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

No registrations found.

| | |
|---|---|
| **Ethical review** | Not applicable |
| **Status** | Recruiting |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON26517

**Source**
NTR

**Brief title**
GENPAD

**Health condition**

Peripheral arterial disease

### Sponsors and support

**Primary sponsor:** Radboudumc
**Source(s) of monetary or material Support:** ZonMW ZE&GG

### Intervention

### Outcome measures

**Primary outcome**

The primary outcome is the number of participants that experienced a major adverse

cardiovascular events, major adverse limb events or death from any cause during a median follow-up of 24 months.(range 6 to 36 months)

### Secondary outcome

The secondary endpoints are:
- The number of participants that experienced major adverse cardiovascular events (MACE) during a median follow-up of 24 months.(range 6 to 36 months). MACE is defined as the composite of myocardial infarction, stroke, transient ischemic attack or cardiovascular death
- The number of participants that experienced a major adverse limb event (MALE) during a median follow-up of 24 months.(range 6 to 36 months). MALE is defined as the composite of acute limb ischemia, chronic limb ischemia or peripheral vascular intervention.
- The number of participants that experienced a major bleeding event during a median follow-up of 24 months.(range 6 to 36 months). Major bleeding includes: 1) fatal bleeding, 2) symptomatic bleeding into a critical organ, 3) 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, and 4) bleeding into a surgical site requiring a second intervention.
- The number of participants that experienced a clinically relevant bleeding during a median follow-up of 24 months.(range 6 to 36 months). Clinically relevant bleeding includes bleeding that led to: 1) hospitalization (including presentation to an acute care facility without an overnight stay), 2) a physician guided medical or surgical treatment for bleeding, and 3) a change in antithrombotic treatment.

## Study description

### Background summary

Rationale: Peripheral arterial disease (PAD) is a common presentation of atherosclerosis, resulting in intermittent claudication, pain at rest or gangrene. For the prevention of adverse events related to arterial thrombosis in PAD patients, clopidogrel is recommended. Clopidogrel in itself is inactive and needs to be metabolized by cytochrome P450 2C19 (CYP2C19) into the active metabolite. About 30% of PAD patients receiving clopidogrel is carrying one or two CYP2C19 loss-of-function allele(s) and do not or to a limited extent convert the prodrug into its active metabolites, and are therefore at increased risk of adverse clinical events related to arterial thrombosis and subsequent cardiovascular death. We hypothesize that genotype-guided prescription of antithrombotic treatment reduces adverse clinical events related to arterial thrombosis.
Objective: 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 PAD patients. Adverse clinical events of interest are major adverse cardiovascular events (myocardial infarction, stroke, transient ischemic arrack), major adverse limb events (acute/chronic limb ischemia of peripheral vascular intervention including amputation) and death. Secondary objectives 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. Other objectives are to evaluate cost-effectiveness, to explore health state scores and health-related quality of life between study groups and metabolizer states and to set-up a biobank.
Study design: A randomized, controlled, open label, multicenter trial.
Study population: Patients (n=2276) with PAD consulting a vascular surgeon for diagnosis and/or treatment, receiving clopidogrel according to the guidelines.
Intervention: Testing for carriage of the CYP2C19*2 and *3 loss-of-function 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.
Main study parameters/endpoints: The primary combined outcome is the occurrence of adverse clinical events related to arterial thrombosis at 24 months. The occurrence of major adverse cardiovascular events, major adverse limb events, death and clinically relevant bleedings are the secondary endpoints. Health state, quality of life and medical consumption will be measured with validated questionnaire. Tailormade questionnaires will be used to assess which antithrombotic treatment the participant is receiving during follow-up, medication adherence and the occurrence of extramural adverse events at 6, 12, 24 and 36 months.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will visit the hospital once for informed consent procedure, blood sample withdrawal and/or buccal sample collection This visit will be combined with a routine visit to the vascular surgeon or vascular laboratory. Patients might experience some discomfort while taking blood samples and buccal sample collection for a short amount of time. The follow-up of participants will range from 6 months (minimum) to 36 months (maximum). Participants are sent questionnaires at baseline and at 6, 12, 24 and 36 months, dependent on the duration of their follow-up. Completing the questionnaires will take approximately 30 minutes. Risks regarding the study are negligible and consist of the possible adverse events related to doubling the daily dose of clopidogrel or related to rivaroxaban and acetylsalicylic acid.

## Study objective

We hypothesize that genotype-guided prescription of antithrombotic treatment reduces adverse clinical events related to arterial thrombosis.

## Study design

24 months

## Intervention

Testing for carriage of the CYP2C19*2 and *3 loss-of-function 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).

# Contacts

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# Eligibility criteria

## 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 peripheral arterial disease

## Exclusion criteria

- known CYP2C19 genotype or metabolizer state
- treated with coumarins, Non-vitamin K Oral Anti-Coagulants (NOACs), unfractionated heparin (UFH), low molecular weight heparins (LMWH) or double antiplatelet therapy (DAPT) with ASA and a P2Y12 inhibitor for other indications
- contraindication for clopidogrel, ASA and/or rivaroxaban
- pregnant or breastfeeding women
- unable to give informed consent (including not being able to understand the Dutch language)

# Study design

## Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 01-03-2021 |
| Enrollment: | 2276 |
| Type: | Anticipated |

## IPD sharing statement

**Plan to share IPD:** Yes

**Plan description**
Data will be accessible through the DANS EASY repository, using Dublin Cor metadata scheme

# Ethics review

Not applicable

| | |
|---|---|
| Application type: | Not applicable |

# Study registrations

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

ID: 50838
Bron: ToetsingOnline
Titel:

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

No registrations found.

## In other registers

| Register | ID |
|---|---|
| NTR-new | NL9027 |
| CCMO | NL75567.091.20 |
| OMON | NL-OMON50838 |

# Study results