# Does cafeine reduce rosuvastatin-induced protection against ischemia-reperfusion injury?

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Primary Objective: The objective of this project is to explore the role of adenosine receptor stimulation in the protective effect of rosuvastatin against ischemia-reperfusion injury after ischemic exercise of the forearm.Secondary Objective(s):...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Arteriosclerosis, stenosis, vascular insufficiency and necrosis |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON30751

**Source**
ToetsingOnline

**Brief title**
rosucof

### Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

**Synonym**
heart infarction, Ischemia-reperfusion injury

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Sint Radboud
**Source(s) of monetary or material Support:** Ministerie van OC&W,ZonMW

## Intervention

**Keyword:** Cafeine, Ischemia, Reperfusion, Rosuvastatin

## Outcome measures

### Primary outcome

Annexin A5 targeting (% difference in radioactivity (counts per pixel) between experimental and control thenar muscle after ischemic exercise, as a indicator for ischemia reperfusion injury.

### Secondary outcome

-Workload (product of 50% of the maximum forearm force and duration of the ischemic exercise)

-The effect of one-week treatment of rosuvastatine 20mg once daily on lipid spectrum.

-The caffeine serum concentration after 24 hour abstinence, and after infusion of cafeine (4mg/kg) or placebo.

# Study description

### Background summary

Rosuvastatin is a proven cholesterol lowering medicine, which hereby is assumed to achieve a reduction in cardiovascular events. Apart from it*s cholesterol lowering action, rosuvastatin may also increase tolerance against ischemia-reperfusion injury. In dogs rosuvastatin increases the endogenous concentration of adenosine, by enhancing the activity of the enzyme ecto-5*-nucleotidase, which converts adenosine monophosphate into adenosine. We hypothesize that rosuvastatin increases tolerance against ischemia-reperfusion injury by induction of ecto-5*-nucleotidase and thereby increasing adenosine activity. This protective effect of rosuvastatin can be abbrogated by using the adenosine receptor antagonist caffeine.

### Study objective

Primary Objective: The objective of this project is to explore the role of adenosine receptor stimulation in the protective effect of rosuvastatin against ischemia-reperfusion injury after ischemic exercise of the forearm.

Secondary Objective(s): Workload (Half of the maximum arm force multiplied with the duration of this exercise). The effect of one-week treatment of rosuvastatine 20mg once daily on lipid spectrum. The caffeine serum concentration after 24 hour abstinence and after infusion of caffeine 4mg/kg or placebo.

### Study design

This study is a randomized double-blind placebo-controlled trial

### Intervention

24 healthy male volunteers receive a one week treatment with 20 mg rosuvastatin daily. On day 7, after at least 24 hours of caffeine abstinence all volunteers will be randomised to receive either placebo (n=12) or caffeine (4mg/kg, n=12) intravenously in a double blind fashion. 30 Minutes after intravenous administration both the groups will perform ischemic isometric muscle contraction of the non dominant forearm. Thereafter 99mTc labelled Annexin A5 will be administered intravenously and gamma scans will be made of both hands after 60 en 240 minutes.

### Study burden and risks

Treatment with rosuvastatin, caffeine or placebo is not expected to harm the volunteers. Most reported side effects of rosuvastatin are gastro-intestinal complains and myalgia. Ischemic hand gripping will temporarily result in pain in the forearm. This is completely reversible upon reperfusion. 24 Hours of caffeine abstinence can lead to mild headache. Administration of radiolabeled Annexin A5 results in an effective dose of less than 5 mSv, well within the range of accepted exposure to radioactivity for human research. Occurrence of an allergic reaction is theoretically possible upon administration of Annexin A5, however there have been no allergic reactions reported in all volunteers exposed to Annexin A5. The volunteers will not benefit directly from participating in this study.

## 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

Male
age between 18-50 yrs
signed informed consent

## Exclusion criteria

-Cardiovascular disease
-Hypertension (systole > 140 mmHg, diastole > 90 mmHg)
-Hypercholesterolemia (fasting total cholesterol > 6,0 mmol/l)
-Drug abuse
-Concomittant medication use
-Inability to perform the ischemic isometric muscle contraction
-Diabetes Mellitus (fasting glucose > 7.0 mmol/L or random glucose > 11.0 mmol/L)
-Alanine-Amino-Transferase (ALAT) >90U/L (more than twice the upper level of the normal range)
-Creatinine Kinase (CK) >340U/L (more than twice the upper level of the normal range)
-Participation in any trial concerning medicinal products

during the last 60 days prior to this study.
-Participation in clinical trial involving administration of radioactivity more than 5mSv, during the 5 years prior to this study.

# Study design

## Design

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|---|---|
| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-03-2007 |
| Enrollment: | 24 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Crestor |
| Generic name: | Rosuvastatin |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 09-02-2007 |
| Application type: | First submission |

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 | EUCTR2007-000151-33-NL |
| CCMO | NL16118.091.07 |