RESEARCH PROTOCOL

Full title:

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

Short title:

Apixaban versus Antiplatelet drugs or no antithrombotic drugs after Cerebral HaEmorrhage under anticoagulation for Atrial Fibrillation.

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

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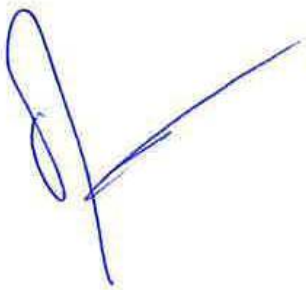
Coordinating investigators: Prof. C.J.M. Klijn, MD, PhD (Principal Investigator) H.B. van der Worp, MD, PhD (Co-principal investigator)	 	14 okt 2020 14/5/2020
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DOCUMENT HISTORY

Document version	Changes to protocol
Amendement 8, Protocol version 8.0 June 1, 2020	Change of follow-up period after last included patient to 6 months Change of local PI of Medisch Spectrum Twente Change of name of AMC to Amsterdam UMC – location AMC Minor textual changes
Amendment 7, Protocol version 7.0 January 1, 2018	Addition of Haaglanden MC Change of inclusion duration from 2.5 to 4.5 years and number of centres from 10 to 16 (paragraph 3 study design) Change of inclusion period from 30 months to 54 months (paragraph 4.4 sample size calculation). Removal of modified Morisky Scale for medication adherence (paragraph 7.3 follow-up visit)
Amendment 6, Protocol version 1.9 December 13, 2016	Changed the fourth inclusion criterion from a CHA_2DS_2-Vasc of 3 to a CHA_2DS_2-Vasc of 2 (4.2 Inclusion criteria). Clarified the fourth inclusion criterion regarding the interpretation of stroke in the CHA_2DS_2-Vasc risk prediction model (4.2 Inclusion criteria and Appendix A – CHA2DS2-VASc score). Added a statement about the how this study complies with *Good Manufacturing Practice* Annex 13 (6.7 Preparation and labelling). Changed the drug accountability procedure (6.8 Drug accountability and 7.3 Study procedures).

	Added a procedure to document if an incapacitated subject regains capacity (10.2 Recruitment and consent). Removed the paragraph that states that the coordinating investigators receive identifying information for each patient (11.1 Handling and storage of data and documents). Changed the name of the St. Elisabeth Ziekenhuis, Atrium MC and St. Lucas Andreas Ziekenhuis due to reflect the new name after mergers, changed the PI of the OLVG and Radboudumc sites.
Amendment 5, Protocol version 1.8 March 25, 2016	Changed study roles of Prof. Klijn and Dr. Van der Worp Changed the Principal Investigator of the Academisch Medisch Centrum to Dr. Coutinho. Several changes are made to implement the change of section 10, subsection 1, of the Medical Research Involving Human Subjects Act version 1 July 2012 into section 10, subsection 4, of the WMO version 1 October 2015 and the subsequently updated CCMO template research protocol. They are listed below. 8.1 Section 10 WMO event This paragraph was replaced by a new paragraph and renamed *'8.1 Temporary halt for reasons of subject safety'.* 8.2.2 Serious adverse events (SAEs) Added the sentence *An elective hospital admission will not be considered as a serious adverse event.* 11.5 End of study report Added the *sentence The sponsor will notify the METC immediately of a temporary halt of the study, including*

	the reason of such an action. Renamed the paragraph *'11.5 Temporary halt and (prematurely) end of study report'*
Amendment 4, Protocol version 1.7, May 21, 2015	Added Atrium MC as site. 4.3 Inclusion criteria Added the clarification *(including isolated spontaneous intraventricular haemorrhage)* to the first inclusion criterion.
Amendment 3 Protocol version 1.6, January 23, 2015	Added Document history 4.3 Exclusion criteria Replaced exclusion criterion *Rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair* with *Mechanical prosthetic heart valve (biological prosthetic heart valves are allowed) or rheumatic mitral valve disease.*
Amendment 2, Protocol version 1.5, December 1, 2014	Addition of Maastricht University Medical Center, Erasmus MC, Leiden University Medical Center, Radboud university medical center and St. Elisabeth Ziekenhuis as sites.
Amendment 1, Protocol version 1.4, October 13, 2014	Addition of Rijnstate Ziekenhuis, St. Lucas Andreas Ziekenhuis, Universitair Medisch Centrum Groningen, Medisch Spectrum Twente, Albert Schweitzer Ziekenhuis, Academisch Medisch Centrum, Gelre Ziekenhuizen and Amphia Ziekenhuis as sites.
First METC approval, Protocol version 1.3, August 21, 2014	

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AF	Atrial fibrillation
APD	Antiplatelet drugs
AR	Adverse Reaction
BID	Twice daily
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRF	Case report form
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
ICH	Intracerebral haemorrhage
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
OAC	Oral anticoagulants
OAC-ICH	Oral anticoagulant-associated intracerebral haemorrhage
(S)AE	(Serious) Adverse Event
SmPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

SUSAR	Suspected Unexpected Serious Adverse Reaction
TTR	Time in therapeutic range (e.g. therapeutic INR when using VKAs)
VKA	Vitamin K antagonist (e.g. acenocoumarol, phenprocoumon or warfarin)
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: There is a marked lack of evidence on the optimal prevention of ischaemic stroke and other thrombo-embolic events in patients with non-valvular atrial fibrillation (AF) and a recent intracerebral haemorrhage (ICH) during treatment with oral anticoagulation. These patients are currently treated with oral anticoagulants, antiplatelet drugs, or no antithrombotic treatment, depending on personal and institutional preferences. Randomised trials in patients with AF but without ICH have convincingly shown that vitamin K antagonists (VKAs, such as warfarin) reduce the risk of ischaemic stroke and other thrombo-embolic events, but increase the risk of bleeding as compared to no anticoagulant therapy. In the recent ARISTOTLE trial, the direct oral anticoagulant (DOAC) apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. In other trials, the other DOACs, rivaroxaban, edoxaban, and dabigatran had a similar benefit as compared with warfarin. DOACs have not been tested in patients with AF and a recent ICH. Apixaban is the only DOAC tested against aspirin in a large randomised trial, in which patients with AF who were treated with apixaban had a lower risk of stroke or systemic embolism than those treated with aspirin, whereas ICH rates were similar in both treatment groups. We hypothesize that in patients with AF who survived an anticoagulation-associated ICH, apixaban is an attractive alternative to antiplatelet drugs or no antithrombotic treatment at all in terms of a low risk of recurrent ICH, while at the same time being more effective for the prevention of ischaemic stroke.

Objective: 1) 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 haemorrhage who are treated with apixaban versus those who are treated with an antiplatelet drug or no antithrombotic drugs. 2) To compare the rates of all-cause death, stroke, ischaemic stroke, ICH, other major haemorrhage, systemic embolism, and functional outcome between patients treated with apixaban and those who are treated with an antiplatelet drug or no antithrombotic drugs.

Study design: A randomised, open, multi-center clinical trial with masked outcome assessment.

Study population: 100 adults with a history of atrial fibrillation and a recent intracerebral haemorrhage during treatment with anticoagulation in whom clinical equipoise exists on the optimal stroke prevention therapy.

Intervention: Apixaban 5 mg twice daily versus antiplatelet therapy or no antithrombotic drugs.

Primary outcome: Vascular death or non-fatal stroke during follow-up.

Time frame: We aim to include 100 patients in 5.5 years. All patients will be followed up for the duration of the study, but at least for 6 months.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The main risks associated with this study are the risk of bleeding (ICH, other major bleeding, minor bleeding) and the risk of ischaemic stroke or systemic embolism. It is currently uncertain which of the treatment strategies mentioned above is most effective and safe. The burden will consist of 3 visits in the first year, with yearly follow-up thereafter.

1. INTRODUCTION AND RATIONALE

Stroke is a major cause of death and disability and is associated with high healthcare expenditure.[1,2] About 80% of strokes are ischaemic, 15% intracerebral haemorrhage (ICH), and 5% subarachnoid haemorrhage. In the Netherlands, each year around 35,600 patients have a first stroke.[3]

Cardioembolism, most often caused by non-valvular atrial fibrillation (AF), accounts for 13 – 27%[4,5] of ischaemic strokes. The average annual risk of ischaemic stroke in patients with AF not treated with antithrombotic drugs is 4.5%.[6] The risk of ischaemic stroke can be estimated with the CHA_2DS_2-VASc score.[7] The annual thrombo-embolic event rate increases from 2.2% with a CHA_2DS_2-VASc score of 2 to 15.2% with the maximum score of 9.[8] In patients with AF and a CHA_2DS_2-VASc score ≥ 2 treatment with oral anticoagulants (OAC) is recommended.[9,10] Traditionally, vitamin K antagonists (VKA) were the drug of choice within this group. While VKA therapy deceases the risk of ischaemic stroke, it increases the risk of ICH, the most devastating complication of oral anticoagulant therapy. This complication leads to death in 42% of cases, and only 8% of patients recover without disability.[11] The risk of ICH in patients with AF treated with vitamin K antagonists is 0.3 to 3% per year, and increases with increasing age.[12–15]

In patients with AF who are unsuitable for VKA therapy because of poor compliance or allergy, or who are unwilling to receive this therapy, antiplatelet drugs (APDs, e.g. acetylsalicylic acid, clopidogrel) are recommended.[9] However, antiplatelet treatment only results in a modest reduction in the risk of ischaemic stroke[16] and increases the risk of major bleeding as compared to no antithrombotic therapy.[17]

In patients with AF who survive an anticoagulation-related ICH, a longstanding and pressing clinical dilemma is whether or not to resume treatment with oral anticoagulation to prevent ischaemic stroke and other thrombotic and embolic complications in the future.[18,19]
Randomized trials have not been performed and reliable estimates of the risk of recurrent ICH or ischaemic stroke after resumption of oral anticoagulation on the one hand or permanent discontinuation of anticoagulants on the other are lacking.[20]
In retrospective studies of small patient cohorts, the annual risk of recurrent ICH after resumption of VKAs varied between 2.5 and 20% and that of ischemic stroke between 0 and 33%. In patients in whom VKAs were discontinued permanently, the risk of ICH varied between 0 and 9% and the risk of ischaemic stroke between 10 and 48%.[21–25]

In small observational studies of patients who survived an ICH - regardless of whether this occurred during the use of an OAC - no difference was found in the risk of recurrent ICH between patients treated with acetylsalicylic acid after the initial ICH and those who used no antithrombotic drugs,[24,26–29] with an annual risk of recurrent ICH between 2.3 and 8.2%.[26,28,29] The annual risk of ischaemic stroke in these patients the risk varied between 1.3 and 9.4%.

The above-mentioned estimates for the risk of ischaemic stroke or recurrent ICH during treatment with VKA or APD are not reliable because of selection bias, the inclusion of patients with different indications for the use of antithrombotic drugs, and variation in target INRs. In addition, estimates varied widely between studies and had wide confidence intervals because of the small numbers of patients included.

The above demonstrates that there is a need for evidence-based recommendations for the prevention of stroke and other thrombo-embolic complications in patients with anticoagulation-related ICH who have survived the first few days to weeks.[30,31] Because guidelines for the treatment of patients with ICH do not provide such recommendations, patients are currently treated - based on ‘expert opinion’- with oral anticoagulation, APDs, or no antithrombotic medication at all, resulting in a marked practice variation.[24,32]

In the past few years, novel antithrombotic drugs have been introduced in clinical practice: the direct oral anticoagulants (DOACs). These drugs reduce coagulation by stoichiometric inhibition of factor Xa (rivaroxaban, apixaban and edoxaban) or factor IIa (dabigatran), resulting in a reduced thrombin generation, diminished enzymatic conversion of fibrinogen to fibrin and thus less efficient clot formation.

In the randomised Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, the oral factor Xa inhibitor apixaban at a dose of 5 mg twice daily was more effective than warfarin (target international normalized ratio, 2.0 to 3.0) in preventing stroke or systemic thromboembolism in patients with AF: hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority. Patients treated with apixaban less often had an ICH (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001) than patients treated with warfarin.[33] These beneficial effects were seen throughout different TTR ranges.[34]

Of the direct oral anticoagulants, only apixaban has been compared with acetylsalicylic acid in a randomised controlled trial in patients with AF. In the trial Apixaban Versus

Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), patients with AF who were treated with apixaban 5 mg twice daily also had a lower risk of stroke or systemic embolism than patients treated with acetylsalicylic acid at a dose of 81 to 324 mg per day (hazard ratio 0.45; 95% CI 0.32 to 0.62; P<0.001). In this trial, the rates of ICH in the two groups were similar.[35]

In phase III randomised trials comparing other DOACs with warfarin, these were non-inferior to warfarin in the prevention of stroke and systemic embolism and were associated with a reduced risk of intracranial bleeding.[36–38]

In a meta-analysis of phase III randomised trials of patients with atrial fibrillation who were randomised to receive DOACs or warfarin, the DOACs had a favourable risk-benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients.[39]

The DOACs have not been compared against each other in clinical trials. A meta-analysis using a Baysian random effects model suggested that these compounds have an equal risk reduction of ICH compared to warfarin.[40] There are no clinical trials testing the effect of a DOAC in patients with AF and a recent OAC-associated ICH.

We hypothesize that in patients with AF who survived an anticoagulation-associated ICH, treatment with apixaban may be the best long-term alternative for the prevention of recurrent stroke and systemic thrombo-embolism. To test this hypothesis, a conclusive phase III, randomised clinical trial comparing the long-term effects of apixaban with those of APDs or no antithrombotic treatment in these patients is required. Before such a trial can commence, a phase II trial is needed to provide reliable estimates of the risk of ischaemic stroke and ICH in these patients when treated with apixaban or with APDs or no antithrombotic treatment. This phase II trial is described in this protocol.

2. OBJECTIVES

2.1 Primary Objective

To obtain reliable estimates of the rates of vascular death or non-fatal stroke in patients with AF and a recent anticoagulation-associated ICH who are treated with apixaban versus those who are treated with APDs or no antithrombotic drugs.

2.2 Secondary Objective

To compare the rates of all-cause death, vascular death, stroke, ischaemic stroke, recurrent ICH, other major haemorrhage, systemic embolism, myocardial infarction, and functional outcome between patients treated with apixaban and those who are treated with APDs or no antithrombotic drugs.

3. STUDY DESIGN

APACHE-AF will be a phase II, randomised, open, multi-centre clinical trial with masked outcome assessment (PROBE design),[41] comparing apixaban as the first treatment arm with APDs or no antithrombotic treatment as the second arm in patients with AF and a recent anticoagulation-associated ICH. An adjudication committee blinded to treatment allocation will perform the adjudication of endpoints.

The choice for an open-label design was made to ensure feasibility of this phase II trial. To minimize the risk of bias associated with open-label treatment,[42,43] it will be of paramount importance to capture all potential outcome events. We will ensure strictly equal follow-up between both treatment arms and will use active surveillance to enable us to notice all potential outcomes. Furthermore, a member of the adjudication committee will review all hospitalizations during follow-up after removing information on treatment allocation.

A total of 100 patients will be included in 16 regional and academic centres in the Netherlands over a period of 5.5 years. Follow-up will continue until six months after inclusion of the last patient. The total study period is expected to be six years.

3.1 Rationale for study treatment

This protocol allows the treating physician (the neurologist attending to the patient) to decide on any of six treatment regimens in the comparator group, five (combinations of) APDs or no antithrombotic treatment. This design is based on the lack of evidence that any of the treatment options in the comparator arm has a more favorable risk/benefit ratio in this population than others. [18,19,44–46]

Allowance of variable treatment regimens enables us to include patients with and without a medical history of atherosclerotic disease, which could warrant the use of antiplatelet drugs. The choice for these treatment options in the comparator arm enables us to closely resemble current clinical practice and include as many eligible patients as possible to answer the research question.

The physician can include other indications for APDs (e.g., a history of myocardial infarction) in this decision on the treatment in the comparator arm (any of five (combinations of) APDs or no antithrombotic treatment.

Treatment with any of the drugs in this study can commence anywhere between 7 and 90 days after the ICH, at the discretion of the treating physician. There are reports that show VKAs can be resumed after 3 days,[47] while others recommend resumption of antithrombotic drugs anywhere between 70 and 210 days.[23] European guidelines recommend resumption

between 10 and 14 days. [30] In the absence of evidence on the optimal timing of the resumption of antithrombotic drugs after ICH, we chose this interval that reflects clinical practice.

4. STUDY POPULATION

4.1 Population (base)

The study population will consist of 100 patients with AF who recently had an ICH while using anticoagulation, in whom there is clinical equipoise regarding the optimal medical treatment for the prevention of stroke.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- 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).
- The haemorrhage has occurred between 7 and 90 days before randomization.
- Diagnosis of (paroxysmal) non-valvular AF, documented on electrocardiography.
- A CHA_2DS_2VASc score[7] ≥ 2. The item Stroke in the Stroke/TIA/TE item refers to ischaemic stroke, not haemorrhagic stroke.
- Score on the modified Rankin scale (mRS)[48] ≤4.
- Equipoise regarding the optimal medical treatment for the prevention of stroke. The clinical equipoise should be self-reported by the attending neurologist after reviewing all relevant information available for the individual patient.
- Age ≥ 18 years.
- Written informed consent by the patient or by a legal representative

4.3 Exclusion criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

- Conditions other than atrial fibrillation for which the patient requires long-term anticoagulation
- A different clinical indication for the use of an APD even if treated with apixaban, such as clopidogrel for recent coronary stenting.
- Mechanical prosthetic heart valve (biological prosthetic heart valves are allowed) or rheumatic mitral valve disease.
- Serious bleeding event (see 7.1.4) in the previous 6 months, except for intracerebral haemorrhage.

- High risk of bleeding (e.g., active peptic ulcer disease, a platelet count of <100,000.mL^{-1} or haemoglobin level of <6.2 $mMol.L^{-1}$, ischaemic stroke in the previous 7 days (patients are eligible thereafter), documented haemorrhagic tendencies, or blood dyscrasias).
- Current alcohol or drug abuse.
- Life expectancy of less than 1 year.
- Severe renal insufficiency (a serum creatinine level of more than 221 µmol per liter or a calculated creatinine clearance of <15 ml per minute).
- Alanine aminotransferase or aspartate aminotransferase level greater than 2 times the upper limit of the normal range or a total bilirubin more than 1.5 times the upper limit of the normal range, unless a benign causative factor (e.g. Gilbert's syndrome) is known or identified.
- Allergy to apixaban.
- Use of strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors (e.g. systemic azole-antimycotics as ketoconazole or HIV protease inhibitors such as ritonavir).
- Pregnancy or breastfeeding.
- Women of childbearing potential: any woman who has begun menstruation and is not postmenopausal or otherwise permanently unable to conceive. A postmenopausal woman is defined as a woman who is over the age of 45 and has not had a menstrual period for at least 12 months.

4.4 Sample size calculation

For the population under study, there are no reliable estimates of the occurrence of the primary outcome measure for each of the tested treatments, and the main aim of this study is therefore to obtain such estimates, to inform the design of a phase III clinical trial. Inclusion of a total of 50 patients in each of the treatment arms during the first 66 months of the study and six months of follow-up after the last inclusion will result in at least 100 patient-years of follow-up in each treatment arm. Ten primary outcome events in 100 patient-years of follow up will yield a 95% confidence interval (CI) of 4.9 to 17.6. This estimate will not only be more reliable because selection bias will not play a major role in this phase II trial, but also be more precise in comparison with the previous retrospective cohort studies.

5. TREATMENT OF SUBJECTS

5.1 Investigational product

Patients will be randomised between:

- apixaban 5 mg orally twice daily
- treatment with one or two oral APDs (ATC group B01AC[49]; acetylsalicylic acid, carbasalate calcium, clopidogrel, or dipyridamole) or no antithrombotic treatment at all, at the discretion of the treating physician.

Patients will be treated for the duration of the study, according to the respective marketing authorisations, professional guidelines, and in case of apixaban, following the Dutch Guideline on the Introduction of New Oral Antiacoagulants.[50] If during the course of their participation in this study the treating physician feels that a particular antithrombotic drug is clearly indicated or contra-indicated, the choice of the antithrombotic drug may be changed at his/her discretion.

5.2 Use of co-intervention

Patients in both treatment groups will be treated according to the relevant guidelines for the prevention of stroke or systemic embolism, except for the choice of the antithrombotic treatment, for which they will be randomised as part of the proposed study.

Patients in the apixaban arm should consult their physician if interacting medication is considered. The main compounds with the risk for interaction are inducers of CYP3A4 and P-gp.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal products

Apixaban (Eliquis®) 2.5 mg or 5 mg tablets. Apixaban is an oral, reversible, direct and selective active site inhibitor of factor Xa. Apixaban inhibits free and clot-bound factor Xa and prothrombinase activity. By inhibiting factor Xa, resulting in a reduced thrombin generation, diminished enzymatic conversion of fibrinogen to fibrin and thus less efficient clot formation.

Patients in the comparator arm can be treated with APDs or with no antithrombotic medication at all. Other indications, besides AF, can influence the clinical decision.

The following treatment regimens are allowed in the comparator arm:

- No antitrombotic treatment
- Acetylsalicylic acid 80 mg once daily
- Carbasalate calcium 100 mg once daily
- Clopidogrel 75 mg once daily
- Acetylsalicylic acid 80 mg once daily and dipyridamole 200 mg twice daily
- Carbasalate calcium 100 mg once daily and dipyridamole 200 mg twice daily

We do not specify a specific version or marketing authorisation holder of the drug. An Investigational Medicinal Product Dossier (IMPD) - consisting of a Summary of Product Characteristics (SmPC) for a random generic version of the APD - is filed under section D2.

APDs interfere with a number of platelet functions, including aggregation, release of granule contents, and platelet-mediated vascular constriction. They can be classified according to their mechanism of action:

COX-inhibitors (acetylsalicylic acid, carbasalate calcium) inhibit thrombocyte aggregation by irreversibly inhibiting platelet cyclooxygenase (COX)-1, an enzyme in the synthesis of thromboxane A_2.

The $P2Y_{12}$ receptor blocker clopidogrel blocks the binding of adenosine diphosphate (ADP) to a platelet receptor $P2Y_{12}$, thereby inhibiting activation of the glycoprotein IIb/IIIa complex and platelet aggregation.

Dipyridamole increases the intracellular cyclic adenosine monophosphate concentration by inhibiting phosphodiesterase and blocking the reuptake of adenosine, leading to decreased platelet activation and aggregation.

The dose of any APD is at the discretion of the treating physician and is not set out in the protocol. However, the dose should be consistent with recommendations in the relevant SmPC.

6.2 Summary of findings from non-clinical studies

Apixaban: we refer to the summary of product characteristics of apixaban, filed under section D2, page 32.

Clopidogrel: we refer to the summary of product characteristics of clopidogrel, filed under section D2, page 15.

Acetylsalicylic acid, carbasalate calcium, dipyridamole: there are no pre-clinical data of relevance.

6.3 Summary of findings from clinical studies

Apixaban: we refer to the summary of product characteristics of apixaban, filed under section D2, pages 28-31 and to the summary of the findings from clinical studies for apixaban, also under section D2.

APDs: the use of APDs in the prevention of ischaemic stroke has been established for decades.

6.4 Summary of known and potential risks and benefits

We refer to the to the structured risk analysis in chapter 12.

6.5 Description and justification of route of administration and dosage

Apixaban (Eliquis®) 2.5 or 5 mg film-coated tablets, Bristol-Myers Squibb / Pfizer EEIG, for oral intake.

Apixaban is available in an oral formulation only. The dose used in the large phase III clinical trials[33,35] was 5 mg BID, or 2.5 BID if a patient had two of the three following characteristics:

age ≥ 80 years, body weight ≤ 60 kg or serum creatinine ≥ 133 µmol. We will use the dose reduction advise recommended in the SmPC (see chapter 6.6).

The dose of 5 mg BID was based on phase II studies, where 5 mg BID proved superior to 2.5 mg BID, without increasing the risk of bleeding complications.[51]

Only oral formulations of APDs can be used in this trial. Their dosage will be decided by the treating physician but will be consistent with recommendations in the relevant SmPC.

6.6 Dosages, dosage modifications and method of administration

Apixaban: oral, 5 mg twice daily. If two of the three following criteria are met, the dose will be reduced to 2.5 mg twice daily:

- Age ≥ 80 years
- Body weight ≤ 60 kg
- Serum creatinine ≥ 133 µmol.

Additionally, if the creatinin clearance is below 30 ml per minute, the dose will be reduced to 2.5 mg twice daily.

6.7 Preparation and labelling

Preparation and labelling for both apixaban and the APDs in the comparator arm will be performed by the pharmacy of the patient. These drugs will be prescribed, dispensed and used in the same way as in routine clinical practise, according to (among other regulations) their marketing authorisations. This complies with Good Manufactoring Practise Annex 13 as detailed in the document ‘verklaring geen activiteiten KGO’. All patients receive a patient card as described in 7.3 which contains additional information required in Annex 13.

6.8 Drug accountability

IMPs will be prescribed by the investigator. They will be stored and dispensed by the pharmacy of the patient, pursuant to the SmPC. Patients are requested to bring the empty packaging of the study drug(s) to each follow up visit. The amount of used IMPs will be recorded, as well as the batch number and expiry date.

As no IMPs will be delivered to investigational and/or Sponsor sites, no records op product delivery, storage, return, disposal, and/or dispensation will be kept.

7. METHODS

7.1 Study parameters and endpoints

7.1.1 Primary outcome

The combination of vascular death or non-fatal stroke (cerebral infarction, intracerebral haemorrhage, or subarachnoid haemorrhage) during follow-up.

7.1.2 Secondary outcomes

- Vascular death.
- Death from any cause.
- All stroke.
- Ischaemic stroke.
- Intracerebral haemorrhage.
- Other major extracranial haemorrhage
- Any intracranial haemorrhage other than ICH.
- Systemic embolism.
- Myocardial infarction.
- Functional outcome as assessed with the score on the modified Rankin Scale at 6 and 12 months; thereafter annually and at the end of the study.

7.1.3 Other study parameters

Baseline

- Date, location, and volume of the ICH (see 7.1.5), assessed on CT or MRI.
- Blood pressure.
- Antithrombotic medication and international normalized ratio (INR) at the time of the ICH.
- Cardiovascular risk factors.
- Previous cardiovascular events, including ischaemic stroke and TIA.
- Neurological examination (score on the National Institutes of Health Stroke Scale (NIHSS).[52]
- Score on the modified Rankin Scale.
- Concurrent medication.
- Screening for cognitive decline prior to index ICH using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[53]
- Blood levels of haemoglobin, liver enzymes, and creatinine, and calculated. glomerular filtration rate, assessed as part of routine clinical care.

- CHA_2DS_2VASc score (see appendix A): a risk stratification score for the risk of thrombo-embolic events in patients with AF.
- HAS-BLED score (see appendix B): a risk stratification score for the risk of major bleeding during treatment with VKA in patients with AF.

Follow-up (at 1, 6 and 12 months, thereafter every 12 months)

- Blood pressure.
- Score on the NIHSS.
- Compliance to allocated treatment.
- Concurrent medication.
- Any SAE (see chapter 8.2.2) or other outcome event.

7.1.4 Definitions of outcomes

Ischaemic stroke

Clinical evidence of the sudden onset of an new neurological deficit, or an increase in an existing deficit, persisting for more than 24 hours, without evidence of a intracerebral haemorrhage on a CT or MRI scan or at post-mortem investigation.

Intracerebral haemorrhage

Clinical evidence of the sudden onset of a new neurological deficit, or an increase in an existing deficit, persisting for more than 24 hours, with a corresponding intracerebral haemorrhage on a CT or MR scan or at post-mortem investigation.

Unclassified stroke

Clinical evidence of the sudden onset of a new neurological deficit, or an increase in an existing deficit, persisting for more than 24 hours, without imaging or post-mortem investigations performed.

Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) demonstrated by CT, lumbar puncture, or at post-mortem investigation.

Myocardial infarction

Myocardial infarction will be considered to have occurred when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI[54]:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin] with at least one value above the 99th percentile upper reference limit and with at least one of the following:
    - Symptoms of ischemia.
    - New or presumed new significant ST-segment–T wave changes or new left bundle branch block.
    - Development of pathological Q waves in the ECG.
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
    - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Vascular death

Death from cerebral infarction; intracerebral, subarachnoid, epidural, or subdural haemorrhage; unclassified stroke; myocardial infarction; extracranial haemorrhage; or systemic embolism. Death should have been unlikely without the events mentioned above. Other events classifying as vascular death: fatal arterial or gastric bleeding, terminal heart failure, fatal pulmonary embolism, and sudden death, defined as death within one hour after onset of symptoms.

Major extracranial haemorrhage

Major extracranial bleeding will be defined using the ISTH criteria.[55]

1) Fatal bleeding, and/or

2) Symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or

3) Bleeding causing a fall in haemoglobin level of 1.24 mmol L^{-1} or more, or leading to transfusion of two or more units of whole blood or red cells.

Clinically relevant non-major bleeding

Clinically relevant non-major bleeding will be defined as acute clinically overt bleeding that does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least one of the following criteria:[51]

- Hospital admission for bleeding
- Physician-guided medical or surgical treatment for bleeding
- Change in antithrombotic (anticoagulant or antiplatelet) therapy.

Intracranial haemorrhage

Intracerebral haemorrhage (see above), subarachnoid haemorrhage (see above), subdural haemorrhage: evidence of a subdural haematoma on a CT or MRI scan or at post-mortem investigations; epidural hematoma: evidence of an epidural haematoma on a CT or MRI scan or at post-mortem investigations.

Systemic embolism

The diagnosis of systemic embolism requires a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries) supported by evidence of embolism from surgical specimens, post-mortem investigations, angiography, vascular imaging, or other objective testing.

7.1.5 Definitions of other study parameters

Haematoma size

Haematoma volumes will be measured using computer-assisted image segmentation.

Cardiovascular risk factors

- Ethnicity.
- Family history of vascular disease (ischaemic stroke, ICH, myocardial infarction, peripheral artery disease, [familial] amyloid angiopathy).
- Intoxications: smoking, alcohol use, drug use (cannabis, MDMA [XTC], GHB, amphetamines, cocaine, opiates).

Medical history

History of ischaemic stroke, transient ischaemic attack, ICH, subarachnoid haemorrhage, hypertension, hyperlipidaemia, diabetes mellitus, malignancy, myocardial infarction, heart

failure, systemic emboli, renal disease, liver disease, major bleeding (see 7.1.4), or peripheral artery disease.

7.2 Treatment allocation and blinding

Allocation to treatment groups will be based on proportional minimisation through a web-based allocation service hosted at or on behalf of the UMC Utrecht. Treatment allocation will be stratified by the choice of treatment in the comparator arm (antiplatelet drug vs. no antiplatelet drug) and will use a minimization algorithm for age (≤ 75 years vs. > 75 years) and location of the haemorrhage (lobar vs. non-lobar). This treatment allocation ensures that both treatment groups will be comparable with regard to the intended treatment in the comparator arm

Treatment allocation will be open but outcomes will be assessed by a blinded adjudication committee.

7.3 Study procedures

Imaging

Imaging will be performed as part of routine clinical care and at the discretion of the treating physician and radiologist, and is therefore not a study procedure. Confirmation of the index ICH with at least one CT or MRI scan is an inclusion criterion. Patients will consent to the retrieval of all imaging data concerning the ICH and subsequent imaging for any possible outcome event from the participating sites for analysis and adjudication at the coordinating centre.

Venepuncture

Venepunctures will only be performed as part of routine care and are not considered to be study procedures. In patients randomised to apixaban, laboratory investigation of the blood will follow standard clinical guidelines.

Screening for cognitive decline

At inclusion patients will be screened for pre-ICH cognitive decline with the IQCODE.[53] The questionnaire will be administered to a person who is close to the patient (partner, family member or friend). The questionnaire is filed under section F1.

Inclusion visit

Before enrolment, inclusion and exclusion criteria will be verified. The patient will receive oral and written information on the study. After written informed consent, the patient will be randomised.

The patient will receive written information on the course of the study related to the assigned treatment to maximize treatment adherence, consisting of a patient alert card for this trial in general (section F3) and a specific patient alert card for apixaban users. The baseline case record form will be completed by the investigator. The investigator will send a letter to the general practitioner (see K6).

Follow up visit

At 1 (± 7 days), 6 (± 14 days), and 12 (± 28 days) months and subsequently every 12 months (± 28 days), follow-up visits will be scheduled.
The treating physician will perform each follow-up visit. Patients will bring the packaging of used IMPs to the follow up visit. Treatment adherence will be monitored by comparing the amount of dispensed and used drugs. Batch numbers and expiry dates will be recorded. Blood pressure will be measured. Disability will be measured using the mRS. Patients will be questioned about the occurrence of outcome events or (other) SAEs in the preceding period. If there is any reason to reduce the dose of apixaban (see 6.6), the dose will be reduced.

Endpoint adjudication

An outcome adjudication committee will meet on a regular interval and adjudicate new endpoints. This committee will consists of clinical specialists and include at least one neurologist and one cardiologist. The committee will receive endpoint information blinded to patient identifiers and treatment allocation. The committee will work according to a standard operating procedure.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator or the treating physician can decide to withdraw a subject from the study for urgent medical reasons. After withdrawal, a withdrawal case report form should be filled out based on the most recent information available when the patient was still in the trial, including the reason for withdrawal, if available. This switching from or to apixaban should be done in accordance with the procedure described in the SmPC for apixaban (filed under section D2, paragraph 4.2, page 20).

7.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced after withdrawal.

7.6 Follow-up of subjects who discontinue their allocated treatment

In patients who discontinue their allocated treatment, this event will be recorded, including the reason for discontinuation and the new treatment strategy. Follow-up will be carried out as planned.

7.7 Premature termination of the study

This study is under surveillance of a Data Safety Monitoring Board, which can advise the sponsor to terminate the study prematurely; see paragraph 8.5.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the allocated treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded in the medical record on site. Only (suspected) thrombo-embolic or haemorrhagic adverse events and all serious adverse events will be reported to the sponsor.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

An elective hospital admission will not be considered as a serious adverse event.

Patients, their partners or families, as well as their general practitioner are informed to report any possible SAE as soon as possible to the local investigator. If the local investigator is notified of a possible SAE or if the local investigator or his staff detect a possible SAE themselves, the local investigator will assess the severity of the adverse event using the criteria described above.

A local investigator will inform the appointed employee of the sponsor within 24 hours after he has first knowledge of the event by email and by filling out the provided SAE form in the electronic CRF system. All possible SAEs will also be recorded in the patients' medical record at the site of the local investigator.

The sponsor will report any SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol within 15 days after the sponsor has first knowledge of the event.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 8.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Summary of Product Characteristics (SmPC) for an authorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

For SUSAR reporting, the same procedure as SAE reporting (see 8.2.2) will be followed in reporting the SUSAR to the sponsor.

As the present study is an open-label study, there is no need for deblinding in case of a SUSAR.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC and the competent authority.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs will be reported until the end of the study within the Netherlands, as defined in the protocol.

8.5 Data Safety Monitoring Board (DSMB)

The safety, efficacy, and futility of the study are monitored by an independent Data Safety Monitoring Board, consisting of a neurologist, a cardiologist, and an epidemiologist/statistician. For the DSMB charter we refer to section K5. The interim analyses performed by the DSMB are described in 9.4.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

9. STATISTICAL ANALYSIS

The primary analysis will be based on the intention-to-treat principle. As a secondary analysis, we will perform a per-protocol analysis for the primary study parameter. Before statistical analysis, a final statistical analysis plan will be completed.

9.1 Primary study parameter

The occurrence of the primary outcome (occurrence of vascular death or a non-fatal stroke) in each of the two treatment groups will be expressed as an annual event rate with a 95% confidence interval (CI). An additional analysis will be done to compare the occurrence of the primary outcomes between the two treatment groups. This analysis will be reported in terms of the hazard ratio with corresponding 95% CIs, calculated with the Cox proportional hazard model.

9.2 Secondary study parameters

The effect of the allocated treatment on the various other outcome events (see 7.1.2) and SAEs will be assessed in the same fashion as the primary study parameter.

We will dichotomise the mRS scores at the different follow up visits into 3 to 6 (poor outcome) and 0 to 2 (good outcome). The effect of the treatment on the mRS will be analysed using risk ratio's with a corresponding 95% CI.

9.3 Other study parameters

We will adjust the crude hazard ratios and risk ratios for possible baseline incomparability given the limited size of the study.

9.4 Interim analysis

Interim analysis will be performed by the DSMB following the DSMB charter, section K6. These analyses are performed after 50, 100, and 150 patient years of follow-up, and *ad hoc* as needed.

The interim analyses on both safety and efficacy will be performed on the primary outcome: the occurrence of vascular death or non-fatal stroke. This combined outcome consists of both the main efficacy outcome (ischaemic stroke) events as well as the main outcomes for harm (intracerebral haemorrhage, fatal vascular event).

The DSMB will compare both treatment arms using a Poisson's test (Conditional Test) with two-sided testing. For all interim analyses of the primary outcome, a boundary of $p < 0.01$ will be used for any recommendation to terminate the trial.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

10.2 Recruitment and consent

Patients will be recruited by the local investigator, after he is notified of an eligible patient by the treating physician. The treating physician will ask the patient's or his proxy's permission to inform the local investigator.

The person obtaining consent will inform the patient orally and provide the patient with the patient information letter and informed consent form. The first contact with the local investigator will occur no later than on the 76th day after the ICH. The patient will be offered all available time he deems necessary until the ninetieth day after the ICH to consider his decision.

During each follow up, the investigator verifies if the patient has regained capacity. If the subject has regained capacity, the person obtaining consent will inform the patient orally and provide the patient with the patient information letter and informed consent form.

Informed consent must be obtained before any study specific procedures (randomisation). The process of obtaining informed consent should be documented in the medical record of the subject.

10.3 Benefits and risks assessment, group relatedness

The objective of this study can only be accomplished in patients with AF and a recent ICH during treatment with anticoagulants, as we wish to estimate the annual rates of vascular endpoints in patients with both AF and a recent ICH when treated with apixaban, APDs, or no antithrombotic treatment. A large proportion of patients who survived an ICH will be incapacitated due to language or cognitive deficits. The clinical dilemma addressed above equally applies to these patients. The inclusion of (temporarily) incapacitated subjects is needed because patients with the capacity to provide informed consent are likely to differ from those without this capacity with respect to lesion location and size, and results obtained in patients with the capacity to consent can therefore not readily be extrapolated to patients without this capacity.

For all antithrombotic drugs, a recent ICH is a relative contra-indication to their use and current clinical evidence on this topic is scarce or non-existent, as explained in chapter 1. Physicians currently have to rely on their personal clinical judgment to weigh the benefits and risks in prescribing or withholding any antithrombotic therapy in this group. APDs, DOACS such as apixaban, VKAs, and withholding antithrombotic drugs are all strategies used by clinicians today. In this trial, we will include patients in whom there is equipoise on the optimal antithrombotic strategy.

Potential risks

Both a previous ICH and antithrombotic therapy are risk factors for recurrent ICH. There is a risk of recurrent ICH or other major bleeding for all participants, but this is likely to be higher when treated with apixaban or an APD. Conversely, the risk of ischaemic stroke or other thrombo-embolism is probably increased in patients in whom antithrombotic therapy is withheld. The risk/benefit ratios of all proposed treatments are uncertain.

Apixaban use is a contra-indication for intravenous thrombolysis for acute ischaemic stroke. Patients using apixaban therefore cannot be treated with thrombolysis in case of ischaemic stroke during follow-up. However, the risk of ischaemic stroke in patients treated with apixaban will most likely be lower than in patients without antithrombotic therapy or treated with APD, and therefore we consider this potential disadvantage of apixaban acceptable.

Aside from the bleeding risk, participants allocated to the use of apixaban or an APD are exposed to other side effects of these drugs, as reported in their SmPCs (section D2). The risks of these other side effects are limited.

Investigators will follow their local protocols regarding the management of bleeding in patients using apixaban (see section K6). Such protocols are available at each study site.

Potential benefits

The main potential benefit in patients allocated apixaban is better protection against ischaemic stroke and systemic embolism, compared to patients allocated APD or no antithrombotic treatment.

Benefit/risk assessment

Because both drugs are currently used in this group of patients without any reliable evidence for their net benefit, and because we only include patients in whom clinical equipoise with

regard to the optimal treatment strategy exists, we feel we do not expose participants to a significant additional risk in participating in this study compared to current clinical practise.

10.4 Compensation for injury

Each investigator and the Sponsor are insured for liability through the liability insurance for their institute, in accordance with article 7, subsection 9 of the WMO.

The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

All patient data are collected into an electronic case report from (eCRF) platform. Only authorized users will be provided access to this system. This software is installed on a server owned and maintained by the study sponsor. Database backups will be made regularly.

The subjects will be identified using successive numbers, generated by the randomisation system. The key to the code will be maintained by the local investigators in the Investigator Master File.

Data will be handled according to the Dutch Personal Data Protection Act, Good Clinical Practise and other relevant regulations.

11.2 Monitoring and Quality Assurance

This study has a moderate risk, based on the risk classification of the Dutch Federation of University Medical Centers[57] (NFU).

For the monitoring plan, we refer to section K6.

11.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.6 Public disclosure and publication policy

Results of the described project will be disclosed and published in peer-reviewed international scientific journals. If the sponsor and/or the investigator will initiate or participate in a phase III trial based on the results of the present study, publication of the results of the present trial may be deferred until the results of the phase III trial can be reported.

12. STRUCTURED RISK ANALYSIS

12.1 Synthesis

An extensive structured risk analysis is not necessary for this study as patients will be exposed to drugs that are already applied in clinical practice for the present indication. We will only include patients in whom there is clinical equipoise on the optimal treatment strategy. Prescription of apixaban in patients with AF and a recent ICH by a neurologist is in accordance with the Dutch Guideline on the Introduction of New Oral Antiacoagulants.[50] There is extensive experience with apixaban in large phase III clinical trials (over 23.000 patients) in patients with AF and experience with this drug in routine clinical practice is accumulating. APDs have been prescribed to patients with atherosclerosis or AF since decades. We therefore do not expect many SUSARs. During the course of the treatment, we will monitor participants for changes in their health status which warrant dose reduction or termination of study treatment.

Ultimately, we do not know which treatment has the best benefit/risk ratio in our population. The study proposed is an important first step in gaining evidence to optimise treatment of patients who had an ICH while on anticoagulation treatment for atrial fibrillation.

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Appendix A – CHA_2DS_2VASc score

Table 2—The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA2DS2-VASc, from Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263–72.

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE *	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex **c**ategory (ie female gender)	1

The item Stroke in the Stroke/TIA/TE item refers to ischaemic stroke, not haemorrhagic stroke.

Appendix B – HAS-BLED score

Table 2— Clinical Characteristics Composing the HAS-BLED from Pisters R, Lane D a, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093–100.

Letter	Clinical Characteristic	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (>65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2