# Effects of low-dose aspirin taken at bedtime vs. on awakening on circadian rhythm of platelet function in healthy subjects

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To study the effect of 80 mg aspirin intake at bedtime compared with 80 mg aspirin intake on awakening on circadian rhythm of platelet function in healthy subjects.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Platelet disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON38423

**Source**
ToetsingOnline

**Brief title**
Aspirin AM or PM?: effect on circadian rhythm of platelet reactivity

### Condition

- Platelet disorders
- Myocardial disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

**Synonym**
arterial thrombosis

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** aspirin, chronotherapy, circadian rhythm, platelet reactivity

## Outcome measures

### Primary outcome

Platelet reactivity, measured by the VerifyNow® Aspirin Assay

### Secondary outcome

Platelet function and factors involved in coagulation pathways, measured in

blood samples

# Study description

### Background summary

Low-dose aspirin is a cornerstone in the secondary prevention of cardiovascular disease (CVD) and is usually taken on awakening, although evidence regarding optimal time of intake is lacking. Platelets play a crucial role in the development of acute thrombotic events and it has been convincingly shown that platelet activity follows a circadian rhythm, with a peak of platelet reactivity in the morning. This might in part explain the peak of cardiovascular events in the morning between 6 and 12 AM1. Due to its short half life, aspirin only inhibits platelets which are present at the time of intake. Thus, the timing of aspirin intake may influence its inhibitory effect on platelets and intake of aspirin at bedtime may attenuate the morning peak of platelet reactivity. The time-dependent effect of aspirin on circadian rhythm of platelet function has never been studied before.

### Study objective

To study the effect of 80 mg aspirin intake at bedtime compared with 80 mg aspirin intake on awakening on circadian rhythm of platelet function in healthy subjects.

### Study design

The design of our study is a randomized, open-label, blinded endpoint (PROBE) crossover trial. Benefits of the PROBE design and its validity as compared to double-blind, placebo-controlled trials have been previously documented. 12 healthy volunteers, as calculated below, will randomly use aspirin on awakening and aspirin at bedtime during two intervention periods of two weeks. The two intervention periods are separated by a wash-out period of 4 weeks, which is approximately 4 times the duration of action of aspirin (7-10 days), and long enough to guarantee washout of the effect of two weeks of aspirin intake in the preceding period. At the end of both treatment periods, subjects will be admitted for 24 hours to the LUMC to assess the effect of aspirin intake on awakening or at bedtime on the circadian rhythm of platelet function.

### Intervention

aspirin 80mg on awakening (2 weeks)
aspirin 80mg at bedtime (2 weeks)

### Study burden and risks

Extensive knowledge is available about AEs associated with use of aspirin. Related to its effect on platelet aggregation is impairment of primary haemostasis. Unless it is given to patients with an underlying haemostatic defect, it does not cause a generalized bleeding abnormality. The most well-known effect is the gastrointestinal toxicity. By dose-related inhibition of prostaglandin synthesis, erosions in the gastric mucosa may occur. In several reviews, the use of low dose aspirin (30-300mg a day) was associated with a relative risk of severe upper gastrointestinal bleeding or perforation of 1.6 - 2.2 versus placebo. A recent meta-analysis reported a total of 0.53 major gastrointestinal and other extracranial bleeds per 10.000 person-years. Given the short duration of exposure to the study drug in a healthy population, we consider the bleeding- and gastrointestinal risk very low for this study. Additionally, medical and hematological screening before entry into the study excludes entry of subjects with an increased risk of side effects or platelet dysfunction. In our opinion, there is a tolerable risk for healthy study subjects during the study period, regarding the minimal risk of side effects with the short term use of low-dose aspirin.

## 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

• Healthy subject
• Age >18yrs
• Capacity to give informed consent

## Exclusion criteria

• Active chronic disease
• Use of any other medication
• History of: major bleeding events, known bleeding diathesis or disorder, cardiovascular disease, malignancy
- allergy to salicylates
• Platelet count < 150 * 109/L
• VerifyNow Aspirin Reaction Units <550 ARU
• Smoking
• Shift work in the preceding 2 months
• Extreme chronotypes, defined as regular (>2 days/week) bedtime <22:00h or >24:00h and/or awakening <6:00h or >9:00h

• Pregnancy

# Study design

## Design

| | |
|---|---|
| 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): | 01-08-2013 |
| Enrollment: | 12 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | acetylsalicylic acid |
| Generic name: | aspirin |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

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|---|---|
| Date: | 27-06-2013 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

Approved WMO

| | |
|---|---|
| Date: | 01-07-2013 |
| Application type: | First submission |
| 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 | EUCTR2013-001410-16-NL |
| CCMO | NL44378.058.13 |

# Study results

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|---|---|
| Date completed: | 01-03-2014 |
| Actual enrolment: | 14 |