Body Weight Adjusted Clopidogrel treatment in patients with CORonary artery Disease (BW-ACCORD)

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This study has been transitioned to CTIS with ID 2024-518890-33-00 check the CTIS register for the current data. To determine if clopidogrel treatment can be optimized in patients with a low or high BW/BMI compared to patients with a normal BW by...

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

Summary

ID

NL-OMON53494

Source
ToetsingOnline

Brief title
BW-ACCORD

Condition

- Coronary artery disorders

Synonym
chronic coronary syndrome, coronary artery disease, stable coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: ACE Pharmaceuticals,Alggen,St. Antonius Onderzoeksfonds

Intervention

Keyword: Body weight, Chronic Coronary Syndrome, Clopidogrel, Pharmacodynamics

Outcome measures

Primary outcome

The primary endpoint will be the level of platelet reactivity, measured as Platelet Reaction Unit (PRU) as measured by the VerifyNow system in the different treatment groups and different treatment regimens.

HTPR will be assessed, defined by a PRU >208.

PRU values in the low and high BW/BMI group will be compared to the PRU values in the normal BW/BMI group.

Secondary outcome

- To determine if the CYP2C19 genotype has additional effect on the platelet reactivity in the different treatment groups.

- To assess the difference between PRU values in the high BW/BMI group during clopidogrel treatment and prasugrel treatment.

- To assess possible confounders for high on-treatment platelet reactivity.

- During the conduct of the study all clinical endpoints will be registered according to the definitions reported in the appendix. The following clinical endpoints will be reported: mortality (and cause of mortality), myocardial infarction, stent thrombosis, revascularization, stroke and bleedings.

Study description

Background summary

Dual antiplatelet therapy (DAPT), consisting of aspirin combined with a P2Y12-inhibitor (preferably clopidogrel), is the standard treatment for patients with chronic coronary syndrome (CCS) treated with percutaneous coronary intervention (PCI) according to European guidelines (class I) to prevent recurrent ischemic events. In patients with acute coronary syndrome (ACS) and any contra-indication for ticagrelor/prasugrel or a high bleeding risk, de-escalation from ticagrelor/prasugrel to clopidogrel, blind or by the use of CYP2C19 genotyping or platelet function testing is optional.

In CCS patients the 2017 focused update on dual antiplatelet therapy ESC guideline recommends DAPT for 6 months, which can be shortened based on the bleeding risk. The trade-off of thrombotic prevention by DAPT is an increased incidence of bleeding, while major bleeding is associated with an increase in mortality. With the recent developments of better stents with less stent-thrombosis, new strategies to reduce bleeding and optimize treatment are being explored.

Extreme body weights (BW) or body mass index (BMI) affect the pharmacokinetics of antithrombotic drugs and consequently may affect cardiovascular risk during treatment. As a consequence the ESC Working group on Thrombosis has addressed the following as a pending issue: *Determining whether the benefit: risk ratio of oral fixed-dose antiplatelet and anticoagulant drugs can be improved using a BW and/or BMI dose adjustment**.
Standard therapeutic regimens and dosing of antithrombotic drugs are largely based on patients with normal-overweight or class 1 obesity. Therefore, fixed-dose drugs might be over- or under-dosed in severely underweight or severely obese patients. This has the potential of impacting the bleeding and thrombosis balance of each drug regimen, considering also the bodyweight-associated thrombotic and bleeding risk, independently of antithrombotic drug use.
Several studies have reported poor responsiveness to clopidogrel, expressed as reduced platelet inhibition and/or active metabolite concentration, associated with a high BMI or BW. On the contrary, (extreme) low BW has been associated to a higher bleeding risk.

As high BW is associated with an increased risk for coronary artery disease (CAD), there are proportionally more overweight than underweight patients in the CAD population. As a result, there is little data on underweight patients and cardiovascular risk, (on-treatment) platelet activity and risk of cardiovascular events, such as bleeding and recurrent atherothrombotic events. A large single-center prospective cohort study with 9738 Dutch patients at risk for cardiovascular disease (due to risk factors or symptomatic arterial disease), showed that the patients with the lowest BMI (BMI 15.90-23.94) had the highest risk of bleeding. In a smaller observational study (N = 774) low BMI (< 18.5) was associated with deep intracranial bleeding risk (OR = 1.76, p = 0.011). In patients undergoing PCI, a low BMI (BMI <18.5) increased risk the risk of bleeding, while class 1-2 obesity has a reduced risk. Both minor and

major bleeding appeared to be most prevalent in the low BMI group.

Explained both by pathophysiological as by clinical observations, a high BMI is associated with a higher risk on cardiovascular disease and mortality. In obesity adipose tissue consists of adipocytes and different cell types in the vascular stroma. During weight gain, adipocytes become hypertrophic, hypoxic and dysfunctional, releasing pro-inflammatory molecules that attract pro-inflammatory cells (neutrophils, CD8 T cells, B cells, mast cells, and interferon-c-Th1). Moreover, obesity increases lipid peroxidation and isoprostane formation, which can activate platelets. Consequently, a state of low-grade chronic inflammation can develop, which by impaired fibrinolysis and endothelial dysfunction can lead to hypercoagulability and platelet activation, ultimately resulting in a higher thrombotic risk. In the clinical practice a high BMI is associated with venous thromboembolism, a higher frequency of plaque rupture in coronary atherosclerosis and higher cardiovascular mortality. In the LEADERS trial, BMI independently predicted major adverse cardiac events at 1-year in patients on clopidogrel 75mg daily.

Clopidogrel therapy and BMI/BW
As stated earlier, previous research has shown that the response to clopidogrel, assessed by platelet inhibition or active metabolite concentration can be influenced by extreme weights. Angiolillo et al. showed that suboptimal platelet aggregation inhibition was significantly higher in overweight than in normal weight patients at baseline, at 24 hours and during the overall study time. An elevated BMI was the only independent predictor of suboptimal platelet response.
In a study by Bonello-Palot et al. clopidogrel dose adjustments were made to overcome high on-treatment platelet reactivity (HTPR) in patients after PCI. Though also influenced by the CYP2C19 gene allel, the only independent predictor of a failed dose adjustment was a high BMI. Pankert et al. analyzed the platelet reactivity in post-PCI patients treated with clopidogrel (both 75mg and 150mg) and prasugrel (10mg). HTPR was more present in obese patients with all treatments, though prasugrel 10mg seemed to be more potent than clopidogrel 150mg in obese patients. A study by Nawaz et al. showed that BMI was inversely related to platelet inhibition by clopidogrel. Additionally they saw, although in a small number of patients, that none of the underweight patients (BMI <18.5) were found to be clopidogrel resistant.

The importance of adequate platelet inhibition by clopidogrel increases as clopidogrel monotherapy can be a more prevalent treatment strategy in the future, as more studies arise in which clopidogrel monotherapy is superior to aspirin monotherapy in patients with CAD. The STOP-DAPT2 trial showed in mostly stable CAD patients that clopidogrel monotherapy after 1 month of DAPT was superior to 12 months of DAPT, reducing the risk of major and minor bleeding without an increase in thrombotic events. The HOST-EXAM trial showed that clopidogrel monotherapy is superior to aspirin monotherapy as chronic maintenance therapy among patients who had successfully completed the required

duration of DAPT therapy post-PCI, both reducing the risk for thrombotic as for bleeding events.

Clopidogrel 25mg
The dosage of clopidogrel 25mg is not yet routinely used in Europe. This lower dosage has been produced to lower the bleeding risk in Asian patients and is applied in the clinical practice in China. In a retrospective study aspirin (100mg), clopidogrel (25mg) and clopidogrel (75mg) were compared in patients after 12-month of DAPT after PCI. There was no significant difference in the overall composite incidence of cardiac death, myocardial infarction and target vessel revascularization in the three groups at three years after PCI. The rates of bleeding (especially minor bleeding), gastrointestinal side-effects, drug discontinuation and any blood transfusion were markedly lower in the low-dose clopidogrel (25 mg) group than in the other two treatment groups ($P<0.05$). Low-dose clopidogrel (50mg) plus aspirin was assumed safe in Japanese patients directly after PCI, with only one stent-thrombosis (0.65%) in 126 patients after a follow-up of almost 14 months. In a small randomized pilot study with 200 patients after PCI comparing clopidogrel 50mg vs clopidogrel 75mg, no myocardial infarction or stent-thrombosis occurred after more than 20 month of follow-up, suggesting that a low-dose clopidogrel treatment is safe in the Japanese population.
In a study evaluating pharmacokinetics and bioequivalence of clopidogrel 25mg, the absorption rate was lower and the absorption extent was higher than under fasted condition, meaning that the pharmacokinetics

Study objective

This study has been transitioned to CTIS with ID 2024-518890-33-00 check the CTIS register for the current data.

To determine if clopidogrel treatment can be optimized in patients with a low or high BW/BMI compared to patients with a normal BW by adjusting the dosage of clopidogrel and evaluating platelet reactivity measured using the VerifyNow.

Study design

This is a non-randomized single centre, prospective, experimental study in patients with CCS treated with clopidogrel 75mg (and aspirin). This study is designed to be pragmatic and is intended to be hypothesis generating. Patients have to be treated with clopidogrel for at least one month without the occurrence of a major bleeding event, an ischemic event (stroke, myocardial infarction, or coronary revascularization) and have to be free of angina complaints.

Eligible patients will be divided into three groups based on their BW or BMI(according to ESC-consensus).

- Group 1 - Low BW: patients with a BW of <60kg or BMI <=18.5
- Group 2 - Normal BW: patients with a BW of 60-100kg and BMI of 18.5-30.
- Group 3 - High BW: patients with a BW of >=100 kg or BMI of >=30.

At baseline each patient is treated with clopidogrel 75mg and aspirin. At baseline platelet reactivity will be measured and CYP2C19 genotype will be analysed. For safety reasons patients in group 1 with high on-treatment platelet reactivity when treated with clopidogrel 75mg, will be excluded for further treatment adjustments, as it is possible that lowering the dosage of clopidogrel will further worsen platelet reactivity and hence it would not be ethical to lower the clopidogrel dose in these patients. Then the dosage of clopidogrel treatment will be adapted for each group. After each alteration of treatment a blood withdrawal takes place to measure platelet reactivity.

Intervention

- Group 1: Clopidogrel 50mg QD for at least 10 days, then clopidogrel 25mg QD for at least 10 days.
- Group 2: Clopidogrel 75mg
- Group 3: Clopidogrel 150mg QD for at least 10 days, then prasugrel 10mg QD for at least 10 days.

In group 3 prasugrel is used as previous research has shown that a higher clopidogrel dose of 150mg still is associated to high on-treatment platelet reactivity, while with prasugrel high on-treatment platelet reactivity was less common

Study burden and risks

There are no major risks or benefits for patients included in this study. A maximum of three blood withdrawals obtained by venipuncture will be performed in all study patients and patients will undergo pharyngeal swabs to analyse the CYP2C19 genotype. All study patients have to be event-free for a month after elective PCI and have to be treated with clopidogrel without any complications, as the first month after PCI is the period that patients have the highest risk for recurrent events.

Patients with a high BW/BMI are at higher risk for cardiovascular events and have been associated with an inadequate response to clopidogrel treatment. We hypothesize that these patients would benefit an dose adjustment to ensure adequate platelet inhibition. In this study these patients possibly could benefit the higher dose of clopidogrel as their risk for thrombotic events could be lower. However, patients will be treated with the higher dose for a short period of time, so the real benefit is estimated to be low. On the contrary, a higher clopidogrel dose could lead to a higher bleeding risk. We hypothesize that this bleeding risk is not higher than the bleeding risk in the normal weight population treated with clopidogrel 75mg. On top of that, again

the period of time that patients are treated with the higher dose is short, so the risk is estimated to be negligible.

Patients with a low BW/BMI will be treated with a lower dose of clopidogrel. Treatment with a lower dose will lower their risk for bleeding. On the contrary, this would potentially increase their thrombotic risk, however we measure the degree of platelet reactivity before adjusting the dose and will exclude patients who are already have HTPR. Hereby, we insure that only patients with adequate platelet inhibition are treated with the lower dose. Apart from the existing literature, showing that low dose clopidogrel can be used safely in CAD patients in the Asian population, the period of time that patients are treated with this lower dose is very short, further reducing the potential risk for thrombotic events during the conduct of this study.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Patients, male or female, >=18 years of age
- Patients treated for coronary artery disease with clopidogrel 75mg QD (aspirin 100mg QD).
- Patients must be treated with clopidogrel 75mg for at least one month
- Patients must give consent by means of a signed informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Contra-indication for aspirin
- Contra-indication for clopidogrel or prasugrel
- Occurrence of an ischemic event after PCI or ACS (stroke, myocardial infarction, or coronary revascularization)
- Presence of unstable angina complaints.
- Presence of two CYP2C19 Loss-of-function (LOF) alleles (*2 or *3)
- Scheduled for cardiac valve surgery
- Indication for chronic oral anticoagulants
- Expected life span of less than one year
- Pregnancy
- Suboptimal stent placement as determined by the cardiologist.
- Patients at increased risk of bleeding with two of the following characteristics: liver cirrhosis with portal hypertension, enhanced bleeding tendency, active malignancy in the past 12 months, thrombocytopenia, major surgery in the past month, spontaneous intracerebral haemorrhage, traumatic intracerebral haemorrhage in the past 12 months, major bleeding requiring hospitalisation or blood transfusion in the past month, ischaemic CVA in the past 5 months.
- Known with established stent thrombosis

Study design

Design

Study phase: 4

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-04-2023
Enrollment:	80
Type:	Actual

Medical products/devices used

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 outside intended use

Ethics review

Approved WMO Date:	23-02-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-08-2024
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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-518890-33-00
EudraCT	EUCTR2022-001290-31-NL
CCMO	NL81095.100.22