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

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Primary objectiveTo assess whether prevention of aspiration, infections, and fever with metoclopramide, ceftriaxone, paracetamol, or any combination of these in the first 4 days after stroke onset improves functional outcome at 90 days in elderly…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Body temperature conditions
Study type	Interventional

Summary

ID

NL-OMON50714

Source
ToetsingOnline

Brief title
PRECIOUS

Condition

- Body temperature conditions
- Bacterial infectious disorders
- Central nervous system vascular disorders

Synonym
stroke

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,European Commission;Horizon 2020 programme

Intervention

Keyword: Complications, Prevention, Stroke

Outcome measures

Primary outcome

The primary outcome measure is the score on the modified Rankin Scale (mRS) at

90 days (± 14 days), as analysed with multiple regression.

Secondary outcome

At 7 days (± 1 day) or at discharge, if earlier:

- Infections in the first 7 days (± 1 day; frequency, type, and C. difficile

overgrowth syndrome). Infections will be categorised as diagnosed by the

clinician, and as judged by an independent adjudication committee (masked to

treatment allocation);

- 3rd generation cephalosporin resistance in the first 7 days (± 1 day),

detected as part of routine clinical practice;

- 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;

- In a subgroup of patients: presence of Extended-Spectrum Beta-Lactamase

(ESBL)-producing bacteria as detected by PCR in a rectal swab.

At 90 days (± 14 days):

- Death;

- Unfavourable functional outcome, defined as mRS 3 to 6;

- Disability assessed with the score on the Barthel Index (BI);

- Cognition assessed with the Montreal Cognitive Assessment (MoCA);

- Quality of life assessed with the EuroQol 5D-5L (EQ-5D-5L);

- Home time: duration of stay in the patient*s own home or a relative*s home

over the first 90 days;

- Patient location over first 90 days (± 14 days): hospital; rehabilitation

service; chronic nursing facility; home.

- SAEs in the 7 days.

Study description

Background summary

Every year, 1.3 million Europeans have a first stroke. One fifth to one third of stroke patients die in the first month after stroke, and one third remain dependent on the help of others. The annual costs for stroke care in Europe have been estimated at ¤64.1 billion. Stroke incidence increases almost exponentially with age, and the personal, societal, and economic burden of stroke is therefore largely driven by its frequent occurrence in the elderly. Elderly patients are at the highest risk of complications after stroke, such as infections and fever. These complications are strongly and independently associated with a higher risk of death or dependency. The risk of developing these complications can be reduced by very simple, safe, and cheap measures, such as metoclopramide for the management of dysphagia, antibiotics for the prevention of infections, and paracetamol for the prevention of fever, but it is uncertain whether these measures also improve functional outcome.

Study objective

Primary objective
To assess whether prevention of aspiration, infections, and fever with

metoclopramide, ceftriaxone, paracetamol, or any combination of these in the first 4 days after stroke onset improves functional outcome at 90 days in elderly patients with acute stroke.

Secondary objective
- To assess the effect of prevention of infections and fever in the first days after stroke onset with metoclopramide, ceftriaxone, paracetamol, or any combination of these, on the following outcomes at 90 days: death, death or dependency, quality of life, cognition, costs
- To detect specific populations classified by age, sex, stroke severity, body temperature, co-morbidities, and geographic region, in which the proposed treatments are particularly effective or not effective.
- To assess the effects of prophylactic treatment with ceftriaxone on antimicrobial resistance and the occurrence of infections with Clostridium difficile.

Study design

International, multi-centre, multi-factorial, randomised, controlled, open-label clinical trial with blinded outcome assessment (PROBE) of metoclopramide, ceftriaxone, paracetamol, or any combination of these, in 3800 elderly patients with acute ischaemic stroke or intracerebral haemorrhage. The trial will be performed according to ICH-GCP principles, the Declaration of Helsinki as most recently amended in 2013, and national and international regulatory requirements.

Intervention

Patients will be randomly allocated in a 2*2*2 factorial design to any combination of open-label oral, rectal, or intravenous metoclopramide (10 mg thrice daily), intravenous ceftriaxone (2000 mg once daily), oral, rectal, or intravenous paracetamol (1000 mg four times daily), or usual care, started within 24 hours after symptom onset and continued for 4 days or until complete recovery or discharge from hospital, if earlier. In patients with moderate to severe renal impairment or with severe hepatic impairment, the dose of metoclopramide is reduced to 5 mg thrice daily, and in patients with end-stage renal disease to 2.5 mg thrice daily. 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.

Study burden and risks

About half of all patients develop complications after stroke, including infections and fever. Advanced age and pre-existing co-morbidities increase the

risk of developing these events. In addition, patients with severe, disabling strokes are particularly vulnerable. These complications can impede functional recovery, prolong hospital admissions, and are independently associated with an increased risk of death or long-term dependency. Earlier trials have suggested that the prevention of these complications may improve outcomes after stroke. The medication tested in PRECIOUS has been used for decades in patients with acute stroke to treat nausea and vomiting (metoclopramide), infections (ceftriaxone), and fever (paracetamol). Serious side effects of these drugs are uncommon when used according to their marketing authorisations. Their use in clinical trials on the prevention of complications in patients with acute stroke was safe and not associated with an increase in serious adverse events (SAEs). According to the Dutch NFU guideline, the risk associated with participation in this study is therefore small. Given the potential benefit of the prevention of complications to the included subjects, future stroke patients, their caregivers, and society on the one hand and the limited risks to trial subjects on the other hand, the trial*s Steering Committee and Ethics Advisory board conclude on a risk-benefit balance strongly in favour of conducting this clinical trial.

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

1. A clinical diagnosis of acute ischaemic stroke or intracerebral haemorrhage, confirmed with CT or MRI scan. A normal CT scan is considered compatible with ischaemic stroke;
2. A score on the National Institutes of Health Stroke Scale (NIHSS) * 6, indicating moderately severe to severe stroke;
3. Age 66 years or older;
4. The possibility to start treatment within 24 hours of symptom onset;
5. Written informed consent.

Exclusion criteria

1. Active infection requiring antibiotic treatment, as judged by the treating physician;
2. Pre-stroke score on the mRS (modified Rankin Scale) *4
3. Death appearing imminent at the time of assessment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	02-04-2016
Enrollment:	740
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alle bestaande merken
Generic name:	Ceftriaxone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Alle bestaande merken
Generic name:	Metoclopramide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Alle bestaande merken
Generic name:	Paracetamol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-11-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-02-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2016
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	12-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-06-2018
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-003179-32-NL
ISRCTN	ISRCTN82217627
CCMO	NL54304.041.15