Clopidogrel for the prevention of late cardiac events in patients with asymptomatic perioperative acute coronary syndrome.

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The primary objective of this study is to determine whether clopidogrel + best medical treatment is superior to best medical treatment only in preventing:A) cardiovascular death, MI, stroke, or severe ischemia of the coronary or peripheral arterial...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON32253

Source
ToetsingOnline

Brief title
DECREASE VII

Condition

- Coronary artery disorders
- Vascular therapeutic procedures
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Cardiac ischemia / cardiac damage

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: Cardiac complications, Clopidogrel, Vascular surgery

Outcome measures

Primary outcome

UNSTABLE ANGINA WITH ECG CHANGES

An episode of angina lasting greater than 15 minutes which is refractory to the

patients usual medications which leads to hospital admission and is associated

with ECG changes consistent with coronary ischemia.

MYOCARDIAL INFARCTION (2 of 3 criteria)

1. Typical ischemic chest pain,

2. Elevation of troponin values,

3. New ECG changes which include new persistent ST/T changes, new BBB or new Q

-

waves in at least 2 consecutive leads

SEVERE CORONARY ISCHEMIA LEADING TO AN INTERVENTION

Unstable angina with ECG changes requiring hospitalization which leads to

coronary revascularization (PTCA, CABG) (or transfer for revascularization)

during the hospitalization

Revascularization of coronary arteries

PTCA: Percutaneous Transluminal Coronary Angioplasty

CABG: Coronary Artery Bypass Graft Surgery

SEVERE LIMB ISCHEMIA LEADING TO AN INTERVENTION

Severe ischemia of the lower extremity which is deemed to threaten the viability of the limb, and is associated with continuing ischemic pain, and neurological deficit, or inadequate skin capillary circulation, or inaudible arterial flow signals by Doppler of the pedal arteries AND which leads to hospitalization for an intervention such as thrombolytic therapy, angioplasty, bypass surgery or amputation.

Reperfusion/reconstruction of peripheral arteries

1. Catheter directed thrombolytic therapy of a peripheral artery

2. Percutaneous transluminal angioplasty of the iliac or femoral arteries (or their main

branches)

3. Surgical revascularization of the aorta or infrainguinal arteries

Amputation

Amputation of the limb secondary to vascular insufficiency - subdivided into Major (proximal to the transmetatarsal level) and Minor (distal to the transmetatarsal level)

STROKE

New focal neurological deficit thought to be vascular in origin lasting greater than 24 hours. Confirmation with CT scan/MRI is recommended but not mandatory. Strokes will be further classified as ischemic, hemorrhagic, or uncertain

TIA

Transient Ischemic Attack: New Onset Focal neurological deficit that resolves within 24 hours

DEATH

Subdivided as cardiovascular and non-cardiovascular. All deaths with a clear cardiovascular cause including haemorrhagic or unknown cause will be classified as cardiovascular. Only deaths due to a documented non-cardiovascular cause (e.g. cancer) will be classified as non-cardiovascular.

Secondary outcome

LIFE-THREATENING BLEEDING

Fatal or intra-cranial bleeding, or bleeding requiring surgical intervention or transfusion of at least 4 units of blood or plasma expanders.

MODERATE AND MINOR BLEEDING

Bleeding which requires <=3 units of blood or blood products will be classified as moderate. All other bleeding not requiring transfusion (but leading to the temporary or permanent cessation of study medication and/or aspirin) will be classified as minor.

TERTIARY STUDY PARAMETERS / OUTCOME OF THE STUDY:

Identification of preoperative risk factors for the occurence of the primary

endpoint

Identification of novel biomarkers that predict the occurence of the primary

endpoint

Study description

Background summary

Patients undergoing vascular surgery are at increased risk for perioperative and long-term cardiovascular events. Despite rigorous preoperative risk assessment and subsequent initiation of appropriate medical therapy and coronary revascularization, approximately 20% of these patients experience asymptomatic perioperative myocardial damage as assessed by troponin T release. Late outcome of these patients is severely compromised: the incidence of death in the first year after surgery is approximately 25%, mostly attributable to cardiac causes.

Studies in non-surgical patients with acute coronary syndromes have shown that clopidogrel on top of aspirin might improve cardiovascular outcome. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomly assigned 12,562 patients who had presented within 24 hours after the onset of symptoms of an acute coronary syndrome to receive clopidogrel or placebo in addition to aspirin for 3 to 12 months. In this trial it was shown that clopidogrel was associated with a 20% relative risk reduction for the composite of cardiovascular death, nonfatal myocardial infarction or stroke.

Routinely patients undergoing vascular surgery are treated with low molecular heparins, beta-blockers, statins and aspirin. The addition of clopidogrel might be beneficial in these patients although safety with respect to bleeding complications is an important issue. Reassuring are previous study results. The CASPAR-trial, that was designed to test whether the addition of clopidogrel would improve patency in 801 patients with peripheral arterial bypass grafts, showed that the incidence of bleeding episodes increased from 1.2% in patients with aspirin alone to 2.1% in patients on both aspirin and clopidogrel. However, the number of episodes of life-threatening bleedings was not significantly increased in patients on dual antiplatelet therapy. A recent

study performed at Erasmus MC, in which patients with previous coronary stent placement underwent surgery, showed that the continuation of dual antiplatelet therapy did not increase the demand for blood transfusion.

Thrombosis caused by a ruptured or eroded atherosclerotic plaque is the usual underlying mechanism of acute coronary syndromes. Aspirin seems to reduce the risk of plaque rupture and subsequent death from cardiovascular causes and nonfatal myocardial infarction but there is still a substantial risk of such events in both the short term and the long term. The thienopyridine derivative clopidogrel is an antiplatelet agent that inhibits the platelet aggregation induced by adenosine diphosphate, thereby reducing ischemic events. Combining one of this drug with aspirin, which blocks the thromboxane-mediated pathway, may have an additive effect. Therefore the current study has been set up to investigate whether the addition of clopidogrel to aspirin in a group of vascular surgery patients at high cardiac risk is safe and improves long term cardiac outcome.

Study objective

The primary objective of this study is to determine whether clopidogrel + best medical treatment is superior to best medical treatment only in preventing:

A) cardiovascular death, MI, stroke, or severe ischemia of the coronary or peripheral arterial circulation leading to an intervention in patients with asymptomatic perioperative troponin release during or shortly after major vascular surgery.

Secondary objectives include determining the effect of clopidogrel on:

B) Bleeding complications, defined as life-threatening bleeding, moderate and minor bleeding in patients with asymptomatic perioperative troponin release after major vascular surgery.

Tertiary objectives also include determining:

C) Identify preoperative risk factors for the occurrence of the primary endpoint in patients scheduled for major vascular surgery

D) Identify novel biomarkers that predict the occurrence of the primary endpoint in patients scheduled for major vascular surgery

Study design

PATIENT RECRUITMENT:

All patients at the vascular surgery outpatient clinic will be screened for eligibility in the study. Those that meet one of the inclusion criteria but none of the exclusion criteria will be asked to participate in the study. After informed consent is obtained the preoperative case record forms will be completed and pertinent data will be entered into the study database. Those patients that do not develop asymptomatic postoperative troponin release will not be randomized. However these patients will remain in the database and will be followed according to a prespecified protocol. Data of these patients will be used for the tertiary objectives of this study. Patients that do develop asymptomatic troponin release will be randomized to receive, in a double-blind way, either clopidogrel 75 mg once daily (with an initial dose of 300mg) plus aspirin or aspirin alone.

PREOPERATIVE WORK UP

Preoperative work up will be done according to current ACC/AHA guidelines but must include at least:

Risk factor assessment:
Of all screened patients the following risk factors will be assessed:
1. Age > 70 years
2. History of angina pectoris or current angina pectoris
3. History of myocardial infarction
4. History of transient ischemic attack (TIA) or cerebrovascular accident (CVA)
5. History of congestive heart failure or current congestive heart failure
6. Diabetes mellitus, insulin dependent (IDDM) or non-insulin dependent (nIDDM)
7. Renal dysfunction (creatinine > 160 mmol/l), and creatinine clearance
8. History of hypertension or current untreated hypertension
9. Chronic obstructive pulmonary disease

Laboratory measurements:
Of all screened patients the following laboratory results will be obtained preoperatively:
1. NT-proBNP
2. fasting glucose
3. Troponin T
4. Total cholesterol, LDL, HDL, triglycerides
5. High-sensitive CRP
6. Interleukin-6, sTNF-alfa
7. An additional 10 ml blood sample of all patients for storage

Echocardiography:
All screened patients will undergo preoperative echocardiography to assess
1. Left ventricular function
2. Wall motion abnormalities
3. Valve abnormalities

Stress testing:
Patients referred for stress testing are patients with 3 or more cardiac risk factors (MI, stroke, AP, CHF, renal failure, age > 70 years). Preoperative stress test results will guide perioperative management. Patients with evidence of left main disease will undergo coronary revascularization.

Electrocardiography:
All screened patients will undergo preoperative electrocardiography.

Ankle-arm index:
During admission the ankle-arm index will be measured in all patients

Medical therapy:
All patients without contraindication will receive at least the following medication:
1. Beta-blocker therapy, preferably bisoprolol, with dose titration to a target heart rate of 60 -65 beats/minute
2. Statin therapy, preferably fluvastatin XL 80mg
3. Aspirin therapy
4. Proton pump inhibitor therapy, preferably pantoprazol 40mg

PERIOPERATIVE MANAGEMENT:

Perioperative management will be done according to current ACC/AHA guidelines but must include:
1. Troponin T measurement preoperatively and on day 1, 2, 3, and 7 postoperatively.
2. ECG recording on day 1, 3, and 7 postoperatively or whenever clinically indicated.
3. Randomization of patients to clopidogrel or placebo in case of asymptomatic troponin
release, using a computer generated randomization list with stratification according to participating centre.
4. Ensurement of adequate medical therapy if medication cannot be given orally; i.v. administration of beta-blockers and restart of statins and aspirin as soon as
possible.

Management after discharge
Patients will be treated according to current ACC/AHA guidelines but must include at least a follow-up visit 30 days, 3 months, 6 months and 12 months after surgery. During these visits case record forms will be completed to assess the occurrence of the predefined (safety) endpoints. Completed case record forms will be faxed to the Project Office.

Intervention

Patients who develop asymptomatic troponin release during the perioperative phase, will be randomised to either clopidogrel or not on top of standard medical treatment.

Study burden and risks

NATURE AND EXTENT OF THE BURDEN ASSOCIATED WITH PARTICIPATION
Laboratory measurements: no extra tests associated with participation
Doctor / follow up visits: No extra visits associated with participation
Physical examination: No extra burden associated with participation

RISKS ASSOCIATED WITH PARTICIPATION
Patients treated with clopidogrel simultaniously with aspirin have an slighty increased risk for non-fatal bleedings complications, sometimes requiring transusions. However, studies show (see background) no increase in the risk for life-threatening bleeding complications.

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) age above 18 years
2) patients scheduled for major vascular surgery, one of the following
- Abdominal aortic aneurysm repair
- Aortic stenosis repair
- Femoropopliteal bypass surgery, above and below knee
3) asymptomatic troponin T release during or after surgery

Exclusion criteria

1) Active bleeding
2) Untreated left main disease
3) Active cardiac condition such as unstable angina pectoris, active CHF, serious cardiac arrhythmias, symptomatic valvular disease, recent < 6 months.
4) Preoperative positive troponin T
5) Inability to take clopidogrel orally
6) Clear indication for long-term clopidogrel use
7) Previous allergy or intolerance to clopidogrel
8) Renal failure requiring dialysis
9) Significant liver disease (i.e. ALAT, ASAT >3x ULN)
10) Cancer with an expected life expectancy < 6 months
11) Anticipated non-adherence to clopidogrel
12) Excessive alcohol use
13) Pregnancy or planning to become pregnant
14) Failure to provide informed consent

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2009
Enrollment:	500
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:	03-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	21-01-2009
Application type:	First submission
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: 29444
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2008-004016-12-NL
CCMO	NL22179.078.08
OMON	NL-OMON29444