# Rosuvastatin use to improve the coagulation profile in patients with venous thrombosis: The STAtins Reduce Thrombophilia (START) Study

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To understand why statins are able to decrease the risk of developing venous thrombosis, by analyzing whether statins can influence pathways that inhibit coagulation.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Coagulopathies and bleeding diatheses (excl thrombocytopenic) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON39948

**Source**
ToetsingOnline

**Brief title**
START

### Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Coronary artery disorders
- Embolism and thrombosis

**Synonym**
blood clot in vein of the leg, Venous thrombosis

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Coagulation, Epidemiology, Statin use, Venous thrombosis

## Outcome measures

### Primary outcome

Primary Objective:

The primary objective of this study will be to demonstrate that 28 days of rosuvastatin 20 mg once daily treatment will improve the coagulation profile in persons who had venous thrombosis.

Coagulation profile includes: thrombin generation, factor VIII, fibrinogen, von Willebrand factor, protein C, protein S, antithrombin, TAT and fragment 1,2

### Secondary outcome

Secondary Objective(s):

To investigate whether the effect on coagulation factors are correlated with changes in levels of markers of endothelial activation and inflammation. We will also assess potential effect modification of rosuvastatin on coagulation factors by genes involved in coagulation regulation.

Endothelium and inflammation: IL-6, IL-8, CRP, soluble P-selectin, trombomodulin and EPCR.

Genetic variants: rs6025 (factor V Leiden), rs1799963 (prothrombin G20210A),

ABO blood group, rs2066865 (FGG 10034 C>T) and rs2289252 (F11)

Acquired risk factors: (hormone use, surgery, malignancy, etc)

# Study description

### Background summary

Venous thrombosis affects 2-3 per thousand inhabitants per year, has a 2.6% immediate death rate and recurrence rates of 25% within 5 years. Recurrence usually leads to life-long anticoagulant treatment, which has serious potential side effects, most notably major bleeding. Moreover, epidemiological studies have shown a 2-3 fold increased long-term risk of arterial cardiovascular disease after venous thrombosis, most predominant in the first year following initial venous thrombosis. The results of recent observational studies that showed 40-50% risk reductions for first venous thrombosis occurrence when using a statin are in this aspect promising. However, these results are primarily obtained from non randomised studies, and therefore leave open the possibility of confounding issues. The results are also somewhat surprising, because the mechanism behind this effect is unclear. Dyslipidaemia may be the most plausible explanation to be considered. However, as dyslipidaemia is not related to an increased risk of venous thrombosis, it is unlikely that statins decrease venous thrombosis risk by lipid lowering activities. Recent observations indicated that coagulation can activate the initial formation of atherosclerosis. Our hypothesis is therefore that the coagulation profile in persons with venous thrombosis is improved when using a statin, ultimately leading to less atherosclerosis: another well known property of statin use. Such a causal relation makes the observation that statins decrease venous thrombosis risk biologically plausible. A confirmation of our hypothesis will be an important step towards a rationale for conducting randomised clinical trials of statin/placebo with recurrent venous thrombosis as outcome event.

### Study objective

To understand why statins are able to decrease the risk of developing venous thrombosis, by analyzing whether statins can influence pathways that inhibit coagulation.

### Study design

Prospective randomised controlled, open label, clinical trial.

### Intervention

After informed consent, participants will be screened on acquired risk factors for thrombosis through a questionnaire and tested on blood parameters that may exclude a particpant from taking rosuvastatin (baseline visit). After a time window of four weeks (to allow a wear off of anticoagulant drugs), a blood sample (approximately 25 mL) will be drawn at randomisation visit. At randomisation, participants will be allocated to receive either rosuvastatin 20 mg/day or no study medication. The study will be continued for 28 days. After stopping rosuvastatin one month later, a final blood sample will be drawn. Blood will be sampled for the measurement of specific inflammatory, endothelial and coagulation factors (of which high or low levels are known to increase the risk). The study is powered on coagulation factor VIII, as a high factor VIII level is well associated with recurrent venous thrombosis. With an amount of 2*125=250 participants, we should be able to find a mean difference of 17 IU/dL with alpha=0.05/beta=0.80. The expected inclusion time is 1.5 years.

### Study burden and risks

The risks that are related to this study are related to risks of blood withdrawal and rosuvastatin use. A maximum of 60 ml of blood will be drawn per participant. The use of riosuvastatin leads very rarely to side effects (0.01-0.1% of cases). Most frequuent side effects are muscle ache and gastrointestinal side effects.

## Contacts

**Public**
Leids Universitair Medisch Centrum

Albinusdreef 2
Liden 2300 RC
NL
**Scientific**
Leids Universitair Medisch Centrum

Albinusdreef 2
Liden 2300 RC
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Persons with venous thrombosis who are allowed to discontinue oral anticoagulant treatment by their treating physician and do not receive a statin.

## Exclusion criteria

Persons already using statins or lipid lowering drugs
History of statin-induced myopathy, or serious hypersensitivity reaction to other HMG-CoA reductase inhibitors (statins), including rosuvastatin
Pregnancy
Current active liver disease
Kidney disease
Mental or physical disability to fulfil study requirements

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Basic science

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-12-2012 |
| Enrollment: | 250 |
| Type: | Actual |

## Medical products/devices used

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

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 27-04-2012 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 03-05-2012 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 31-03-2014 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

# 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 | EUCTR2012-000223-41-NL |
| CCMO | NL39080.058.12 |