# Effects of ivabradine on plaque burden, morphology and composition in patients with clinically indicated coronary angiography. A randomised double-blind placebo-controlled international multicentre study.

Published: 21-02-2013
Last updated: 24-04-2024

The purpose of this study is to demonstrate the beneficial effect of ivabradine on plaque burden, morphology and composition, as well as on arterial wall shear stress (WSS) in patients with CAD who have a clinical indication for coronary angiography...

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| **Ethical review** | Not approved |
| **Status** | Will not start |
| **Health condition type** | Coronary artery disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON38424

**Source**
ToetsingOnline

**Brief title**
MODIFY

### Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

**Synonym**
Atherosclerosis/ hardening of the coronary arteries

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Institut de Recherches Internationales Servier I.R.I.S
**Source(s) of monetary or material Support:** Institut de Recherches Internationales Servier (IRIS)

## Intervention

**Keyword:** Ivabradine, Plaques burden, Plaques composition, Plaques morphology

## Outcome measures

### Primary outcome

The primary endpoint for the assessment of atherosclerotic disease progression is the nominal change in coronary Percent Atheroma Volume (PAV) from baseline to the study end for all anatomically comparable slices in a 30-mm segment of the target coronary artery assessed by Intravascular Ultrasound (IVUS).

### Secondary outcome

- Coronary IVUS endpoints, nominal changes from baseline to study end:

Total atheroma volume for all anatomically comparable slices in the 30-mm target coronary artery segment.

Atheroma volume for the 5-mm segment centered on the cross-section with largest plaque area at baseline.

Atheroma volume for the 5-mm segment centered on the cross-section with smallest plaque area at baseline.

Total vessel volume for all anatomically comparable slices in the 30-mm target coronary artery segment.

Plaque characterisation indices (arc index and inner perimeter index).

- Coronary VH-IVUS endpoints, assessed in a sub-population (see section 8.2.2.5), nominal changes from baseline to study end:

Necrotic core volume.

Volumes of fibrofatty plaque and fibrous plaque.

- Coronary QCA endpoints, nominal changes from baseline to study end:

Coronary artery score (defined as the per-patient mean of the minimal lumen diameter for all lesions measured).

Cumulative coronary stenosis score (calculated by adding all percent diameter stenoses in SI units).

- Coronary OCT endpoints, assessed in a sub-population (see section 8.2.2.5), nominal changes from baseline to study end:

Surface area of fibrous cap thickness < 65 *m.

Surface area of fibrous cap thickness between 65 - 150 *m.

Absolute thickness at thinnest point/region: single measurement + average.

Lipid rich core plaque morphology: presence, overall length and extent (% circumference).

Calcium rich core plaque morphology: presence, overall length, extent (% circumference) and volume.

Macrophage cluster volume: total + associated with lipid rich plaque.

Semi-quantitative plaque composition: fibrous, lipid rich, calcium rich.

- WSS endpoints:

Endothelial Shear Stress (kPal).

# Study description

### Background summary

An elevated heart rate is associated with increased mortality and morbidity in patients with coronary heart disease and has been shown to be correlated with greater progression of coronary atherosclerosis. Experimental data showed a benificial effect of ivabradine in different vascular ?This study will investigate the effect of ivabradine, a heart reate reducing agent, on coronary plaque burden, morphology and/or composition, as well as arterial shear stress in patients with coronary heart disease.

### Study objective

The purpose of this study is to demonstrate the beneficial effect of ivabradine on plaque burden, morphology and composition, as well as on arterial wall shear stress (WSS) in patients with CAD who have a clinical indication for coronary angiography.

### Study design

This is a multicentre, double-blind, randomised, placebo controlled, parallel group study.
Approximately 500 patients will be randomised, to either active ivabradine treatment (250 patients) or placebo (250 patients).

The study is divided into a pre-randomisation period and a post-randomisation period. During pre-randomisation phase, potentially eligible study patients, who fulfill clinical and laboratory entry criteria at selection will undergo a clinically indicated catheterisation and coronary angiography, followed by IVUS assessment of at least one coronary artery, and if the techniques are available: VH-IVUS and OCT. These imaging modalities will be used to evaluate coronary atherosclerotic disease progression. The planned duration of this pre-randomisation period is 7 to 45 days.

Patients who fulfil all inclusion and non-inclusion criteria will enter the post-randomisation period. It will include a 18-month period of double-blind treatment with ivabradine or matching placebo with visits at the following scheduled time-points: 1 month, 2 months, 3 months, 6 months, 12 months and 18 months.

After 18 months of treatment, patients will undergo repeat coronary imaging (IVUS, VH-IVUS, OCT, QCA and WSS).
The follow-up period after end of treatment will last 14 ± 7 days.

Patients will receive test drug on a background of contemporary evidence-based usual care for CAD, including statins at optimal dose.

**Study burden and risks**

cfr. E9

## 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 or female of any ethnic origin aged 18 years or older at the date of selection,;- Patients with a clinically indicated coronary angiography,;- Patients in sinus rhythm and heart rate equal or higher than 70 bpm,;- Treatment with optimal dose of lipid lowering therapies

including statins (unless not-tolerated) to ensure that LDL dosage is within recommended range following local practice, as well as recommended treatment for CAD.

### Exclusion criteria

- Primary percutaneous coronary intervention for acute myocardial infarction with ST elevation at selection visit;;- Previous coronary artery bypass graft (CABG) surgery or probable need for CABG in the next 18 months;;- Valvular disease likely to require surgery during the treatment period of the study;;- Patients with transplanted heart;;- Implanted pacemaker, implantable cardioverter defibrillator, cardiac resynchronisation therapy;;- Known hypersensitivity to ivabradine;;- Known hereditary problems of galactose intolerance, Lapp lactase deficiency or glucosegalactose;malabsorption;;- Myocardial infarction in the target coronary artery for IVUS.

## Study design

### Design

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|---|---|
| Study phase: | 3 |
| Study type: | Observational invasive |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Prevention |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 80 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Procoralan |
| Generic name: | Ivabradine |

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| Registration: | Yes - NL outside intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 21-02-2013 |
| Application type: | First submission |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 16-04-2013 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Not approved Date: | 03-05-2013 |
| Application type: | First submission |
| Review commission: | METC Noord-Holland (Alkmaar) |

## 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 | EUCTR2012-004779-38-NL |
| CCMO | NL43449.094.13 |