Cost-effectiveness of CYP2C19 genotype guided treatment with antipaletelet drugs in patients with ST-segment-elevation myocardial infarction undergoing immediate percutaneous coronary intervention with stent implantation: optimization of treatment.

Published: 31-03-2011
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To assess the efficacy, safety and cost-effectiveness of the CYP2C19 genotype guided antiplatelet treatment strategy, using clopidogrel or prasugrel/ticagrelor.

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

Summary

ID

NL-OMON47500

Source
ToetsingOnline

Brief title
Pharmacogenetics in STEMI

Condition

- Coronary artery disorders

Synonym
heart attack, myocardial infarction

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Subsidie ZonMW

Intervention

Keyword: clopidogrel, pharmacogenetics, prasugrel, STEMI

Outcome measures

Primary outcome

To determine whether the CYP2C19 genotype guided antiplatelet treatment strategy is not inferior to a treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel in terms of the composite of death, recurrent myocardial infarction (MI), definite stent thrombosis, stroke and PLATO major bleeding at 1 year, in patients undergoing primary PCI for STEMI. If non-inferiority is proven, analysis will be performed for superiority.

To determine whether the CYP2C19 genotype guided antiplatelet treatment strategy is superior to a treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel in terms of a composite endpoint of PLATO major and minor bleeding.

To assess the quality of life of patients and health-care resource use in both treatment groups i.e. the CYP2C19 genotype guided antiplatelet treatment and the treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel, to calculate Quality Adjusted Life Years (QALY*s) and net costs per

life-year and QALY.

Secondary outcome

Secondary objectives:

To compare the efficacy of the CYP2C19 genotype guided antiplatelet treatment strategy versus the treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel in terms of clinical outcome parameters taken separately or combinations of parameters i.e. death, cardiovascular death, cerebrovascular death, recurrent myocardial infarction (MI), definite stent thrombosis, probable stent thrombosis, possible stent thrombosis, urgent target vessel revascularisation (TVR), hospital admission for ACS or stroke at 30 days and 1 year, in patients undergoing primary PCI for STEMI.

To compare the safety of the CYP2C19 genotype guided antiplatelet treatment strategy to the treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel in terms of safety outcome parameters taken separately or combinations of these parameters i.e. (non-)CABG-related major bleeding, major bleeding, minor bleeding, life threatening bleeding, fatal bleeding, intracranial bleeding, bleed requiring transfusion at 30 days and 1 year in patients undergoing primary PCI for STEMI. Different bleeding classifications will be used i.e. TIMI, PLATO and BARC bleeding scales to make the study comparable to previous and future publications.

To compare the CYP2C19 genotype guided antiplatelet treatment strategy

(subdivided into patients included before protocol version 05, 16-02-2012 and patients included starting with protocol version 05, 16-02-2012) to a treatment strategy with either clopidogrel in all patients or a treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel in terms of the composite of death, recurrent myocardial infarction (MI), definite stent thrombosis, stroke and PLATO major and minor bleeding at 30 days and 1 year, in patients undergoing primary PCI for STEMI.

To compare the efficacy and safety of CYP2C19 genotype guided antiplatelet treatment strategy to the treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel in subgroups (subgroups are described in the protocol) in terms of death, recurrent myocardial infarction (MI), definite stent thrombosis, stroke and PLATO major and minor bleeding (or one of the other bleeding classifications, i.e. TIMI, BARC) and net adverse clinical events , in-hospital, at 30 days and at 1 year in patients undergoing primary PCI for STEMI.

To compare the efficacy and safety of using a loading dose of clopidogrel versus not using a loading dose of clopidogrel in the CYP2C19 genotype guided antiplatelet group in terms of the composite death, recurrent myocardial infarction (MI), definite stent thrombosis, stroke and PLATO major and minor bleeding (or one of the other bleeding classifications, i.e. TIMI, BARC) at 30 days and 1 year, in patients undergoing primary PCI for STEMI.

To compare the efficacy and safety of using glycoprotein IIB/IIIA inhibitors (GPI) in patients undergoing primary PCI for STEMI in terms of death, recurrent myocardial infarction (MI), definite stent thrombosis, stroke and PLATO major and minor bleeding (or one of the other bleeding classifications, i.e. TIMI, BARC) and net adverse clinical events , in-hospital, at 30 days and at 1 year in patients undergoing primary PCI for STEMI. The use of GPI will be compared between patients on ticagrelor with GPI versus ticagrelor without GPI, in patients on ticagrelor with GPI versus clopidogrel with GPI and there will be further sub-group analysis based on the CYP2C19 genome.

To compare the number of patients in whom the antiplatelet drug is prematurely discontinued or switched to another drug in the CYP2C19 genotype guided antiplatelet treatment versus the treatment strategy with the newer antiplatelet drugs i.e. ticagrelor and prasugrel.

Tertiary objectives:

To evaluate whether clopidogrel in non carriers of a reduced CYP2C19 function allele is not inferior to prasugrel and ticagrelor in CYP2C19 reduced function allele carriers in terms of clinical outcome and safety parameters taken separately or combinations of these parameters i.e. death, cardiovascular death, cerebrovascular death, recurrent myocardial infarction (MI), definite stent thrombosis, probable stent thrombosis, possible stent thrombosis, urgent target vessel revascularisation (TVR), hospital admission for ACS, stroke,

(non-)CABG-related major bleeding, major bleeding, minor bleeding, life threatening bleeding, fatal bleeding, intracranial bleeding or bleed requiring transfusion at 30 days and 1 year, in patients undergoing primary PCI for STEMI.

To evaluate the effect of genetic variants on the response to clopidogrel, ticagrelor or prasugrel in terms of efficacy and safety in a candidate gene approach, Genome Wide Association Study or (next generation) sequencing.

Study description

Background summary

The use of antiplatelet drugs (i.e. clopidogrel, ticagrelor or prasugrel) are crucial as antiplatelet drug in the treatment in of patients undergoing percutaneous coronary intervention (PCI) with stent implantation and during one year after PCI, to prevent atherothrombotic complications. New antiplatelet drugs, i.e. prasugrel and ticagrelor, are more effective in preventing atherothrombotic complications, but exhibit a higher risk of bleeding complications, compared to clopidogrel. Clopidogrel is converted into its active metabolite by CYP2C19. Carriers of the non functional CYP2C19*2 and *3 alleles have an impaired CYP2C19 capacity, making clopidogrel less effective in CYP2C19*2 and *3 carriers. For these subjects prasugrel orticagrelor is an alternative, because the antiplatelet effect of those drugs is not influenced by CYP2C19 metabolizer status. It is hypothesized that the net clinical benefit, taking atherothrombotic and bleeding complications into account, of a CYP2C19 guided antiplatelet strategy is not inferior to a strategy with the newer antiplatelet drugs and reduces drug costs.

Study objective

To assess the efficacy, safety and cost-effectiveness of the CYP2C19 genotype guided antiplatelet treatment strategy, using clopidogrel or prasugrel/ticagrelor.

Study design

The design is a randomized, open label, multicenter study. STEMI patients who underwent primary PCI will be randomized to the CYP2C19 genotype guided

antiplatelet treatment strategy (intervention group) or treatment with prasugrel or ticagrelor (usual care in the control group). Patients in both treatment groups will receive the antiplatelet drugs for the duration of one year.

Intervention

The intervention group will be genotyped for the CYP2C19*2 and *3 alleles within 48 hours after PCI. Carriers of a CYP2C19*2 or *3 allele will receive prasugrel at a dosage of 10 mg once daily or ticagrelor at a dosage of 90mg twice daily starting after PCI for one year. Patients older than 75 years or with a body weight of less than 60 kg will receive prasugrel at a dosage of 5 mg once daily. Non-carriers will be treated with clopidogrel at a dosage of 75mg once daily. The control group receives prasugrel or ticagrelor at the same dosage as described above. The choice for prasugrel or ticagrelor will be made by the attending doctor. Antiplatelet therapy will be continued for one year after PCI. Follow-up using questionnaires will be performed for one year.

Study burden and risks

The burden for patients participating in the study is that patients will be contacted after 1,6 and 12 months to fill out a follow-up and a quality of life questionnaire.

Depending on the randomisation result patients can be treated with prasugrel or ticagrelor (routine treatment) or clopidogrel (if genotyping result is 'extensive metabolizer'). The use of prasugrel and ticagrelor is associated with a decrease in atherothrombotic events, compared to clopidogrel, but with an increase in bleeding events. Evidence suggests that by selecting patients based on CYP2C19 metabolizer status the best net clinical benefit can be achieved related to atherothrombotic and bleeding events.

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) more than 21 years of age with symptoms of acute myocardial infarction of more than 30 minutes but less than 12 hours
2) performed primary PCI with stenting for STEMI

Exclusion criteria

1) unable to give informed consent or have a life expectancy of less than one year
2) active malignancy with increase in bleeding risk, in the investigator*s opinion
3) women who are known to be pregnant or who have given birth within the past 90 days or who are breastfeeding
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
8) cardiogenic shock (SBP <= 80mmHg for >30 mins) or needing Intra-Aortic Balloon Pump (IABP)
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.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-06-2011
Enrollment:	2475
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Brilique
Generic name:	ticagrelor
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Efient
Generic name:	Prasugrel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plavix
Generic name:	Clopidogrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-03-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-10-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-06-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	28-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-05-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-04-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

(Nieuwegein)

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: 24886
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2010-024667-40-NL
CCMO	NL35106.100.11
OMON	NL-OMON24886