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

Published: 07-07-2014
Last updated: 19-03-2025

Primary Objective: to obtain reliable estimates of the rates of vascular death and non-fatal stroke in patients with atrial fibrillation and a recent anticoagulation-associated ICH who are treated with apixaban versus those who are treated with APDs...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Cardiac arrhythmias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50507

**Source**
ToetsingOnline

**Brief title**
APACHE-AF

### Condition

- Cardiac arrhythmias
- Central nervous system vascular disorders
- Embolism and thrombosis

**Synonym**
brain haemorrhage, Intracerebral haemorrhage

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht
**Source(s) of monetary or material Support:** ZonMW,Nederlandse Hartstiching

## Intervention

**Keyword:** Antiplatelet drugs, Apixban, Atrial fibrillation, Intracerebral haemorrhage

## Outcome measures

### Primary outcome

The combination of vascular death or non-fatal stroke (cerebral infarction,

intracerebral haemorrhage, or subarachnoid haemorrhage) during follow-up.

### Secondary outcome

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.

# Study description

### Background summary

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. Patients are currently treated with vitamin K antagonists (VKAs), direct oral anticoagulant drugs (DOACs), 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 VKAs reduce the risk of ischaemic stroke and other thrombo-embolic events, but increase the risk of bleeding as compared to no anticoagulant therapy. In a more recent large randomised trial, the direct oral anticoagulant (DOAC) apixaban was superior to VKAs in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. Other DOACs had similar effects. Unfortunately, DOACs have not been tested in patients with AF and a recent ICH. 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.

### Study objective

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

Secondary Objective: to compare the rates of vascular death and non-fatal stroke, all-cause death, disabling stroke, recurrent ICH, other major haemorrhage, systemic embolism, and functional outcome between patients treated with apixaban and those who are treated with APDs or no antithrombotic drugs.

### Study design

This will be a phase II, randomized, open, multi-centre clinical trial with masked outcome assessment (PROBE design), comparing apixaban with APDs or no antithrombotic treatment in patients with AF and a recent anticoagulation-associated ICH.

The adjudication of the endpoints will be performed by an adjudication committee blinded to 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 will be six years.

## Intervention

Patients will be randomised between:
* apixaban 5 mg orally twice daily
* treatment with one or two oral APDs (ATC group B01AC; acetylsalicylic acid, carbasalate calcium, clopidogrel, or dipyridamole) or no antithrombotic treatment at all, at the discretion of the treating physician.

## Study burden and risks

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. Practitioners 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 potential increased risk of ICH or other major bleeding for all participants, but this is likely to be higher when treated with apixaban or an APD. The risk for a new intracranial haemorrhage is probably higher when treated with apixaban compared to treatment with APDs. Conversely, the risk of ischaemic stroke or other thrombo-embolism is probably increased in patients in whom antithrombotic therapy is withheld. The risk for thrombo-embolic complications is probably higher when using APDs than when using apixaban. The risk/benefit ratio of all proposed treatments is 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. The risk of these other side effects however appears acceptable.

Investigators will be provided with a protocol regarding the management of bleeding in patients using apixaban.

POTENTIAL BENEFIT
The main potential benefit in patients allocated apixaban is better protection against ischaemic stroke and thrombo-embolism, compared to patients allocated APD or no antithrombotic treatment. The risk for thrombo-embolism is probably higher during treatment with APDs compared to the risk during treatment with apixaban.

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.

# Contacts

**Public**
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
**Scientific**
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion 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 CHA2DS2VASc score * 2. The item Stroke in the Stroke/TIA/TE item refers to ischaemic stroke, not haemorrhagic stroke.*
Score on the modified Rankin scale (mRS) *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 the all relevant information available for the individual patient.
Age * 18 years.
Written informed consent by the patient or by a healthcare proxy

## Exclusion criteria

Conditions other than atrial fibrillation for which the patient requires long-term anticoagulation.
A different clinical indication for the use of an APD even when 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 protocol chapter 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 or haemoglobin level of <6.2 mMol/L, 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 *mol 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 an 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.

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Prevention |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 15-01-2015 |
| Enrollment: | 100 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Ascal |
| Generic name: | carbasalate calcium |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Aspirin |

| | |
|---|---|
| Generic name: | Acetylsalicylic acid |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Eliquis |
| Generic name: | Apixaban |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Persantin |
| Generic name: | dipyridamole |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Plavix |
| Generic name: | clopidogrel |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 07-07-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 01-09-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 30-10-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 12-11-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 16-01-2015 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 12-02-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 13-02-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 01-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 08-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 19-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 23-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 10-01-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 22-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 01-05-2018 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 09-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 01-12-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 10-12-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

ID: 27026
Source: Nationaal Trial Register
Title:

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2014-000112-33-NL |
| CCMO | NL47761.041.14 |
| Other | NTR4526, NCT02565693 |
| OMON | NL-OMON27026 |

# Study results

| | |
|---|---|
| Date completed: | 15-01-2021 |
| Results posted: | 08-12-2021 |
| Actual enrolment: | 101 |

**Summary results**
Trial is onging in other countries

**First publication**
01-11-2021