Clinical trial results:
Apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation. A randomised phase II clinical trial.

Summary

EudraCT number	2014-000112-33
Trial protocol	NL
Global end of trial date	15 January 2021

Results information

Result version number	v1 (current)
This version publication date	05 January 2024
First version publication date	05 January 2024
Summary attachment (see zip file)	summary APACHE-AF (summary APACHE-AF.pdf)

Trial information

Trial identification

Sponsor protocol code	NL47761.041.14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02565693
WHO universal trial number (UTN)	U1111-1154-5474
Other trial identifiers	NTR: 4395

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584CX
Public contact	Dept. of Neurology & Neurosurgery, University Medical Center Utrecht, 31 0887557975, h.b.vanderworp@umcutrecht.nl
Scientific contact	Dept. of Neurology & Neurosurgery, University Medical Center Utrecht, 31 0887557975, h.b.vanderworp@umcutrecht.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2021
Global end of trial reached?	Yes
Global end of trial date	15 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To obtain reliable estimates of the rates of vascular death or non-fatal stroke in patients with atrial fibrillation and a recent anticoagulation-associated intracerebral hemorrhage who are treated with apixaban versus those who are treated with antiplatelet drugs or no antithrombotics.

Protection of trial subjects:

Participants were protected by means of careful in- and exclusion criteria, thus reducing the risk of potential harm from allocation to active treatment. Additionally, participants allocated to active treatment underwent 2-3/year venapuncture to determine EGFR and, if necessary, allow for dose adjustments of apixaban.

Background therapy:

Not applicable

Evidence for comparator:

At the time of the design of the trial, there was no data on what treatment option was best to prevent new cardiovascular events.

Actual start date of recruitment	01 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	78
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

We included 101 participants from 16 hospitals in the Netherlands between January 15, 2015 and July 6, 2020

Pre-assignment

Screening details:

We included adults with a spontaneous ICH (including isolated intraventricular haemorrhage) in the previous seven to 90 days during treatment with anticoagulation (vitamin K antagonist, NOAC, or (low-molecular-weight) heparin at therapeutic dose) because of documented (paroxysmal) non-valvular atrial fibrillation.

Period 1

Period 1 title	baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Outcome event adjudication was performed blinded to the patient’s identity, treatment allocation, and antithrombotic drug use.

Arms

Are arms mutually exclusive?	Yes
Arm title	apixaban

Arm description:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Arm type	Experimental
Investigational medicinal product name	apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Arm title	avoid anticoagulation

Arm description:

Treatment in the avoiding anticoagulation arm consisted of no antithrombotic treatment or oral antiplatelet treatment (acetylsalicylic acid 80mg once daily; carbasalate calcium 100mg once daily; clopidogrel 75mg once daily; or a combination of dipyridamole 200mg twice daily with either acetylsalicylic acid 80mg once daily or carbasalate calcium 100mg once daily), at the discretion of the treating physician.

Arm type	avoid anticoagulation

No investigational medicinal product assigned in this arm

Number of subjects in period 1	apixaban	avoid anticoagulation
Started	50	51
Completed	50	51

Period 2	
Period 2 title	follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Outcome event adjudication was performed blinded to the patient's identity, treatment allocation, and antithrombotic drug use.

Arms	
Are arms mutually exclusive?	Yes
Arm title	apixaban

Arm description:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Arm type	Experimental
Investigational medicinal product name	apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Arm title	avoid anticoagulation

Arm description:

Treatment in the avoiding anticoagulation arm consisted of no antithrombotic treatment or oral antiplatelet treatment (acetylsalicylic acid 80mg once daily; carbasalate calcium 100mg once daily; clopidogrel 75mg once daily; or a combination of dipyridamole 200mg twice daily with either acetylsalicylic acid 80mg once daily or carbasalate calcium 100mg once daily), at the discretion of the treating physician

Arm type	avoid anticoagulation

No investigational medicinal product assigned in this arm

Number of subjects in period 2	apixaban	avoid anticoagulation
Started	50	51
Completed	50	51

Baseline characteristics

Reporting groups	
Reporting group title	apixaban

Reporting group description:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Reporting group title	avoid anticoagulation

Reporting group description:

Treatment in the avoiding anticoagulation arm consisted of no antithrombotic treatment or oral antiplatelet treatment (acetylsalicylic acid 80mg once daily; carbasalate calcium 100mg once daily; clopidogrel 75mg once daily; or a combination of dipyridamole 200mg twice daily with either acetylsalicylic acid 80mg once daily or carbasalate calcium 100mg once daily), at the discretion of the treating physician.

Reporting group values	apixaban	avoid anticoagulation	Total
Number of subjects	50	51	101
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	0	3
From 65-84 years	37	41	78
85 years and over	10	10	20
Age continuous Units: years			
median	77	79	
inter-quartile range (Q1-Q3)	74 to 83	72 to 83	-
Gender categorical Units: Subjects			
Female	23	23	46
Male	27	28	55

Subject analysis sets	
Subject analysis set title	Primary analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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.

Reporting group values	Primary analysis		
Number of subjects	101		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	3		
From 65-84 years	78		
85 years and over	20		
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	apixaban

Reporting group description:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Reporting group title	avoid anticoagulation

Reporting group description:

Treatment in the avoiding anticoagulation arm consisted of no antithrombotic treatment or oral antiplatelet treatment (acetylsalicylic acid 80mg once daily; carbasalate calcium 100mg once daily; clopidogrel 75mg once daily; or a combination of dipyridamole 200mg twice daily with either acetylsalicylic acid 80mg once daily or carbasalate calcium 100mg once daily), at the discretion of the treating physician.

Reporting group title	apixaban

Reporting group description:

Patients assigned to apixaban received an oral dose of 5mg twice daily or a reduced dose of 2·5mg twice daily in case the creatine clearance was ≤30mL/min, or if two of three of the following criteria were present: age ≥80 years; body weight ≤60kg; or serum creatinine ≥133µmol/l.

Reporting group title	avoid anticoagulation

Reporting group description:

Treatment in the avoiding anticoagulation arm consisted of no antithrombotic treatment or oral antiplatelet treatment (acetylsalicylic acid 80mg once daily; carbasalate calcium 100mg once daily; clopidogrel 75mg once daily; or a combination of dipyridamole 200mg twice daily with either acetylsalicylic acid 80mg once daily or carbasalate calcium 100mg once daily), at the discretion of the treating physician

Subject analysis set title	Primary analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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.

Primary: non-fatal stroke or vascular death

End point title	non-fatal stroke or vascular death

End point description:

The primary outcome was the combination of non-fatal stroke (ischaemic stroke, ICH or subarachnoid haemorrhage) or vascular death, whichever came first, during follow-up.

End point type	Primary

End point timeframe:

Entire follow-up period

End point values	apixaban	avoid anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: numbers	13	12		

Statistical analyses

Statistical analysis title	Analysis primary outcome

Statistical analysis description:

We quantified the annual event rate with 95% CI for occurrence of the primary outcome in each of the two treatment arms, based on the intention-to-treat (ITT) population, compromising all participants who had been randomised, 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

Comparison groups	apixaban v avoid anticoagulation
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	Regression, Cox

Notes:

[1] - No formal cut-off was pre-specified. The above is the default option

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Full duration of follow-up.	
Adverse event reporting additional description: Adverse events are reported on an intention-to-treat basis.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	apixaban
Reporting group description: patients randomised to apixaban	
Reporting group title	avoid anticoagulation
Reporting group description: patients randomised to avoiding anticoagulation	

Serious adverse events	apixaban	avoid anticoagulation	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 50 (52.00%)	25 / 51 (49.02%)	
number of deaths (all causes)	9	11	
number of deaths resulting from adverse events	9	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
cancer			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular disorders			
Retinal vein thrombosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Sudden death			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Arrhythmia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac decompensation			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Withdrawal of life support			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgery			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
intracerebral hemorrhage			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
ischemic stroke			
subjects affected / exposed	7 / 50 (14.00%)	6 / 51 (11.76%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	

Nervous system disorder			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
clinically relevant non-major bleeding			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
major extracranial bleeding			
subjects affected / exposed	2 / 50 (4.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 50 (0.00%)	4 / 51 (7.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
exacerbation COPD			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 50 (10.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	5 / 50 (10.00%)	3 / 51 (5.88%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	apixaban	avoid anticoagulation	
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 50 (12.00%)	5 / 51 (9.80%)	
Nervous system disorders transient ischemic attack subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 7	2 / 51 (3.92%) 2	
Blood and lymphatic system disorders Epistaxis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3	0 / 51 (0.00%) 0	
General disorders and administration site conditions Fall subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 51 (1.96%) 1	
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all) hematuria subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0 1 / 50 (2.00%) 1	1 / 51 (1.96%) 1 2 / 51 (3.92%) 2	
Musculoskeletal and connective tissue disorders muscle hematoma subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 51 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2014	amendment 1: study sites added
16 January 2015	amendment 2: study sites added
12 February 2015	amendment 3: study sites added; exclusion criterion 'Rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair' replaced by 'Mechanical prosthetic heart valve (biological prosthetic heart valves are allowed) or rheumatic mitral valve disease;' change in monitoring plan.
08 June 2015	amendment 4: study site added; inclusion criterion 'Intracerebral haemorrhage (including isolated spontaneous intraventricular haemorrhage), documented with CT or MRI, during treatment with anticoagulation (VKA, any direct thrombin inhibitor, any factor Xa inhibitor, or (low-molecular-weight) heparin at a therapeutic dose)' replaced by 'Intracerebral haemorrhage, documented with CT or MRI, during treatment with anticoagulation (VKA, any direct thrombin inhibitor, any factor Xa inhibitor, or (low-molecular-weight) heparin at a therapeutic dose).'
23 November 2016	amendment 5: change in titles and personal details principal investigator and co-principal investigator; change in local principal investigator at study site; change in adverse event reporting section in study protocol; update of Summaries of Product Characteristics; based on the update of the Summaries of Product Characteristics: adding three potential side effects to the patient information letter; change in Chair of DSMB.
22 March 2017	amendment 6: change in exclusion criterion: the minimum CHA2DS2-Vasc-score for inclusion is reduced from 3 to 2; change in section 6.7 of study protocol (Preparation and labelling) to clarify that GMP Annex 13 is adhered to; change in study protocol and patient information letter with respect to drug accountability; change in paragraph 9.2 of study protocol (Recruitment and consent) with regard to the inclusion of incapacitated patients; change in section 10.1 (Handling and storage of data and documents) of study protocol and relevant section in patient information letter: central collection of personal data is terminated; change in local principal investigator at study site and administrative changes with regard to naming of study sites.

09 May 2018	amendment 7: study site added; extension of inclusion period; amendment of monitor plan; update of Summary of Product Characteristics; update of patient information letter based on update of Summary of Product Characteristics; deletion of modified Morisky Scale from study protocol.
01 December 2020	amendment 8: extension of inclusion period; change in name of one study site; change in local principal investigator at study site; editorial changes study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34687635