# The role of corticosteroids on coagulation and inflammation in asthma

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Primary objective:- To evaluate the effects of a 10 day-course of prednisolon on coagulation and fibrinolysis parameters in patients with mild-moderate astma, patients with severe asthma, and healthy controls.Secondary objectives:- To compare the...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Respiratory disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON36375

**Source**
ToetsingOnline

**Brief title**
ROCOCO

### Condition

- Respiratory disorders NEC

**Synonym**
corticosteroid induced hypercoagulability in asthma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** collectebusfondsen

## Intervention

**Keyword:** asthma, coagulation, corticosteroids, inflammation

## Outcome measures

### Primary outcome

Primary endpoint will be the change in TATc and PAPc in blood.

### Secondary outcome

Secondary endpoints will be changes in markers of hemostasis and inflammation

in blood and induced sputum.

# Study description

### Background summary

Asthma is a chronic inflammatory disease of the airways characterised by variable airways obstruction and although asthma can be well controlled in most patients by treatment with inhaled corticosteroids, there is a small subset of patients requiring oral corticosteroids for asthma control. High levels of glucocorticoids, either endogenous or exogenous, have been shown to induce hypercoagulability and an increased risk of venous thromboembolism.
In asthma corticosteroids, either inhaled or oral, have been shown to influence hemostasis. In patients with moderate asthma inhaled corticosteroids decrease the activation of hemostasis, while in severe asthmatic patients a further activation of hemostasis may occur. Oral corticosteroids further activate hemostasis during an acute exacerbation.
In addition, asthma itself has also been associated with a prothrombotic state, and preliminary data from our group have shown an increased risk of pulmonary embolism in patients with severe asthma that was associated with chronic oral corticosteroid use and frequent asthma exacerbations.
Therefore, an activated coagulation system might enhance the inflammatory process in the airways of asthmatics and contribute to therapy resistance in those with severe disease.

Hypothesis
We hypothesize that:
1. Patients with mild-moderate and severe asthma have an increased procoagulant activity as compared to healthy controls.
2. Oral corticosteroids activate coagulation in healthy controls and increase

the procoagulant activity in mild-moderate and severe asthmatic patients.
3. Increase of hypercoagulation is correlated with asthma severity and use of high dose corticosteroids.

## Study objective

Primary objective:
- To evaluate the effects of a 10 day-course of prednisolon on coagulation and fibrinolysis parameters in patients with mild-moderate astma, patients with severe asthma, and healthy controls.

Secondary objectives:
- To compare the parameters for coagulation and fibrinolysis between patients with severe asthma, well-controlled mild-moderate asthma and healthy controls.
- To assess the relationship between asthma severity and coagulation activation.
- To disentangle the effects of asthmatic disease and prednisolon on coagulation activation.

## Study design

Study 1:
A cross-sectional study in which the haemostatic activity in peripheral blood and induced sputum is compared between three groups of 30 subjects each: patients with mild-moderate and severe asthma, and healthy controls,

Study 2:
A randomised, placebo-controlled, double blind, parallel intervention trial with oral prednisolon (0.5 mg/kg/day for 10 days) in the same three groups of 30 subjects each, as mentioned in study 1. Study participants will undergo pulmonary function testing, sputum induction and venous blood sampling three times in a period of 2 weeks (days -1, 1 and 11).

## Intervention

All patients will receive prednison 0,5mg/kg/dag of placebo for 10 days.

## Study burden and risks

For patients with severe, refractory asthma, there are hardly any therapeutic options except oral corticosteroids that are associated with serious long-term side effects. Preliminary data from our group suggests an increased risk of pulmonary embolism in this group of patients. This study will investigate what the effect of prednisolon is on hemostasis and the interaction with inflammation. Adverse effects of prednisolon for the time and dose prescribed in this study are expected to be nihil.

# 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

All subjects
• Age between 18 - 75 years
• Non-smoking or stopped smoking more than 12 months ago and 10 pack years or less
• Able to give written and dated informed consent prior to any study-specific procedures;Healthy controls:
• Baseline FEV1 > 80% of predicted
• Methacholine PC20> 8 mg/ml
• No usage of steroids by any dosing route
• Negative allergy testing by skin prick test or specific IgE
• Negative history of pulmonary and any other relevant diseases;Patients with asthma
• All patients have previous evidence of variable airways obstruction within the last 5 yrs, as documented by at least one of the following:

- Reversibility in forced expiratory volume in one second (FEV1) of >=9% predicted after 4 puffs of a 100 µg salbutamol dose-aerosol, administered via a spacer.
*- A mean diurnal variation in peak expiratory flow (PEF) >=15% (highest PEF - lowest PEF) per mean PEF on >=4 days per week for a minimum of 2 weeks.
*- An increase in FEV1 of >=400 mL after a course of prednisolone 0.5 mg•kg*1•day*1 for 14 days.
*- A provocative concentration causing a 20% fall in FEV1 with histamine or methacholine <8 mg/mL.
• Clinically stable, for patients with mild asthma this means no exacerbations within the last 8 weeks prior to the study.
• No other clinically significant abnormality on history and clinical examination
• The use of short and long-acting beta2-agonists, leukotriene receptor antagonist, short or long acting anticholinergic agonists are allowed provided that the dose of these drugs remains stable during the study.;Mild/Moderate asthmatic patients:
• Baseline FEV1 > 70% of predicted
• Low- to medium-dose use of inhaled corticosteroids (ICS) (fluticason <= 500 µg/day or equivalent drug);Severe asthmatic patients:
• Severe asthma according to the recently published consensus criteria of the Innovative Medicine Initiative (IMI)31
• High- and ultrahigh dose of ICS (Fluticasone >=1000 µg/day or equivalent drug).
• On stable doses of inhaled corticosteroids during the previous 4 weeks and during the study.

## Exclusion criteria

Exclusion criteria for all patient-groups are as follows:
• Women who are pregnant or lactating or who have a positive urine pregnancy test at screening
• Participation in any clinical investigational drug treatment protocol within the preceding 30 days
• Use of heparin, LMWH, NSAID or vitamin K antagonists.
• Use of omalizumab during the last 6 months before randomization
• Use of oral corticosteroids during the last 8 weeks before randomization
• Ongoing use of tobacco products of any kind or previous usage with a total pack year >= 10 years
• General contraindications for the use of corticosteroid use, including a known diagnosis of peptic ulcers, osteoporosis, psychoses, infections, diabetes and hypertension, or symptoms and signs compatible with one of the above diagnoses.
• Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the patient in this study
• Unwillingness or inability to comply with the study protocol for any other reason

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 27-02-2012 |
| Enrollment: | 90 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Prednison |
| Generic name: | Prednisolon |
| Registration: | Yes - NL intended use |

# Ethics review

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| Approved WMO Date: | 01-09-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-10-2011 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

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| Date: | 22-11-2013 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# 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 | EUCTR2010-023931-40-NL |
| CCMO | NL34709.018.11 |
| Other | NTR in aanvraag |