# Randomised trial to investigate possible differences in biological availability and effectiveness between vitamin K solution in oil and vitamin K tablets.

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1. Determining whether or not the vitamin K tablets have the same biological availability in humans as the vitamin K solution has.2. Determining whether or not the vitamin K tablets are as effective as the vitamin K solution is.

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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-OMON39217

**Source**
ToetsingOnline

**Brief title**
Comparison

### Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

**Synonym**
normalising the INR, Reducing the INR

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum

**Source(s) of monetary or material Support:** Ministerie van OC&W,Nederlandse Hartstichting

## Intervention

**Keyword:** Biological availability, Effectiveness, Vitamin K, Vitamin K antagonist

## Outcome measures

### Primary outcome

Healthy volunteers:

Difference in the ammount of vitamin K in the blood at different times between the vitamin K tablets en solution. Also we will examine the area under the curve for the entire period of 24 hours.

Patients undergoing (small) elective surgery / invasive diagnostic procedure:

The difference in the number of INR-values beneath 2.0 between both groups after 24 and 48 hours.

Patients having an INR between 7.0 and 10.0:

The difference in INR reduction between both groups after 24 and 48 hours.

### Secondary outcome

Patients having an INR between 7.0 and 10.0:

The difference in the number of INR-values beneaht 2.0 after 24 and 48 hours between both groups.

The difference of the ammount of vitamin K in the blood between both groups.

# Study description

### Background summary

Anticoagulation therapy with vitamin K antagonists is an effective way to counteract the formation of clots in diseases like atrial fibrillation.
However, in several situations the anticoagulation effect must be reduced or even normalised. In case of the shortacting acenocoumarol this can be achieved by suspending treatment for one of two days. With the longacting phenprocoumon (of, internationally, warfarin) this does not work because of the long half life of both drugs. In these case treatment with vitamin K is necessary.
In the Netherlands there is sufficient experience in dosing vitamin K solution in oil. Recently vitamin K tablets were presented which should have the same effect in theory. However, since these tablets are marketed as medication but as dietary supplement these tablets have not been subjected to the same rigorous testing as they would have been had these tablets been marketed as medication.
Vitamin K as tablets do have a practical advantage for both the pharmacy and the patient when dealing with transport, storage, production and intake. Also dosing vitamin K tablets could be more accurate than dosing the vitamin K solution.

### Study objective

1. Determining whether or not the vitamin K tablets have the same biological availability in humans as the vitamin K solution has.
2. Determining whether or not the vitamin K tablets are as effective as the vitamin K solution is.

### Study design

Step 1:
25 healthy volunteers will receive 5 mg vitamin K in either tablet or solution. 5 will receive 5 mg vitamin K in solution and 5 will receive tablets. Participants are asked to postpone their breakfast untill ingestion of the vitamin K. Before intake and 7 times after (after 2, 4, 5, 6, 8, 10 and 24 hours) blood will be drawn to determine the ammount of vitamin K in the blood. Additionally, participants are asked to follow a low-vitamin K diet during 24 hours. In a crossover model with a wash out period of 2 weeks this will be repeated with the ones who first received tablets now receiving the vitamin K solution and vice versa.

Step 2:
72 patients who need to undergo (small) surgery or an invasive diagnostic procedure according to which they need to be treated with 5 mg vitamin K

according to the protocols from the Leiden anticoagulation clinic will be randomised over two groups. One group will receiver 5 mg vitamin K as tablets and one group will receive the vitamin K solution. Before intake and after 24 and 48 hours the INR will be determined. The effectiveness of the vitamin K will be expressed as the difference in the number of INR values below 2.0 between the two groups.

Step 3:
72 patients who have an INR between 7.0 and 10.0 will be randomised over two groups: one receiving 5 mg vitamin K as tablets while the other group receives the vitamin K solution. Before intake and after 24 and 48 hours the INR will be measured. Also, before intake and 24 hours after intake some extra blood will be taken to determine the ammount of vitamin K in the blood. The endpoints consist of the difference in the INR reduction between both groups and the difference in the increase of the ammount of vitamin K in the blood.

**Intervention**

De healthy volunteers will receive both 5 mg vitamin K tablets and 5 mg vitamin K solution with a wash out period of 2 weeks in between.

The patients will receive either 5 mg vitamin K tablets or 5 mg vitamin K solution depending on the randomisation.

**Study burden and risks**

There is no risk involved for the healthy volunteers since no adverse effects of vitamin K intake are known.
The burden excist in the need of a multiple blood sampling over a period of two times 24 hours.

The risk for the patients undergoing either (small) elective surgery or invasive diagnostic procedures lies in the fact the planned procedures need to be cancelled should the INR respond inadequately to the vitamin K tablets. Also, there is a theoretical risk the vitamine K tablets have a higher biological availability or effectiveness than the solution, causing an increased thrombo-embolic risk,
In these patients either one or two additional INR measurements need to be done.

The risk in the patientgroup that has a high INR excist in the extended duration of the bleeding risk should the biological availability or the effectiveness be less for the vitamin K tablets. Also in this groups of patients there is a theoretical risk of thrombo-embolic complications should the biological availibility or the effectiveness of the vitamin K tablets be superior to the vitamin K solution.
These patients will need to ondergo another blood sampling the day of the

initial INR monitoring in order to determine the ammount of vitamin K in the blood. Furthermore this group will also have two additional INR measurements and, 24 hours after vitamin K intake, an additional ammount of blood for vitamin K measurement in the blood.

## 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 above 18.

### Exclusion criteria

Liver failure
Dialysis (both hemodialysis and peritoneal dialysis)
Pregnancy, pregnancy wish or breastfeeding.
Participation in the self management program
Inability to manage medication intake or proven (previously) non-compliance with treatment.

# Study design

## Design

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|---|---|
| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 18-07-2011 |
| Enrollment: | 169 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Vitamin K1 |
| Generic name: | Phytomenadion solution in oil FNA |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Vitamin K1 |
| Generic name: | Phytomenadion tablets |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 11-10-2010 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 28-04-2011 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 01-05-2013 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

## 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 | EUCTR2010-022826-34-NL |
| CCMO | NL33919.058.10 |

## Study results

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| Date completed: | 06-09-2013 |

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| Actual enrolment: | 194 |