, an indication for anticoagulation, and a score of 4 or less on the modified Rankin Scale.[14] Enrolment occurred from 14 days to 12 months (initially 6 months) after the index intracerebral haemorrhage. Exclusion criteria included intracerebral haemorrhage resulting from vascular malformation or trauma and the presence of or the plan to implant a left atrial appendage occlusion device. Full eligibility criteria are presented in the appendix (p 7). Eligible patients or their legal representatives were approached by local investigators. Written informed consent was obtained from the patient or their legal representative (after an amendment) if the patient lacked capacity to consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive a DOAC or no anticoagulation using a central web-based randomisation system (secuTrial), stratified according to intracerebral haematoma location (lobar *vs* non-lobar, determined by each site) and sex. Haematoma location and volume were reassessed by the imaging core laboratory (Medical University of Graz) using the Cerebral Haemorrhage Anatomical RaTing instrument.[15]

Treatment allocation was known to patients, treating clinicians, and investigators including patients into the trial and completing follow-up. Outcome events were assessed by an event adjudication committee masked to treatment allocation, drug use, and participant identity, by redaction of source documents.

Procedures

Patients assigned to the DOAC group received apixaban, dabigatran, edoxaban, or rivaroxaban at the discretion of local investigators. A dose licensed for stroke prevention in atrial fibrillation by the European Medicines Agency was prescribed. All DOACs were labelled by the central pharmacy (Heidelberg University Hospital). Patients in the no anticoagulation group received antiplatelet medication (eg, aspirin 100 mg once per day) or no antiplatelet medication as decided by local investigators. The use of dual antiplatelets was not permitted at enrolment but was allowed during follow-up if clinically warranted (appendix p 8).

At screening and enrolment, demographics, cardiovascular risk factors, medical history, concomitant medication, and vital signs were recorded. Data were collected to calculate the risk of stroke using the CHA_2DS_2-VASc score (for which points are assigned for the following risk factors: congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, previous stroke [doubled], vascular disease, and female sex), with scores ranging from 1 to 9 and higher scores indicating a greater risk of stroke. Risk of major bleeding was calculated using the HAS-BLED score (for which points are assigned for the following risk factors: uncontrolled hypertension or systolic blood pressure >160 mm Hg, abnormal renal or liver function, previous stroke, bleeding history or predisposition, labile international normalised ratio, age >65 years, concomitant drugs, and alcohol use), with scores ranging from 0 to 9 and higher scores indicating a greater risk of bleeding.

Patients were followed up for at least 6 months, and up to 36 months, with in-person follow-up visits scheduled at 1, 6, 12, 24, and 36 months. Off-site or remote visits were permitted if the patient was unable to attend the site. Essential procedures included blood pressure measurements, blood sample collection, outcome and adverse event recording, and drug accountability. All sites with enrolled patients underwent repeated on-site monitoring with source data verification. Trial conduct, data quality, and patient safety were centrally monitored throughout the study.

Outcomes

The two coprimary binary endpoints were first incident ischaemic stroke and first recurrent intracerebral haemorrhage (definitions of all endpoints and outcomes are provided in the appendix pp 8–10). Prespecified secondary endpoints were all stroke and systemic embolism, major adverse cardiac events, cardiovascular mortality, all-cause mortality, and net clinical benefit comprising all stroke and systemic embolism, myocardial infarction, cardiovascular mortality, and major bleeding.[16] Secondary safety endpoints were all events of intracranial haemorrhage and all events of major bleeding according to the International Society on Thrombosis and Haemostasis classification.[17] All prespecified primary and secondary endpoints were centrally assessed by the event adjudication committee. All serious adverse events were reviewed centrally by the sponsor and presented periodically to the independent data safety monitoring board.

Statistical analysis

The original sample size calculation was based on a meta-analysis of observational studies in which patients mostly received vitamin K antagonists as anticoagulants.[7] The calculation yielded a total of 654 participants (327 per group in a 1:1 randomisation). A revision of the power analysis was performed in 2022 after data from two pilot-phase trials became available.[10,11] This power analysis also accounted for the slower than expected recruitment rate and considered different recruitment scenarios during the remaining funding period (full details are provided in the appendix). The different recruitment scenarios resulted in 294–340 participants in total. For the coprimary endpoint of ischaemic stroke, the corresponding power analysis calculated more than 80% power at a significance level of 0·05 for hazard ratios (HRs) less than 0·348, assuming a 10% dropout rate and a 5% change of treatment regimen. The scenario considered most realistic was a recruitment rate of 12 participants per month, yielding an expected sample size of 312 participants.

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See Online for appendix

Within the primary analysis, statistical tests for the two coprimary endpoints were combined by a fixed sequence hierarchical test procedure (ie, the null hypothesis for recurrent intracerebral haemorrhage was only tested if the null hypothesis for incident ischaemic stroke could be rejected at a significance level of 0·05). Therefore, the overall significance level of the analyses of 0·05 was preserved. The primary efficacy statistical test procedure for the first coprimary endpoint was a two-sided log-rank test for the time from randomisation to the first incident ischaemic stroke. The hypothesis for the second coprimary endpoint was tested with a non-inferiority log-rank test for the time from randomisation to the first event of recurrent intracerebral haemorrhage. Assignment to the DOAC group was assessed as non-inferior compared with the no anticoagulant group if the absolute increase in hazard rate was no more than 0·03 (ie, hazard rate in no anticoagulant group was 0·0408 *vs* 0·0708 in DOAC group). Non-inferiority could be concluded if the upper limit of a two-sided 90% CI for the HR was less than the non-inferiority boundary of 1·735.

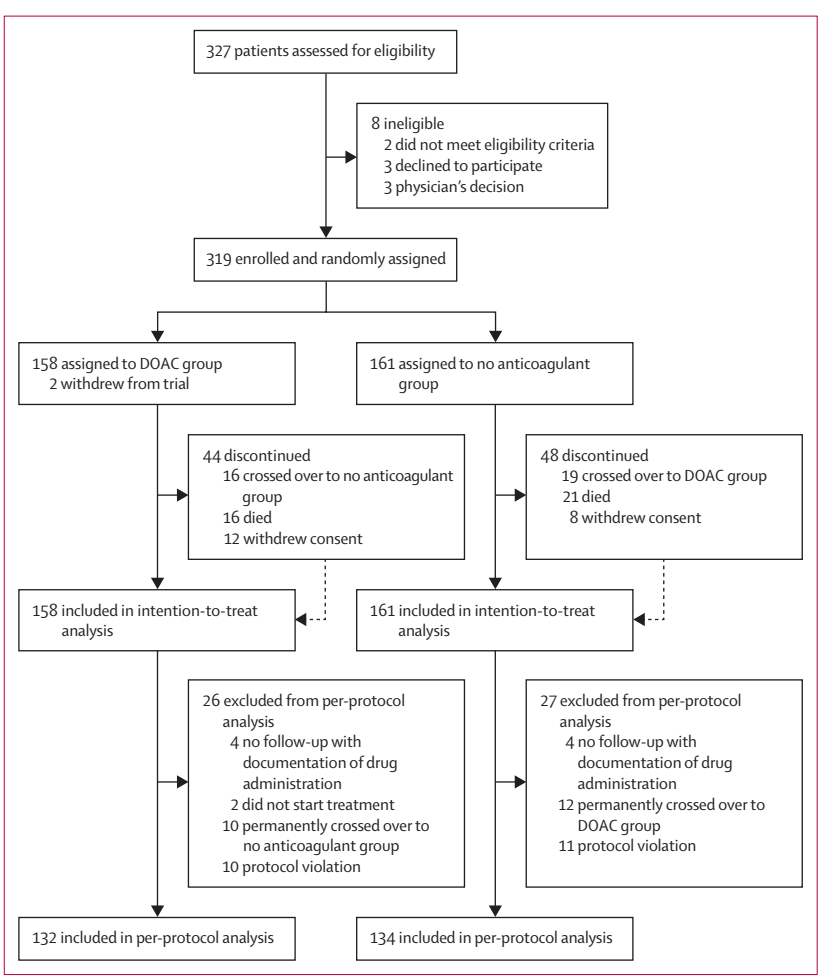

Figure 1: **Trial profile**
DOAC=direct oral anticoagulant.

All patients randomly assigned to treatment groups were included in the intention-to-treat population and were tested for superiority. To establish non-inferiority, a significant result was required from the intention-to-treat analysis and the per-protocol analysis. Patients with no follow-up examination with documentation of drug administration or who permanently crossed over treatments, or those who never started the assigned treatment or with other protocol violations were excluded from the per-protocol analysis.

As randomisation was stratified according to two dichotomous factors (lobar or non-lobar location of index intracerebral haemorrhage and sex), variables were adjusted for in sensitivity analyses. For both coprimary endpoints, Cox proportional hazards regression was performed for the time-to-first ischaemic stroke or first recurrent intracerebral haemorrhage, with treatment group as the main factor and location of index intracerebral haemorrhage, sex, and age (<80 years *vs* ≥80 years) as covariates. Additionally, event rates (per 100 person-years) of all primary endpoint events were calculated as a sensitivity analysis. Within another sensitivity analysis, the variability of the treatment effect across hospitals was estimated by using frailty models incorporating a random centre effect within the hazard function. A sensitivity analysis using a risk-score imputation approach was also conducted to censor patient information by creating multiple imputations of event times for patients whose event times were censored non-administratively.

Secondary endpoints were compared between treatment groups by calculating estimates for event rates (per 100 patient-years) and event rate ratios with accompanying 95% CIs. For adjusted results, Cox proportional hazards regression with treatment group as the main factor and location of index intracerebral haemorrhage, sex, and age as covariates was used for both mortality endpoints. Similarly, count data regression models with treatment group as the main factor, location of index intracerebral haemorrhage, sex, and age as covariates, and individual time under observation as an offset term were used for all other secondary and safety endpoints.

The proportional hazards assumption for Cox regression analyses was affirmed by graphical methods. For all secondary endpoints and sensitivity analyses of the coprimary endpoints, the width of the CI around the risk estimates were not adjusted for multiplicity and should not be used in place of hypothesis testing. All statistical analyses were performed using R version 4.4.1.

Role of the funding source

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

Results

Between May 31, 2019, and Nov 30, 2023, 319 patients were enrolled; 158 were assigned to the DOAC group and 161 to the no anticoagulant group (figure 1). Of 158 patients in the DOAC group, 85 (54%) received apixaban, 33 (21%) received dabigatran, 29 (18%) received edoxaban, nine (6%) received rivaroxaban, and two (1%) did not receive any anticoagulant (appendix p 11). Of 161 patients in the no anticoagulant group, 53 (33%) received antiplatelet therapy and 108 (67%) received no antithrombotic treatment. 266 (83%) of 319 patients were included in the per-protocol analysis. No patients were lost to follow-up.

	DOAC group (n=158)	No anticoagulant group (n=161)
Age, years	78 (73–83)	79 (73–84)
Sex		
Female	56 (35%)	57 (35%)
Male	102 (65%)	104 (65%)
Ethnicity*		
White	153 (97%)	153 (95%)
Mixed	1 (1%)	1 (1%)
Asian	0	1 (1%)
Black	0	1 (1%)
Unknown	4 (3%)	5 (3%)
Medical history		
Hypertension	151 (96%)	154 (96%)
Diabetes	41 (26%)	38 (24%)
Myocardial infarction	10 (6%)	16 (10%)
Ischaemic stroke	32 (20%)	30 (19%)
Transient ischaemic attack	9 (6%)	7 (4%)
ICH†	6 (4%)	8 (5%)
Other major bleeding†	13 (8%)	20 (12%)
Modified Rankin Scale score	3 (1–3)	3 (2–3)
CHA_2DS_2-VASc score‡	4 (3–6)	4 (3–6)
HAS-BLED score§	3 (2–3)	3 (2–3)
Blood pressure at enrolment, mm Hg		
Systolic	129 (15)	128 (16)
Diastolic	76 (11)	75 (10)
Time from index ICH to enrolment, days	48 (29–96)	49 (32–91)
Location of ICH¶		
Lobar	53 (34%)	42 (26%)
Non-lobar	105 (66%)	119 (74%)
ICH volume, mL¶‖	4·2 (1·4–8·9)	3·2 (1·1–10·2)
Antithrombotic medication before index ICH		
Anticoagulant agent	135 (85%)	133 (83%)
Antiplatelet agent	8 (5%)	8 (5%)
Anticoagulant and antiplatelet agent	3 (2%)	3 (2%)
No antithrombotic medication	12 (8%)	17 (11%)

Data are median (IQR), n (%), or mean (SD). DOAC=direct oral anticoagulant. ICH=intracerebral haemorrhage. *Percentages do not add up to 100 due to rounding. †Before index intracerebral haemorrhage. ‡CHA_2DS_2-VASc score (for which points are assigned for the following risk factors: congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, previous stroke [doubled], vascular disease, and female sex). §HAS-BLED score (for which points are assigned for the following risk factors: uncontrolled hypertension or systolic blood pressure >160 mm Hg, abnormal renal or liver function, previous stroke, bleeding history or predisposition, labile international normalised ratio, aged >65 years, and concomitant drugs and alcohol use). ¶Based on central reading by the imaging core laboratory. ‖Index ICH volume could not be determined in nine participants (two in the DOAC group and seven in the no anticoagulant group).

Table 1: **Patient baseline characteristics**

Baseline characteristics were similar between groups (table 1; appendix p 11). The median age of patients was 79 years (IQR 73–83); 113 (35%) of 319 patients were women and 206 (65%) were men. Median time from index intracerebral haemorrhage to enrolment was 49 days (IQR 31–93). Based on central assessment, the index intracerebral haemorrhage was in non-lobar locations in 224 (70%) of 319 patients and in lobar locations in 95 (30%) of 319 patients. Median haematoma volume was 4·2 mL (IQR 1·4–8·9) in the DOAC group and 3·2 mL (1·1–10·2) in the no anticoagulant group. The median length of follow-up was 1·4 years (0·7–2·3). 11 patients underwent left atrial appendage closure during follow-up (appendix p 12). There were no key variables with missing data. Blood pressure was well controlled in both groups at baseline and during follow-up (appendix p 12).

First ischaemic stroke occurred significantly less frequently in the DOAC group than in the no anticoagulant group (HR 0·05 [95% CI 0·01–0·36]; log-rank p<0·0001; table 2; figure 2). The rate of all ischaemic stroke events was 0·83 (95% CI 0·14–2·57) per 100 patient-years in the DOAC group versus 8·60 (5·43–12·80) per 100 patient-years in the no anticoagulant group (appendix p 12). Treatment with a DOAC was associated with an absolute reduction in the event rate of ischaemic stroke by 7·77 events per 100 patient-years resulting in a number needed to treat of 13 patients to prevent one ischaemic stroke per year. Treatment effects from Cox regression models including a random centre effect revealed no indication for a possible variability in the treatment effect across hospitals. The effect size estimates from the sensitivity analysis addressing informative censoring yielded similar results as in the primary efficacy analyses (appendix p 13).

The comparison of the first recurrence of intracerebral haemorrhage between the DOAC group and the no anticoagulant group did not meet the prespecified non-inferiority margin (HR 10·89 [90% CI 1·95–60·72];

	DOAC group (n=158)	No anticoagulant group (n=161)	Unadjusted HR (95% or 90% CI)*	Adjusted HR† (95% or 90% CI)*
Ischaemic stroke	1	20	0·05 (0·01–0·36)	0·05 (0·01–0·38)
Recurrent intracerebral haemorrhage	11	1	10·89 (1·95–60·72)	11·2 (2·01–62·86)

Data are number of events, unless otherwise specified. DOAC=direct oral anticoagulant. HR=hazard ratio. *95% CI for ischaemic stroke, 90% CI for intracerebral haemorrhage as the hypothesis for intracerebral haemorrhage endpoint was non-inferiority. †Adjusted for location of index intracerebral haemorrhage, sex, and age.

Table 2: **Coprimary endpoints during follow-up**

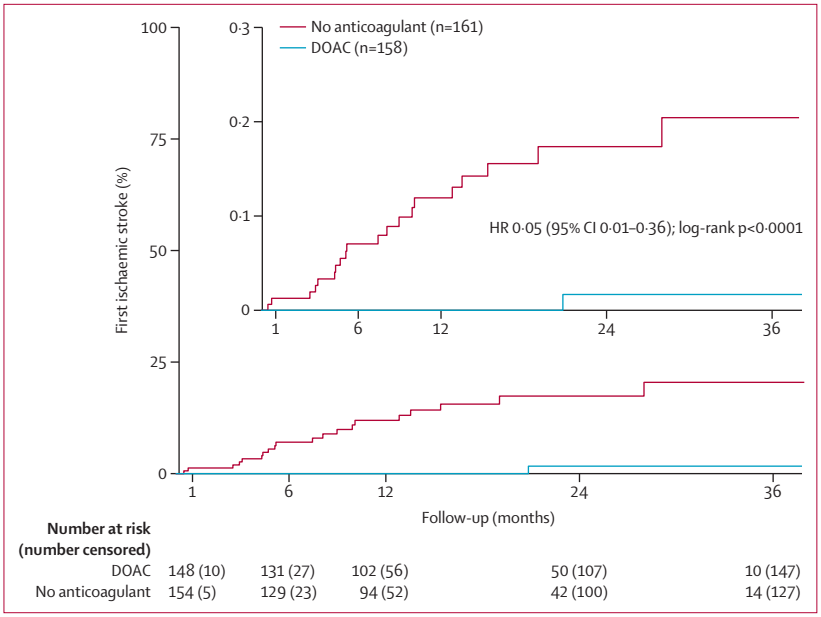

Figure 2: **Kaplan–Meier analysis of first incident ischaemic stroke**
DOAC=direct oral anticoagulant. HR=hazard ratio.

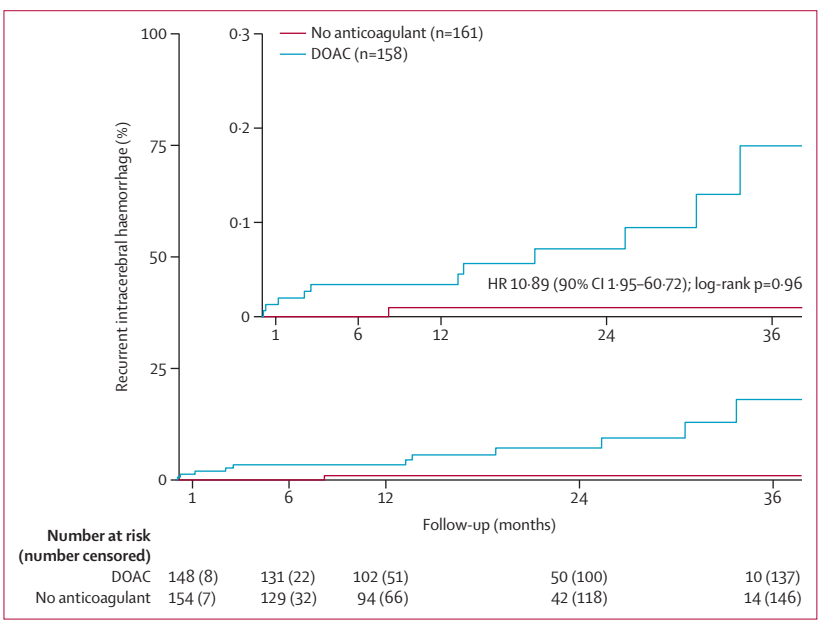

Figure 3: **Kaplan–Meier analysis of first recurrent intracerebral haemorrhage**
DOAC=direct oral anticoagulant. HR=hazard ratio.

log-rank p=0·96; table 2; figures 3, 4). The rate of all intracerebral haemorrhage was 5·00 (95% CI 2·68–8·39) per 100 patient-years in the DOAC group compared with 0·82 (0·14–2·53) per 100 patient-years in the no anticoagulant group (appendix p 12). DOACs increased the event rate of recurrent intracerebral haemorrhage by 4·18 events per 100 patient-years resulting in a number needed to harm of 24 patients to cause one more intracerebral haemorrhage per year. Differential risks of

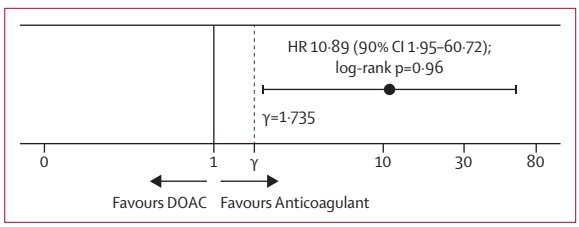

Figure 4: **Intracerebral haemorrhage in relation to prespecified non-inferiority margin**
DOAC=direct oral anticoagulant. HR=hazard ratio.

recurrent intracerebral haemorrhage based on haematoma location were not identifiable (appendix p 13).

Point estimates for event rates for secondary mortality endpoints were lower in the DOAC group than in the no anticoagulant group (6·67 events *vs* 8·60 events per 100 patient-years for all-cause mortality and 2·92 events *vs* 5·73 events per 100 patient-years for cardiovascular mortality; table 3). The secondary safety endpoints of any intracranial bleeding (6·25 events per 100 patient-years *vs* 0·82 per 100 patient-years) and any major bleeding (8·75 *vs* 2·05) occurred more often in the DOAC group than in the no anticoagulant group (table 3; appendix p 13). Fewer patients in the DOAC group met the secondary composite endpoint of all stroke and systemic embolism than patients in the no anticoagulant group (5·83 events per 100 patient-years *vs* 11·06 events per 100 patient-years; table 3). Similarly, fewer patients in the DOAC group met the net clinical benefit endpoint (all stroke and systemic embolism, myocardial infarction, cardiovascular mortality, and major bleeding) than in the no anticoagulant group (19·20 *vs* 26·52). Kaplan–Meier estimates for time to first event of the composite endpoints showed lower risks for patients in the DOAC group than the no anticoagulant group (appendix pp 4–5).

The HR for the rate of first recurrent intracerebral haemorrhage in the per-protocol population was 7·42 (90% CI 1·30–42·50). The results of a post-hoc sensitivity analysis, excluding eight patients who had left atrial appendage occlusion without having a previous primary outcome event, were not different to the results from the intention-to-treat analysis (appendix p 15).

A post-hoc power calculation for the endpoint ischaemic stroke on the final sample size of 319 patients resulted in a power of 84·7%. In post-hoc analyses, the event rate of recurrent intracerebral haemorrhage did not seem to be higher in patients with lobar location than non-lobar location of the index intracerebral haemorrhage, as assessed by core laboratory reading. Serious adverse events occurred in 70 (44%) of 158 patients in the DOAC group and 89 (55%) of 161 patients in the no anticoagulant group. 16 (10%) patients in the DOAC and 21 (13%) in the no anticoagulant group died (appendix p 13).

	DOAC group (n=158)		No anticoagulant group (n=161)		Unadjusted HR or event rate ratio (95% CI)	Adjusted HR or event rate ratio* (95% CI)
	Number of events	Event rate per 100 patient-years	Number of events	Event rate per 100 patient-years		
All-cause mortality	16	6·67	21	8·60	0·78 (0·41–1·49)	0·81 (0·42–1·55)
Cardiovascular mortality	7	2·92	14	5·73	0·51 (0·21–1·27)	0·52 (0·21–1·28)
Major adverse cardiac events	9	3·75	15	6·14	0·61 (0·27–1·40)	0·60 (0·25–1·36)
Any major bleeding†	21	8·75	5	2·05	4·27 (1·74–12·80)	4·47 (1·82–13·44)
Any intracranial bleeding	15	6·25	2	0·82	7·63 (2·15–48·43)	7·53 (2·11–47·87)
All stroke and systemic embolism	14	5·83	27	11·06	0·53 (0·27–0·99)	0·55 (0·28–1·04)
Net clinical benefit‡	32	19·20	45	26·52	0·67 (0·33–1·36)	0·69 (0·33–1·40)

DOAC=direct oral anticoagulant. HR=hazard ratio. *Adjusted for location of index intracerebral haemorrhage, sex, and age. †Definition according to International Society on Thrombosis and Haemostasis bleeding assessment tool. ‡All stroke and systemic embolism, myocardial infarction, cardiovascular mortality, and major bleeding.

Table 3: **Prespecified secondary endpoints during follow-up by treatment allocation**

Discussion

In this multicentre, randomised, phase 3 trial, survivors of intracerebral haemorrhage with atrial fibrillation assigned to no anticoagulation had a high event rate of ischaemic strokes. Treatment with DOACs substantially decreased the risk of ischaemic stroke but also increased the risk of recurrent intracerebral haemorrhage and other types of major bleeding.

PRESTIGE-AF is the first completed phase 3 trial showing a significant reduction in the risk of ischaemic stroke using DOACs in survivors of intracerebral haemorrhage with atrial fibrillation. The reduction in ischaemic stroke was consistent with the efficacy of anticoagulation in trials using DOACs in patients with atrial fibrillation without previous intracerebral haemorrhage.[18,19] A meta-analysis of observational trials in survivors of intracerebral haemorrhage with atrial fibrillation found a 53% risk reduction of ischaemic stroke with vitamin K antagonists.[7] The pilot-phase, randomised APACHE-AF trial did not find any effect of apixaban on the risk of ischaemic stroke.[11] A meta-analysis of randomised data[12] encompassing the SoSTART trial[10] reported a reduction of major adverse cardiovascular events including ischaemic stroke, consistent with the effects of DOACs seen in the PRESTIGE-AF trial.

A meta-analysis of observational data suggested that vitamin K antagonists do not increase the risk of recurrent intracerebral haemorrhage in patients with intracerebral haemorrhage and atrial fibrillation.[7] In prevention trials in patients without previous intracerebral haemorrhage, DOAC use conferred a 50% lower risk of intracerebral haemorrhage than vitamin K antagonists.[19] Two pilot-phase trials in survivors of intracerebral haemorrhage with atrial fibrillation reported unadjusted HRs of 2·31 (95% CI 0·69–7·68) to 4·12 (0·46–36·94) for the risk of recurrent intracerebral haemorrhage associated with DOACs.[10,11] In a meta-analysis of randomised data,[12] use of anticoagulants was not associated with a significant increase in haemorrhagic major adverse cardiovascular events compared with DOACs (15 [7%] of 212 *vs* nine [5%] of 200; pooled HR 1·80 [95% CI 0·77–4·21]) but the investigators expressed a need for data from larger studies. PRESTIGE-AF tested the non-inferiority hypothesis that DOACs do not substantially increase the risk of recurrent intracerebral haemorrhage compared with no anticoagulation. However, PRESTIGE-AF did not show non-inferiority but instead found a higher risk (HR 10·89) of recurrent intracerebral haemorrhage in patients assigned to the DOAC group than the no anticoagulant group. Moreover, the event rate of all major haemorrhages was higher in the DOAC group, which was largely driven by recurrent intracerebral haemorrhage. Taken together, these findings suggest that use of DOACs in survivors of intracerebral haemorrhage is associated with a substantially increased risk of severe bleeding complications compared with no anticoagulation. This higher risk difference between treatment groups versus previous studies might be explained by the low rate of recurrent intracerebral haemorrhage in the no anticoagulant group, which might be attributed to close and structured follow-up during PRESTIGE-AF, which was conducted as a clinical trial with investigational medicinal products.[20]

Whether haematoma location should affect the decision to start anticoagulation in patients with intracerebral haemorrhage with atrial fibrillation is controversial. Lobar haemorrhages were associated with a two-fold to three-fold higher risk of recurrent intracerebral haemorrhage than non-lobar haematomas in observational studies.[3,21] An observational study pooling data from three registries reported a similar benefit of anticoagulation in lobar and non-lobar intracerebral haemorrhage and no differential effect on major bleedings.[22] An interim safety analysis of the ongoing ENRICH-AF trial (NCT03950076) found an excessive risk of recurrent intracerebral haemorrhage in patients receiving anticoagulation treatment with lobar intracerebral haemorrhage.[23] Consequently, the

steering committee discontinued anticoagulation in patients with lobar intracerebral haemorrhage and excluded further enrolment of such patients.[23] By contrast, a meta-analysis of the SoSTART and APACHE-AF trials found no clear dependency of the safety of anticoagulation on haematoma location.[12] Similarly, in PRESTIGE-AF, the increased risk of recurrent intracerebral haemorrhage in patients in the no anticoagulant group did not seem to depend on haematoma location (appendix p 13) but there are too few events for intracerebral haemorrhage recurrence to draw definitive conclusions.

The benefits and risks of anticoagulation should be carefully balanced in patients with intracerebral haemorrhage and atrial fibrillation. The Kaplan–Meier analyses in this trial might suggest a particular benefit of DOACs for prevention of ischaemic strokes in the first year after the index event, whereas the risk of intracerebral haemorrhage recurrence in the DOAC group appeared to continue thereafter. However, this finding should be interpreted with caution due to the short observation time. Another approach to balance the opposing risks is to use composite endpoints. The composite of all (ischaemic and haemorrhagic) strokes and systemic embolism has been widely used as a primary endpoint in trials of stroke prevention in patients with atrial fibrillation without previous intracerebral haemorrhage.[19,24] The present study found a reduction in risk of all strokes and systemic embolism in patients who were assigned to receive a DOAC. The composite endpoint of net clinical benefit occurred less frequently in the DOAC group. A large observational study suggested that anticoagulation might reduce the mortality of patients with atrial fibrillation.[9] A meta-analysis of randomised data did not find a significant benefit of DOACs on cardiovascular or all-cause mortality.[12] In the PRESTIGE-AF trial, point estimates for mortality were lower in the DOAC group. However, the findings regarding all secondary endpoints should be interpreted with caution due to the wide CIs of effect estimates, which were not adjusted for multiplicity, and should not be used in place of hypothesis testing.

In view of the opposing risks that survivors of intracerebral haemorrhage with atrial fibrillation face with and without anticoagulation, individual patient preferences should be considered in shared decision making.[25] This discussion should include the different effects of ischaemic versus haemorrhagic types of stroke. The establishment of tools including clinical, neuroimaging, and genetic patient features for enhancing individualised risk prediction is desirable. New anticoagulants with a lower bleeding risk[26] or mechanical interventions, such as left atrial appendage occlusion, might become better alternatives to DOACs, at least for selected patients;[27] however, their efficacy and safety in survivors of intracerebral haemorrhage remains to be established (A3ICH NCT03243175; STROKECLOSE NCT02830152; CLEARANCE NCT04298723).

This study has some limitations. The low number of primary outcome events and short follow-up period resulting in broad CIs surrounding effect estimates limit the overall interpretation and clinical impact of the results. The study had an open design, but outcome events were adjudicated by independent experts masked to treatment allocation and potential under-reporting of events was addressed by prespecified procedures including monitoring. Furthermore, the study was not powered for secondary endpoints, and any trends suggesting a potential net benefit require confirmation in larger ongoing trials. The putatively differential impact of ischaemic strokes and recurrent intracerebral haemorrhages on disability were difficult to determine because the event rates were low and the levels of disability at the time of enrolment varied. The generalisability of the trial to different ethnicities and other systems of stroke care might be limited and requires assessment in ongoing trials (ENRICH-AF NCT03950076; ASPIRE NCT03907046). For example, only 113 (35%) of 319 participants were female, indicating that women are under-represented as in many other cardiovascular and stroke prevention trials. Recruitment of patients into PRESTIGE-AF was slowed by the COVID-19 pandemic, as in other trials in cardiovascular medicine.[28] This lower than expected recruitment rate led to a revised power calculation in view of a planned sample size reduction, resulting in a minimum power of 80% for the primary endpoint of ischaemic stroke. Additionally, a post-hoc power calculation on the final sample size of 319 patients resulted in a power of 84·7%. The trial protocol excluded the enrolment of survivors of intracerebral haemorrhage with severe disability, which might have led to the enrolment of patients with small haematoma volumes[29] limiting the study's generalisability. The number of patients with lobar intracerebral haemorrhage was slightly different between groups due to different interpretations of local and core imaging of available brain scans. A supplementary analysis stratified by DOAC type (accounting for uneven prescription frequencies in the study cohort) was not possible due to the small number of events. Subgroup analyses were not reported as stated in the original protocol, as only one event of first ischaemic stroke was observed in the DOAC group and one event of first recurrent intracerebral haemorrhage was observed in the no anticoagulation group. 33 (10%) of 319 participants crossed over to the opposite treatment. However, this rate was lower than anticipated in our sample size calculations, and the results of the per-protocol analysis were consistent with the intention-to-treat analysis. Finally, 11 (3%) participants underwent left atrial appendage closure for various reasons, but in most cases, this occurred at later timepoints during follow-up. This study has several strengths including rigorous study conduct, adequate power, regulatory standards of clinical trials of investigational medicinal products followed, performed across six countries with a homogeneous standard of care, and no patients lost to follow-up.

In conclusion, DOACs are effective in preventing ischaemic strokes in survivors of intracerebral haemorrhage with atrial fibrillation. However, this benefit is partly offset by an increased risk of intracerebral haemorrhage and other major bleeding complications. To further improve stroke prevention in these vulnerable patients, additional evidence is needed from ongoing trials and the COCROACH meta-analysis of randomised data, as well as the evaluation of safer medical or mechanical alternatives for selected patients.

Contributors

RV composed the first draft of the manuscript. RV, PUH, JM, CE, and DAL formulated the overarching research goals and aims. KHH, ERH, CF, UM, GPT, CS, SU, CE, SF-H, VR, KHaa, SR, and RdTC curated the data. RV and CF directly accessed and verified the underlying data. CF, UM, SR, SD, and TD completed the formal analysis. EK, PUH, JM, GYHL, DAL, WEH, KIF, VSW, PBN, CDAW, and IS acquired funding. RV, EK, JM, GPT, CS, SU, CE, SF-H, DAL, WEH, KIF, VSW, PBN, SP, LD, JP, MB, RW, GN, EP, PM, MH, YS, RdTC, CDAW, IS, KHaj, MGM, MLai, OH, PM-S, SD, TD, VCas, VCan, PR, and SR conducted the trial. RV, EK, PUH, UM, CE, DAL, WEH, PBN, BN, VR, KHaa, and YW developed and designed the methodology. RV, KHH, ERH, KHü, GPT, CS, SU, CE, GYHL, WEH, KIF, VSW, CDAW, EP, MLac, PM, RdTC, IS, MGM, OH, VCas, VCan, and PR were responsible for the management and coordination of the research planning and execution. RV, EK, KHH, ERH, CF, UM, KHü, GPT, CS, SU, CE, SP, LD, YS, SR, IS, MGM, SD, TD, VCas, VCan, and PR provided resources. RV, KHH, ERH, PUH, JM, PR, KHü, CE, BN, GP, CDAW, RdTC, IS, SP, MLai, VCas, and WEH were responsible for the oversight and leadership for the research activity planning and execution. CF, UM, RV, EK, GPT, CS, SU, SP, RW, VR, YS, and RdTC validated the overall results and research outputs. RV, KHH, ERH, CF, and PM prepared, created, and presented the draft manuscript. RV, EK, KHH, ERH, CF, and JM wrote the original draft. All authors reviewed and edited the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The data which can be made publicly available will be compiled and deposited in the OpenAIRE's Zenodo (https://zenodo.org/) 6 months after publication. Data which cannot be made openly available will be available to researchers upon request to the corresponding author (r.veltkamp@imperial.ac.uk) and will be subject to approval by an independent review committee identified for this purpose.

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