Platelet reactivity in diabetic patients and the effects of different antithrombotic agents on the results of multiple platelet function tests

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Primary Objectives:1. To compare the magnitude of baseline (or intrinsic) platelet reactivity between T2DM patients and healthy volunteers using multiple platelet function assays 2. To compare the magnitude of baseline (or intrinsic) platelet...

Ethical review	Not approved
Status	Will not start
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON34970

Source
ToetsingOnline

Brief title
PREDATOR

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes, diabetes mellitus type 2

Research involving
Human

Sponsors and support

Primary sponsor: Internal Medicine

Source(s) of monetary or material Support: St Antonius ziekenhuis (R&D Interne geneeskunde en R&D Cardiologie)

Intervention

Keyword: aspirin, clopidogrel, diabetes mellitus, platelet reactivity, prasugrel

Outcome measures

Primary outcome

1. The magnitude of baseline (or intrinsic) platelet reactivity among male and female T2DM patients and among male and female healthy volunteers as measured with multiple platelet function assays

2. Tthe magnitude of *on-aspirin once daily platelet reactivity* and *on-aspirin twice daily platelet reactivity* among male and female T2DM patients and among male and female healthy volunteers as measured with multiple platelet function assays

3. The magnitude of *on-clopidogrel platelet reactivity* and *on-prasugrel platelet reactivity* among male and female T2DM patients and among male and female healthy volunteers as measured with multiple platelet function assays

4. The magnitude of *on-dual antiplatelet therapy* platelet reactivity* among male and female T2DM patients and among male and female healthy volunteers as measured with multiple platelet function assays

Secondary outcome

nvt

Study description

Background summary

Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) mellitus. Specifically, recent studies have demonstrated that T2DM is associated with a twofold to fourfold risk of developing coronary artery disease (CAD), peripheral arterial disease (PAD), and stroke. Several mechanisms account for the increased atherothrombotic risk in diabetes mellitus patients, including a high intrinsic (or baseline) platelet reactivity status.
As a consequence, two recent primary prevention trials in T2DM patients attempted to provide proof of the principle that primary prevention by means of aspirin therapy reduces the incidence of atherothrombotic events on the long-term. Although both trials did not show a superiority of aspirin therapy when compared to placebo, a trend favoring aspirin therapy was clearly visible. Abovementioned results have fueled the discussion why low-dose aspirin failed to show superiority and currently, the body of evidence is growing that the efficacy of low-dose aspirin in patients with diabetes on the platelet level is substantially lower than in individuals without diabetes.
Another interesting subgroup of patients in whom aspirin therapy has failed to show superiority in primary prevention includes women. Are there any apparent reasons for these sex-related differences? The answer is yes. First of all, women tend to develop heart disease between 10 and 15 years later than men. This may explain why consistent benefits of aspirin on all major cardiovascular endpoints, including myocardial infarction and stroke, were observed only among women aged 65 years or older. Second and probably more important, sex differences in salicylate metabolism, platelet responses, vascular reactivity, and the nature of atherosclerotic disease also cause different biological responses between men and women
In the present study, we sought to explore the differences in baseline (intrinsic) platelet reactivity status between T2DM and healthy volunteers with multiple platelet function assays. Moreover, we will investigate the response to different forms and intensities of antiplatelet therapies and lastly, we will explore any sex-related differences within the group of T2 diabetics and healthy volunteers.

Study objective

Primary Objectives:
1. To compare the magnitude of baseline (or intrinsic) platelet reactivity between T2DM patients and healthy volunteers using multiple platelet function assays

2. To compare the magnitude of baseline (or intrinsic) platelet reactivity

between male and female healthy volunteers using multiple platelet function assays

3. To compare the magnitude of baseline (or intrinsic) platelet reactivity between male and female T2DM using multiple platelet function assays

4. To investigate the effects of different antiplatelet agents (low-dose aspirin alone once daily, followed by low-dose aspirin twice daily), (clopidogrel alone followed by prasugrel alone) or (low dose aspirin once daily followed by dual antiplatelet therapy with aspirin and clopidogrel) on the change in absolute magnitude of baseline (or intrinsic) platelet reactivity between T2DM patients and healthy volunteers

5. To investigate the effects of different antiplatelet agents (low-dose aspirin alone once daily, followed by low-dose aspirin twice daily), (clopidogrel alone followed by prasugrel alone) or (low dose aspirin once daily followed by dual antiplatelet therapy with aspirin and clopidogrel) on the change in absolute magnitude of baseline (or intrinsic) platelet reactivity among male and female healthy volunteers

6. To investigate the effects of different antiplatelet agents (low-dose aspirin alone once daily, followed by low-dose aspirin twice daily), (clopidogrel alone followed by prasugrel alone) or (low dose aspirin once daily followed by dual antiplatelet therapy with aspirin and clopidogrel) on the change in absolute magnitude of baseline (or intrinsic) platelet reactivity among male and female T2DM patients

Secondary Objectives:
1. To investigate the magnitude of baseline (or intrinsic) platelet reactivity among T2DM patients and to compare the results of multiple platelet function assays with one and another

2. To investigate the magnitude of baseline (or intrinsic) platelet reactivity among healthy volunteers and to compare the results of multiple platelet function assays with one and another

3. To investigate the effects of different antiplatelet agents (low-dose aspirin alone once daily, followed by low-dose aspirin twice daily), (clopidogrel alone followed by prasugrel alone) or (low dose aspirin once daily followed by dual antiplatelet therapy with aspirin and clopidogrel) among healthy volunteers and to compare results of multiple platelet function assays with one and another

4. To investigate the effects of different antiplatelet agents (low-dose aspirin alone once daily, followed by low-dose aspirin twice daily), (clopidogrel alone followed by prasugrel alone) or (low dose aspirin once daily followed by dual antiplatelet therapy with aspirin and clopidogrel) among T2DM

patients and to compare results of multiple platelet function assays with one and another

Tertiairy (exploratory) Objectives:
1. To explore the relationship between the magnitude of Baseline platelet reactivity (as measured with various platelet function tests) among T2DM patients and healthy volunteers and the occurrence of atherothrombotic events at 5 years follow-up

2. To explore possible relationships between the magnitude of platelet reactivity (as measured with various platelet functions tests) and genetic variations in selected candidate genes

3. To explore possible relationships between antiplatelet therapy responsiveness and genetic variations in selected candidate genes

Study design

This is an open label, randomized trial

Intervention

nvt

Study burden and risks

Suitable candidates (male and female T2DM patients and male and female healthy volunteers) will be invited to the outpatient clinical of our department of Research and Development for intrinsic (baseline) platelet function evaluation, physical examination and a standardized interview. After checking all the in- and exclusion criteria, written informed consent will be obtained before initiating any study procedure.
Study site personnel will question each patient and will record on the CRF the occurrence and nature of pre-existing conditions. These include: demographics, medical history and vital signs. After drawing of the baseline blood samples, subjects will be randomly assigned in an open-label fashion to one of the three treatment arms of the study. Randomization will be performed with sealed envelopes.
At baseline, 1 week and after 4 weeks, platelet function evaluation will be performed with different platelet function assays to measure the effects of the different antiplatelet regimens on the magnitude of platelet reactivity.

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

Cases
-Male and female patients with a diagnosis of Type 2 Diabetes Mellitus according to the WHO-criteria
->40 years
-willing to provide informed consent;Controls
->40 years
-willing to provide informed consent

Exclusion criteria

Cases

- a history of coronary heart disease (either stable angina with angiographic confirmed significant coronary artery disease or an acute coronary syndrome)
- a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack
- a history of arteriosclerotic disease necessitating medical treatment
- <=40 years or >75 years
- weight <60kg
- no Diabetes Mellitus
- atrial fibrillation
- Women who are known to be pregnant or who have given birth within the past 90 days, or who are breastfeeding.
- use of antiplatelet or antithrombotic therapy within the last 10 days (aspirin, NSAIDS, clopidogrel, prasugrel, ticlopidine, dipyridamole, acenocoumarol, fenprocoumon, argatroban, LMW) heparin
- a history of severe gastric or duodenal ulcer
- severe liver dysfunction
- use of steroid-treatment within the last 30 days
- severe renal dysfunction
- Allergy to either aspirin, clopidogrel or prasugrel.
- Patients who are unwilling and/or unable to give informed consent;
- Patients at increased risk of death from a pre-existing concurrent illness;Controls
- a history of coronary heart disease (either stable angina with angiographic confirmed significant coronary artery disease or an acute coronary syndrome)
- a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack
- a history of arteriosclerotic disease necessitating medical treatment
- <=40 years or >75 years
- weight <60kg
- Diabetes Mellitus
- atrial fibrillation
- Women who are known to be pregnant or who have given birth within the past 90 days, or who are breastfeeding.
- use of antiplatelet or antithrombotic therapy within the last 10 days (aspirin, NSAIDS, clopidogrel, prasugrel, ticlopidine, dipyridamole, acenocoumarol, fenprocoumon, argatroban
- a history of severe gastric or duodenal ulcer
- severe liver dysfunction
- use of steroid-treatment within the last 30 days
- severe renal dysfunction
- Allergy to either aspirin, clopidogrel or prasugrel.
- Patients who cannot communicate reliably with the investigator;
- Patients who are unwilling and/or unable to give informed consent;
- Patients at increased risk of death from a pre-existing concurrent illness

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-04-2010
Enrollment:	600
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ASA Cardio 80 PCH
Generic name:	acetylsalicylic acid
Product type:	Medicine
Brand name:	Effient
Generic name:	prasugrel
Product type:	Medicine
Brand name:	Plavix
Generic name:	clopidogrel

Ethics review

Not approved

Date:	04-05-2010
Application type:	First submission

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-014524-27-NL
CCMO	NL30402.100.10