Prevalence and impact of high on-treatment platelet reactivity in patients with peripheral arterial disease

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Primary Objective: Investigate the difference in composite endpoint MACE, major amputation, or target vessel revascularization in PAD Fontaine II patients with and without antiplatelet resistance as measured by a. VerifyNow b. Genetic testing of...

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

Summary

ID

NL-OMON53864

Source
ToetsingOnline

Brief title
HTPR in peripheral arterial disease

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
intermittent claudication, peripheral arterial disease

Research involving
Human

Sponsors and support

Primary sponsor: Haaglanden Medisch Centrum
Source(s) of monetary or material Support: Bronovo Research Fonds

Intervention

Keyword: Clopidogrel, HTPR, MACE, Peripheral arterial disease

Outcome measures

Primary outcome

Investigation of antiplatelet therapy resistance

a. Study parameters: antiplatelet resistance, genetic testing CYP2C19.

b. Primary endpoint:

ii. MACE, major amputation, target vessel revascularisation in PAD Fontaine II patients.

Definitions of study parameters/endpoints

All definitions pertinent to PAD are based on the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Disease, in collaboration with the European Society for Vascular Surgery (ESVS).(8)

Adherence to drug treatment: Medication use includes therapy initiated 6 months prior to the index date and up to 30 days after the index date. Treatment adherence can be defined as the number of physiotherapy sessions prescribed for walking therapy, and the estimated number of sessions completed. Drug adherence can be estimated by calculating the number of pills prescribed and the estimated number of pills taken each day.

Ankle-brachial Index of <0.90 is considered diagnostic for PAD, as well as a significant decrease in ABI after exercise testing (see below).

Antiplatelet resistance is defined as that which is the result of high antiplatelet reactivity or is associated with undesirable ischemic clinical outcomes.(10) Table 2 in the protocol highlights the various definitions provided in the literature(11):

Death will be defined as death from cardiovascular causes or cerebrovascular causes and any death without another known cause. The information will be obtained from patient files, referring vascular surgeons, general practitioners or death certificates.

Exercise/treadmill test is usually performed using the Strandness protocol at a speed of 3km/h and 10% slope. The test is stopped when the patient is unable to walk further because of pain, defining maximal walking distance. Furthermore, a post-exercise ankle SBP decrease of >30mmHg or a post-exercise ABI >20% is diagnostic of PAD.

Exercise therapy is usually applied using the Strandness protocol at a speed of 3km/h and 10% slope. The test is stopped when the patient is unable to continue walking due to limb pain. This is defined as the maximal walking distance. A post-exercise ankle SBP decrease >30 mmHg or a post-exercise ABI decrease >20% are diagnostic of PAD.(8)

Fontaine Classification: Clinical stages of lower extremity artery disease, see Table 1(8)

MACE: Major adverse cardiovascular events include hospitalisation with the diagnosis of nonfatal myocardial infarction, cardiovascular death or nonfatal stroke.

Toe pressure <50mmHg is considered abnormal

Toe brachial Index <0.70 is considered abnormal

Secondary outcome

Investigate the prevalence of clopidogrel and aspirin resistance in the PAD patient population

1. Progression of disease according to the Fontaine Classification.

Progression of disease is defined as:

i. Fontaine IIa/b and an intervention (endovascular/operation)

ii. Fontaine II to Fontaine III (with/without intervention)

iii. Fontaine II/III to Fontaine IV (with/without intervention)

2. Investigate the prevalence of CYP2C19 loss-of-function alleles in The Hague region

3. Investigate the prevalence of antiplatelet therapy resistance with the point-of-care VerifyNow Platelet Function Analyser.

4. Evaluate the percentage increase or decrease in all-cause mortality, revascularisation, stent thrombosis in patients with and without antiplatelet therapy resistance as measured by

i. VerifyNow

ii. Genetic testing of CYP2C19 loss-of-function alleles

Study description

Background summary

Epidemiology
Peripheral arterial disease (PAD) is a common vascular disease with a preference for the lower extremities, and is estimated to affect 200 million people worldwide, with the burden of disease presenting in the elderly population.(1) PAD is caused by atherosclerosis, and progresses due to increased arterial plaque formation and thus reduction in blood flow and oxygen supply to the extremities. Reduced oxygen supply in the extremities leads to symptoms such as ischemic pain, and the development and impaired healing of ulcers. Risk factors for PAD include age, gender, ethnicity, smoking and Diabetes Mellitus (DM).(2)

It is estimated that the population of persons 65 years old and over will increase 44% in the coming 20 years. The prevalence of PAD in the general population in the Netherlands is an estimated 7% to 56% in patients over 55 and 85 years old, respectively. For the larger The Hague area, this PAD prevalence may be an underestimation as the population is of lower socio-economic status (SES) and of larger multinational background including a large Surinam-Hindustan community with a high-risk cardiovascular profile including high rates of DM.

PAD can be divided into four stages according to the Fontaine classification system, see Table 1.(3) Fontaine II includes patients with intermittent claudication, and has a 5-year overall and vascular mortality rate of 9% and 3%, respectively.(4, 5) One-fifth of Fontaine II patients experience worsening symptoms, and in some eventual amputation. Furthermore, Fontaine II is often the index presenting symptom in patients with underlying cardiovascular disease, with 21% of Fontaine II patients developing other cardiovascular events in the course of five years.(5) While these numbers warrant extensive secondary prevention and surveillance in PAD patients, current guidelines are based on either recent small studies or dated larger American studies that may no longer be relevant due to changing diagnostic and treatment strategies.(6) There is thus a need for large contemporary studies on the epidemiology and natural progression of Fontaine II patients.

Table 1: Fontaine Classification

FONTAINE CLASSIFICATION
STAGE Symptoms
I Asymptomatic
II IIa Non-disabling intermittent claudication

IIb Disabling intermittent claudication
III Ischaemic rest pain
IV Ulceration or gangrene

Treatment of Fontaine II PAD
Fontaine II PAD is generally considered a benign disease, but it has a large impact on quality of life, as claudication symptoms can lead to limited mobility with the potential for amputation in advancing cases. Prevention of progression of disease and relief of intermittent claudication should initially be attempted with supervised exercise therapy (SET).(7) By encouraging patients to continue to walk, despite experiencing ischemic pain, collateral blood vessel formation can be stimulated, improving the blood flow to the peripheries. Furthermore, secondary prevention is initiated, including smoking cessation advice and commencement of statins and platelet aggregation inhibitors according to local guidelines.

Secondary prevention with platelet aggregation inhibitors
European PAD guidelines advocate for the treatment of PAD with clopidogrel, with aspirin as the second-choice antiplatelet agent.(8) However, despite adhering to antiplatelet therapy, a significant proportion of the PAD patient population will suffer an ischemic cardiovascular event. Increasing evidence shows aspirin resistance or clopidogrel resistance to be associated with a higher risk of ischemic events in adherent patients.(9) Current research focuses on the presence of antiplatelet resistance in patients with advanced cardiovascular disease with significant results, but with limited studies exploring this phenomenon in PAD patients.(10) Historically, light transmission aggregometry was used to measure platelet aggregation, but this procedure is time intensive and requires laboratory technical skills.(11) Antiplatelet resistance testing has advanced into point-of-care analysers, such as the VerifyNow system. The VerifyNow assay can be used to measure clopidogrel or aspirin resistance, depending on the use of a P2Y12- or Arachadonic Acid Assay, respectively.(12, 13) No consensus has been reached as to the optimal cut-off value for antiplatelet resistance, largely due to the small retrospective nature of the studies conducted in this field.(10)
Clopidogrel resistance can be due to a genetic polymorphism, as well as patient-related factors such as DM or renal failure. A polymorphism in the CYP2C19 gene can result in reduced metabolism of clopidogrel, diminishing its* antiplatelet inhibitor function.(14) The most common CYP2C19 loss-of-function alleles are 1-3. Allele 2 loss-of-function most frequently occurs, in ~15% of Caucasians and Africans and 29-35% of Asians.(15) Patients can be classified according to the CYP2C19 polymorphism expression. Individuals homozygous for two loss-of-function alleles are said to be poor metabolisers (PM); those heterozygous for one loss-of-function allele are intermediate metabolisers (IM); and subjects with a wild type genetic profile are extensive metabolisers (EM). (16, 17) Previous research has shown that being a poor metaboliser has a

negative effect on clinical outcomes.(14, 16) The prevalence of loss-of-function alleles therefore differs per ethnic group and as such it is unclear what the prevalence is in the multi-ethnic population of the Hague, and whether it would be appropriate to adapt the antiplatelet treatment strategy based on regional epidemiological data.

Hypothesis and Rationale
It is hypothesized that resistance to antiplatelet therapy is a risk factor for progression of disease, MACE and secondary outcomes such as increased need for revascularisation, or a higher incidence of in-stent thrombosis.

Study objective

Primary Objective:
Investigate the difference in composite endpoint MACE, major amputation, or target vessel revascularization in PAD Fontaine II patients with and without antiplatelet resistance as measured by
a. VerifyNow
b. Genetic testing of CYP2C19 loss-of-function alleles

Study design

This study will be performed in The Hague, the Netherlands and include patients receiving care in the Haaglanden Medical Centre and the General Practitioners in this region.

Prospective cohort study
To prospectively determine the prevalence and effect of antiplatelet therapy resistance on disease progression and adverse events.

Point-of-care antiplatelet resistance blood tests and CYP2C19 genotyping will be performed in patients in a hospital setting.
1. VerifyNow: clopidogrel and aspirin resistance blood tests
2. Genotyping: gold standard - laboratory genetic tests

Patients will be divided into cases (antiplatelet resistant) and controls (not antiplatelet resistant) based on VerifyNow results. According to genetic testing patients will be divided into extensive-, intermediate- and poor metabolisers. Blood sample for genetic testing will be collected at inclusion and collectively analysed upon completion of the study.

Study burden and risks

An added risk for participants of this study is due to venipuncture. This procedure is low risk, and subject may develop a hematoma post-procedure. Participation in this study will require venipuncture for the VerifyNow and

CYP2C19 genetic test during the primary consultation. Furthermore, at a regular follow-up visit at 4 months a second VerifyNow measurement will be performed. The patient will be required to fill out a questionnaire four times during the study period.

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

18 years of age and older
Suggestion of peripheral arterial disease Fontaine II: claudication pain in the limb; ABI <0.9, DUS >50% stenosis.
Antiplatelet therapy: clopidogrel

Exclusion criteria

Unable to give informed consent or have a life expectancy of less than one year due to a non-cardiovascular risk profile

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-09-2024
Enrollment:	246
Type:	Actual

Ethics review

Approved WMO Date:	10-08-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL81458.058.22