The Rotterdam Antiplatelet Therapy in Vascular Patients Study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON46172

Source
ToetsingOnline

Brief title
RAVE

Condition

- Vascular therapeutic procedures
- Embolism and thrombosis

Synonym
arteriosclerosis and trombosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Lijf en Leven

Intervention

Keyword: Clopidogrel, MACE, Troponin, Vascular Surgery

Outcome measures

Primary outcome

In patients with asymptomatic troponin release BEFORE and AFTER major vascular surgery the following objectives will be investigated:

The primary objective is to assess the efficacy of clopidogrel, as compared to placebo, on top of standard treatment with aspirin on;

A. the composite endpoint of MACE, defined as;

- cardiovascular death
- non-fatal myocardial infarction
- stroke
- severe ischemia of the coronary or peripheral arterial circulation leading to intervention

Secondary outcome

Secondary objectives

B. Individual components of MACE

C. Bleeding complications, defined as life-threatening bleeding, moderate and minor bleeding.

In patients with asymptomatic troponin release BEFORE major vascular surgery

the following objective will be investigated:

Tertiairy objectives

In all patients undergoing vascular surgery and preoperative troponin release,

the following objectives will be determinded;

D. Presence of significant occlusive coronary artery disease and the

impact of presence of vulnerable plaques according to PROSPECT criteria

Study description

Background summary

In the past few years there efficacy and safety of double antiplatelet therapy, as compared to aspirin, has been investigated increasingly for prevention of cardiovascular complications after non-cardiac surgery.
The CURE study showed that in patients with myocardial damage, but not having a myocardial infarction, improvement in first year survival can be achieved by adding Clopidogrel to standard therapy with aspirin. A significant reduction in incidence of the primary endpoint, defined as death from cardiovascular cause, myocardial infarction and stroke, from 11.4% to 9.3% was found in patients undergoing non-cardiac surgery, when treated with double antiplatelet therapy. The CHARISMA trial was next in line to investigate the same study population but having multiple atherosclerotic risk factors. Results also showed a reduction of primary endpoint of 7.3% to 6.8%, although not significant. A desirable effect of treatment with double antiplatelet therapy was seen among patients with proven coronary artery disease. A meta-analysis by Bowry et al of 2008 displayed favourable effects of double antiplatelet therapy on the compound endpoint death, new myocardial infarction and stroke, having an odds ratio reduction of 15 % in patients having an acute coronary syndrome and 34% in patients undergoing percutaneous coronary intervention. A significant reduction in fatal and non-fatal myocardial infarction was also shown. On the contrary, double antiplatelet therapy is associated with a significant increased risk on major bleeding when used > 30 days, OR 1.80, if compared to aspirin monotherapy resulting in an absolute risk increase of 1.5% on major bleeding. Aspirin has a baseline risk of 1.9% on major bleeding when used for a period of 13 months. Subsequently, an meta-analysis by Zhou et al (2012) showed

comparable results when using double antiplatelet therapy on the same primary endpoints and risk on major bleeding. Gualandro et al showed that amongst 480 patients having an acute coronary syndrome (ACS) perioperatively, 50 % had coronary plaque rupture, displaying evidence for type 1 myocardial infarction. This is in contradiction with the for many years generally accepted hypothesis that patients having an ACS perioperatively, suffered from type 2 myocardial infarction. This new insight, combined with increased knowledge on stress induced plaque inflammation leading to plaque instability and subsequent thrombus formation, creates the basis to reexamine the potential beneficial effect of double antiplatelet therapy in a (not previously examined) high risk patient category such as vascular patients, in preventing cardiovascular (atherothrombotic) complications. This specific subgroup has not been investigated previously.

Study objective

The objective of the proposed study is to evaluate if results as are written above, are to be extrapolated on high risk patients who underwent vascular surgery. In this group of patients, there is a substantial risk of 15-20% to die in the first year postoperatively. In contrast, patients who underwent myocardial infarction have a chance of 'only' 10%. Differences could be explained simply by failure to provide adequate treatment of atherosclerotic cardiovascular diseases and adding extra antiplatelet therapy would be a logical next step given the presumed pathofysiological process in this specific subgroup of patients.

Study design

Patients are eligible for inclusion in case of outpatient clinic elevated troponin value above the 99th percentile of that specific assay. During this visit, patients will be informed about participation into the study. Second, patients will be evaluated for significant coronary obstructive disease by a cardiologist through angiography. Next, vascular surgery will be performed without interference. Postoperatively, troponin values will be measured on day 1 through 3. Randomisation will be accorded definitely if at least one of these measurements is above the 99th percentile and elevated with respect to baseline value. A cardiologist will be consulted to exclude myocardial infarction if necessary. If patients meet all of the inclusion criteria, but non of the exclusion criteria, randomization to study medication can be accorded (treatment with either clopidogrel or placebo), on top of standard treatment with aspirin for 12 months. At 30-days after surgery and after that every 3 months, patients are seen on outpatient clinic visits for blood samples and quality of life questionnaires. Study ends after completion of 12 month follow-up.

This will be a randomized controlled double blind clinical trial with an

intention-to-treat analysis.

Intervention

Patients will be randomized to receive either clopidogrel or placebo on top of standard treatment with aspirin for 12 months postoperatively, in case of postoperative troponin elevation, above the 99th percentile and elevation with respect to the baseline value, within the first 3 days after surgery. Randomization will only be accorded if patients meet all of the inclusion- but non of the exclusion criteria.

During the 12 month follow-up period, patients will be seen 5 times at out outpatient clinical visit at 30days after surgery and thereafter every 3 months. In total, 6 blood samples (a 10mL) will be collected important for analysis of the primary endpoint: one during index hospitalization (=standard of care) and 5 during outpatient clinic visits (additional measurements in this study).

Patients with preoperative troponin elevation will be refferend to a cardiologist for analysis of the presence of significant occlusive coronary artery disease through angiography. Significant and intermediate lesions will be assessed using Fractional Flow Reserve (conform international guidelines).

Study burden and risks

Burden
Patients will be asked for outpatient clinic visits on 30 days and therafter every 3 months, for 12 months follow-up (5 visits). In total, 6 blood samples and 2 questionnaires on quality of life will be taken (1 bloodsample is considered standard of care directly after surgery, other 5 are additional measurements). Patients are asked for a total of 5 extra outpatient clinic visits.

Risks
Patients will be exposed to a higher risk of major bleeding when compared to aspirin monotherapy. According to a meta-analysis performed by Bowry et al, there is an absolute risk increase of 1.5% when using clopidogrel combined with aspirin for 1 year (the baseline risk on bleeding on Aspirin monotherapy is 1.9% over a 13 month period of treatment).
Other adverse events reported with clopidogrel: bruising, epistaxis, diarrhea and abdominal pains.

We do not suspect unexpected adverse events hence there is extensive clinical experience using clopidogrel.

Patients will be asked for changes in health status during routine outpatient

clinical visits through the entire study and actions will be taken according to good clinical practice if required.

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

1.Preoperative myocardial injury (baseline value), defined as a troponin release above 99th percentile.
2.Absence of significant occlusive coronary artery disease as diagnosed through angiography (and confirmed by FFR).
3.Postoperative myocardial injury, defined as troponin release above the 99th percentile, which exceed the baseline value.

Exclusion criteria

1. if troponin elevation is diagnosed as myocardial infarction by cardiologist.
2. Presence of significant occlusive coronary artery disease, as diagnosed through preoperative angiography, requiring treatment.
3. No postoperative troponin values above the 99th percentile and no rise with respect to baseline value.
4. Active bleeding.
5. Active cardiac conditions at the time of randomisation such as unstable angina pectoris, active congestive heart failure (CHF), serious cardiac arrhythmias, symptomatic valvular disease.
6. Clear indication for long-term P2Y12 inhibitor use.
7. Preoperative use of P2Y12 inhibitors.
8. Previous allergy or intolerance to clopidogrel.
9. Use of oral anticoagulants after surgery.
10. Use of intravenous glycoprotein IIB/IIA receptor inhibitors in the previous three days.
11. Coronary revascularization therapy in the previous six months.
12. Renal failure requiring dialysis.
13. Significant liver disease (i.e. ALAT, ASAT > 3x ULN).
14. Cancer with an expected life expectancy less than 6 months.
15. Excessive alcohol use.
16. No informed consent.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-08-2016

Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Plavix
Generic name:	Clopidogrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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: 28641
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-000686-23-NL
CCMO	NL54577.078.16
OMON	NL-OMON28641