PRIMARY: postoperative biomarker measurements after coronary bypass surgery; towards an improved understanding and definition of the concepts of periprocedural myocardial injury and infarction

Published: 08-12-2023
Last updated: 18-01-2025

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

Summary

ID

NL-OMON56115

Source
ToetsingOnline

Brief title
PRIMARY

Condition

- Coronary artery disorders

Synonym
Periprocedural myocardial injury

Research involving

Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Hartstichting - Dekkersubsidie 'Clinical Scientist' - https://professionals.hartstichting.nl/actualiteiten/de-hartstichting-kent-37-miljoen-euro-toe-aan-tien-dekkerlaureaten

Intervention

Keyword: biomarkers, coronary artery bypass grafting, imaging, myocardial injury

Outcome measures

Primary outcome

1. The diagnostic accuracy of the various assessed cardiac biomarkers for objectively quantified new myocardial cell necrosis on CMR at one month follow-up, in relation to the pre-operative baseline CMR imaging results. The area under the ROC curve will be used as the main diagnostic accuracy parameter.

2. The prognostic value of the various assessed cardiac biomarkers for the incidence of 1-year clinically relevant outcomes (defined as mortality, myocardial infarction, and/or unplanned revascularisation). The prognostic value of cardiac biomarkers will be compared using hazard ratios with 95% confidence intervals derived from multivariable Cox regression models.

Secondary outcome

- The diagnostic accuracy of the continuous visual and functional coronary CTA measurements will be assessed using the area under the ROC curve (AUC) as primary parameter. The test results of invasive coronary angiography will be used as reference standard. Presence of severe coronary stenosis based on the

invasive coronary angiography will be defined as a visual stenosis of >70% and a fractional flow reserve (FFR) of <0.80.

- Bland-Altman plots of the objectively quantified volumes of myocardial necrosis according to delayed enhancement on CTA and delayed enhancement on CMR will be realized to evaluate the agreement between the two cross-sectional imaging modalities.

- Biomarker release peaks, curves and patterns (normalized to the 99%-percentile of the biomarker in a reference population of seemingly healthy adults).

- ECG changes, objectively quantified by an advanced ECG analytical method (cine-ECG). The occurrence of classical true ECG-changes will be considered (left bundle branch block de novo, Q-waves, and ST-elevation with reciprocal depression), as well as percentual change as compared to baseline, quantified by the advanced analytical method (cine-ECG).

- (Silent) graft failure upon postoperative coronary CTA, defined as non-patent grafts.

- The objectively quantified amount of loss of viable myocardium (expressed as mean and standard deviation or median and interquartile range, depending on the distribution) as assessed by cross-sectional cardiac imaging studies at various points in time (pre-operative, 3-days/1-month, one year)

Study description

Background summary

Coronary artery bypass grafting (CABG) is the most commonly performed cardiac surgical procedure (approximately 500 patients per year in MUMC+, 7000 patients in the Netherlands, and 1 million patients worldwide undergo CABG yearly). This procedure is usually performed through sternotomy, and by use of cardiopulmonary bypass (the heart-lung machine) under cardioplegic arrest (the cessation of the heart). The surgery comprises the realization of bypass grafts, rerouting the blood flow to myocardial territories beyond stenosed vessels. Therefore, this intervention is aimed at the improvement of survival and quality of life in patients with (extensive) coronary artery disease by, amongst others, a reduction in future spontaneous myocardial infarction (MI). Despite that the prevention of future MI is the aim of CABG, the occurrence of periprocedural MI (PMI, also known as type 5 myocardial infarction) can be a complication of this procedure. The prevalence of PMI is 3-40%(!) in patients undergoing CABG, but is highly definition-dependent. Indeed, several conflicting definitions of PMI are being applied, incorporating contradicting statements.

The importance of a uniform definition of PMI:
The non-uniform use of the definitions of PMI in clinical practice and the application in trials has led to substantial controverse, as it predisposes patients to under- or overdiagnosis of PMI, and potential manipulability of trials* outcomes. Still, a timely diagnosis of PMI is imperative, as prompt (<12 hours) revascularization improves prognosis. Therefore the accurate and timely diagnosis of PMI is of utmost importance to improve the outcomes of patients undergoing coronary bypass surgery.

Causes of periprocedural myocardial infarction and injury:
Periprocedural myocardial infarction has a pluriform aetiology, which can roughly be divided in irreversible and reversible causes. Although adequate diagnosis of irreversible PMI is important for long-term medical treatment, the adequate and timely diagnosis of reversible PMI is relevant, as immediate treatment improves long-term prognosis. Still, some amount of myocardial injury is inherent to the nature of cardiac surgery and CABG. During CABG, the heart is cannulated, cardiopulmonary bypass and cardioplegic arrest are initiated, and the heart is incised for graft anastomosis. Such injury can be monitored postoperatively by measuring biomarker release, for which the causative mechanisms are multifactorial. However, disproportionate myocardial injury, resulting in excessive loss of viable myocardium, may lead to impaired long-term prognosis. At a certain level of injury, such loss can be considered an infarction, which is known as PMI.

Study objective

The current research project aims to improve the care of CABG patients, by a redefinition of PMI. In this research proposal, we focus on the diagnostic and clinical relevance of postoperative biomarker increases and will determine the association between the release of various biomarkers and actual loss of viable

myocardium in relation to prognosis, using state-of-the-art diagnostic modalities. As such, we divided our primary objective in two parts:

1. Diagnostic
To compare the diagnostic accuracy of CK-MB and high-sensitivity cardiac troponin I and T in the direct postoperative phase after CABG for new loss of viable myocardium as determined by cross-sectional cardiac imaging. This endpoint will be primarily analysed based on the 1-month CMR study in relation to baseline CMR findings. The 3-day and 1-year imaging studies will be used to validate the definitiveness of the 1-month findings.

2. Prognostic
To compare the prognostic value of CK-MB, high-sensitivity cardiac troponin I and T for the one year probability of all-cause mortality and major adverse cardiovascular events in patients undergoing CABG.

Study design

This study comprises a prospective longitudinal observational cohort study of patients undergoing CABG, with incorporation of state-of-the-art imaging modalities and 1-year follow-up. The primary objectives are divided in a diagnostic part (focused on the detection of myocardial injury at 1 month and 1 year as quantified by CMR) and a prognostic part (relating the direct postoperative biomarker measurements and 30-day imaging findings to clinically relevant events at 1-year follow-up).

Study burden and risks

The ionizing radiation exposure is limited to a minimal amount by the use of most contemporary scanners and protocols. The use of contrast agent carries a low risk of an adverse reaction. Finally, blood draws are limited to clinically indicated points in time, posing minimal burden to the patients. Based on this protocol and in agreement with the NFU* Kwaliteitsborging Mensgebonden Onderzoek, there is a small chance of little to moderate injury. Therefore the proposed study constitutes a *negligible risk*. We therefore believe that the clinical importance of this study outweighs its minor risk.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adult patients (>18 years of age).
- Surgery preceded by a heart-team discussion, in which the patient is planned for multivessel CABG, receiving more than one graft (i.e., more than only left internal mammary artery [LIMA] to left anterior descending artery [LAD]).
- Isolated on-pump planned multivessel CABG (defined as using cardiopulmonary bypass and cardioplegic arrest).
- Able and willing to provide written informed consent.
- Elective or urgent surgery (defined as either planned surgery, or a surgical procedure without which the patients cannot leave the hospital before the surgery is performed24).

Exclusion criteria

- Non-adult patients (<18 years of age)
- Emergency surgery (defined as within 24 hours of indication and not waiting until the following working day24).
- Recent acute coronary syndromes (including ST-elevation myocardial infarction [STEMI] and non-STEMI [NSTEMI], recent defined as <14 days prior to surgery).
- Patients with contraindications to undergo cardiac magnetic resonance imaging

(including claustrophobia and CMR-incompatible implants).
- Prior adverse reactions to gadolinium- or iodine-based contrast agents.
- Moderate-severely compromised renal function (estimated glomerular filtration [eGFR] <45mL/min/kg)
- In clinical heart failure upon admission for surgery.
- Pregnant or breast-feeding patients

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-04-2024
Enrollment:	143
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	08-12-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL85076.068.23