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Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial

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Summary

Background In patients with atrial fibrillation who survive an anticoagulation-associated intracerebral haemorrhage, a decision must be made as to whether restarting or permanently avoiding anticoagulation is the best long-term strategy to prevent recurrent stroke and other vascular events. In APACHE-AF, we aimed to estimate the rates of non-fatal stroke or vascular death in such patients when treated with apixaban compared with when anticoagulation was avoided, to inform the design of a larger trial.

Methods APACHE-AF was a prospective, randomised, open-label, phase 2 trial with masked endpoint assessment, done at 16 hospitals in the Netherlands. Patients who survived intracerebral haemorrhage while treated with anticoagulation for atrial fibrillation were eligible for inclusion 7–90 days after the haemorrhage. Participants also had a CHA_2DS_2-VASc score of at least 2 and a score on the modified Rankin scale (mRS) of 4 or less. Participants were randomly assigned (1:1) to receive oral apixaban (5 mg twice daily or a reduced dose of 2·5 mg twice daily) or to avoid anticoagulation (oral antiplatelet agents could be prescribed at the discretion of the treating physician) by a central computerised randomisation system, stratified by the intention to start or withhold antiplatelet therapy in participants randomised to avoiding anticoagulation, and minimised for age and intracerebral haemorrhage location. The primary outcome was a composite of non-fatal stroke or vascular death, whichever came first, during a minimum follow-up of 6 months, analysed using Cox proportional hazards modelling in the intention-to-treat population. APACHE-AF is registered with ClinicalTrials.gov (NCT02565693) and the Netherlands Trial Register (NL4395), and the trial is closed to enrolment at all participating sites.

Findings Between Jan 15, 2015, and July 6, 2020, we recruited 101 patients (median age 78 years [IQR 73–83]; 55 [54%] were men and 46 [46%] were women; 100 [99%] were White and one [1%] was Black) a median of 46 days (IQR 21–74) after intracerebral haemorrhage. 50 were assigned to apixaban and 51 to avoid anticoagulation (of whom 26 [51%] started antiplatelet therapy). None were lost to follow-up. Over a median follow-up of 1·9 years (IQR 1·0–3·1; 222 person-years), non-fatal stroke or vascular death occurred in 13 (26%) participants allocated to apixaban (annual event rate 12·6% [95% CI 6·7–21·5]) and in 12 (24%) allocated to avoid anticoagulation (11·9% [95% CI 6·2–20·8]; adjusted hazard ratio 1·05 [95% CI 0·48–2·31]; p=0·90). Serious adverse events that were not outcome events occurred in 29 (58%) of 50 participants assigned to apixaban and 29 (57%) of 51 assigned to avoid anticoagulation.

Interpretation Patients with atrial fibrillation who had an intracerebral haemorrhage while taking anticoagulants have a high subsequent annual risk of non-fatal stroke or vascular death, whether allocated to apixaban or to avoid anticoagulation. Our data underline the need for randomised controlled trials large enough to allow identification of subgroups in whom restarting anticoagulation might be either beneficial or hazardous.

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Introduction

In patients with atrial fibrillation who survive an anticoagulation-associated intracerebral haemorrhage, a long-standing and pressing clinical dilemma is whether restarting or avoiding anticoagulation is the best long-term strategy to prevent recurrent stroke and systemic thromboembolism.[1] For a long time, physicians have been reluctant to recommend oral anticoagulation, with treatment resumed in only a minority of patients and often many months after the intracerebral haemorrhage.[2–4] More

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For the Dutch translation of the abstract see **Online** for appendix 1

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Research in context

Evidence before this study

Anticoagulation with a vitamin K antagonist reduces the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation at the expense of an increased risk of haemorrhagic complications, including intracerebral haemorrhage. In large randomised clinical trials, non-vitamin K antagonist oral anticoagulants, including apixaban, were equally effective in reducing the risk of ischaemic stroke in patients with atrial fibrillation as the vitamin K antagonist warfarin, but were associated with a lower rate of intracranial haemorrhage. In a large randomised trial in patients with atrial fibrillation, apixaban reduced the rate of ischaemic stroke compared with aspirin, without increasing the risk of intracranial haemorrhage. However, these trials excluded patients with previous intracerebral haemorrhage. The best long-term treatment strategy for patients with atrial fibrillation and previous intracerebral haemorrhage is therefore uncertain, especially if the intracerebral haemorrhage occurred while the patient was being treated with an anticoagulant. We searched the Cochrane Central Register of Controlled Trials, PubMed, Embase, and bibliographies of relevant publications from database inception to June 14, 2021, for randomised controlled trials of restarting versus avoiding oral anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation, without language restrictions (appendix p 5). We found no completed randomised controlled trials. The authors of a 2017 Cochrane review on this topic concluded that there is not enough evidence from trials to support or discourage the use of antithrombotic treatment after intracerebral haemorrhage.

Added value of this study

APACHE-AF is a randomised controlled trial comparing the effects of apixaban versus avoiding anticoagulation in patients with atrial fibrillation who had an intracerebral haemorrhage while on anticoagulant therapy no more than 3 months before randomisation. This phase 2 trial was intended to provide reliable estimates of the risk of ischaemic stroke or intracerebral haemorrhage for both treatment strategies, to inform the design of a larger and conclusive trial. During a median follow-up of almost 2 years, the annual event rate of the composite outcome of non-fatal stroke or vascular death was about 12% in patients allocated to apixaban and in those allocated to avoid anticoagulation. More participants allocated to apixaban than allocated to avoid anticoagulation had a recurrent intracerebral haemorrhage but there was no difference between the treatment groups in the rate of ischaemic stroke.

Implications of all the available evidence

Our findings underline the importance of including patients with atrial fibrillation who have had an intracerebral haemorrhage in randomised trials of restarting anticoagulation versus avoiding anticoagulation. Pooled analysis of our trial with other trials is probably required to assess which patients benefit most from either treatment strategy.

recently, observational studies have provided arguments in favour of recommencing anticoagulation. In survivors of anticoagulation-related intracerebral haemorrhage who have atrial fibrillation, resuming oral anticoagulation was associated with a lower risk of death[5,6] and a better functional outcome than avoiding anticoagulation.[6] These associations were similar in patients with non-lobar and lobar intracerebral haemorrhage,[6] even though patients with lobar intracerebral haemorrhage have a higher risk of recurrent intracerebral haemorrhage than those with non-lobar intracerebral haemorrhage.[7] Additionally, the risk of ischaemic stroke after intracerebral haemorrhage might be as high as that of recurrent intracerebral haemorrhage.[8–11] In two systematic reviews and meta-analyses of observational studies, survivors of intracranial haemorrhage who restarted anticoagulation had a lower risk of ischaemic stroke than those in whom anticoagulants were withheld, whereas the risk of intracerebral haemorrhage was similar.[12,13] However, the results of these observational studies could have been confounded by indication, and most patients on anticoagulation were treated with vitamin K antagonists. Non-vitamin K-antagonist oral anticoagulants, known as direct oral anticoagulants (DOACs), have a lower risk of haemorrhagic complications than vitamin K antagonists in primary prevention[14] and secondary prevention after transient ischaemic attack and ischaemic stroke in patients with atrial fibrillation.[15] DOACs might therefore be a safer option, particularly in patients with anticoagulation-associated intracerebral haemorrhage. Randomised trials of restarting or avoiding anticoagulation have not been done in patients with atrial fibrillation who were required to have had an intracerebral haemorrhage while on anticoagulation.[16] As a result, guidelines do not provide strong recommendations on which patients with anticoagulation-associated intracerebral haemorrhage, if any, should resume anticoagulation.[15,17] We hypothesised that in patients with atrial fibrillation who survived an anticoagulation-associated intracerebral haemorrhage, treatment with the DOAC apixaban might be the best long-term alternative, by reducing the risk of ischaemic stroke and other occlusive vascular events without increasing the risk of intracerebral haemorrhage and other haemorrhagic complications to the extent that this benefit is offset. To test this hypothesis, a conclusive phase 3, randomised clinical trial comparing the long-term effects of apixaban with avoiding anticoagulation is required. To inform the sample size calculation of such a trial, a phase 2 trial is needed. We did the apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation (APACHE-AF) trial with the aim to

provide reliable estimates of the rates of non-fatal stroke or vascular death in patients with atrial fibrillation and a recent anticoagulation-associated intracerebral haemorrhage who were treated with apixaban versus those in whom anticoagulation was avoided.[18] Additionally, we estimated the effect of apixaban compared with no anticoagulation on the occurrence of non-fatal stroke or vascular death, on the occurrence of other haemorrhagic and ischaemic events, and on functional outcome.

Methods

Study design

APACHE-AF was an investigator-led, prospective, randomised, open-label, phase 2 trial with blinded endpoint assessment in 16 hospitals in the Netherlands. The trial rationale and design have been published.[18] The Medical Research Ethics Committee of the University Medical Center Utrecht, Netherlands, approved the study. The trial steering committee approved the trial protocol (appendix 2 p 3) and the statistical analysis plan (appendix 2 pp 6–9).

Participants

We included adults with a spontaneous intracerebral haemorrhage (including isolated intraventricular haemorrhage) in the previous 7–90 days during treatment with anticoagulation (vitamin K antagonist, DOAC, or heparin or low-molecular-weight heparin at therapeutic dose) because of documented paroxysmal or non-paroxysmal non-valvular atrial fibrillation. Other inclusion criteria were a CHA_2DS_2-VASc score of at least 2 and a score on the modified Rankin scale (mRS) of 4 or less. Patients were ineligible if they: had conditions other than atrial fibrillation requiring long-term anticoagulation (eg, mechanical prosthetic heart valve); had other serious bleeding events besides intracerebral haemorrhage in the previous 6 months; had a high risk of bleeding; had ischaemic stroke in the previous 7 days; had active alcohol or drug misuse; had a life expectancy of less than 1 year; had severe renal insufficiency; had liver test abnormalities; or were women with childbearing potential or who were pregnant or breastfeeding (appendix 2 pp 50–51).[18] If the treating physician had clinical equipoise regarding the optimal medical treatment for stroke prevention, patients could be enrolled when they or their legal representative had provided written informed consent.

Randomisation and masking

A central computerised randomisation system randomly assigned participants (1:1) to apixaban or to avoid anticoagulation. Treatment allocation was stratified by intention to start an antiplatelet agent or not in the avoid group, and subsequently based on proportional minimisation, according to age (≤75 years *vs* >75 years) and location of the intracerebral haemorrhage (lobar *vs* non-lobar). Participants, their treating physicians, and local investigators were aware of treatment allocation. Outcome event adjudication was done by LJK and GJER masked to the patient's identity, treatment allocation, and antithrombotic drug use.

Procedures

Local investigators completed information about participants' demographics, comorbidities, functional status, and concurrent medication into a database via a secure web interface. At baseline, a proxy (if available) provided information on cognitive decline before the index intracerebral haemorrhage using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[19] Patients assigned to apixaban received an oral dose of 5 mg twice daily, or a reduced dose of 2·5 mg twice daily if their creatine clearance was 30 mL/min or less, or if two of three of the following criteria were present: age 80 years or older, bodyweight 60 kg or lower, or serum creatinine 133 μmol/L or greater. In the avoid anticoagulation group, patients either received no antithrombotic treatment or received oral antiplatelet treatment (acetylsalicylic acid 80 mg once daily; carbasalate calcium 100 mg once daily; clopidogrel 75 mg once daily; or a combination of dipyridamole 200 mg twice daily with either acetylsalicylic acid 80 mg once daily or carbasalate calcium 100 mg once daily) at the discretion of the treating physician. The allocated treatment was started between days 7 and 90 after the index intracerebral haemorrhage, at the discretion of the treating physician in the absence of evidence on the optimal timing of resumption of antithrombotic therapy after intracerebral haemorrhage.[15,17]

Imaging characteristics of the qualifying intracerebral haemorrhage were centrally read by one of two trained assessors (CJMK or HBvdW) who were masked to treatment allocation, and were intracerebral haemorrhage location, presence of intraventricular haemorrhage, subdural or subarachnoid extension, small vessel disease score, and Edinburgh CT criteria for cerebral amyloid angiopathy.[20,21] Intracerebral haemorrhage volume was measured using a previously published deep-learning algorithm[22] combined with manual check and adjustment. Participants were scheduled for follow-up at 1 month (±7 days), 6 months (±14 days), and 12 months (±28 days), and subsequently every 12 months (±28 days) after inclusion until the end of the study. As per a protocol amendment on Sept 1, 2020, the minimum duration of follow-up was reduced from 12 months to 6 months (appendix 2 p 81). At follow-up, participants were questioned on the occurrence of outcome events, other adverse events, and adherence to the allocated treatment by the local investigators in the outpatient clinic. Participants could start or discontinue antithrombotic therapy if clinically indicated by events during follow-up, regardless of treatment allocation. We recorded blood pressure and mRS score at each visit. In participants allocated to apixaban, we assessed renal function twice a year. Qualified monitors not involved in the trial design or

For the **APACHE-AF trial website** see https://www.apache-af.nl

See **Online** for appendix 2

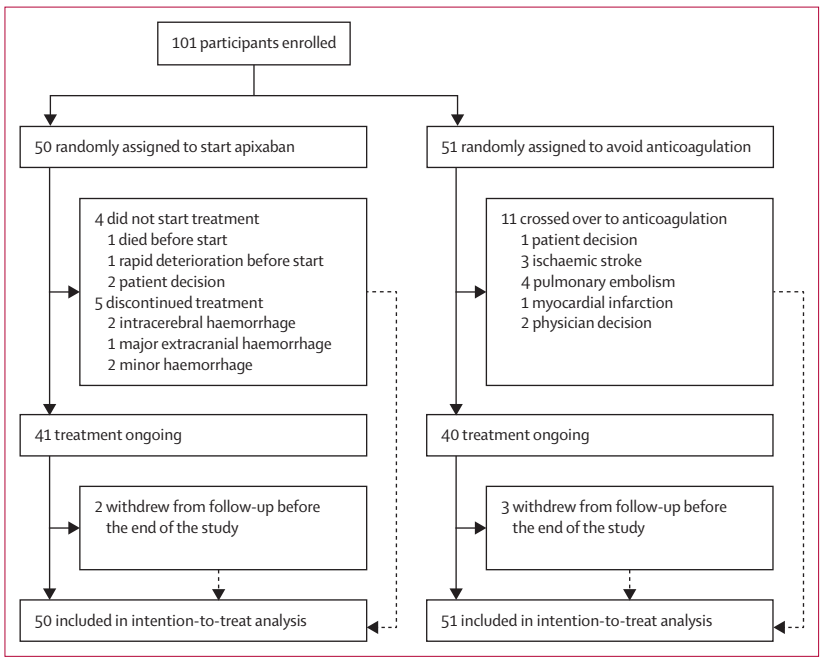

Figure 1: **Trial profile**

execution conducted on-site monitoring visits to ensure data quality.

All potential outcomes were assessed by an adjudication committee masked to patient identity, treatment allocation, and drugs used; the committee was composed of two neurologists with neurovascular expertise (LJK and GJER) and a cardiologist (H M Nathoe). Adjudication was done independently by two individuals using all available source documentation from follow-up visits, including clinical records and imaging in routine clinical care. In the case of disagreement between adjudicators, a consensus meeting was held. Additionally, investigators reported serious adverse events (other than prespecified outcome events), adverse events, and suspected unexpected serious adverse drug reactions to the trial coordinating centre. The trial coordinating centre reported serious adverse events and potential unexpected adverse drug reactions to the medical research ethics committee and the sponsor.

Outcomes

The primary outcome was non-fatal stroke (ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage) or vascular death, whichever came first, during follow-up (appendix 2 p 4). Secondary outcomes were intracerebral haemorrhage, subarachnoid haemorrhage, traumatic intracranial haemorrhage, major extracranial haemorrhage, clinically relevant non-major bleeding, ischaemic stroke, unclassified stroke, any stroke, myocardial infarction, pulmonary embolism, systemic embolism, vascular death, and all-cause death. Definitions of all outcomes are in the appendix 2 (pp 4–5).

Statistical analysis

We aimed to recruit 100 participants and follow them up for at least 100 patient-years per treatment group. Ten primary outcome events per 100 patient-years of follow-up would then yield a 95% CI of 4·9–17·6. At 50, 100, and 150 patient-years of follow-up or at least annually, prespecified interim analyses were performed by the trial epidemiologist (AA) and evaluated by an independent data safety monitoring board to assess trial conduct, safety, and efficacy, and to make recommendations to the trial steering committee. The data safety monitoring board compared treatment groups using a Poisson's test (conditional test) with two-sided testing of the primary outcome, for which a boundary of $p<0·01$ was used for any recommendations to end the trial. Without reference to the data, the chief investigators (CJMK and HBvdW) prepared the statistical analysis plan, which was approved by the steering committee (on Nov 12, 2020), before database lock.

We did not perform imputation for missing data. Baseline patient and imaging characteristics were summarised per treatment group. We also described adherence to treatment (including the reasons for change) and mean blood pressure at 6 months and 12 months and at each subsequent annual follow-up by treatment group.

We quantified the annual event rate with 95% CI for occurrence of the primary outcome in each of the two treatment groups, in the intention-to-treat (ITT) population, compromising all participants who had been randomly assigned, irrespective of whether they used their allocated treatment.

We estimated the survival function by Kaplan-Meier survival analysis of time from randomisation to first outcome event during follow-up by treatment group. Follow-up was censored at death (unrelated to an outcome event), last available follow-up, or time of withdrawal from the study. Proportionality of hazards was assessed graphically. We compared the time to the primary outcome in the two treatment groups by a Cox proportional hazards regression model, adjusting for one aggregated risk variable, expressed as hazard ratio (HR) with 95% CI. The aggregated risk variable was constructed as the sum of the coefficients of the two minimisation variables (age [continuous variable] and intracerebral haemorrhage location [lobar *vs* non-lobar]), and any of the baseline characteristics if they changed the relative risk of the primary outcome between treatment groups by more than 10% in the Poisson regression model.

For secondary outcomes with events in both groups, we present the absolute number and percentage for each treatment group, and the crude and adjusted HRs and corresponding 95% CIs. We assessed the effect of treatment allocation on functional outcome by means of the mRS score at 6, 12, and 24 months, using ordinal logistic regression yielding common odds ratios with corresponding 95% CIs. We also assessed the following prespecified composite outcomes: recurrent intracerebral

haemorrhage, all major haemorrhagic events (all intracranial haemorrhage and major extracranial haemorrhage), all major occlusive events (ischaemic stroke, myocardial infarction, or pulmonary or systemic embolism), all major haemorrhagic or occlusive vascular events (all major haemorrhagic or occlusive events or vascular death), and all major vascular events as defined by the Antithrombotic Trialists' Collaboration (myocardial infarction, stroke, or vascular death).[23]

In a secondary analysis, we analysed the population as treated, by calculating the annual event rate with 95% CI for occurrence of the primary outcome for the time participants were on anticogulation (apixaban or other anticoagulant) and the time participants were not on anticoagulation. Furthermore, we calculated the crude and adjusted HRs and corresponding 95% CIs for the primary and secondary outcomes using Cox regression analyses with time varying covariates, comparing hazard for the outcome during the time on anticoagulation treatment and off anticoagulation treatment (irrespective of treatment allocation).

We did prespecified exploratory subgroup analyses of the effect of treatment allocation on the primary outcome, based on location of index intracerebral haemorrhage (lobar *vs* non-lobar), age (<75 years *vs* ≥75 years), sex (male *vs* female), time since intracerebral haemorrhage onset (<7 weeks *vs* ≥7 weeks), CHA_2DS_2-VASc score (less than median *vs* median or greater), the intention to start antiplatelet treatment versus no antiplatelet treatment in the comparator group, and CT small vessel disease score (0 *vs* 1–3). Analyses were done by including an interaction term between treatment group and relevant covariate in the Cox proportional hazards regression model. We summarised serious adverse events other than outcome events grouped by body system and tabulated by treatment group.

Statistical analyses were done with R, version 3.6.2, with packages coxme, epiR, epitools, forestplot, gmodels, ggplot2, plyr, rms, rmeta, survival, and MASS. The APACHE-AF trial is registered with ClinicalTrials.gov (NCT02565693) and the Dutch trial registry (new ID NL4395; old ID NTR4526).

Role of the funding source

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

Results

We enrolled 101 participants between Jan 15, 2015, and July 6, 2020 (figure 1). 50 participants were randomly assigned to start apixaban and 51 patients to avoid anticoagulation. Of the 51 participants assigned to the avoid group, 26 (51%) received antiplatelet medication. All 101 participants were included in the intention-to-treat analysis and none were lost to follow-up. Median age of participants was 78 years (IQR 73–83); 55 (54%) were men and 46 (46%) were women, and 100 (99%) were White and one (1%) was Black (table 1). 95 (94%) participants had a history of hypertension, 24 (24%) had a previous ischaemic stroke, and seven (7%) had an intracerebral haemorrhage before the qualifying one. The median CHA_2DS_2-VASc

	Apixaban group (n=50)	Avoid anticoagulation group (n=51)
Sex		
Men	27 (54%)	28 (55%)
Women	23 (46%)	23 (45%)
Age		
Median, years	77 (74–83)	79 (72–83)
≥75 years	36 (72%)	30 (59%)
Ethnicity		
White	49 (98%)	51 (100%)
Black	1 (2%)	0
CHA_2DS_2-VASc score	4 (3–5)	4 (3–5)
Cardiovascular risk factors		
Previous ischaemic stroke	10 (20%)	14 (27%)
Previous intracerebral haemorrhage	4 (8%)	3 (6%)
Previous myocardial infarction	8 (16%)	4 (8%)
Hypertension	45 (90%)	50 (98%)
Diabetes	9 (18%)	7 (14%)
Oral anticoagulant at time of intracerebral haemorrhage		
Vitamin K antagonist	33 (66%)	37 (73%)
Non-vitamin K oral antagonist	17 (34%)	14 (27%)
Intracerebral haemorrhage characteristics		
Volume, mL	5·7 (1·8–11·9)	6·6 (2·3–14·3)
Location		
Lobar	14 (28%)	14 (27%)
Deep	27 (54%)	25 (49%)
Brainstem	2 (4%)	1 (2%)
Cerebellum	7 (14%)	10 (20%)
Intraventricular only	0	1 (2%)
Small vessel disease CT score >0	21 (42%)	18 (35%)
Edinburgh CT criteria for cerebral amyloid angiopathy*	3 (6%)	6 (12%)
Time from intracerebral haemorrhage to randomisation, days	45 (22–70)	46 (20–76)
Blood pressure at randomisation†, mm Hg		
Systolic	142 (130–159)	140 (129–157)
Diastolic	80 (74–88)	82 (71–90)
Modified Rankin scale at randomisation	2 (1–3)	3 (1–4)
IQCODE‡	3·2 (3·0–3·4)	3·3 (3·1–3·5)

Data are n (%) or median (IQR). IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. *These criteria might underestimate the prevalence of cerebral amyloid angiopathy.[24] †Available for 93 of 101 participants. ‡Available for 75 of 101 participants.

Table 1: **Baseline characteristics**

	Apixaban group (n=50)		Avoid anticoagulation group (n=51)	
	Patients with first event	All events	Patients with first event	All events
Primary outcome				
Non-fatal stroke or vascular death	13 (26%)	14	12 (24%)	12
Secondary outcomes				
Major haemorrhagic events	6 (12%)	6	3 (6%)	3
Intracerebral haemorrhage	4 (8%)	4	1 (2%)*	1
Subarachnoid haemorrhage	0	0	0	0
Traumatic intracranial haemorrhage	0	0	0	0
Major extracranial haemorrhage	2 (4%)	2	2 (4%)	2
Clinically relevant non-major bleeding	1 (2%)	1	0	0
Major occlusive events	6 (12%)	7	11 (22%)†	12
Ischaemic stroke	6 (12%)	7	6 (12%)	6
Myocardial infarction	0	0	2 (4%)	2
Pulmonary embolism‡	0	0	4 (8%)	4
Systemic embolism	0	0	0	0
Unclassified stroke	0	0	0	0
Any stroke	10 (20%)	11	7 (14%)	7
Vascular death	5 (10%)	5	7 (14%)	7
All-cause death	9 (18%)	9	11 (22%)	11

*Event occurred while on treatment with rivaroxaban that had been prescribed because of pulmonary embolism at an earlier timepoint during follow-up. †One patient had a pulmonary embolism and then an ischaemic stroke later. ‡Not prespecified as a secondary outcome.

Table 2: **Primary and secondary outcome events**

score was 4 (IQR 3–5). 28 (28%) participants had lobar intracerebral haemorrhage. Participants were randomly assigned a median of 46 days (IQR 21–74) after intracerebral haemorrhage onset. Participants' characteristics were well balanced for prognostic factors and potential confounders.

Median follow-up at database lock on April 20, 2021, was 1·9 years (IQR 1·0–3·1), with a total of 222 person-years. Five participants (two assigned to apixaban and three to avoid anticoagulation) decided to discontinue participation before the end of the study at a median of 1·7 years (IQR 0·5–3·3) after randomisation. In the apixaban group, four patients did not start treatment and five discontinued treatment; in the avoid group, 11 crossed over to receive anticoagulation. Median systolic blood pressure during different follow-up timepoints was between 123 mm Hg (at 60 months) and 140 mm Hg (at 6 and 24 months) in participants assigned to apixaban and between 130 mm Hg (at 24 months) and 146 mm Hg (at 36 months) in those assigned to anticoagulation (appendix 2 p 21).

The primary outcome occurred in 13 (26%) of 50 participants allocated to apixaban (annual event rate 12·6% [95% CI 6·7–21·5]) and in 12 (24%) of 51 allocated to avoid anticoagulation (11·9% [95% CI 6·2–20·8]; adjusted HR 1·05 [95% CI 0·48–2·31], p=0·90; tables 2, 3, figure 2).

With regard to the secondary outcomes related to haemorrhage, four (8%) of 50 participants (two with lobar and two with non-lobar index intracerebral haemorrhage) assigned to apixaban had an intracerebral haemorrhage (fatal in one) compared with one (2%) of 51 participants (non-lobar index intracerebral haemorrhage) allocated to avoid anticoagulation (tables 2, 3). All four participants with intracerebral haemorrhage who had been assigned to apixaban were receiving apixaban at the time the intracerebral haemorrhage occurred. The participant assigned to avoid anticoagulation had recurrent intracerebral haemorrhage while on treatment with rivaroxaban that had been prescribed because of pulmonary embolism during follow-up (appendix 2 p 23). Six (12%) participants allocated to apixaban compared with three (6%) participants assigned to avoid anticoagulation had a major haemorrhage, including intracerebral haemorrhage (tables 2, 3).

With regard to the secondary outcomes related to occlusive events, six (12%) participants in each treatment group had ischaemic stroke (tables 2, 3). Of the six participants assigned to apixaban who had ischaemic stroke (fatal in two), three used apixaban whereas three others were not taking apixaban at the time of the ischaemic stroke (stopped after intracerebral haemorrhage in one, participant decision in two). Of the six participants who were assigned to avoid anticoagulation and had an ischaemic stroke (fatal in one), three were on antiplatelet medication, two had no antithrombotic medication, and one patient had crossed over to apixaban because of pulmonary embolism. Six (12%) participants assigned to apixaban compared with 11 (22%) participants allocated to avoid anticoagulation had a major occlusive event (tables 2, 3).

14 (28%) of 50 participants in the apixaban group had a major vascular event according to the protocol compared with 16 (31%) of 51 participants in the avoid anticoagulation group (tables 2, 3). For the composite of a major vascular event according to the definition of the Antithrombotic Trialists' Collaboration, the number of events in both groups were similar (tables 2, 3).

In the on-treatment analysis for the primary outcome, 12 participants had non-fatal stroke or vascular death during 106 person-years of follow-up on anticoagulation (annual event rate 11·3 [95% CI 5·8–19·7]) compared with 13 participants who were not on anticoagulation during 98 person-years of follow-up (annual incidence 13·3 [95% CI 7·1–22·7]; adjusted HR 0·87 [95% CI 0·39–1·94], p=0·74; appendix 2 pp 25–27). In exploratory subgroup analyses for the primary outcome, we found no evidence of heterogeneity (appendix 2 p 19). We also found no differences in the distribution of the mRS score during follow-up (appendix 2 pp 17–18). Serious adverse events that were not outcome events occurred in 29 (58%) of 50 participants assigned to apixaban and 29 (57%) of 51 assigned to avoid anticoagulation (appendix 2 p 28).

	Apixaban group (n=50)	Avoid anticoagulation group (n=51)	Unadjusted analysis		Adjusted analysis	
			HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Primary outcome						
Non-fatal stroke or vascular death	13 (26%)	12 (24%)	1·07 (0·49–2·34)	0·87	1·05 (0·48–2·31)	0·90
Secondary outcomes*						
Intracerebral haemorrhage	4 (8%)	1 (2%)	4·12 (0·46–36·94)	0·21	4·08 (0·45–36·91)	0·21
All major haemorrhagic events	6 (12%)	3 (6%)	2·14 (0·53–8·57)	0·29	2·11 (0·52–8·51)	0·29
Ischaemic stroke	6 (12%)	6 (12%)	0·97 (0·31–3·00)	0·96	0·96 (0·31–2·97)	0·94
All major occlusive events	6 (12%)	11 (22%)	0·46 (0·17–1·25)	0·13	0·46 (0·17–1·25)	0·13
All major vascular events according to the protocol†	14 (28%)‡	16 (31%)§	0·81 (0·39–1·66)	0·56	0·80 (0·39–1·64)	0·54
All major vascular events (myocardial infarction, stroke, or vascular death)¶	13 (26%)	13 (25%)	0·94 (0·43–2·02)	0·87	0·93 (0·43–2·00)	0·85

Adjusted analyses included an aggregated risk variable consisting of the sum of the coefficients of the two minimisation variables and no other baseline characteristics. HR=hazard ratio. *Intracerebral haemorrhage and ischaemic stroke are analysed separately, whereas other secondary outcomes are analysed as composites of major haemorrhagic events, major occlusive events, or all major vascular events. †All major haemorrhagic events, all major occlusive events, or vascular death, whichever occurred first. ‡One participant had a major extracranial haemorrhage and then an ischaemic stroke. §Three participants had pulmonary embolism followed by another major vascular event (intracerebral haemorrhage in one participant, major extracranial haemorrhage in one, and ischaemic stroke in another). ¶As defined by the Antithrombotic Trialists' Collaboration.

Table 3: **HRs for first occurrence of primary and secondary outcome events**

Discussion

This randomised controlled trial of patients with atrial fibrillation and intracerebral haemorrhage while on anticoagulation treatment shows a high annual risk of non-fatal stroke or vascular death of around 12%, irrespective of allocation to apixaban or to no anticoagulation.

These results provide estimates of the risk of non-fatal stroke or vascular death for patients treated with apixaban and for those in whom anticoagulation is avoided. In previous estimates from observational studies, patients who restarted anticoagulation after intracerebral haemorrhage were most often treated with a vitamin K antagonist and not with a DOAC.[5,6] In a pooled analysis of two population-based studies, the rate of non-fatal stroke, myocardial infarction, or vascular death in 147 intracerebral haemorrhage survivors with atrial fibrillation was 15·5 per 100 person-years (95% CI 10·0–24·1), but no information was provided on whether, and if so what type of, anticoagulation was started or restarted.[7] In two systematic reviews of observational studies assessing long-term antithrombotic treatment in intracranial haemorrhage survivors, studies also included patients with subdural haematoma or subarachnoid haemorrhage[12,13] and patients with indications for anticoagulation other than atrial fibrillation.[13] Estimates for the composite outcome of non-fatal stroke or vascular death were not reported.[12,13] Our results do not support the notion that in intracerebral haemorrhage survivors with atrial fibrillation, the impact of ischaemic stroke on functional outcome is less than that of recurrent intracerebral haemorrhage, but a difference might have been missed because of small numbers of outcome events.

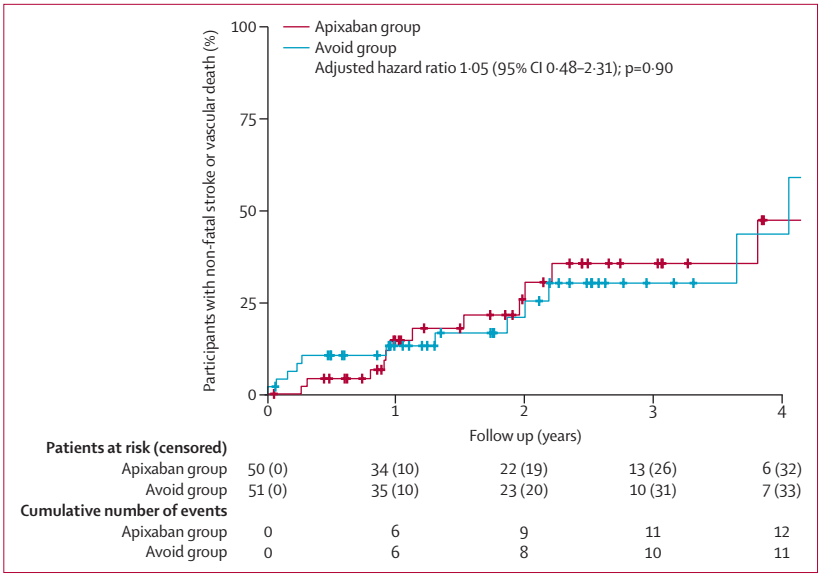

Figure 2: **Kaplan-Meier plot of the first occurrence of a non-fatal stroke or vascular death**
Numbers at risk refer to participants under follow-up at the start of each year according to treatment allocation. Cumulative events indicate the participants in follow-up with a non-fatal stroke or vascular death.

In contrast to observational studies suggesting benefit of restarting anticoagulation, we found that the risk of non-fatal stroke or vascular death was similar in participants allocated to apixaban and in those assigned to avoiding anticoagulation. This difference might be explained by confounding by indication in the observational studies (recommencing anticoagulation in those considered at low risk of haemorrhagic complications, including intracerebral haemorrhage) and the use of different outcomes (overall mortality, and ischaemic stroke and intracerebral haemorrhage separately in the observational studies,

rather than the composite of non-fatal stroke and vascular death).

Our study has several strengths. In APACHE-AF, we restricted inclusion to patients with intracerebral haemorrhage (excluding those with subdural haematoma) and the time between the intracerebral haemorrhage and randomisation was 7–90 days, which resulted in a homogeneous group of participants. Randomisation with a minimisation algorithm secured well balanced patient and imaging characteristics between treatment groups, despite the small sample size. To avoid heterogeneity in the intervention group, we chose one treatment with a relatively favourable safety profile in patients with atrial fibrillation without previous intracerebral haemorrhage, apixaban,[25] thus avoiding the use of vitamin K antagonists. The median duration of follow-up was almost 2 years and attrition bias was low because no patients were lost to follow-up. Outcome assessors were masked to treatment allocation and to the actual treatment and adjudicated all outcome events according to predefined definitions. We did analyses according to a prespecified statistical analysis plan, including on-treatment analyses and exploratory prespecified subgroup analyses.

This study also has limitations. Despite the 222 person-years of follow-up, during which 25 primary outcome events occurred, this study is small. As a result, the estimates of the annual event rates of the primary outcome still have wide 95% CIs and the assessment of the efficacy and safety of apixaban in this patient population is inconclusive. Additionally, the prospective, randomised, open-label trial with blinded endpoint assessment design might have led to reporting, observation, and detection bias, which could have led to either overestimation or underestimation of the effects of apixaban.[26] Moreover, subgroup analyses, although predefined, should be interpreted with considerable caution. We have nevertheless made these available because they can be helpful for meta-analyses and to inform future studies.[27] The small median size of the index intracerebral haemorrhage probably reflects the clinical practice of considering restarting anticoagulants in patients who have recovered well from their intracerebral haemorrhage more often than in those who have a poor outcome. Blood pressure control during follow-up could have been stricter, but probably reflects current clinical practice in this population of older adults (median age 78 years). Also, it is not certain whether stricter regulation would have resulted in a lower annual incidence of the primary outcome. Finally, all but one participant was White, thus we cannot be sure whether our findings also apply to patients from other ethnic backgrounds.

Results of seven other randomised controlled trials should further inform the decision on optimal secondary prevention after intracerebral haemorrhage in patients with atrial fibrillation. In the start or stop anticoagulants randomised trial (SoSTART),[28] after spontaneous intracranial haemorrhage, 203 patients with intracranial haemorrhage (intracerebral haemorrhage, intraventricular haemorrhage, subarachnoid haemorrhage, or subdural haematoma) were randomly assigned to any DOAC (or a vitamin K antagonist if a DOAC could not be used) or to avoid anticoagulation. In SoSTART, the index haemorrhage could have occurred under any antithrombotic treatment strategy (including no antithrombotic drug), whereas in APACHE-AF the index intracerebral haemorrhage should have occurred while using anticoagulation. Another difference with APACHE-AF is that there were no restrictions with regard to the time between the intracranial haemorrhage and randomisation. In another small feasibility and safety trial (NASPAF-ICH, NCT02998905), patients with atrial fibrillation and intracerebral haemorrhage on or off anticoagulants were randomly allocated to a DOAC or aspirin; this study was stopped early after the inclusion of 30 patients. Five other studies are ongoing: ENRICH-AF (NCT03950076), a study of edoxaban versus no anticoagulation in 1200 patients with intracranial haemorrhage and atrial fibrillation; ASPIRE (NCT03907046), which is assessing apixaban versus aspirin in 700 patients with intracerebral haemorrhage and atrial fibrillation; PRESTIGE-AF (NCT03996772), assessing DOAC versus no anticoagulation in 654 patients with intracerebral haemorrhage and atrial fibrillation; A3ICH (NCT03243175), assessing apixaban versus left atrial appendage occlusion versus no anticoagulation and no left atrial appendage occlusion in 300 patients with intracerebral haemorrhage and atrial fibrillation; and STATICH (NCT03186729),[29] assessing antithrombotic medication versus no antithrombotic medication in 500 patients with intracranial haemorrhage and an indication for antithrombotic drugs (including but not restricted to atrial fibrillation).

Based on the 13% lower hazard of non-fatal stroke or vascular death with apixaban compared with avoiding anticoagulation observed in our on-treatment analysis, a phase 3 trial would need 5744 participants in each treatment group to provide a reliable estimate of a treatment difference. If the effect of apixaban was twice as high, 1346 participants would be needed in each treatment group. Either approach would require a global effort and poses a feasibility challenge. In our view, the potential net benefit of anticoagulation in a phase 3 trial would be evident as the overall decrease in the risk of the combination of vascular events. Therefore, we would recommend the composite of non-fatal stroke or vascular death as the primary outcome in such a trial, in combination with individual thrombotic and haemorrhagic complications, functional outcome, and all-cause mortality as secondary outcomes.

The results of our study do not yet have direct implications for clinical practice. Our results neither support nor rule out the benefit of recommencing

anticoagulation as suggested by the results from observational studies. Hence, the clinical dilemma remains. However, we do think that the results of APACHE-AF might aid in the prevention of a potentially inappropriate shift in treatment towards anticoagulation on the basis of results of observational studies. Our results support the inclusion of patients with atrial fibrillation and intracerebral haemorrhage in the five ongoing trials. Additionally, an individual patient data meta-analysis has been prospectively planned and will start with the first three studies that have now been completed (APACHE-AF, SoSTART, and NASPAF-ICH).

In our study, blood pressure was not tightly controlled in all patients. This should raise awareness among clinicians of the potential of better blood pressure control for the prevention of vascular complications. A randomised controlled trial investigating the effects of more intensive blood pressure control by means of a fixed low-dose combination of antihypertensive drugs (triple pill) on top of standard care in patients with intracerebral haemorrhage is ongoing (TRIDENT, NCT02699645).

In summary, the high annual risk of non-fatal stroke or vascular death in patients with atrial fibrillation who had an anticoagulation-associated intracerebral haemorrhage, either when assigned to apixaban or when assigned to avoid anticoagulation, underscores the need for large randomised controlled trials and identification of subgroups in whom the effect of restarting anticoagulation might be either beneficial or hazardous.

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Contributors

CJMK and HBvdW (chief investigators) conceived the idea of the study and CJMK obtained funding. KMvN, CJMK, and HBvdW designed the study and wrote the protocol with input from ICvG, REGS, LJK, and GJER. FHBMS, KMvN, CJMK, and HBvdW implemented the study with support from BZ. FHBMS processed the data, with oversight from CJMK and HBvdW. FHBMS and CJMK accessed and verified the data. Statistical analysis was performed by FHBMS with the help of JWvD and oversight from AA, CJMK, and HBvdW. FHBMS and CJMK wrote the first draft of the manuscript. All authors had full access to all the data in the study, reviewed the analyses and drafts of the manuscript, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data can be made available to other researchers in a fully anonymised format 1 year after publication. Written proposals can be addressed to the corresponding author and will be assessed by APACHE-AF investigators (including the principal investigators CJMK and HBvdW) for appropriateness of use, and a data-sharing agreement in accordance with Dutch regulations will be put in place before data are shared.

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