Less Bleeding by Omitting Aspirin in Non-ST-segment Elevation Acute Coronary Syndrome Patients

Published: 02-02-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-504360-42-00 check the CTIS register for the current data. The Less Bleeding by Omitting Aspirin in Non-ST-segment Elevation Acute Coronary Syndrome Patients (LEGACY) trial will investigate...

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

Summary

ID

NL-OMON54035

Source
ToetsingOnline

Brief title
LEGACY

Condition

- Coronary artery disorders

Synonym
'acute coronary syndrome', 'heart attack'

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,-

Intervention

Keyword: P2Y12-inhibitor monotherapy, percutaneous coronary intervention

Outcome measures

Primary outcome

The primary bleeding endpoint at 12 months is:

- Major or minor bleeding defined as Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 bleeding

The primary ischemic endpoint at 12 months is the composite of:

- All-cause mortality
- Myocardial infarction (according to the 4th universal definition of MI)
- Stroke

Secondary outcome

- Primary bleeding and ischemic endpoints at 1, 3 and 6 month(s)
- Individual components of the primary endpoints at 1, 3, 6 and 12 month(s)
- Net adverse clinical events at 1, 3, 6 and 12 month(s) defined as all-cause mortality, MI, stroke and major bleeding (BARC type 3 or 5 bleeding)
- Academic Research Consortium (ARC) defined definite or probable stent thrombosis at 1, 3, 6 and 12 month(s)
- Repeat revascularization at 1, 3, 6 and 12 month(s) including periprocedural medication during repeat revascularization
- Modifications to aspirin or P2Y12-inhibitor regimen at 1, 3, 6 and 12 month(s)

Study description

Background summary

Approximately 15,000 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are admitted to Dutch hospitals each year. The vast majority of these patients is treated with percutaneous coronary intervention (PCI) using intracoronary stents. Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12-inihibitor, reduces the risk of stent thrombosis, myocardial infarction (MI) and stroke as compared to aspirin monotherapy after coronary stent implantation. However, DAPT inevitably increases the risk of bleeding, which in turn is associated with increased mortality, morbidity and reduced quality of life (all associated with high healthcare costs). In recent decades, improvements in stent design, interventional technique and antithrombotic therapy have substantially reduced the risk of stent thrombosis and subsequent ischemic complications.

Among these improvements is the development of new generation drug-eluting stents (DES). The bulky, thick-strut bare-metal stents that were used when DAPT was introduced, have therefore become obsolete. The advent of safer, thinner-strut, new generation DES equipped with biocompatible coatings has led to low rates of stent thrombosis. These DES are now commonly used in all patients. Pharmacological therapy has improved as well. New P2Y12-inhibitors, i.e. prasugrel and ticagrelor, which result in a more potent and reliable inhibition of platelet activity, have been shown to significantly reduce the incidence of stent thrombosis as compared to clopidogrel. These novel agents are currently used alongside aspirin as the standard-of-care for acute coronary syndrome (ACS) patients. The combined improvements in stent design and antithrombotic therapy have led to very low rates of stent thrombosis.

Consequently, the status of aspirin as the cornerstone of antithrombotic therapy has been challenged. Aspirin use is associated with an increased risk of bleeding (in particular gastrointestinal bleeding), especially when combined with other antithrombotic agents (e.g. a P2Y12-inhibitor). The advent of potent P2Y12-inhibitors has raised questions as to whether the additional antithrombotic benefit of aspirin outweighs the increase in bleeding complication. Ex-vivo data on thrombogenicity under dynamic flow conditions have shown that the antithrombotic potency of P2Y12-inhibitor monotherapy is similar to that of a P2Y12-inhibitor combined with aspirin in high-risk patients who underwent PCI with DES. Furthermore, contemporary pharmacologic therapies for cardiovascular risk factors, such as hypertension, dyslipidemia and impaired glucose metabolism, have led to reductions in an individual*s cardiovascular risk. These therapies were not available at the time of the pivotal studies evaluating aspirin in the setting of secondary prevention. Therefore, relative benefits of adding aspirin might translate into much

smaller absolute risk reductions in current clinical practice as compared to several decades ago.

In recent years, multiple randomized controlled trials (RCT) have evaluated the efficacy and safety of P2Y12-inhibitor monotherapy, but this always involved concurrent aspirin use during at least 1-3 month(s). A recent meta-analysis of these trials investigating P2Y12-inhibitor monotherapy after PCI concluded that P2Y12-inhibitor monotherapy preceded by a short period of DAPT was associated with a 40% lower incidence of major bleeding compared to standard DAPT without a significant differences in cardiovascular events after one year. In fact, even complete omission of aspirin after PCI is now a topic of investigation. Recently, the Acetyl Salicylic Elimination Trial (ASET) pilot has shown that an aspirin-free strategy directly following PCI was feasible in chronic coronary syndrome patients. Besides improving clinical outcomes, omitting aspirin can reduce healthcare costs (e.g. by reducing costs associated with bleeding complications). Likewise, omitting aspirin might reduce polypharmacy and therefore improve medication adherence.

Study objective

This study has been transitioned to CTIS with ID 2023-504360-42-00 check the CTIS register for the current data.

The Less Bleeding by Omitting Aspirin in Non-ST-segment Elevation Acute Coronary Syndrome Patients (LEGACY) trial will investigate whether omitting aspirin reduces the rate of major or minor bleeding while remaining non-inferior to the current standard of care, DAPT, with respect to the rate of ischemic events in NSTE-ACS patients undergoing PCI. Importantly, we hypothesize that omitting aspirin will vastly improve the cost-effectiveness of the care for these patients. Our study addresses an important gap in evidence as highlighted by the European Society of Cardiology (ESC). Completely omitting aspirin is unique and could positively alter the treatment of a large number of patients.

Study design

Open-label, multicenter randomized controlled trial

Intervention

No aspirin during 12 months

Study burden and risks

Patients will be contacted by phone after 1, 3, 6 and 12 month(s) for follow-up. Omitting aspirin may lead to a reduction in (major) bleeding events,

while reducing the number of medications patients use. However, it is unknown if 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)

Inclusion criteria

- Adult patients presenting with NSTE-ACS undergoing PCI
- Written informed consent

Exclusion criteria

- Known allergy or contraindication for aspirin or P2Y12-inhibitors
- Concurrent use of oral anticoagulants (e.g. because of atrial fibrillation)

- Overwriting indication for DAPT (e.g. recent PCI or ACS)
- Planned surgical intervention within 12 months of revascularization
- Pregnant or breastfeeding women at time of enrolment
- Participation in another trial with an investigational drug or device (i.e. stent)

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:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-05-2022
Enrollment:	3090
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aspirin
Generic name:	Acetylsalicylic acid
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-02-2022

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
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Approved WMO Date:	25-01-2023
Application type:	Amendment
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Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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
Other	-
EU-CTR	CTIS2023-504360-42-00
EudraCT	EUCTR2021-005550-28-NL
CCMO	NL79129.018.21