The metformin in CABG (MetCAB) trial

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To study whether pretreatment with metformin can reduce myocardial injury during CABG surgery in patients without diabetes mellitus.

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

Summary

ID

NL-OMON38069

Source
ToetsingOnline

Brief title
MetCAB trial

Condition

- Coronary artery disorders

Synonym
CABG, cardiac surgery

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: CABG, Ischemia-reperfusion injury, Metformin

Outcome measures

Primary outcome

High-sensitive troponin-I levels measured before and 6,12 and 24 hours after CABG.

Secondary outcome

Secondary endpoints will include the post-operative occurrence of arrhythmias, the need for inotropic support, time to detubation, and time to discharge from the intensive care unit. Moreover, renal injury and function will be secondary endpoints of the study. Renal ischemia-reperfusion will be assessed by measuring urinary excretion of the markers of tubular damage Kidney Injury Molecule (KIM)-1 and neutrophil gelatinase-associated lipocalin (NGAL), and renal function will be assessed by plasma and urine concentrations of creatinine. Finally, the right auricle will be harvested during surgery to determine whether metformin augments recovery of contractile function of isolated atrial trabeculae after ex vivo simulated ischemia-reperfusion (vide infra) and to determine the effect of metformin on the expression and activation of protein kinases involved in ischemia-reperfusion injury (Western blotting).

Study description

Background summary

In patients with a myocardial infarction, occlusion of a coronary artery induces myocardial ischemia and cell death. The only way to limit final infarct size, is timely reperfusion of the occluded artery. Paradoxically, however, reperfusion itself can also damage myocardial tissue and contribute to the

final infarct size (*reperfusion injury*). Also during coronary artery bypass grafting (CABG), the myocardial tissue is exposed to ischemia and reperfusion, which will induce cell death. Indeed, postoperatively, the plasma concentration of troponin I is increased, and associated with adverse outcome. The anti-hyperglycaemic drug metformin has been shown in preclinical studies to be able to reduce ischemia-reperfusion injury and to limit myocardial infarct size. Moreover, metformin therapy improves cardiovascular prognosis in patients with diabetes mellitus. Paradoxically, in patients with diabetes, current practice is to temporarily stop metformin before major surgery for the presumed risk of lactic acidosis, which is a rare complication of metformin. However, here is no evidence that this practice benefits the patient. Therefore, we hypothesize that pretreatment with metformin can reduce myocardial injury in patients undergoing elective CABG surgery.

Study objective

To study whether pretreatment with metformin can reduce myocardial injury during CABG surgery in patients without diabetes mellitus.

Study design

Randomised, double-blinded, placebo-controlled clinical trial

Intervention

Pretreatment with metformin (500 mg three times a day for at least 3 days - max 7 days -) or placebo until the day of surgery

Study burden and risks

This study will be executed at the Radboud University Nijmegen Medical Centre,Groningen University Medical Centre and Maastricht University Medical Centre, under close medical supervision. Treatment metformin or placebo is not expected to harm the participants. We expect patients receiving metformin will be suffer less myocardial injury after CABG. In some patients, metformin treatment can give mild gastro-intestinal side effects, such as nausae, bloating, and diarrhea. Lactic acidosis is an extremely rare side-effect with an incidence of 1-5 per 100.000 patients, which can occur during metformin accumulation during longterm treatment in the setting or renal insufficiency. By excluding patients with renal insufficiency and due to the short-term treatment with metformin, the risk of a lactic acidosis is even further reduced.

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

- Acceptation for CABG
- Informed consent
- Age >= 18 years

Exclusion criteria

- Diabetes mellitus
- Renal dysfunction (MDRD < 60 ml/min)
- Elevated liverenzymes (ALAT > 3 times upper limit of reference range)
- Treatment with dipyridamole or xanthine derivatives
- Recent myocardial infarction (<2 weeks before inclusion)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2011
Enrollment:	110
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	03-05-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-05-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	07-06-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-000099-33-NL
CCMO	NL35358.091.11