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# Prevention of complications to Improve outcome in elderly patients with acute stroke - A randomised clinical trial

**Submission date**
29/08/2015

**Recruitment status**
No longer recruiting

**Registration date**
22/09/2015

**Overall study status**
Completed

**Last Edited**
11/12/2023

**Condition category**
Circulatory System

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

Background and study aims
About 85% of strokes are ischemic strokes. Ischemic strokes happen when the arteries that supply the brain with oxygen (the carotid arteries) become narrowed or blocked, causing severely reduced blood flow (ischemia). As we age, a gradual build-up of a sticky substance called plaque can occur in one or both of the carotid arteries. When there is a lot of plaque, particularly with a rough or irregular surface, blood clots can develop, depriving the brain of oxygen and leading to an acute ischemic stroke (AIS). Intracerebral haemorrhages (ICH) are much less common than ischemic strokes, and make up about 12% of all strokes. ICH happens when a diseased blood vessel in the brain bursts, causing bleeding within the brain. This causes a sudden increase of pressure on the brain, and can quickly lead to unconsciousness and even death. About 70% of patients who suffer from a ICH experience long-term side-effects, and depending on the area of the brain that is affected, it can affect their ability to move, speak or even their cognitive function (memory loss, difficulty reasoning, confusion). Elderly patients who have experienced a stroke have a high risk of immediate complications, such as infections or fever. It has been found that these complications are strongly related to a higher risk of death or long-term disability (dependency). These complications are usually treated only when they become apparent by paracetamol (for pain or fever), infections (ceftriaxone) and nausea and vomiting (metoclopramide). The aim of this study is to find out whether giving these medications to stroke patients straight away can prevent these complications from occurring in the first place, and reduce the risks of long-term side-effects.

Who can participate?
Adults over 66 years of age with a clinical diagnosis of AIS or ICH.

What does the study involve?
Participants are randomly allocated into groups who will receive treatment with a combination of paracetamol, ceftriaxone and metoclopramide, or none of these drugs (usual care). The treatment is started within 12 hours of the stroke, and continues for four days (or until the

patient is discharged from hospital, if sooner). Three months later, participants are interviewed in order to assess whether they have any handicap following their stroke, and if so, how severe it is. Survival rates, quality of life and cognition (mental processes) are also measured.

What are the possible benefits and risks of participating?
A benefit of participating is that one or more of the drugs used in this study could help to reduce the change of death or dependency after a stroke, but this cannot be guaranteed. There are no significant risks of participating as the drugs used in this study have been used for decades in patients with acute stroke to treat fever (paracetamol), infections (ceftriaxone), and nausea and vomiting (metoclopramide). Common side effects from these drugs include diarrhoea and allergic reactions, however serious side effects are rare.

Where is the study run from?
1. Tartu University Hospital (Estonia)
2. Larissa University Hospital (Greece)
3. University of Debrecen (Hungary)
4. Carlo Poma Hospital (Italy)
5. University Medical Center Utrecht (Netherlands)
6. Oslo University Hospital (Norway)
7. Institute of Psychiatry and Neurology, Warsaw (Poland)
8. Royal Infirmary of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
June 2015 to September 2022

Who is funding the study?
European Union's Horizon 2020 Research and Innovation Programme (Belgium)

Who is the main contact?
Dr Bart van der Worp

### Study website
http://www.precious-trial.eu/

# Contact information

### Type(s)
Public


### Contact name
Dr Bart van der Worp

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## Additional identifiers

### EudraCT/CTIS number
2015-003179-32

### IRAS number

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
ToL54304

## Study information

### Scientific Title
PRECIOUS: PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke. A randomised, open, phase III, clinical trial with blinded outcome assessment

### Acronym
PRECIOUS

### Study objectives
Prevention of infections, fever, or aspiration with ceftriaxone, paracetamol, metoclopramide, or any combination of these in the first 4 days after stroke onset improves functional outcome at 3 months in elderly patients with acute stroke.

### Ethics approval required
Old ethics approval format

## Ethics approval(s)
Not provided at time of registration

## Study design
International multi-centre multi-factorial randomized controlled open-label clinical trial with blinded outcome assessment

## Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet

## Health condition(s) or problem(s) studied
Acute ischaemic stroke or intracerebral haemorrhage

## Interventions
Patients will be randomly allocated in a 2*2*2 factorial design to any combination of open-label oral or rectal metoclopramide (10 mg thrice daily), intravenous ceftriaxone (2000 mg once daily), oral, rectal, or intravenous paracetamol (1000 mg four times daily), or to usual care, started within 12 hours after symptom onset and continued for 4 days or until complete recovery or discharge from hospital, if earlier. Allocation will be based on proportional minimisation through a web-based allocation service. Investigators will have the opportunity to censor a single specific randomisation arm in a specific patient before randomisation, for example in case of an allergy to one of the interventions. Patients will have follow-up at 7 and 91 days.

## Intervention Type
Drug

## Phase
Phase III

## Drug/device/biological/vaccine name(s)
Paracetamol, ceftriaxone, metoclopramide

## Primary outcome measure
Handicap as assessed with the score on the modified Rankin Scale at 91 days (± 14), and analysed with ordinal logistic regression.

## Secondary outcome measures
At 7 days (± 1 day) or at discharge, if earlier:
1. Infections in the first 7 days (± 1 day; frequency, type, and C. difficile infections). Infections will be categorised as diagnosed by the clinician, and as judged by an independent adjudication

committee (masked to treatment allocation);
2. Third generation cephalosporin resistance in the first 7 days (± 1 day), detected as part of routine clinical practice;
3. Antimicrobial use during the first 7 days (± 1 day), converted to units of defined daily doses according to the classification of the WHO Anatomical Therapeutic Chemical Classification System with Defined Daily Doses Index;
4. In a subgroup of patients: presence of Extended-Spectrum Beta-Lactamase (ESBL)-producing bacteria as detected by PCR in a rectal swab.
At 91 days (± 14 days):
1. Death;
2. Unfavourable functional outcome, defined as mRS 3 to 6;
3. Disability assessed with the score on the Barthel Index (BI);
4. Cognition assessed with the Montreal Cognitive Assessment (MoCA);
5. Quality of life assessed with the EuroQol 5D-5L (EQ-5D-5L);
6. Home time: duration of stay in the patient's own home or a relative's home over the first 90 days;
7. Patient location over first 91 days (± 14 days): hospital; rehabilitation service; chronic nursing facility; home;
8. SAEs in the first 14 days.

### Overall study start date
01/06/2015

### Completion date
30/09/2022

## Eligibility

### Key inclusion criteria
1. Clinical diagnosis of acute ischaemic stroke or intracerebral haemorrhage (confirmed with CT or MRI scan)
2. Score on the National Institutes of Health Stroke Scale58 (NIHSS) ≥6, indicating moderately severe to severe stroke
3. Aged 66 years or older
4. Possibility to start trial treatment within 12 h of symptom onset

### Participant type(s)
Patient

### Age group
Senior

### Lower age limit
66 Years

### Sex
Both

### Target number of participants
3800

### Total final enrolment
1493

### Key exclusion criteria
All participants:
1. Active infection requiring antibiotic treatment, as judged by the treating physician;
2. Pre-stroke score on the modified Rankin Scale ≥4
3. Death appearing imminent at the time of assessment.

For the ceftriaxone arm:
1. Known hypersensitivity to beta-lactam antibiotics

For the paracetamol arm:
1. Known hypersensitivity to paracetamol or any of the excipients
2. Known severe hepatic insufficiency
3. Chronic alcoholism

For the metoclopramide arm:
1. Hypersensitivity to the metoclopramide or to any of the excipients
2. Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk
3. Confirmed or suspected pheochromocytoma
4. History of neuroleptic or metoclopramide-induced tardive dyskinesia
5. Epilepsy
6. Parkinson's disease
7. Use of levodopa or dopaminergic agonists
8. Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency

### Date of first enrolment
01/02/2016

### Date of final enrolment
30/06/2022

## Locations

### Countries of recruitment
Estonia

Germany

Greece

Hungary

Italy

Netherlands

Norway

Poland

Scotland

United Kingdom

**Study participating centre**
**Tartu University Hospital**
Ülikooli 18
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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### Study participating centre
**University Medical Center Utrecht**
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### Study participating centre
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### Study participating centre
**Institute of Psychiatry and Neurology**
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### Study participating centre
**Royal Infirmary of Edinburgh**
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## Sponsor information

### Organisation
University Medical Center Utrecht

### Sponsor details
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### Sponsor type
Hospital/treatment centre

### Website
www.umcutrecht.nl

### ROR
https://ror.org/0575yy874

## Funder(s)

### Funder type
Research organisation

### Funder Name
European Union’s Horizon 2020 Research and Innovation Programme

## Results and Publications

### Publication and dissemination plan
The research data will be publicly disclosed and published independent of the outcome of the study in scientific, peer-reviewed, international journals and at international conferences.

### Intention to publish date
31/12/2022

### Individual participant data (IPD) sharing plan

### IPD sharing plan summary
Data sharing statement to be made available at a later date

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | protocol | 01/09/2018 | | Yes | No |
| Statistical Analysis Plan | statistical analysis plan | 26/10/2020 | 28/10/2020 | No | No |
| Abstract results | | 03/05/2022 | 10/10/2023 | No | No |
| Abstract results | | 16/05/2017 | 10/10/2023 | No | No |
| Results article | | 01/12/2023 | 11/12/2023 | Yes | No |