Prospective Randomised Open-label Trial to Evaluate risk faCTor management in patients with Unruptured intracranial aneurysms (PROTECT-U)

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This study has been transitioned to CTIS with ID 2024-517236-22-00 check the CTIS register for the current data. The main purpose of this study is to assess the hypothesis that a strategy with ASA 100mg/day and intensive blood pressure treatment (…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Aneurysms and artery dissections
Study type	Interventional

Summary

ID

NL-OMON52612

Source
ToetsingOnline

Brief title
PROTECT-U

Condition

- Aneurysms and artery dissections

Synonym
Intracranial aneurysm - Dilated brain artery

Research involving
Human

Sponsors and support

Primary sponsor: Ruprecht-Karls-University Heidelberg, Medical Faculty Mannheim

Source(s) of monetary or material Support: Dr Rolf Schwiete Foundation;Mannheim;Nederlandse Hartstichting;Stichting Phoenix

Intervention

Keyword: acetylsalicylic acid, growth, intracranial aneurysm, rupture

Outcome measures

Primary outcome

The primary outcome measure will be aneurysm rupture or growth on serial imaging (MR- or CT-angiography). Aneurysm growth is defined as an increase in any aneurysm diameter by >= 1mm at 36±6 months on the intervention. Aneurysm rupture or growth will be assessed centrally by two independent trial radiologists, who will be blinded to the treatment allocation.

Secondary outcome

1. Any growth or rupture of aneurysm during follow-up irrespective of the duration of trial participation

2. Difference of aneurysm volume (defined as increase of aneurysm volume in computerized measurements from source images by >10% and >3mm3) or aneurysm shape (e.g. development of daughter sac)

3. Development of de novo aneurysm on serial imaging

4. Clipping/coiling during the study period

5. Any ischemic or hemorrhagic stroke, defined as clinical symptoms of stroke AND a compatible lesion on imaging

6. Myocardial infarction defined as increase of Troponin, CKMB and/or presence of new significant Q waves obtained in ECG

7. Vascular death (including fatal stroke, fatal myocardial infarction, sudden

death)

8. Death from all other causes

9. Major spontaneous bleeding requiring hospitalisation defined as

substantially disabling bleeding, intraocular bleeding leading to the loss of

vision, or bleeding necessitating the transfusion of at least 2 units of

erythrocyte concentrates

10. Blood pressure; any data on blood pressure management used

11. Safety aspects (adverse and serious adverse events)

12. Quality of life

Study description

Background summary

In the Netherlands, approximately 300.000 people have an intracranial aneurysm. Most people are not aware of having an intracranial aneurysm until brain imaging is made for another reason, such as traumatic head injury. An intracranial aneurysm can then be found by accident. If such an aneurysm is found, it needs to be considered if preventive aneurysm treatment should occur to prevent bleeding. Preventive aneurysm treatment can be done by neurosurgical clipping or endovascular coiling. However, both treatment options have a risk of treatment complications, such as ischemic or hemorrhagic stroke. It will only be decided to do preventive aneurysm treatment if the risk of aneurysm rupture is larger than the risk of treatment complications. Because most aneurysm are relatively small and have a low risk of rupture, most aneurysms remain untreated. Patients with such an aneurysm receive a 'wait-and- scan' policy to determine if the aneurysm growths. Aneurysm growth increases the risk of rupture, and therefore in these patients it can be decided in a later phase to perform preventive aneurysm treatment.

In the PROTECT-U trial, we focus on patients in whom the risk of aneurysm rupture is lower than the risk of treatment complications: the untreated group of patients. Previous studies suggested that acetylsalicyl acid decreases inflammation in the aneurysm wall and hereby the risk of aneurysm rupture. In addition, high blood pressure is a risk factor for aneurysm rupture. In the PROTECT-U trial we will randomize 776 patient to either treatment with daily

acetylsalicylic acid and intensive blood pressure treatment in combination with weakly home blood pressure measurements OR current standard of care (this is the control group, there is no need to take a placebo).

Study objective

This study has been transitioned to CTIS with ID 2024-517236-22-00 check the CTIS register for the current data.

The main purpose of this study is to assess the hypothesis that a strategy with ASA 100mg/day and intensive blood pressure treatment (targeted systolic blood pressure below 120mmHg) with advice to patients to do weekly measurements using a home blood pressure measuring device reduces the risk of aneurysm growth or rupture compared with standard care (i.e. no ASA, blood pressure management according to guidelines which advise treatment if systolic blood pressure exceeds 140mmHg, and no home device for weekly blood pressure measuring).

Study design

International, phase III multicenter, randomised, controlled trial with a PROBE design (prospective, randomised, open-label trial with blinded outcome assessment)

Intervention

Patients will be randomized to either:
- a strategy with ASA 100mg/day and intensive blood pressure treatment (targeted systolic blood pressure below 120 mm Hg) with daily measurements using a home blood pressure measuring device
- standard care (i.e. no ASA, blood pressure management according to guidelines which usually advise treatment if systolic blood pressure exceeds 140 mm Hg, and no home device for daily blood pressure measurements).

Blood pressure lowering drugs will not be part of the IMP. Both in the intervention arm and the control arm of the trial, the general practitioner will control the blood pressure target and prescribe blood pressure lowering drugs (but with different targets of systolic blood pressures in the two arms).

Study burden and risks

If a recent (<6 months) GFR (determined at the lab of the trial center or at another lab that provides a copy of the appropriate lab certificate) is not available, a blood test will be done to measure GFR after informed consent has been obtained. In women with child-bearing potential, a pregnancy test will be done.

The patients included in this study will be randomly assigned to either acetylsalicylic acid 100 mg once daily in combination with intensive blood pressure treatment (target systolic BP <120 mm Hg) and a home blood pressure measuring device in addition to standard of care or only standard clinical care. Side effects of acetylsalicylic acid may include nausea, vomiting, dyspepsia, stomach ache, and a gastrointestinal bleeding tendency.

All patients will have a treatment visit every 6 months during which a blood pressure, potential side effects, cardiovascular outcomes, hospital admissions, and quality of life are recorded. There is no risk related to these treatment visits. Treatment visits will take place until the study is finished, 3 years after inclusion of the last patient. Therefore, the patient will be in the trial for 3-5 years, depending on the time of inclusion. There will be a minimum of 9 visits, and a maximum of 13 visits (including the screening-, baseline- and follow-up visits).

Aneurysm imaging is part of patient care, and therefore is no study procedure.

Patients of the treatment group, who consent into an additional data upload, are instructed how to transmit pseudonymised blood pressure measurements into a central database by online transfer.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Patient with at least one intradural, saccular unruptured aneurysm in whom it is decided not to intervene with preventive neurosurgical or endovascular aneurysm repair and who are monitored on a regular basis for aneurysm growth
• 18 years or older
• Last aneurysm imaging with either CTA/MRA within the last 3 months
• Ability of subject to understand character and individual consequences of clinical trial
• Not legally incapacitated
• Written informed consent (must be available before enrolment in the trial)
• For women with childbearing potential adequate contraception

Exclusion criteria

• All non-saccular UIAs or aneurysms related to arteriovenous malformations • Daily ASA already prescribed for another indication • Use of a vitamin K antagonist or direct oral anticoagulant (DOAC) at baseline • History of hypersensitivity to ASA or to any other drug with similar chemical structure or to any excipient present in the pharmaceutical form of ASA • History of asthma induced by ASA or other anti-inflammatory drugs • Other contra-indications for ASA not yet mentioned, in the dosage of 100 mg/day (e.g. bleeding disorders, gastric ulcers and/or intestinal ulcers, acute liver failure of kidney failure, severe heart failure, treatment with methotrexate in a dosage 15 mg/week or above) • Use of another platelet aggregation inhibitor, which in combination with ASA would give an unacceptable risk of side effects/complications • Chronic kidney disease stage IV and V (GFR < 30 mL/min/1.73 m2) • Pregnancy and lactation • Participation in any other clinical trial • Life-expectancy <3 years

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-04-2018
Enrollment:	355
Type:	Actual

Medical products/devices used

Generic name:	Blood pressure measurement device
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	ASS-ratiopharm® PROTECT 100 mg
Generic name:	Acetylsalicylic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-04-2018
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	04-04-2018
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	13-03-2019
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	28-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-08-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-09-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-517236-22-00
EudraCT	EUCTR2017-000514-35-NL
ClinicalTrials.gov	NCT03063541
CCMO	NL63115.041.17