Ticagrelor of prasugrel versus clopidogrel bij oudere patiënten met een acuut coronair syndroom (pijn op de borst en hartinfarct) en een hoog bloedingsrisico: Optimaliseren van bloedplaatjes remming bij ouderen met verhoogd bloedingsrisico

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21629

Source
Nationaal Trial Register

Brief title
POPular AGE

Health condition

Anti-platelet therapy in the elderly with Non ST elevation acute coronary syndrome and CRUSADE score of at least 31

Sponsors and support

Primary sponsor: St. Antonius teaching hospital
Source(s) of monetary or material Support: ZonMw

Intervention

Outcome measures

Primary outcome

The first primary endpoint is the occurrence of any bleeding episode at 30 days and 1 year after diagnosis and second primary endpoint is the net clinical benefit at 30 days and 1 year after diagnosis.

Secondary outcome

Secondary safety endpoints are the number of patients with (non-)CABG-related major bleeding, major bleeding, minor bleeding, life threatening bleeding, fatal bleeding, intracranial bleeding and bleed requiring transfusion or the number of patients with combination of these endpoints at 30 days and 1 year after diagnosis. Different bleeding classifications will be used, i.e. TIMI, PLATO, GUSTO and BARC bleeding scales to make the study comparable to previous and future publications

Secondary net clinical benefit endpoints are the number of patients who either died from any cause other than vascular or bleeding causes, died from vascular causes, died from bleeding causes (= fatal bleeding), developed recurrent myocardial infarction, stroke, unstable angina, trans ischemic attack, other arterial thrombosis, PLATO major and minor bleeding or the number of patients with combinations of these endpoints at 30 days and at one year after diagnosis.

Secondary efficacy endpoints are the number of patients who either died, died from cardiovascular death, from cerebrovascular death, developed recurrent MI, stent thrombosis, underwent urgent target vessel revascularisation (TVR), hospitalization for ACS, developed stroke or the number op patients with combinations of these endpoints at 30 days and at one year after diagnosis.

Secondary endpoints in terms of quality of life are measurements obtained with EuroQol 5D and SF36 questionnaires.

Tertiary endpoints would be the evaluation of genetic variants on the response to clopidogrel and prasugrel or ticagrelor in terms of efficacy and safety in a candidate gene approach,

Genome Wide Association Study or (next generation) sequencing

Study description

Background summary

Rationale: Dual antiplatelet therapy is crucial in patients with an acute coronary syndrome (ACS) to prevent atherothrombotic events. The recent guideline of the European Society of Cardiology (ESC) recommends the use of more potent antiplatelet drugs i.e. ticagrelor or prasugrel, which give more bleeding complications, compared to clopidogrel (1). The “Commissie Farmaceutische Hulp” (CFH) concluded that ticagrelor is superior to clopidogrel, mainly because of a mortality reduction observed in the PLATO study (2). However, the representation of the elderly in clinical trials is low. In a subgroup analysis of patients 75 years of age and older, the difference between cardiovascular event rates in ticagrelor versus clopidogrel treated patients, did not reach statistical significance (3). There is a major gap in the knowledge regarding the optimal strategy for the elderly, who have an increased risk of both atherothrombotic and bleeding complications. The ESC guideline advises on the use of the CRUSADE bleeding risk score for risk stratification. However, based on the currently available data it is not clear which antiplatelet treatment should be initiated in those patients with a high bleeding risk, who often also appear to have the highest atherothrombotic risk.

Objective: To assess the safety, efficacy and net clinical benefit of clopidogrel versus the new antiplatelet drugs i.e. ticagrelor and prasugrel, in elderly with a high bleeding risk.

Study design: Randomized, controlled, open label, multicenter study.

Study population: 1,000 patients hospitalized for either myocardial infarction without ST-segment elevation (NSTEMI) or unstable angina (UA), aged at least 75 years and with a score of at least 31 based on the CRUSADE bleeding risk score.
Intervention: Patients randomized to clopidogrel will receive 75 mg daily for one year. Those randomized to the new antiplatelet drugs will be treated with either ticagrelor 90 mg twice daily or prasugrel 5 mg daily, according to hospital’s local standards. The follow-up duration will be one year.

Main study parameters/endpoints: Any bleeding episode classified according to different bleeding scores, see section 7.1.3. and net clinical benefit defined as composite endpoint of death, non-fatal myocardial infarction, non-fatal stroke, PLATO major life threatening (without fatal bleeding), major and minor bleedings. Efficacy in terms of the combined endpoint of death, myocardial infarction, stroke, stent thrombosis. Quality of life assed by the EuroQol 5D and SF36 questionnaires.

Sample size calculation/data analysis: Assuming an alpha of 0.05, beta 0.2 and the combined end point of non-CABG related PLATO major and minor bleedings of 10% in the clopidogrel group versus 17% in the new antiplatelet drugs group, a lost-to-follow-up rate of 10%, the

inclusion of 1,000 patients (500 per group) would be sufficient. Intention-to-treat principle will be used in data analysis. Kaplan-Meier analysis will be used and groups will be compared by hazard ratios and 95% confidence intervals.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden for patients participating in the study is that patients will be contacted twice during the study; 3 months and 12 months after initial diagnosis to fill out a questionnaire, to get information regarding the use of antiplatelet drugs, changes in prescribed drugs and medical condition. At 3 months and 12 months patients will also be requested to fill out EuroQol 5D and SF36 questionnaires to asses quality of life. The patient may be contacted by telephone if this is necessary to complete follow-up data

Study objective

Since bleeding risk is high in the elderly we hypothesize that clopidogrel is superior to ticagrelor and prasugrel in terms of causing lesser bleeding events and being non inferior in net clinical benefit in patients above 75 years and CRUSADE score ≥ 31 with acuut coronary syndrome.

Study design

3 and 12 months after enrollment

Intervention

clopidogrel versus ticagrelor/prasugrel in patients aged at least 75 year with CRUSADE score of at least 31. At 3 months and 12 months patients will also be requested to fill out questionnaires to asses endpoints of the study. Follow up will be 12 months.

Contacts

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Eligibility criteria

Inclusion criteria

1) At least 75 years of age.

2) Hospitalization for NSTEMI or unstable angina (UA), according to the following definitions NSTEMI (Non-ST-elevation myocardial infarction) will be defined as detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischaemia.

- New or presumed new significant ST-segment–T wave (ST–T) changes other than ST-segment elevation.

- Development of pathological Q waves in the ECG.

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- Identification of an intracoronary thrombus by angiography or autopsy.

UA (unstable angina) will be defined as acute onset of chest pain consistent with symptoms of ischaemia without rise in cardiac biomarker values, which may or may not be consistent with ECG changes suggesting ischaemia.

Diagnosis of UA and NSTEMI should be made by decisional doctor.

3) A CRUSADE bleeding risk score of at least 31

Exclusion criteria

Exclusion criteria

1) Contraindication to P2Y12 inhibitors i.e. clopidogrel, prasugrel or ticagrelor:

- Hypersensitivity to the active substance or to any of the excipients
- History of intracranial bleeding or active pathological bleeding such as peptic ulcer or intracranial haemorrhage
- Moderate to severe (Child-Pugh C) hepatic disfunction.
- Concomitant use of ticagrelor with strong CYP3A4 inhibitors (e.g. itraconazol, voriconazol, ketoconazol, erytromycine, clarithromycine, rifampicine, nefozodon, lopinavir, ritonavir en atazanavir)

2) Unable or unwilling to give informed consent or have a life expectancy of less than one year

3) Active malignancy with increase in bleeding risk, in the investigator’s opinion.

4) Having received thrombolytic therapy within the previous 24 hours or oral anticoagulants during the previous 7 days.

5) Severe renal function impairment needing dialysis.

6) Confirmed or persistent severe hypertension (Systolic Blood Pressure (SBP) > 180 mmHg and/or Diastolic Blood Pressure (DBP) >110 mmHg) at randomization.

7) Contraindication to anticoagulation or at increased bleeding risk, at the investigator’s opinion, i.e. because of active malignancy.

8) Cardiogenic shock (SBP ≤ 80mmHg for >30 mins) or needing Intra-Aortic Balloon Pump (IABP) at presentation.

9) History of major surgery, severe trauma, fracture or organ biopsy within 90 days prior to randomisation.

10) Clinically significant out of range values for platelet count or haemoglobin at screening, in the investigator’s opinion.

11) ACS under dual antiplatelet therapy, e.g. aspirin with a P2Y12 inhibitor; clopidogrel, prasugrel, ticagrelor.

12) Patients either homozygous or heterozygous carriers of a CYP2C19*2 or *3 allele if known at time of randomization.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2013
Enrollment:	1000
Type:	Anticipated

Ethics review

Positive opinion

Date:	14-05-2013
Application type:	First submission

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
NTR-new	NL3804
NTR-old	NTR3991
Other	EudraCT : 2013-001403-37
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results