POPular GUILTY pilot: Genotype-guided clopidogrel monotherapy

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This study has been transitioned to CTIS with ID 2024-518464-12-00 check the CTIS register for the current data. The primary efficacy endpoint is to assess ischemic risk of genotype-guided clopidogrel monotherapy during the first 6 months following...

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

Summary

ID

NL-OMON53943

Source
ToetsingOnline

Brief title
POPular GUILTY

Condition

- Coronary artery disorders

Synonym
Non-ST elevation myocardial infarction (coronary artery disease)

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: St. Antonius Ziekenhuis

Intervention

Keyword: Antiplatelet therapy, CYP2C19 genotyping, Non-ST elevation acute coronary syndrome, P2Y12 inhibitor monotherapy

Outcome measures

Primary outcome

The primary ischemic endpoints at 6 months is the composite of:

• All-cause mortality

• Myocardial infarction

• Academic Research Consortium (ARC) defined definite or probable stent

thrombosis

• Ischemic stroke

The primary bleeding endpoint at 6 months is:

• Major or minor bleeding defined as Bleeding Academic Research Consortium

(BARC) type 2, 3 or 5 bleeding

Secondary outcome

Secondary endpoints will include:

• Primary ischemic and bleeding endpoint at 6 months

• Each individual component of the primary endpoints at 6 months

• Cardiovascular mortality at 3 and 6 months

• Non-cardiovascular mortality at 3 and 6 months

• Any need for revascularization at 3 and 6 months

• Any periprocedural complications

Study description

Background summary

Dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor is the cornerstone of treatment in patients with acute coronary syndrome (ACS) and those receiving coronary stent implantation, reducing the risk of stent thrombosis, myocardial infarction and stroke. [1,2] However, the need for aspirin is currently challenged as both technical (e.g. stent design and interventional technique) and pharmaceutical (e.g. more potent P2Y12 inhibitors) advancements reduced atherothrombotic complications and DAPT is associated with bleeding complications.[3]

Several randomized controlled trials concluded that single antiplatelet therapy (SAPT) with a P2Y12 inhibitor reduces major and clinically relevant non-major bleeding complications and is non-inferior to DAPT with respect to ischemic events, in both acute and chronic coronary syndrome patients.[4-8] However, P2Y12-inhibitor monotherapy was preceded by a 1-3 month period of DAPT in all these trials. The recent Acetyl Salicylic Elimination Trial (ASET) pilot study was the first trial completely omitting aspirin after successful percutaneous coronary intervention (PCI).[9] In the 201 patients treated with prasugrel monotherapy, no stent thrombosis occurred during a 4-month follow-up period.

Whether complete omission of aspirin reduces the rate of major or minor bleeding while maintaining non-inferiority to the current standard of care (DAPT) with respect to ischemic event rate in NSTE-ACS patients undergoing PCI, is currently investigated in The Less Bleeding by Omitting Aspirin in Non-ST-segment Elevation Acute Coronary Syndrome Patients (LEGACY) trial. This open-label, multicenter randomized controlled trial randomizes NSTE-ACS patients undergoing PCI in a 1:1 ratio to the intervention group receiving P2Y12-inhibitor monotherapy (ticagrelor or prasugrel) for 12 months or the standard group receiving DAPT for 12 months.

Previous studies showed that the P2Y12-inhibitors prasugrel and ticagrelor reach more potent and reliable platelet inhibition than clopidogrel, reducing the incidence of myocardial infarction and definite or probable stent thrombosis with 16-24% and 25-52%, respectively.[10,11] The higher incidence of ischemic events in patients using clopidogrel may, however, be explained by the great interindividual variability in P2Y12 inhibition. Clopidogrel is a prodrug requiring bioactivation into its active metabolite, which irreversibly inhibits P2Y12 receptors on platelets and therewith platelet aggregation.[12] Various defective polymorphisms of the CYP2C19 gene have been found, encoding the CYP2C19 enzyme responsible for the bioactivation by hepatic cytochrome P450 enzymes.[13] Approximately 30% of Caucasian patients carry at least one loss-of-function (LOF) allele such as CYP2C19*2 or CYP2C19*3, resulting in high

on-treatment platelet reactivity and an increased risk of atherothrombotic events.[12,14-16 In patients without LOF alleles, however, clopidogrel has similar efficacy in prevention of ischemic complications to ticagrelor and prasugrel.[17-20]

In addition, the more potent P2Y12 inhibitors are associated with a significant increase in bleeding complications. When compared to clopidogrel, patients receiving prasugrel had a 32% higher incidence of TIMI major hemorrhage, including both life-threatening and fatal bleeding, and patients using ticagrelor had a 25% increase in non-CABG related major TIMI bleeding. [10,11]

This single-centre, single-arm pilot study will explore the feasibility and safety of genotype-guided clopidogrel monotherapy in CYP2C19 extensive metabolizers presenting with NSTE-ACS and undergoing successful PCI. We hypothesize that genotype-guided clopidogrel monotherapy is safe with regards to bleeding and ischemic endpoints in Non-ST-Segment Elevation Acute Coronary Syndrome Patients undergoing successful PCI.

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Study objective

This study has been transitioned to CTIS with ID 2024-518464-12-00 check the CTIS register for the current data.

The primary efficacy endpoint is to assess ischemic risk of genotype-guided clopidogrel monotherapy during the first 6 months following successful PCI in NSTE-ACS patients.

The primary safety endpoint is to assess bleeding risk of genotype-guided clopidogrel monotherapy during the first 6 months following successful PCI in

NSTE-ACS patients.

Secondary objective
The secondary endpoints include the individual components of the primary safety and efficacy endpoints (at 3 and 6 months).

Study design

This is a single-center, single-arm, open-label, proof-of-concept trial assessing the safety and efficacy of genotype-guided clopidogrel monotherapy following successful PCI in NSTE-ACS patients. The study design is illustrated in Figure 1 in the protocol.

In this pilot study, patients presenting with NSTE-ACS who have undergone successful PCI will be enrolled in case of CYP2C19 wildtype genotype. Patients will be treated with clopidogrel monotherapy.

After 1, 3, and 6 months (+/- 2 weeks) after hospital discharge, patients will be contacted by phone to discuss clinical events, adverse events and self-reported adherence to medication. In addition, medical files will be reviewed.

Intervention

Treatment before PCI:
• Patients will be treated with a loading dose of 60 mg prasugrel, 180 mg ticagrelor or 600mg clopidogrel at least 2 hours prior to coronary angiography.

Treatment after PCI:
• Patients will be treated with 75mg clopidogrel once daily for 6 months
• After 6 months, medical regimen is at the discretion of the treating physician.

Study burden and risks

Patients will be contacted by phone at 1, 3, and 6 months after successful PCI. Omitting aspirin may lead to a reduction in (major) bleeding events. However, it is unknown whether omitting aspirin affects the risk of ischemic 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

Patients aged 18 years or older are eligible for inclusion if all of the following criteria are met:
- Clinical diagnosis of NSTE-ACS (i.e. NSTEMI or unstable angina)
- Successful PCI (according to the treating physician) with implantation of new generation drugeluting stents.
- CYP2C19 extensive metabolizer

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Known allergy or contraindication for aspirin or clopidogrel.
• Concurrent use of oral anticoagulants (e.g. because of atrial fibrillation)
• Ongoing indication for DAPT at admission (e.g. due to recent PCI or ACS)
• High-risk features for PCI including left main disease, chronic total occlusion, bifurcation lesion requiring 2-stent treatment, saphenous or arterial graft lesion, severely calcified lesion requiring the use of the

Rotablator system, >=3 treated vessels, >= 3 stents implanted and total stent length >60 mm
• Recent stroke, transient ischemic attack (TIA) or intracranial bleeding
• Severe hepatic impairment (Child Pugh class C)
• Planned surgical intervention within 6 months of PCI
• Patients requiring staged procedure (to avoid heterogeneity in the duration of pharmacological treatment between index and staged procedures)
• Pregnant or breastfeeding women at time of enrolment
• Participation in another trial with an investigational drug or device

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-07-2023
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clopidogrel
Generic name:	Clopidogrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	22-03-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-05-2023
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
EU-CTR	CTIS2024-518464-12-00
EudraCT	EUCTR2022-003061-38-NL
CCMO	NL82555.100.22