Can metformin prevent endothelial ischemia and reperfusion injury? The metformin-FMD trial.

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To study the protective effect of pre-treatment with metformin on flow mediated dilation after 20 minutes ischemia and 20 minutes reperfusion. If metformin treatment indeed limits endothelial IR-injury, a second study will be performed in the same...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON37620

Source
ToetsingOnline

Brief title
The Metformin-FMD trial.

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
ischemia and reperfusion injury

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Flow mediated dilation, Ischemia reperfusion injury, Metformin

Outcome measures

Primary outcome

Difference in flow mediated dilation before and after 20 minutes of ischemia.

Secondary outcome

not applicable.

Study description

Background summary

In acute myocardial infarction early restoration of coronary blood flow is the most effective strategy to limit infarct-size. Paradoxically, reperfusion itself also aggravates myocardial injury and contributes to final infarct size, a process termed *reperfusion injury*. Ischemia and reperfusion (IR)-induced endothelial dysfunction seems to play a pivotal role in this process, resulting in vasoconstriction and reduced blood flow to the already ischemic tissue. Recently, it has been shown that the glucose-lowering drug metformin is able to limit IR-injury in murine models of myocardial infarction, probably by increased formation of the endogenous nucleoside adenosine. In the current research proposal, we aim to translate this finding to the human in vivo situation, using flow-mediated dilation (FMD) of the brachial artery as a well-validated model of (endothelial) IR-injury.

Study objective

To study the protective effect of pre-treatment with metformin on flow mediated dilation after 20 minutes ischemia and 20 minutes reperfusion. If metformin treatment indeed limits endothelial IR-injury, a second study will be performed in the same subjects to investigate whether this is mediated by adenosine receptor stimulation.

Study design

Randomized, open label, cross over clinical trial.

Intervention

Main study (metformin FMD trial): Pre-treatment with metformin 500 mg three times a day for 3 days or no treatment. Second study: Pre-treatment with metformin 500 mg three times a day for 3 days or no treatment, combined with caffeine infusion preceding FMD measurement.

Study burden and risks

Healthy volunteers will be treated with metformin (500mg three times a day) for 3 days. Short-term treatment with metformin is not expected to induce serious side-effects. Monotherapy with metformin does not induce hypoglycemia. Metformin can give some gastrointestinal discomfort in the first days of treatment, but this is mild and self-limiting. Lactic acidosis is a rare, but serious, complication of metformin, which can occur in the setting of shock/hypoxia/renal failure in combination with metformin accumulation. This is therefore not to be expected in case of healthy volunteers. The participants will not benefit directly from participating in this study, but if our hypothesis proves to be correct, these findings will help to optimize future medical care of patients suffering from (myocardial) ischemia/infarction.

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

- Age 30-50 years
- Written informed consent

Exclusion criteria

- Smoking
- Hypertension (Psystole > 140mmHg, diastole > 90 mmHg)
- Hyperlipidaemia (fasting total cholesterol >5.5 mmol/L or random > 6.5 mmol/L)
- Diabetes Mellitus (fasting glucose > 7.0 mmol?L or random glucose > 11.0 mmol/L)
- History of any cardiovascular disease
- Concomitant chronic use of medication
- Renal dysfunction (MDRD < 60 ml/min)
- Professional athletes

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-05-2012

Enrollment:	26
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-01-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-01-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2012
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	EUCTR2011-005343-27-NL
CCMO	NL38672.091.11