Genotype-guided strategy for antithrombotic treatment versus conventional clopidogrel therapy in peripheral arterial disease.

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This study has been transitioned to CTIS with ID 2024-518122-33-00 check the CTIS register for the current data. The primary aim of the GENPAD study is to evaluate the ability of genotype-guided antithrombotic treatment to reduce adverse clinical...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON50838

Source
ToetsingOnline

Brief title
GENPAD

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
lower extremity arterial disease, Peripheral arterial disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: ZonMw ZE&GG

Intervention

Keyword: Cardiovascular events, Clopidogrel, CYP2C19 enzyme, Peripheral arterial diseae

Outcome measures

Primary outcome

The primary outcome is the occurrence of adverse clinical events related to arterial thrombosis at 24 months, including death from any cause, major adverse cardiovascular events (MACE) and major adverse limb events (MALE).

MACE is defined as the composite of myocardial infarction, stroke, TIA and CV death.

MALE is defined as the composite of:

- Acute limb ischemia: limb-threatening ischemia that is confirmed by using limb hemodynamic parameters or imaging and leading to an acute vascular intervention within 30 days of onset of symptoms.
- Chronic limb ischemia: continuing ischemic limb, foot, or digit pain leading to hospitalization and intervention and not meeting the definition of acute limb ischemia; or participants with Rutherford classification3 IV, V or VI at baseline who had a peripheral vascular intervention over the course of the trial.
- Peripheral vascular interventions not meeting the definition for acute limb ischemia or chronic limb ischemia.

Peripheral vascular interventions include pharmacological interventions (heparin, thrombolysis), peripheral artery surgery/reconstruction, peripheral artery angioplasty/stent, and (major or minor) amputation.

Major vascular amputation is defined as an amputation above the forefoot due to a vascular event.

Secondary outcome

Secondary endpoints are the occurrence of the separate elements of the primary composite outcome at 24 months.

The secondary safety outcome will be major and clinically relevant minor bleeding complications.

Major bleeding is defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria and include

- fatal bleeding,
- symptomatic bleeding into a critical organ
- bleeding causing a fall in hemoglobin level of 20 g L-1 (1.24 mmol L-1) or more or leading to transfusion of two or more units of whole blood or red cells
- bleeding into a surgical site requiring a second intervention.

All non-major bleedings will be considered minor. Minor bleedings will be further divided into those that are clinically relevant and those that are not.

A clinically relevant minor bleeding leads to at least one of the following:

- hospitalization (including presentation to an acute care facility without an

overnight stay)

- a physician guided medical or surgical treatment for bleeding

- a change in antithrombotic treatment.

Study description

Background summary

In the Netherlands, 1.1 million people have peripheral arterial disease of which 85,000 patients have symptomatic peripheral arterial disease, such as intermittent claudication, pain at rest or gangrene. Patients with peripheral arterial disease are at increased risk of cardiovasculair events - i.e. myocardial infarction, stroke, limb ischemia or death. International PAD guidelines recommend the use of clopidogrel 75mg once daily for secondary prevention of cardiovascular events. Clopidogrel, however, is a prodrug which need to be metabolized by the enzym CYP2C19 to its active metabolite. Thirty per cent of patients with peripheral arterial disease receiving clopidogrel 75mg once daily is carrying one or two CYP2C19 loss-of-function allele(s) and do not or to a limited extent convert the prodrug into active metabolites, and are therefore at increased risk of adverse cardiovascular events.

Study objective

This study has been transitioned to CTIS with ID 2024-518122-33-00 check the CTIS register for the current data.

The primary aim of the GENPAD study is to evaluate the ability of genotype-guided antithrombotic treatment to reduce adverse clinical events related to arterial thrombosis in patients with peripheral arterial disease. Secondary aims are to evaluate the ability of genotype-guided antithrombotic treatment to reduce the separate elements of the primary composite outcome and to assess the risk of clinically relevant bleedings in patients allocated to the genotype-guided antiplatelet treatment versus standard clopidogrel prescription.

Study design

A randomized, controlled, open label, multicenter study.

Intervention

Intervention: Testing for carriage of the CYP2C19*2 and *3 allele, i.e. loss-of-function (LOF) alleles, followed by a genotype guided antithrombotic treatment with either clopidogrel 75mg once daily (normal metabolizers), clopidogrel 75mg twice daily (intermediate metabolizers), or low-dose rivaroxaban plus acetylsalicylic acid (poor metabolizers).

Comparator: All patients receive clopidogrel 75mg once daily without pharmacogenetic guidance.

Study burden and risks

The burden is one visit to the outpatient clinic of 30 minutes or a prolongation of a regular visit to the outpatient clinic with 30 minutes. Additionally, paricipants will be sent questionnaires, two to five times, dependent on the duration of study follow-up, of 30 minutes each time. 85% of the research population will not have any risks associated with participation. For the 30% of the intervention group with one or two loss-of-function allele(s), risks associated with participation are the possible side effects of increased dose of clopidogrel or the possible side effects of acetylsalicylic acid and rivaroxaban.

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

- age > 16 years
- obtained written informed consent
- indication for monotherapy clopidogrel 75mg once daily
- ankle-brachial index < 0.9 and/or toe brachial index < 0.5
- current or previous symptoms due to insufficient vascularization of one or two lower extremities, including intermittent claudication, pain at rest and/or gangrene (Rutherford category 1-6)
- consulting a vascular surgeon for diagnosis, treatment and/or follow-up of PAD symptoms

Exclusion criteria

- known CYP2C19*2 and *3 status
- treated with coumarins, Non-vitamin K Oral Anti-Coagulants, unfractionated heparin, low molecular weight heparins or double antiplatelet therapy for other indications
- contraindication for clopidogrel, acetylsalicylic acid and/or rivaroxaban
- life expectancy of less than 1 year
- pregnant or breastfeeding women
- unable to give informed consent

Study design

Design

Study phase:	4
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-03-2021
Enrollment:	2276
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aspirin
Generic name:	Acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plavix
Generic name:	Clopidogrel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xarelto
Generic name:	Rivaroxaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-02-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	11-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-02-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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: 26517
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-518122-33-00
EudraCT	EUCTR2020-004913-11-NL
CCMO	NL75567.091.20