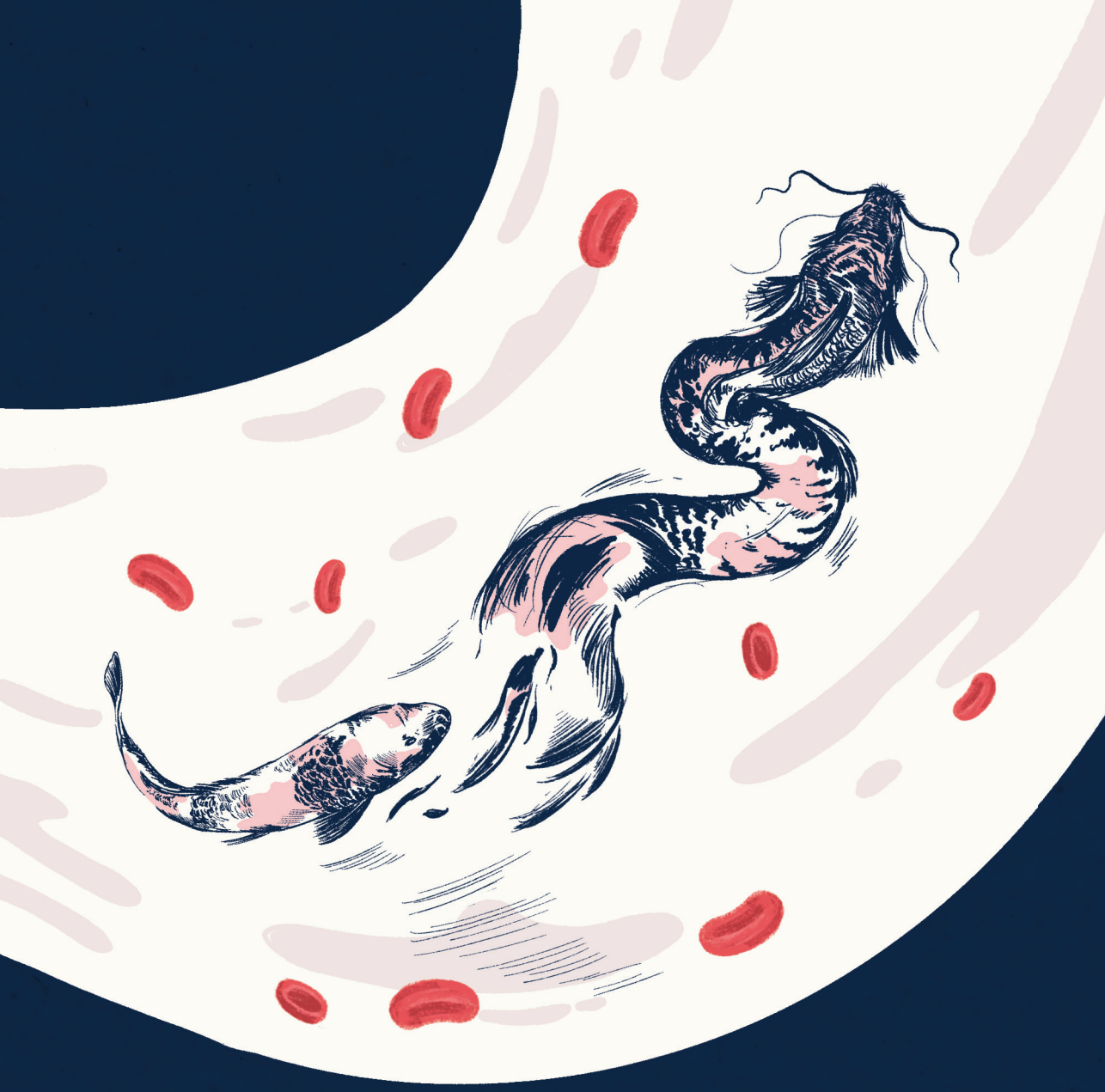

Complications, treatment restrictions and end-of-life care in patients with acute stroke

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Complicaties, behandelbeperkingen en levenseindezorg bij patiënten met een acute beroerte
(met een samenvatting in het Nederlands)

Proefschrift

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Chapter I

General introduction and thesis outline

OUTCOME AFTER STROKE

The treatment of patients with acute stroke has significantly improved during the last decades. Halfway the 1990s, treatment with aspirin and implementation of organised care on a dedicated stroke unit were the only evidence-based treatments for patients with acute ischaemic stroke, but beneficial effects of these treatments on outcomes are only small to modest.[1,2] In recent years, treatment of patients with acute ischaemic stroke has been supplemented by intravenous thrombolysis with alteplase and endovascular treatment. Although these two treatments significantly improve functional outcome,[3,4,5,6] they can only be applied in a limited and highly selected group of patients. For intracerebral haemorrhage, no treatments with proven benefit other than organized stroke unit care are currently available.

As a consequence, stroke still remains a devastating disease. Death in the first month occurs in 13-23% of ischaemic stroke patients and in up to 40% of patients with intracerebral haemorrhage.[7,8] With 6.55 million deaths, stroke was the second-leading cause of mortality worldwide in 2019.[9] In many survivors functional outcome is poor: around 40% of patients with intracerebral haemorrhage and around 30% of ischaemic stroke patients remain dependent on the help of others,[10,11] causing stroke to be the third-leading cause of death or disability worldwide.[9]

COMPLICATIONS AFTER ACUTE STROKE

The clinical syndrome of stroke in the acute phase of the disease is a consequence of the direct dysfunction of brain tissue caused by deprivation of blood flow (ischaemic stroke) or by blood leakage into the tissue (intracerebral haemorrhage), and is characterised by neurological deficits, such as loss of motor skills, visual field defects, ataxia or sensory loss. The severity of these early symptoms, as assessed by the National Institutes of Health Stroke Scale (NIHSS), is an important predictor of functional outcome.[12] Secondary adverse medical events occur in more than half of patients during the first days after stroke onset. These complications may impede neurological recovery and may have a substantial negative effect on stroke-related morbidity and mortality.[13] Older age, pre-existing comorbidity and more severe stroke are associated with an increased risk of these post-stroke complications.[14]

Among the most common of these secondary complications are dysphagia, infections and hyperthermia. Dysphagia is present in about a quarter to half of patients with acute stroke and is associated with increased risk of pneumonia, poor quality of life, and longer hospital stay.[13,15,16] Infections complicate the acute phase in around 30% of patients, and consist mainly of urinary tract infections and pneumonia. Infection in general and pneumonia in particular have been associated with an increased risk of death and unfavourable outcome.[17] Subfebrile temperatures or fever are observed in one third to half of the patients during the first days after stroke, and are also independently associated with an increased risk of a poor functional outcome or death.[18,19]

THE PRECIOUS TRIAL

Current American guidelines require screening for dysphagia in patients with acute stroke. Furthermore, infections should be treated with antibiotics and fever with antipyretic drugs.[20] As these are simple measures, their preventive use might be an option to improve functional outcomes in stroke patients. Current European guidelines conclude that there is insufficient evidence to make a strong recommendation on whether, when, and to whom preventive or early fever treatment should be given and call for new randomised controlled trials to allow for better-informed recommendations in the future.[21,22] The PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) Trial, which was initiated in 2015, addresses this very question. **Chapters 2 and 3** of this thesis focus on the rationale, design and statistical analysis of this phase III randomised clinical trial.

The results of the PRECIOUS trial were not available at the accomplishment of this thesis, mainly due to slow patient recruitment that required an extension of the trial. PRECIOUS is not unique in this respect: approximately half of the clinical trials fail to meet their intended sample size within the planned timeline.[23] Multiple barriers to successful trial completion have been identified and highlighted by neurologists involved in stroke trials throughout Europe.[24,25] Obtaining regulatory and governance approval has become increasingly burdensome and disproportionate to the conceivable risks to research participants.[24,25] However, evidence on the exact extent of these delays on trial progress has been very scarce so far. In **chapter 4** of this thesis, I focus on quantifying delays by regulatory reviews in PRECIOUS and analyse their relationship with patient recruitment.

SPACE-OCCUPYING OEDEMA

Space-occupying oedema is one of the most life-threatening complications in the first days of ischaemic stroke and has a reported mortality up to 80% when treated conservatively.[26] Surgical decompression consistently increased survival and improved functional outcome in pooled analyses of three randomised controlled trials at the beginning of this century.[27,28] Based on these findings, surgical decompression is advocated in guidelines as a reasonable treatment option for these patients.[20] However, subgroup analyses were hampered by small sample sizes and uncertainties remain about optimal timing and the benefit of surgical decompression for specific patient groups.[29] The results of more recently completed randomised clinical trials and the pooling of individual patient data allowed us to better address the effects of surgical decompression in individual patients. The results of this analysis are presented in **chapter 5** of this thesis.

TREATMENT RESTRICTIONS IN STROKE

Most in-hospital deaths of patients with acute stroke follow a decision to withhold or withdraw life-sustaining treatments.[30] Treatment restrictions are usually installed in a clinical setting in which it is expected that extension of lifetime would result in a state of disability that might be against the patient's wishes and would essentially constitute 'a fate worse than death.'[31] These decisions usually evolve from complex discussions that encompass prognosis, institutional and societal norms and values and, of course, patient preferences. However, most stroke patients in whom treatment restrictions are considered have lost their capacity to participate in end-of-life decisions,[32] meaning that clinicians are often dependent on family members to communicate the patient's wishes.

Adequate prognostication is essential for families to make an informed decision on the best medical care for their loved one, but in practice both predictive models and physician estimates are too imprecise to be used in end-of-life-decisions.[31] Previous North American studies in patients with intracerebral haemorrhage have even suggested that the use of do-not-resuscitate orders itself independently increases the risk of death.[33,34] Many uncertainties about the association between treatment restrictions and mortality after stroke remain, including the influence of the type and timing of treatment restrictions and the question if such an association also exists in patients with ischaemic stroke. In addition, the use of treatment restrictions, as well as their association with mortality, may be different in a European setting as a consequence of cultural differences. Therefore, we analysed the relationship between treatment restrictions and mortality in stroke patients in the University Medical Center Utrecht, The Netherlands, as described in **chapter 6** of this thesis.

END-OF-LIFE CARE IN STROKE

Approximately half of stroke-related deaths occur in-hospital.[35] As a consequence, palliative care for these patients is common practice in a stroke unit. In fact, end-of-life care should be an essential core competency for every stroke neurologist.[36] Nonetheless, there is a striking lack of evidence concerning optimal palliative care practices in patients with acute stroke, especially when compared with patients with a more gradually progressive disease, such as cancer or amyotrophic lateral sclerosis.[35] For this reason, we assessed palliative end-of-life care in patients who deceased in our stroke unit in a prospective observational study, which is the topic of **chapter 7** of this thesis.

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2

Chapter 2

PRECIOUS: Prevention of complications to improve outcome in elderly patients with acute stroke. Rationale and design of a randomised, open, phase III, clinical trial with blinded outcome assessment

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Eur Stroke J. 2018; 3(3): 291-298

ABSTRACT

Background
Elderly patients are at high risk of complications after stroke, such as infections and fever. The occurrence of these complications has been associated with an increased risk of death or dependency.

Hypothesis
Prevention of aspiration, infections, or fever with metoclopramide, ceftriaxone, paracetamol, or any combination of these in the first four days after stroke onset will improve functional outcome at 90 days in elderly patients with acute stroke.

Design
International, 3 × 2-factorial, randomised-controlled, open-label clinical trial with blinded outcome assessment (PROBE) in 3800 patients aged 66 years or older with acute ischaemic stroke or intracerebral haemorrhage and an NIHSS score ≥6. Patients will be randomly allocated to any combination of 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 h after symptom onset and continued for four days or until complete recovery or discharge from hospital, if earlier.

Outcome
The primary outcome measure is the score on the modified Rankin Scale at 90 days (± 14 days), as analysed with multiple regression.

Summary
This trial will provide evidence for a simple, safe and generally available treatment strategy that may reduce the burden of death or disability in patients with stroke at very low costs.

Planning
First patient included in May 2016; final follow-up of the last patient by April 2020.

INTRODUCTION

In the first days after stroke, about half of all patients develop complications, including infections and fever. The risk of developing these events is greater in patients of higher age or with more severe stroke.[1–3] Aspiration, infections and fever can impede functional recovery, prolong hospital admissions, and are independently associated with an increased risk of death or long-term dependency.[1,2,4–9] In addition, systematic review of animal studies modelling ischaemic stroke has shown that hyperthermia during or shortly after the onset of ischaemia substantially increases infarct size, suggesting that the relation between fever and poor outcome observed in patients is at least in part causal.[10]

The risk of developing these complications can be reduced by very simple, safe and inexpensive 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.[11–14] In some, generally small, randomised trials, preventive treatment with these drugs not only convincingly reduced the risks of aspiration, infections, or fever by one third to one half, but was also associated with clear trends towards a lower risk of death or poor outcome.[11–14] The cluster-randomised Quality in Acute Stroke Care (QASC) study demonstrated that implementation of nursing protocols for the management of fever, hyperglycaemia and swallowing dysfunction on a stroke unit resulted in better outcomes.[15] However, in two recent large trials, preventive treatment with antibiotics did not improve functional outcomes.[16,17]

American guidelines for the treatment of patients with acute ischaemic stroke advocate screening for dysphagia; the use of antibiotics in patients with infections; and antipyretic drugs such as paracetamol in patients with subfebrile temperatures or fever.[18] Guidelines of the European Stroke Organisation concluded that there is insufficient evidence from randomised trials to make strong recommendations on whether, when and to whom preventive antibiotic or antipyretic treatment should be given after ischaemic stroke or intracerebral haemorrhage.[19,20] The authors called for randomised trials to allow for better-informed recommendations in the future.[20]

The PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) trial will assess whether a pharmacological strategy to prevent aspiration, infections, or fever with metoclopramide, ceftriaxone, paracetamol, or any combination of these in elderly patients with a moderately severe to severe acute stroke is more effective at reducing the risk of death and improving functional outcome than current clinical practice of waiting until these complications are manifest before initiating treatment.

DESIGN

Overview and timelines

PRECIOUS is an international, multi-centre, 3 × 2-factorial, randomised, controlled, open-label clinical trial with blinded outcome assessment (PROBE) of the preventive use of metoclopramide, ceftriaxone, paracetamol, or any combination of these, for four days in elderly patients with acute ischaemic stroke or intracerebral haemorrhage. The primary outcome measure is the score on the modified Rankin Scale (mRS) at 90 days (±14 days).[21] 3800 patients will be recruited over a period of about four years in about 80 hospitals (both academic and regional) in 9 European countries (Figure 1). The first patient was included in May 2016 and the main results are anticipated to be available in 2020. The complete and most recent version of the study protocol is available at www.precious-trial.eu.

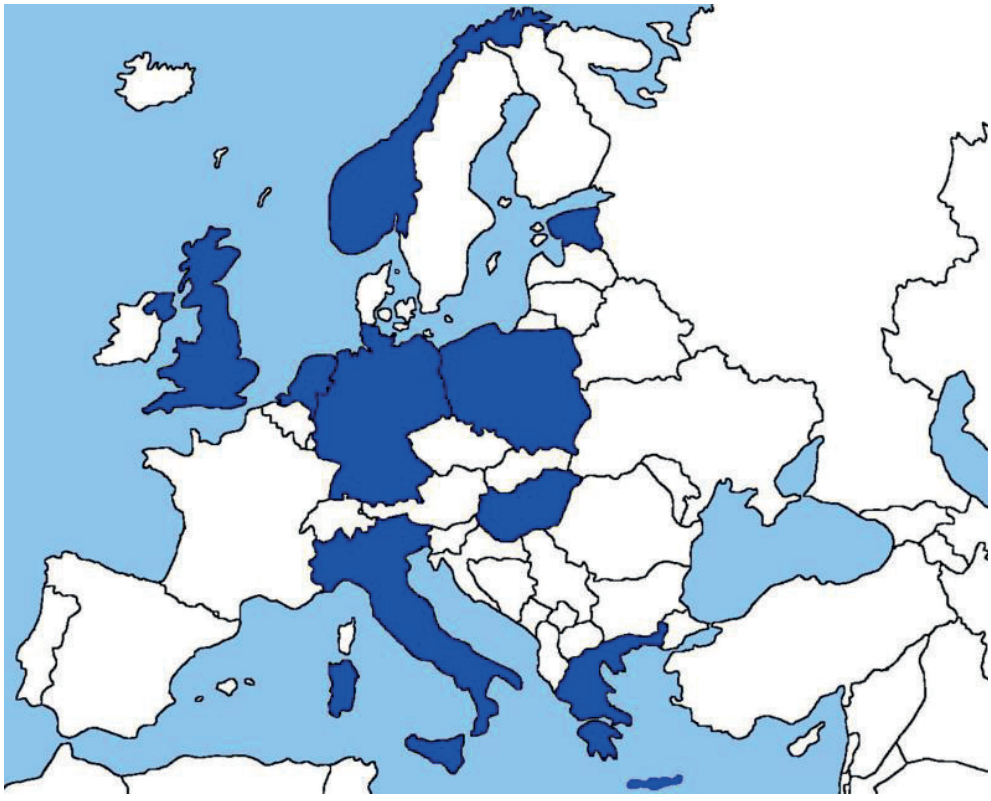

Figure 1. Participating countries in PRECIOUS.

Study population

The study population consists of patients aged 66 years or older who are hospitalised with moderately severe to severe acute ischaemic stroke or intracerebral haemorrhage and can be treated within 24 h of stroke onset. In order to be eligible to participate, a patient must meet all inclusion criteria listed in Table 1 and none of the exclusion criteria listed in Table 2. Patients with an active infection are excluded.

Table 1. Inclusion criteria.

1. A clinical diagnosis of acute ischaemic stroke or intracerebral haemorrhage, confirmed with CT or MRI scan[a]
2. A score on the NIHSS ≥6, indicating moderately severe to severe stroke[b]
3. Age 66 years or older
4. The possibility to start treatment within 24h of symptom onset[c]
5. Written informed consent[d]

CT: computed tomography; MRI: magnetic resonance imaging; NIHSS: National Institutes of Health Stroke Scale.
[a] A normal CT scan is considered compatible with ischaemic stroke.
[b] NIHSS is assessed at the time of inclusion.
[c] In case of a stuttering stroke, treatment should start within 24 h of the moment the first symptoms occurred.
[d] Informed consent is given by the patient, legal representative or independent physician (depending on local and national regulations).

Table 2. Exclusion criteria.

1. Active infection requiring antibiotic treatment[a] 2. Pre-stroke score on the mRS ≥4[b] 3. Death appearing imminent at the time of assessment
Criteria for censoring a treatment stratum:
For the metoclopramide stratum: 1. Hypersensitivity to 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. 9. Clinical indication for the use of metoclopramide. Incidental use of metoclopramide before screening is not an exclusion criterion.
For the ceftriaxone stratum: 1. Known hypersensitivity to beta-lactam antibiotics; 2. Clinical indication for antibiotic treatment. The use of an antibiotic before screening is not an exclusion criterion.
For the paracetamol stratum: 1. Known hypersensitivity to paracetamol or any of the excipients; 2. Known severe hepatic insufficiency; 3. Chronic alcoholism; 4. Clinical indication for the use of paracetamol. Incidental use of paracetamol before screening is not an exclusion criterion.

mRS: modified Rankin Scale.
[a] As judged by the treating clinical physician.
[b] Score 4 mRS: Moderately severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted.

Patient enrolment

After written informed consent, patients are randomly allocated in a 3 × 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 h after symptom onset and continued for four days or until complete recovery or discharge from hospital, if earlier (Figure 2). The daily dose of metoclopramide is reduced to 3 times 5 mg in patients with moderate to severe renal impairment or with severe hepatic impairment, and to 3 times 2.5 mg in patients with end-stage renal disease.

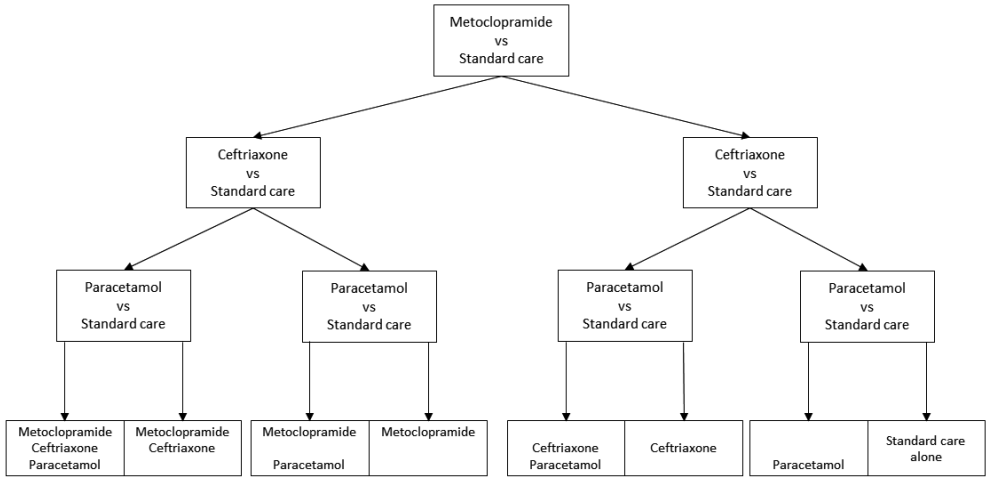

Figure 2. Treatment allocation

Allocation is based on proportional minimisation through a web-based allocation service. Treatment allocation is stratified by country and includes the following minimisation factors for balance in baseline characteristics: age (66–75 years vs. > 75 years); sex (male vs. female); stroke type (ischaemic stroke vs. intracerebral haemorrhage); stroke severity (NIHSS 6–12 vs. > 12); and diabetes mellitus (yes vs. no). Investigators have the opportunity to censor a single randomisation stratum in a specific patient before randomisation, for example in case of an allergy to one of the study medications (Table 2). Alongside the study treatment, all patients receive standard care as recommended by national or international guidelines or local protocols. This may include thrombolysis and endovascular treatment for acute ischaemic stroke, and treatment of hypertension for intracerebral haemorrhage.

Data collection and follow-up

Baseline characteristics assessed are listed in Table 3. The presence of any treatment restriction, the method of food intake and the vital signs (including body temperature) are recorded at baseline and during the first seven days of hospitalisation. The recording and reporting period for all severe or serious adverse events begins after randomisation and ends on day 7, except for serious adverse reactions and suspected unexpected serious adverse reactions (SUSARs), which are recorded and reported up to 90 days. Death occurring before day 90 (±14) is a study secondary outcome and is always documented and recorded.

Table 3. Baseline characteristics.

• Demographics: age; sex; ethnicity
• Comorbidities/medical history: atrial fibrillation; diabetes mellitus; hypertension; pre-stroke mRS
• Concurrent drugs: use of any antipyretic, antibiotic, or antiemetic drug in the three days before randomisation.[a]
• Way of food intake on the day before the stroke[b]
• Treatment restrictions[c]
• Dates and times: stroke onset, hospital admission
• Vital signs: blood pressure; pulse; body temperature[d]
• Neurological examination: NIHSS; location of the lesion
• Laboratory examinations[e]
• Results of chest X-ray and urine analysis if performed as part of routine clinical practice
• Imaging results: stroke type: ischaemic stroke or intracerebral haemorrhage
• Previous treatment: intravenous thrombolysis with alteplase; intra-arterial treatment.

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

[a] Aspirin in any formulation and in a daily dose of up to 300 mg is not considered an antipyretic drug.

[b] The method of feeding on the day before the stroke and at noon of the relevant day will be recorded and classified as 1. normal food; 2. oral, soft or fluids only; 3. nasogastric tube; 4. percutaneous endoscopic gastrostomy (PEG); 5. intravenous only; 6. none.

[c] The presence of any treatment restriction will be recorded at baseline and during the patients stay in the hospital, and will be classified as 1. Do not resuscitate; 2. Do not intubate and ventilate; 3. Withholding other treatments that may prolong life; 4. Withholding food; 5. Withholding fluids; and 6. Palliation with morphine or a benzodiazepine. Any combi- nation of these strategies is possible.

[d] Blood pressure, pulse and body temperature will be assessed at baseline and at 12-h (±3 h) intervals (where assessed as part of routine clinical practice). Both rectal and tympanic thermometry are allowed.

[e] If assessed at baseline as part of routine clinical practice, the following laboratory tests will be collected: serum glucose; glomerular filtration rate; C-reactive protein (CRP); alkaline phosphatase (ALP); gamma-glutamyl transferase (GGT); alanine aminotransferase (ALT); and aspartate aminotransferase (AST); leucocyte count and differential.

At day 7 after admission to the hospital, or at discharge if earlier, the score on the mRS is assessed. During a follow-up visit at day 90 (±14), the mRS is assessed by a trained, certified investigator in a standard fashion according to each centre's normal practice, and the interview is recorded with a digital video camera. During this recording, no reference to the treatment allocation is made. The videos are uploaded and distributed for independent and blinded scoring by three certified expert raters from the same country as the patient. Additionally, the Barthel index (BI),[22] Montreal Cognitive Assessment

(MoCA)[23] and EuroQol 5D-5L (EQ-5D-5L) are assessed at 90 days, as well as the patient's location and number of nights spent at home over the first 90 days after stroke.

Outcome events

The primary outcome measure is the score on the mRS at 90 days (±14).[24] The mRS is an ordinal hierarchical scale incorporating seven categories from 0 up to and including 6 and describes the range of disability encountered post stroke. 'Death' is assigned a score of 6. Secondary outcomes are outlined in Table 4.

Table 4. Study outcomes.

Primary outcome
• Score on the mRS[a]
Secondary outcomes
At 7 days (± 1 day) or at discharge, if earlier: • Infections in the first seven days (± 1 day; frequency, type and C. difficile infections)[b] • 3rd generation cephalosporin resistance in the first seven days (± 1 day)[c] • Antimicrobial use during the complete hospital admission for stroke[d] • SAEs in the first seven days • In a subgroup of patients: presence of ESBL-producing bacteria[e]
At 90 days (± 14 days): • Death • Unfavourable functional outcome[f] • Disability[g] • Cognition[h] • Quality of life[i] • Home time[j] • Patient location[k]

mRS: modified Rankin Scale; SAE: serious adverse event; ESBL: extended-spectrum beta-lactamase.
[a] As assessed by three independent and blinded adjudicators based on a video recording of an mRS interview at the follow-up visit after 90 days.
[b] Infections will be categorised as diagnosed by the clinician, and as judged by an independent adjudication committee (masked to treatment allocation).
[c] Detected as part of routine clinical practice.
[d] Converted to units of defined daily doses according to the classification of the WHO Anatomical Therapeutic Chemical Classification System with Defined Daily Doses Index.
[e] As detected by PCR in a rectal swab.
[f] Defined as mRS 3 to 6.
[g] Assessed with the Barthel index (BI).[28]
[h] Assessed with the Montreal Cognitive Assessment (MoCA).[29]
[i] Assessed with the EuroQol 5D-5L (EQ-5D-5L).
[j] The number of nights among the first 90 since stroke onset that are spent in the patient's own home or a relative's home. Where final follow- up occurs earlier, the last known placement will be extrapolated to 90 days.
[k] Hospital; rehabilitation service; chronic nursing facility; home.

Infections will be categorised as diagnosed by the clinician, and as judged by an independent adjudication committee (masked to treatment allocation) according to modified Centres for Disease Control and Prevention criteria.[25] The scoring algorithms for infections that will be used by this committee have been described previously and are in line with recommendations of the Pneumonia in Stroke Consensus Group.[26] Clostridium difficile infection will be defined as diarrhoea in combination with a positive Clostridium difficile toxin test.

Substudy

To detect selection of bacteria with third generation cephalosporin resistance caused by increased antibiotic pressure, a nested case-control substudy will be performed in 1000 patients in 30 centres in different participating countries. The presence of extended spectrum beta-lactamase (ESBL) producing bacteria will be assessed with polymerase chain reaction (PCR). For this purpose, two rectal swabs will be collected in each patient, after specific informed consent, on admission and at day 7 (±1 day, or at discharge, if earlier).

Sample size calculation and statistical analysis plan

The primary effect estimate will be the difference between groups in the mRS scores obtained through centralised adjudications and assessed using multiple regression, and will be expressed as a mean difference with 95% confidence interval. PRECIOUS is powered to detect a statistically significant shift in the difference in the proportion of patients with mRS 0 to 2 at 90 days, assuming an effect that leads to a 5% absolute increase (from 36 to 41%)[26] in the cumulative proportion of patients with mRS 0 to 2 in any intervention group, compared with controls. The effect size of 5% is based on previous smaller studies and/or meta-analyses thereof, performed in more general stroke populations.[12–14,16] The statistical analyses will be performed according to the intention-to-treat principle and adjusted for the minimisation factors mentioned, other relevant baseline characteristics, and treatment allocation for the other two strata of the trial. Three separate primary analyses will be performed, looking at the main effects of each of the three interventions compared with their respective controls. Although the study is not powered to detect interactions between the three interventions, such interactions will be investigated in secondary analyses. Two sensitivity analyses will be performed in which all patients who are lost to follow-up will be classified as having the worst possible outcome (death) or the best possible outcome (mRS = 0), respectively.

Secondary efficacy outcomes will be analysed using similar methods as for the primary efficacy analysis, with binary logistic regression used for binary outcomes, including death, unfavourable outcome and SAEs. Ordinal logistic regression will be used for ordered categorical data and multiple regression for continuous outcomes. Wilcoxon rank sum test will be used for continuous outcome measures which are not normally distributed. Several subgroup analyses will be performed based on age, sex, stroke type and severity, diabetes mellitus, presence of atrial fibrillation, pre-stroke mRS score,

treatment with alteplase or other recanalisation method, treatment allocation for the other two trial strata and time to treatment. A full statistical analysis plan will be completed before the final follow-up of the last patient.

DISCUSSION

Because several complications in the first days after stroke have consistently been associated with a higher risk of death or poor functional outcome, prevention of these complications appears a logical, simple and safe approach to improve outcome after stroke. In the past two decades, several trials aimed at prevention of complications have been performed, but – besides organised care in a designated stroke unit – no treatment to prevent complications has convincingly shown to improve the functional outcome in patient with stroke.[13,14,16] However, most of these trials were underpowered, started treatment too late after stroke onset, or aimed at only one specific complication after stroke. Strengths of PRECIOUS are the assessment in an elderly population with moderately severe to severe stroke (with an increased risk of complications and poor outcome), the start of treatment within 24 h after stroke onset, and its multifactorial design. The trial will provide high-quality evidence that could be broadly generalizable. Because of its pragmatic design and the use of safe, inexpensive, and generally available drugs, the results of PRECIOUS could be implemented rapidly throughout Europe and the rest of the world.

It may be questioned whether the effects of prophylactic antibiotics in patients with stroke should still be assessed after the neutral results in two recent phase III clinical trials. Ceftriaxone is an off-patent, broad-spectrum antibiotic with proven efficacy against bacteria most frequently causing infection in patients with acute stroke.[12,27] In the PASS trial, 2550 patients with stroke were randomly assigned to standard care or intravenous ceftriaxone, started within 24 h of stroke onset, continued for four days. Preventive ceftriaxone reduced the incidence of infections in general (from 7% to 3%; $p < 0.0001$), but did not have an effect on the occurrence of pneumonia or the risk of a poor outcome at 90 days.[16] However, the median score on the NIHSS of patients in PASS was 5, which could explain the relatively low incidence of infections. In the cluster-randomised STROKE-INF trial, which included 1217 stroke patients with dysphagia, prophylactic antibiotics did not change the incidence of post-stroke pneumonia or poor functional outcome.[17] However, antibiotic treatment may have started too late (up to 48 h after stroke onset) to prevent early infections. In addition, a considerable proportion of patients in the treatment group received only a limited number of antibiotic doses, while 34% of the patients in the control group received an antibiotic at least once during the first seven days. Finally, individual centres included only a small number of patients over an extended period of time; in a cluster-randomised study this may induce selection bias, decreasing the discriminative power. Because of the limitations of these two trials, and the strong association between infections and a poor functional outcome,[4,28] additional evidence on the effect of preventive antibiotics is still strongly needed.

The PRECIOUS trial will also be able to assess whether antibiotics work in isolation, or whether the effect is dependent on the combination of drugs that are used in the trial. The results of PASS and STROKE-INF support the concept that post-stroke pneumonia might be a respiratory syndrome resulting from complex bacterial, chemical and immunological causes that might not be prevented by antibiotics alone. The combination of treatments in PRECIOUS, especially the combination of metoclopramide and ceftriaxone, targets different pathways in the development of post-stroke pneumonia, potentially resulting in a larger reduction in the risk of complications than with the individual treatments alone.

The prevention of complications with the treatments proposed in PRECIOUS was safe in previous trials and not associated with an increased risk of SAEs.[13,14,16] In addition, the risk of developing Clostridium difficile overgrowth was smaller than 1% in previous studies with ceftriaxone, and there was no association with an increase in antimicrobial resistance.[16,17]

PRECIOUS uses paracetamol for the prevention of increases in body temperature because this was safe in doses up to 6 grams per day in randomised clinical trials in patients with acute stroke, reduced the risk of subfebrile temperatures or fever at 24h by 50% and was associated with a trend towards an improvement in functional outcome in the PAIS trial. This trial was underpowered to detect a benefit on functional outcome because this was terminated prematurely due to lack of funding after inclusion of 1400 patients, against a target of 2500 patients.[10] For PRECIOUS, we have selected a maximum daily dose of 4 grams to comply with the drug's summary of product characteristics.

Given the potential benefit of the prevention of complications to the patients included in PRECIOUS, future stroke patients, their caregivers, and society, the risk-benefit balance is strongly in favour of conducting this clinical trial.

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3

Chapter 3

PRECIOUS: prevention of complications to improve outcome in elderly patients with acute stroke. Statistical analysis plan of a randomised, open, phase III, clinical trial with blinded outcome assessment

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ABSTRACT

Rationale
Aspiration, infections, and fever are common in the first days after stroke, especially in older patients. The occurrence of these complications has been associated with an increased risk of death or dependency.

Aims and design
PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) is an international, multi-centre, 3×2 factorial, randomised, controlled, open-label clinical trial with blinded outcome assessment, which will assess whether prevention of aspiration, infections, or fever with metoclopramide, ceftriaxone, paracetamol, respectively, 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.

Discussion
This statistical analysis plan provides a technical description of the statistical methodology and unpopulated tables and figures. The paper is written prior to data lock and unblinding of treatment allocation.

BACKGROUND

In the first days after stroke, about half of all patients develop one or more complications, including aspiration, infections, or fever. The risk of developing these events is greater in patients of higher age or with more severe stroke.[1,2,3] These complications can impede functional recovery, prolong hospital admissions, and are independently associated with an increased risk of death or long-term dependency.[1,2,4,5,6,7,8,9,10,11] The risk of developing these complications can be reduced by very simple, safe, and inexpensive 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.[12,13,14,15] In some generally small, randomised trials, preventive treatment with these drugs not only convincingly reduced the risks of aspiration, infections, or fever by one third to one half, but was also associated with clear trends towards a lower risk of death or poor outcome.[12,13,14,15] However, in two large randomised clinical trials, preventive treatment with antibiotics did not improve functional outcomes.[16,17] Guidelines of the European Stroke Organisation concluded that there is insufficient evidence from randomised trials to make strong recommendations on whether, when, and to whom preventive antibiotic or antipyretic treatment should be given after ischaemic stroke or intracerebral haemorrhage.[18,19] The PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) trial will assess whether prevention of aspiration, infections, or 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 older patients with acute stroke. The current paper describes the statistical analysis plan (SAP) of the trial and conforms to the guidelines set by Gamble et al.[20] The details of the study protocol of the PRECIOUS trial have been published earlier.[21] PRECIOUS has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement no. 634809.

STUDY METHODS

PRECIOUS is an international, multi-centre, multi-factorial, randomised, controlled, phase III, open-label clinical trial with blinded outcome assessment (PROBE). The primary objective is to assess whether prevention of aspiration, infections, or 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 older patients with acute stroke. Patients will be randomly allocated in a $2 \times 2 \times 2$ 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 h 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. Patients will be stratified according to country (Estonia, Germany, Greece, Hungary, Italy, The Netherlands, Norway, Poland,

UK), and there will be 5 minimisation factors: age (66–75 years; > 75 years), sex (male vs. female), stroke type (ischaemic stroke vs. intracerebral haemorrhage), stroke severity (NIHSS 6–12 vs. > 12), and diabetes mellitus (yes vs. no). A total of 3800 patients will be recruited, based on the sample size calculation described in the previously published protocol.[21]

Statistical interim analyses and stopping guidance

An independent Data and Safety Monitoring Board (DSMB) will conduct unblinded interim analyses after 600, 1200, 1800, 2400, and 3000 patients have completed follow-up to assess the safety of the interventions in the trial. With respect to efficacy, the DSMB will conduct unblinded interim analyses after 2400 patients had their final follow-up. DSMB members will receive listings of all SAE reports as well as unblinded aggregate summaries of data by treatment groups for review in closed meetings. The results of these interim analyses are confidential and limited to the members of DSMB.

Timing of final analysis

This statistical analysis plan (SAP) will be signed off by the trial Steering Committee and then submitted for publication prior to data lock and final analysis. The final statistical analysis will be performed once recruitment has ceased, final follow-up and final outcome adjudication have been completed, final data have been checked and any errors corrected, and the database has been locked. The analyses will be carried out according to the current statistical analysis plan. The statistical analyses will be performed by the Nottingham Stroke Trial Unit (NSTU) at the University of Nottingham (UNOTT) in collaboration with the UMC Utrecht.

Trial population

The study population will consist of patients aged 66 years or older who are hospitalised with moderately severe to severe (National Institutes of Health Stroke Scale (NIHSS) ≥ 6) acute ischaemic stroke or intracerebral haemorrhage. Patients will only be included if treatment can be started within 24 h of stroke onset. For a complete overview of the inclusion and exclusion criteria, we refer to the study protocol.[21] Patients are planned to be recruited in about 80 hospitals in 9 European countries over a period of about 4 years. To increase the generalisability of the findings, these countries are distributed across Europe and include Estonia, Germany, Greece, Hungary, Italy, The Netherlands, Norway, Poland, and the UK. For the same reason, the trial will recruit patients both in academic and regional hospitals (Table 1, Figure 1).

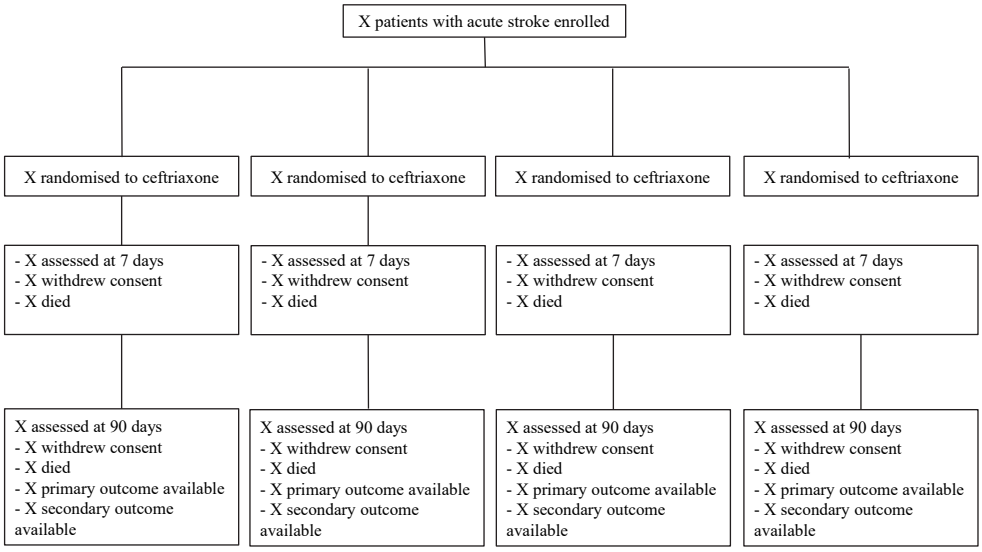

Figure 1. Trial profile

Table 1. Baseline characteristics

	All	Paracetamol	Control	Metoclopramide	Control	Ceftriaxone	Control
Total patients randomised							
Age (years)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Sex, male (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Premorbid mRS [/6]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
Ethnicity, white (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Medical History (%)							
- Atrial fibrillation	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Hypercholesterolaemia	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Hypertension	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Diabetes mellitus	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Obstructive pulmonary disease	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Previous stroke	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Immunocompromised	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Smoking							
- Never	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Ever	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Currently	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pre-stroke method of food intake							
- Normal food	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Oral softened food or fluids only	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Nasogastric tube	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Percutaneous endoscopic gastrostomy	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Intravenous only	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

	All	Paracetamol	Control	Metoclopramide	Control	Ceftriaxone	Control
Use of drugs 3 days before randomisation							
- Paracetamol	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Metoclopramide	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Ceftriaxone	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Time, onset to randomisation (min)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Stroke type (%)							
Ischaemic stroke	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Intracerebral haemorrhage	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other diagnosis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
NIHSS (/42)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Systolic BP (mmHg)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Diastolic BP (mmHg)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Heart rate (bpm)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Body temperature (ºC)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Acute stroke treatment (%)							
- Intravenous thrombolysis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
- Mechanical thrombectomy	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Data are n (%) or median [IQR]. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke scale; BP, blood pressure.

STATISTICAL ANALYSIS

Primary outcome

The primary outcome measure is the score on the modified Rankin Scale (mRS) at 90 days (± 14 days). The mRS is an ordinal scale ranging from 0 to 6.[22] The mRS assessment at 90 days will be during a hospital/home visit or by telephone, and the assessment or a report thereof will be recorded using a digital video camera. Three blinded raters will view the videotape and adjudicate a score on the mRS.

Primary outcome analysis

For each patient, a median mRS score will be calculated from the three mRS scores obtained through centralised adjudications by raters who are blinded to treatment allocation. The use of three scores increases the precision in scoring and statistical power as compared to a single mRS assessment.[23] The primary effect estimate will be the difference in the mRS scores between the active treatment group and controls assessed using ordinal logistic regression, and will be expressed as an odds ratio with 95% confidence interval.[24] The primary analysis will be performed on all randomised patients with a valid mRS score at 90 days. The distribution of the mRS scores will be shown as a figure (Figure 2). Three separate primary analyses will be performed for each intervention vs. their respective controls (e.g., metoclopramide vs. non-metoclopramide). The primary analyses will be adjusted for stratification (country), minimisation (age, sex, stroke type, stroke severity, diabetes), and other baseline prognostic (e.g., premorbid mRS, atrial

fibrillation, reperfusion treatment [alteplase and/or thrombectomy], time from onset to randomisation) factors, and treatment allocation for the other two strata of the trial (Table 2).

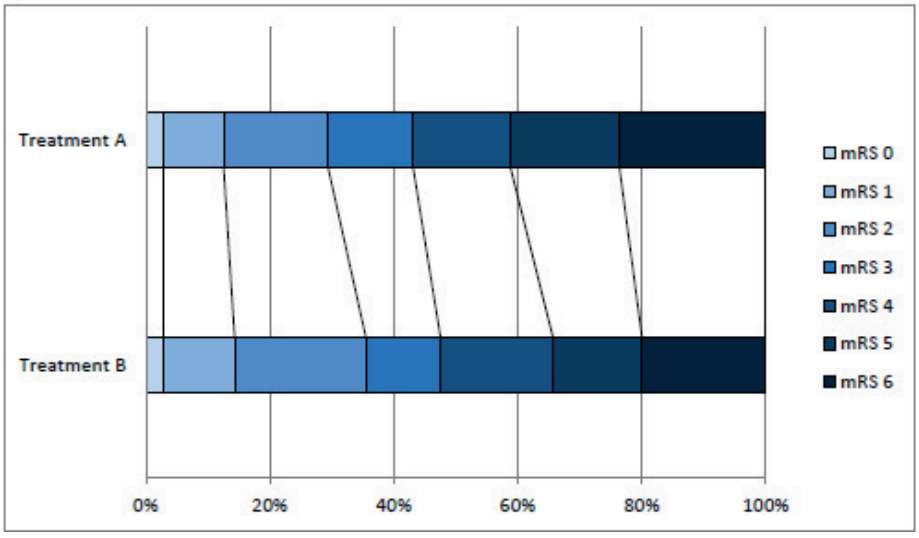

Figure 2. Distribution of modified Rankin Scale for each intervention using median mRS value for each participant. Example of a distribution of the modified Rankin Score at 3 months. The figure is an example, with dummy treatments and scores.

Primary outcome subgroup analysis

Comparison of the effect of the three intervention groups vs. their respective controls on the primary outcome will be performed in the following pre-specified subgroups (assuming sufficient numbers in each subgroup) with assessment of interaction between treatment and the minimisation factors (these subgroup analyses are considered hypothesis-generating) (Table 3):

- Age (≤ 75, > 75 years);
- Sex (male, female);
- Stroke type (ischaemic stroke, intracerebral haemorrhage);
- Stroke severity (NIHSS 6–12, > 12);
- Diabetes mellitus (yes, no).

Table 2. Primary outcome.

	Analysis	Paracetamol	Control	DIM or OR (95% CI)	Metoclopramide	Control	DIM or OR (95% CI	Ceftriaxone	Control	DIM or OR (95% CI)
mRS, median	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Sensitivity analyses										
mRS, unadjusted	OLR	Median [IQR]	Median [IQR]	OR (95% CI)	Median [IQR]	Median [IQR]	OR (95% CI)	Median [IQR]	Median [IQR]	OR (95% CI)
mRS, imputed	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
mRS, mean	aMLR	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)
mRS >2	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Death	aCPHR	n (%)	n (%)	aHR (95% CI)	n (%)	n (%)	aHR (95% CI)	n (%)	n (%)	aHR (95% CI)

Analyses are adjusted except where stated. Data are n (%), median [IQR], mean (SD). aDIM: adjusted difference in means. aHR: adjusted hazards ratio. aOR: adjusted odds ratio. Comparison by adjusted ordinal logistic regression (aOLR), multiple linear regression (aMLR), Cox proportional hazards regression (CPHR) or adjusted binary logistic regression (aBLR)

Table 3. Subgroup analysis—shown as forest plot. Adjusted analysis with interaction term

	Paracetamol	Control	aOR (95% CI)	Interaction P	Metoclopramide	Control	aOR (95% CI)	Interaction P	Ceftriaxone	Control	aOR (95% CI)	Interaction P
Age				+				+				+
Age < 75 years	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Age > 75 years	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Sex				+				+				+
Male	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Female	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Stroke type				+				+				+
Ischaemic stroke	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Intracerebral haemorrhage	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Other diagnosis	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Stroke severity				+				+				+
NIHSS 6–12	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
NIHSS > 12	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Diabetes mellitus				+				+				+
Yes	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
No	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Atrial fibrillation				+				+				+
Yes	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
No	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	

	Paracetamol	Control	aOR (95% CI)	Interaction P	Metoclopramide	Control	aOR (95% CI)	Interaction P	Ceftriaxone	Control	aOR (95% CI)	Interaction P
Pre-stroke mRS				+				+				+
0	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
>0	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Treatment with alteplase				+				+				+
Yes	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
No	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Thrombectomy				+				+				+
Yes	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
No	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Time to treatment				+				+				+
<6 h	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
6–12 h	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
12–24 h	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Treatment allocation to other treatment strata				+				+				+
Paracetamol	–	–	–	–	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)	
Metoclopramide	n/N (%)	n/N (%)	aOR (95% CI)		–	–	–	–	n/N (%)	n/N (%)	aOR (95% CI)	
Ceftriaxone	n/N (%)	n/N (%)	aOR (95% CI)		n/N (%)	n/N (%)	aOR (95% CI)		–	–	–	–

Data are n/N (%). aOR adjusted odds ratio. Comparison by adjusted ordinal logistic regression with adjustment for an interaction term. This table will be presented as forest plots in the final publication.

In addition, the interaction between treatment and other baseline factors will be assessed:

- Presence of atrial fibrillation (yes, no);
- Pre-stroke mRS score (0, > 0);
- Reperfusion treatment (alteplase and/or mechanical thrombectomy);
- Time to treatment (< 6, ≥ 6 h < 12 h, ≥ 12 h);
- Treatment allocation for the other two trial strata (paracetamol—active, control; ceftriaxone—active, control; metoclopramide—active, control). Since the study is not powered to detect interactions between the three interventions, these interactions will be investigated in secondary analyses.

Sensitivity analyses
Four sensitivity analyses of the mRS will also be performed: unadjusted ordinal logistic regression, adjusted analysis of mRS following regression imputation of missing data, multiple linear regression on the mean mRS score for each participant, and binary logistic regression on mRS > 2.

Secondary outcomes
The following secondary outcomes will be assessed at 7 days (± 1 day) or at discharge, if earlier:

- Infections in the first 7 days (± 1 day; frequency, type, and *Clostridium difficile* infections). Infections will be categorised as diagnosed by the clinician and as judged by an independent adjudication committee (masked to treatment allocation);
- Third generation cephalosporin resistance in the first 7 days (± 1 day), detected as part of routine clinical practice;
- Antimicrobial use during the first 7 days, converted to units of defined daily doses according to the classification of the WHO Anatomical Therapeutic Chemical Classification System with Defined Daily Doses Index;
- Serious adverse events (SAEs) in the first 7 days;
- In a subgroup of patients: presence of Extended-Spectrum Beta-Lactamase (ESBL)-producing bacteria as detected by PCR in a rectal swab at day 7 (± 1 day, or at discharge, if earlier).

The following secondary outcomes will be assessed at 90 days (± 14 days) (Table 4):

- 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) and EQ-visual analogue scale (EQ-VAS);
- Home time: the number of nights among the first 90 since stroke onset that are spent in the patient's own home or a relative's home. Resource use will be censored at 90 days. Where final follow-up occurs earlier, the last known placement will be extrapolated to 90 days;
- Patient location over first 90 days (± 14 days): hospital, rehabilitation service, chronic nursing facility, and home.

Table 4. Secondary outcome assessment at 90 days

	Analysis	Paracetamol	Control	OR (95% CI)	Metoclopramide	Control	OR (95% CI)	Ceftriaxone	Control	OR (95% CI)
mRS, median										
Ischaemic stroke	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Intracerebral haemorrhage	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Other diagnosis	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Mortality	aCPHR	n (%)	n (%)	aHR (95% CI)	n (%)	n (%)	aHR (95% CI)	n (%)	n (%)	aHR (95% CI)
mRS, unfavourable outcome	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Patient location	aOLR			aOR (95% CI)			aOR (95% CI)			aOR (95% CI)
Hospital		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Rehabilitation service		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Nursing home		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Home		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Home time (no. of days)	aMLR	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)
Questionnaires										
Barthel Index	aMLR	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)
MoCA	aMLR	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)
EQ-5D-5L	aMLR	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)
EQ-VAS	aMLR	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)	Mean (SD)	Mean (SD)	aDIM (95% CI)

Data are n (%) or median [IQR]. aDIM: adjusted difference in means. aOR: adjusted odds ratio. aHR adjusted hazards ratio. Comparison by adjusted ordinal logistic regression (aOLR), Cox Proportional Hazards regression (aCPHR) or multiple linear regression (aMLR). mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment; EQ-5D-5L, EuroQol 5D-5L; EQ-VAS, EuroQol-Visual Analogue Scale

Analysis of secondary outcomes
Binary logistic regression will be used for binary outcomes (e.g., mRS > 2). Cox proportional hazards regression will be used for time to events (e.g., death). Ordinal logistic regression will be used for ordered categorical data (e.g., mRS). Multiple linear regression will be used for continuous outcomes (e.g., BI, EQ-VAS). Patients with missing outcome data will be excluded from the analysis.

Missing data and death
Patients without a primary outcome assessment at 90 ± 14 days will be considered as a lost to follow-up. The total amount of patients who are lost to follow-up will be recorded and calculated for each treatment arm. The primary analysis will be performed on all randomised patients with a valid mRS score at 90 days. In a sensitivity analysis, missing mRS data will be imputed using multiple regression-based imputation.

For the secondary outcome measures (Barthel Index, MoCA, EQ-5D-5L, EQ-VAS), patients who die will be assigned a value one unit worse than any living value. This way, patients who die cannot be given a score similar to the worst score of patients who are alive, and it ensures that all patients will be included in the analysis. Potential scores, with worst with dead added, are as follows:

- Modified Rankin Scale (mRS), 0 to 5 with death = 6;
- Barthel Index (BI), 100 to 0 with death = – 5;
- EuroQol 5D-5L (EQ-5D-5L), – 0.5 to 1 with death = 0;
- EuroQol visual analogue scale (EQ-VAS), 0 to 100 with death = – 1;
- Montreal cognitive assessment (MoCA), 0 to 30 with death = – 1.

Safety outcomes
In the first 7 days after randomisation, all SAEs will be reported and described by duration (start and stop dates), severity, outcome, treatment, and relation to the investigational medical product (IMP), or if unrelated, the cause. All SAEs will be tabulated per treatment stratum. In addition, any SAE occurring between day 7 and the end of follow-up on day 90 (± 14 days) for which a causal relationship between the IMP and the SAE is considered at least a reasonable possibility (i.e., SARs and SUSARs) should be reported as other SAEs.

Treatment restrictions
The presence of any treatment restriction will be recorded at baseline and during the hospital phase, and classified as (1) do not resuscitate, (2) do not intubate and ventilate, (3) withhold other treatments that may prolong life, (4) withhold food, (5) withhold fluids, and (6) palliation (e.g., with morphine or a benzodiazepine). Any combination of these strategies is possible. The primary study will report on the frequency of each

treatment restriction, and further analyses on this topic will be published in future subgroup analyses.

Minimising bias

PRECIOUS is an open-label clinical trial, and both patients and treating physicians are therefore aware of the assigned treatment. Knowledge of treatment allocation can influence outcome assessment, and unblinded trials like PRECIOUS are therefore at risk of detection bias. In addition, despite its apparent simplicity, assessment of the score on the mRS has been associated with considerable inter-observer variability, especially in multi-centre studies, and may therefore affect trial power and treatment effect size. In PRECIOUS, these two major issues are minimised through (1) online training and certification of outcome assessors via a link on the PRECIOUS website and (2) central outcome assessment by three blinded adjudicators based on digital video recordings of the 90-day outcome interviews. This central adjudication by trained adjudicators offers several benefits:[23]

1. Blinding is assured;

2. Standardisation is possible across multiple regions and cultures;

3. Statistical power is enhanced through the use of three repeated assessments;

4. The estimate of treatment effect size is restored (since statistical noise leads to underestimation);

5. It provides independent validation of the information that is collected, thereby minimising the risk of fraud;

6. Site staff perform to a higher standard when aware that there will be review or audit of their activity.

In addition, the risk of bias is reduced by performing the statistical analyses according to the intention-to-treat principle and adjusting for the minimisation factors, other relevant baseline characteristics, and treatment allocation for the other two strata of the trial.

STATISTICAL PRINCIPLES

Confidence intervals and P values

Analyses will be two-sided $P < 0.05$ with 95% confidence intervals presented. The trial is testing the effect of the interventions on mRS, and analyses in subgroups and on other outcomes are considered hypothesis-generating. Hence, no adjustment will be made for multiplicity of testing.

Alpha spending
The Data Monitoring Committee performs safety assessments using the Haybittle-Peto boundary rule ($P < 0.001$); hence, no significant spending of alpha will occur during the trial. All analyses will be two-tailed, and P values of < 0.05 will denote statistical significance; 95% confidence intervals will be provided. Adjustment for multiple comparisons will not be performed, but all contrasts will be declared.

Compliance
Compliance with allocated treatment will be tabulated. For each of the three study drugs, the number of received dosages will be calculated (maximum of four for ceftriaxone, twelve for metoclopramide, and sixteen for paracetamol). The number of patients who received the first dosage within the time window of 24 h will also be presented; if the dosage was not given within 24 h, the reason will be given (withdrawn informed consent, death, human error, other reason).

Analysis populations
All efficacy analyses will be performed on the intention-to-treat population. The robustness of the primary and key secondary analyses will be assessed in the per-protocol population. Safety analyses will be performed on the safety population.

The following population definitions will be used:

- Intention-to-treat in primary efficacy analysis: all randomised participants who received any study medication and with a valid mRS score recorded at 90 days.

- Intention-to-treat in primary safety analysis: all randomised participants with a vital status recorded at 90 days.

- Per-protocol: all participants in the intention-to-treat population who are deemed to have no major protocol violations that could interfere with the objectives of the study.

- Patients with protocol violations in trial eligibility will be included in the intention-to-treat population, but excluded in the per-protocol analysis. Patients who withdrew informed consent before initiating treatment will be excluded from analysis. If (per accident) multiple randomisations are performed for a single patient, the result of the first randomisation will be used.

Patients with protocol violations in trial eligibility will be included in the intention-to-treat population, but excluded in the per-protocol analysis. Patients who withdrew informed consent before initiating treatment will be excluded from analysis. If (per accident) multiple randomisations are performed for a single patient, the result of the first randomisation will be used.

CURRENT STATUS

The trial received approval from the central Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands, on 3 February 2016. The Dutch National Competent Authority (Centrale Commissie Mensgebonden Onderzoek (CCMO)) declared to have no objection against the execution of the clinical trial within The Netherlands on 17 November 2015. In addition, the national (and local, if applicable) medical ethical committees and competent authorities of the other 8 participating countries have approved the trial. The first patient was included in May 2016. The analysis and reporting of the trial will be in accordance with CONSORT guidelines. After publication of the trial, to promote the independent re-use of PRECIOUS data, a coded dataset will be made available in a public data repository within 18 months of the final follow-up of the last patient. Coded data will also be included in the Virtual International Stroke Trials Archive (VISTA).

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SUPPLEMENTAL MATERIAL

Table 1. Protocol violations in eligibility

	Paracetamol	Control	Metoclopramide	Control	Ceftriaxone	Control
	N	N	N	N	N	N
Other diagnosis than stroke	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
NIHSS score of ≤5	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age ≤65 years	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Start treatment >24 hours	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Inclusion with active infection requiring antibiotic treatment	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pre-stroke mRS ≥4	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Death is imminent	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Inclusion in treatment arm despite contra-indication	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Data are n (%). mRS, modified Rankin Scale.

Table 2. Compliance and cross-over in first 7 days

	Paracetamol	Control	P	Metoclopramide	Control	P	Ceftriaxone	Control	P
	N	N		N	N		N	N	
Received all allocated dosages	n (%)	-	-	n (%)	-	-	n (%)	-	-
Received 75-99% of dosages	n (%)	-	-	n (%)	-	-	n (%)	-	-
Received 50-<75% of dosages	n (%)	-	-	n (%)	-	-	n (%)	-	-
Received 25-<50% of dosages	n (%)	-	-	n (%)	-	-	n (%)	-	-
Received 0-<25% of dosages	n (%)	-	-	n (%)	-	-	n (%)	-	-
Received any antibiotic drug	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Received any antipyretic drug	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Received any antipyretic drug for four days at least once	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Received any anti-emetic drug	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Received any anti-emetic drug for four days at least once	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	

Data are n (%). Comparisons made by binary logistic regression.

Table 3. Secondary outcomes and treatment restrictions at 7 days

	Analysis	Paracetamol	Control	OR (95% CI)	Metoclopramide	Control	OR (95% CI)	Ceftriaxone	Control	OR (95% CI)
mRS, median										
All patients	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Ischaemic stroke	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Haemorrhagic stroke	aOLR	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)	Median [IQR]	Median [IQR]	aOR (95% CI)
Mortality at 7 days	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Any treatment restriction	-	n (%)	n (%)	-	n (%)	n (%)	-	n (%)	n (%)	-
Infection										
All infections	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Pneumonia	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Urinary tract infection	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Other infections	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Infections based on expert panel										
All infections	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Pneumonia	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Urinary tract infection	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Other infections	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Antimicrobial use and resistance										
3rd generation cephalosporin resistance	aBLR	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)	n (%)	n (%)	aOR (95% CI)
Antimicrobial use during first 7 days*		DDD	DDD	-	DDD	DDD	-	DDD	DDD	-

mRS, modified Rankin Scale. Data are n (%) or median [IQR]. aOR: adjusted odds ratio. Comparison by adjusted ordinal logistic regression (aOLR) or binary logistic regression (aBLR).
* Converted to units of defined daily doses according to the classification of the WHO Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (DDD) Index;

Table 4. Overview of safety

	Paracetamol	Control	P	Metoclopramide	Control	P	Ceftriaxone	Control	P
Infections diagnosed by physician	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
- Pneumonia	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
- Urinary tract infection									
- Other infection	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Pneumonia diagnosed by an independent adjudication committee	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Clostridium difficile infection of the gastro-intestinal tract	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Infection with a ceftriaxone resistant micro-organism	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Liver function disturbance or liver failure	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Allergic or hypersensitivity reaction	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Other SAEs:									
Total amount of SAEs	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Total amount of related SAEs (SARs or SUSARs)	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Total amount of SUSARs	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	

Data are n (%). SAE, Severe Adverse Event; SAR, Severe Adverse Reaction; SUSAR, Severe Unexpected Serious Adverse Reaction. Comparisons made by binary logistic regression.

Table 5. List of PRECIOUS partners

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4

Chapter 4

Regulatory delays in a multinational clinical stroke trial

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ABSTRACT

Introduction
The initiation and conduct of randomised clinical trials are complicated by multiple barriers, including delays in obtaining regulatory approvals. Quantitative data on the extent of the delays due to national or local review in randomised clinical trials is scarce.

Materials and methods
We assessed the times needed to obtain regulatory approval and to initiate a trial site for an academic, EU-funded, phase III, randomised clinical trial of pharmacological prevention of complications in patients with acute stroke in over 80 sites in nine European countries. The primary outcome was the time from the first submission to a regulatory authority to initiation of a trial site. Secondary outcomes included time needed to complete each individual preparatory requirement and the number of patients recruited by each site in the first 6 and 12 months.

Results
The median time from the first submission to a regulatory authority to initiation of a trial site was 784 days (IQR: 586–1102). The single most time-consuming step was the conclusion of a clinical trial agreement between the national coordinator and the trial site, which took a median of 194 days (IQR: 93–293). A longer time to site initiation was associated with a lower patient recruitment rate in the first six months after initiation ($B = -0.002$; $p = 0.02$).

Conclusion
In this EU-funded clinical trial, approximately 26 months were needed to initiate a trial site for patient recruitment. The conclusion of a contract with a trial site was the most time-consuming activity. To simplify and speed up the process, we suggest that the level of detail of contracts for academic trials should be proportional to the risks and commercial interests of these trials.

INTRODUCTION

Randomised clinical trials (RCTs) and meta-analyses thereof are generally considered the best instruments to assess whether a specific diagnostic test or treatment is of benefit to patients or healthy persons,[1] but their initiation and conduct are hampered by multiple barriers. Editorials and narrative reviews have reported lack of funding, increasing complexity of regulations, excessive monitoring, overinterpretation of privacy laws, and complex and overly bureaucratic trial procedures, often out of proportion to the conceivable risk to research participants, as important obstacles.[2–5] In addition, delays in obtaining ethical, regulatory, and legal approvals have been identified as major delaying factors in initiating clinical trials sites.[2] As a result of these and other barriers, it has been estimated that approximately half of the clinical trials fail to reach their target sample size within the planned timeline.[6]

Quantitative evidence on the true extent of the delays in RCTs due to institutional or legal review is scarce and limited to a specific part of the approval process, to specific countries and time periods.[5,7,8] New regulations, such as the General Data Protection Regulation in the European Union, have been introduced in recent years, which could have major consequences for institutional review and contractual governance.

In the present study, we aimed to quantify delays caused by legal or institutional review in the PRECIOUS trial (PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke). This is a multicentre, multinational clinical trial, performed in over 80 sites in 9 European countries, and supported by the European Union's Horizon 2020 programme.[9] We provide a systematic overview of the time period required for each regulatory approval procedure needed to open an individual trial site and analyse its relationship with patient recruitment.

METHODS

PRECIOUS is an international, multi-centre, 3*2-factorial, randomised, controlled, open-label clinical trial with blinded outcome assessment (PROBE) of the preventive use of metoclopramide, ceftriaxone, paracetamol, or any combination of these, for four days in elderly patients with acute ischaemic stroke or intracerebral haemorrhage. The trial was initiated in 2015 and aims to recruit 3800 patients in about 80 hospitals (both academic and general) in 9 European countries: Estonia, Germany, Greece, Hungary, Italy, The Netherlands, Norway, Poland, and the UK. An overview of the regulatory requirements for starting the trial on international, national, regional and local levels is provided in Table 1 and described in more detail below.

Overview of preparatory requirements

On an international level, we requested a 'Voluntary Harmonisation Procedure' (VHP) for six countries (Estonia, Germany, Greece, Hungary, Italy, and the United Kingdom). The VHP provides a coordinated assessment of a clinical trial application in multiple

European countries.[10] Three countries were not included in the VHP (The Netherlands, Norway and Poland).

After VHP approval, subsequent evaluation on a national level was needed by the National Competent Authority (NCA) and leading or national Ethics Committee (EC) in each country. The leading EC was usually the EC affiliated to the hospital of the National Coordinator (NC), who is the coordinating investigator for each country. In some countries (Greece, Italy), an independent review by an Ethics Committee on a regional (REC) or hospital (HEC) level was also required, as well as approval from each participating site (usually given by the Board of Directors) was needed to endorse the practicability of conducting the trial at that site in some countries (Table 1).

Table 1. Overview of regulatory requirements for each country

Country	International	National				Regional / local		
	VHP	EC[c]	NCA	CCA	CTA	HEC/ REC	Hospital[d]	SIV
Estonia	X	X	X	X	X	-	X	X
Germany	X	X	X	X	X	X[a]	-	X
Greece	X	X	X	X	X	X	X	X
Hungary	X	X	X	X	X	X[a]	-	X
Italy	X	X	X	X	X	X	X	X
Norway	-	X	X	X	X	-	-	X
The Netherlands	-	X	X	X	X	-	X	X
Poland	-	X	X	X	X	X[a]	-	X
United Kingdom	X	X	X	X	X	X[b]	X	X

VHP indicates voluntary harmonisation procedure; CCA, country coordinator agreement; EC, national ethics committee; NCA, national competent authority; CTA, clinical trial agreement; REC, regional ethics committee; HEC, hospital ethics committee; SIV, site initiation visit. [a] No separate submission is required, the EC or NCA contacts the REC for approval during the approval process. [b] Review by the UK's NHS Research Scotland (NRS) and Health Research Authority (HRA) were categorised under REC. [c] The EC is the national ethics committee of a country or the leading ethics committee affiliated the hospital of the national coordinator. [d] Hospital stands for local hospital approval.

In addition, and often in parallel, two types of required legal documents were completed: a Country Coordinator Agreement (CCA) and a Clinical Trial Agreement (CTA). A CCA is a contract signed between the trial sponsor, University Medical Center Utrecht (UMCU) in The Netherlands, and the institution of the NC of each participating country, which delegated the responsibility for arranging legal agreements for that country from the sponsor to the NC, in order to prevent potential problems due to different national laws between the participating and the Sponsor's country. Subsequently, the institution of the NC contracted each participating trial site in that country by means of a CTA.

After obtaining all necessary regulatory approvals and completing all contracts, the Site Initiation Visit (SIV) was planned. During this meeting with the local PRECIOUS team, a national trial monitor assessed whether all mandatory preparations had been completed and whether the Investigator Site File contained a copy of all the necessary

documents (e.g., approval letters of the regulatory authorities, lists of signatures and CVs of trained site PRECIOUS personnel). After approval of the SIV report by the central monitoring team of European Clinical Research Infrastructure Network, a site was considered ready to start recruiting patients.

Included sites and data collection

We included a trial site in this analysis if the start and end dates ('milestone dates') for one or more of the individual regulatory preparatory processes were available: VHP, EC, NCA, REC/HEC, local hospital approval, CCA or CTA. A trial site was excluded if there were specific circumstances that resulted in exceptional delay in opening the site (e.g., long-term sick leave of the principal investigator that delayed all regulatory approvals). Two authors (JCdJ, HR) retrospectively retrieved milestone dates from correspondence with regulatory authorities (e.g., approval letters) and signed contracts stored in the Trial Master File during the trial. The start of contract negotiations was retrieved from email correspondence and supplemented by information from the relevant national research teams. For each site we collected the number of included patients in the first 6 and 12 months after the date of the SIV from the study's electronic case file.

Measures and outcomes

We distinguished trial sites that were included in the original submissions to the national authorities ('original sites') and trial sites that expressed interest in joining during the course of the trial, which had to be added by means of an amendment because national approvals were already obtained ('additional sites').

The primary outcome was the time needed to initiate the original trial sites ('time to site initiation'), which was defined as the time period between the date of VHP submission and SIV approval (for VHP countries), between submission to the EC and SIV approval (for The Netherlands) or between sending the CCA template to the NC and SIV approval (for Norway and Poland, where this was the first preparatory activity).

Secondary outcomes included (1) time to site initiation for additional sites; (2) time needed to complete each individual preparatory requirement; (3) average time to site initiation in each of the 9 participating countries; (4) average time to site initiation in academic and non-academic hospitals; and (5) number of patients recruited by each site in the first 6 and 12 months after SIV. Time to site initiation for additional sites was defined as the time between the date of the first preparatory activity (either applying for an amendment to the EC or sending the CTA template to the hospital) and the SIV date (defined as the last signature on the SIV report), which means that the time needed to obtain primary (inter)national approvals (VHP, EC, NCA, CCA) was not included in this outcome. The time needed for individual regulatory approvals (VHP, EC, NCA, REC/HEC, local hospital approval) was defined as the time period between submission date to the regulatory authority and their approval. The time needed for concluding a contract (CCA, CTA) was defined as the time period between the date the first draft version of the contract was sent to the trial site (i.e., national coordinator or institution lawyer), and the date of the last signature on the contract. As some regulatory processes

may be done in parallel or may overlap, the time to site initiation is not necessarily the sum of the time periods needed for all individual preparatory requirements.

Statistical analysis

The time to site initiation and the time period needed for each regulatory requirement to be completed are reported in median days with interquartile range. Differences in time to site initiation between original and additional sites, and between academic and non-academic hospitals were analysed with the Mann–Whitney U test. Differences between countries were assessed with one-way non-parametric ANOVA (Kruskal–Wallis test). The association between median time to initiation and patient recruitment in the first 6 and 12 months was assessed with linear regression. The criterion for statistical significance was set at $\alpha = 0.05$. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

During the course of PRECIOUS, 88 trial sites planned to participate in the trial. In the present study, three trial sites were excluded because all of the regulatory approvals of these sites were delayed because of extraordinary circumstances. Therefore, 85 trial sites were included in the analysis (Figure 1). The start date of PRECIOUS was submission to the Sponsor's EC on 16 October 2015.

The median time to initiation was available for 80 sites; 59 of 60 (98%) original sites (one UK site excluded because of delay of the SIV due to long absence of the PI) and 21 of 25 (84%) additional sites. Two additional sites were excluded (both in Italy), because the start date of the preparation period was not available, and two sites (one in Germany, one in UK) were excluded because the SIV was postponed for other reasons (Figure 1). The median time to site initiation was 784 days (IQR: 586–1102) for the 59 original trial sites and 234 days (IQR: 166–315; $p < 0.0001$) for the 21 additional trial sites. For original and additional trial sites combined, the median time to initiation was 698 days (IQR: 409–979; Table 2).

The time needed for each separate regulatory requirement to be completed is shown in Tables 3 and 4. The median EC and NCA review time was 87 (IQR: 37–128) and 91 (IQR: 16–132) days, respectively. For VHP countries, the review by the NCA lasted 105 (IQR: 10–156) days. The signing process of the CCA and CTA were the most time-consuming regulatory requirements (Figure 2). The median time needed to sign a CCA was 201 days (IQR: 104–492) and to sign a CTA was 194 days (IQR: 93–293). On average, 35.9% of the time to initiation was used for signing the CTA.

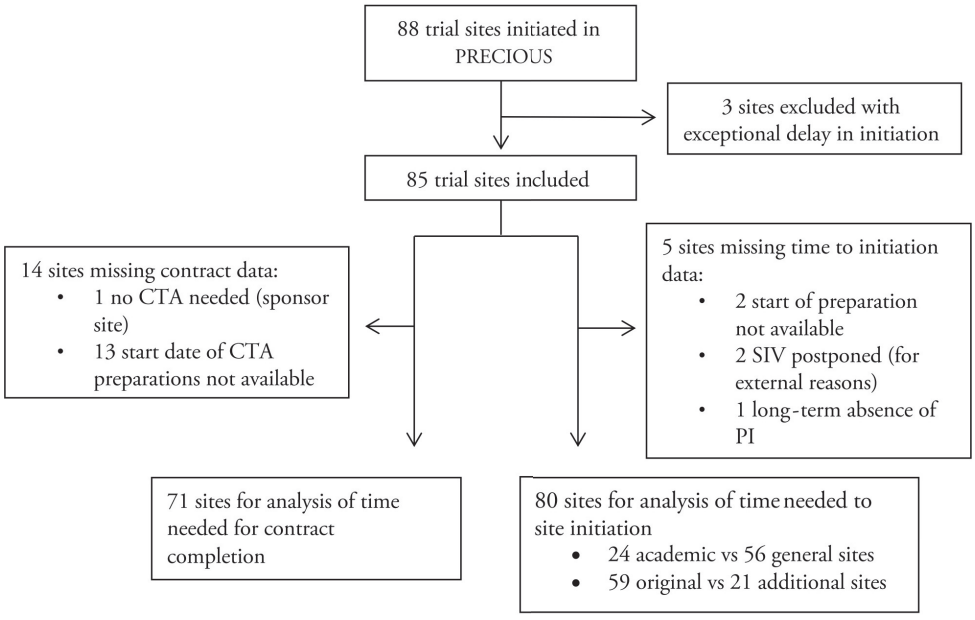

Figure 1. Flowchart of included trial sites in the current study

Table 2. Time to site initiation per country

Country	Original sites			Additional sites		
	Number of sites	Median [IQR]	Range	Number of sites	Median [IQR]	Range
Netherlands	10/10	504 [437-551]	238-700	4/4	175 [166-325]	166-372
Estonia	4/4	591 [573-670]	569-695	-	-	-
Norway	4/4	735 [574-971]	545-1025	-	-	-
United Kingdom	6/7	760 [718-903]	716-987	12/13	212 [163-256]	91-566
Germany	6/6	767 [605-925]	567-1096	1/2	406	-
Greece	3/3	793 [774-821]	774-821	2/2	308	287-329
Italy	9/9	813 [702-1115]	543-1131	0/2	-	-
Poland	6/6	956 [812-1108]	711-1113	1/1	116	-
Hungary	13/13	1235 [1201-1285]	564-1430	1/1	1324	-
Total	59/60	784 [586-1102]	238-1430	21/25	234 [166-315]	91-1324

Time is displayed as days. Countries sorted on duration of time to initiation. Abbreviations: IQR, interquartile range.

Table 3. Time needed for each (inter)national regulatory approval

Country	VHP	EC	NCA	CCA
Estonia	84	44	111	376
Germany	84	149	14	74
Greece	84	57	99	52
Hungary	84	87	153	768
Italy	84	28	163	193
Netherlands	-	110	21	-
Norway	-	136	91	192
Poland	-	29	88	531
United Kingdom	84	119	8	209
Median [IQR]	-	87 [37-128]	91 [16-132]	201 [104-492]

Time is displayed in days. The approval time is the time of the first approval (amendments for adding sites are not included). Abbreviations: EC, Ethics Committee; NCA, National Competent Authority; CCA, Country Coordinator Agreement; IQR, interquartile range.

Table 4. Time needed for each local regulatory approval

Country	CTA		Local hospital approval		REC	
	Number of sites	Median [IQR]	Number of sites	Median [IQR]	Number of sites	Median [IQR]
Estonia	4/4	105 [52-130]	3/4	13 [5-66]	-	-
Germany	8/8	542 [231-779]	-	-	-	-
Greece	5/5	208 [198-281]	4/5	69 [65-82]	5/5	41 [23-61]
Hungary	13/13	328 [277-368]	-	-	-	-
Italy	1/11	51	4/11	39 [6-152]	10/11	51 [24-67]
Netherlands	13/14*	140 [60-179]	13/14*	25 [10-57]	-	-
Norway	1/4	81	-	-	-	-
Poland	6/6	205 [157-252]	-	-	-	-
United Kingdom	20/20	118 [70-196]	20/20	85 [39-108]	20/20	39 [4-131]
Total	71/85	194 [93-293]	44/54	61 [22-88]	35/36	41 [14-69]

Time is displayed in days. Abbreviations: IQR, interquartile range.
* Since the UMCU was the coordinator centre, no CTA or local hospital approval had to be obtained.

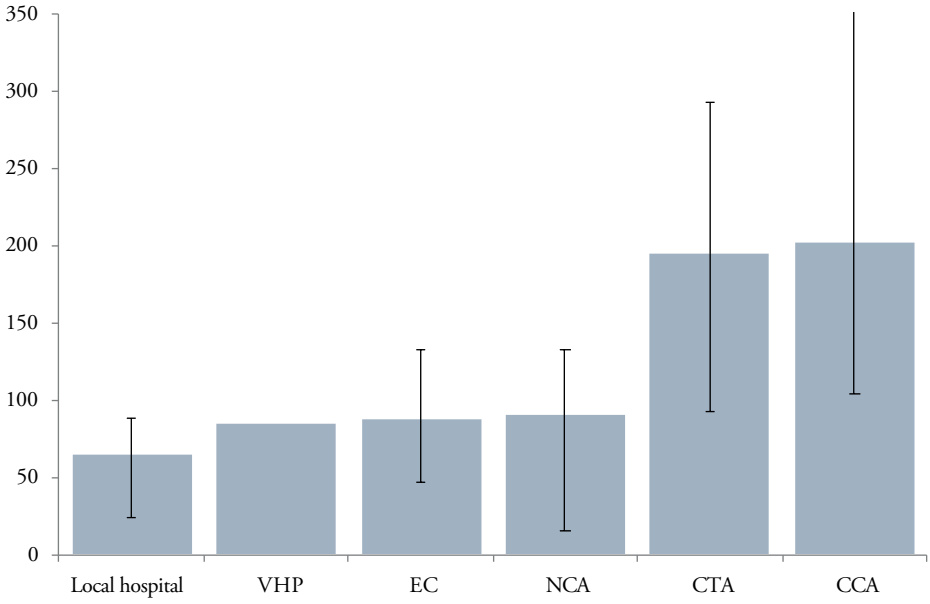

Figure 2. Median time per regulatory requirement
Approval duration of national regulatory requirements, sorted based on duration. Time displayed in median number of days with interquartile ranges.

The median time to initiation was similar for academic (n = 24) and general (n = 56) hospitals (659 vs 703 days, p = 0.77). The median time to initiation differed significantly between countries (p < 0.0001), with the shortest time to initiation for The Netherlands (where approval was requested first) and the longest for Hungary (see Table 2). A longer time to initiation was associated with a slower patient recruitment in the first six months after initiation (B = –0.002; p = 0.02), but not in the first 12 months (B = –0.003; p = 0.12; see Supplemental Table 1).

DISCUSSION

In PRECIOUS, the median time to initiation of a pre-planned trial site was just over two years. Negotiations on contracts between a national coordinator and trial sites were an important delaying factor, responsible for approximately one third of the time needed to initiate a trial site.

PRECIOUS is an investigator-initiated, pragmatic clinical trial testing widely available off-patent medications that have been on the market for several decades and that have proven to be safe in stroke patients.[11,12] As a consequence, the trial was considered as low risk by regulatory authorities. The study Sponsor had almost full-time availability of a chief investigator, trial coordinator, and research nurse to support the submissions and applications. The trial was coordinated in the participating countries by experienced NCs and research teams. In three countries (Greece, Hungary, and Poland), a clinical

research organisation (CRO) was contracted during the course of the trial to speed up the approval process. Nevertheless, we experienced considerable delays in obtaining ethics and hospital management approvals. Considering that the duration of the trial granted by the European Union was 60 months, more than half of the time intended to recruit patients was spent on obtaining regulatory approvals. In addition, we found that longer time to site initiation was negatively associated with the number of included patients in the first six months, possibly because of understandable loss of momentum and enthusiasm among some of the investigators. Delays in obtaining regulatory approval and legal review may therefore be an important reason why about half of the clinical trials fail to reach their target sample size within the planned timeline.[6]

Only a few previous studies evaluated delay due to regulatory review in RCTs.[5] Also, most of these studies only looked at ethics[13,14] or local hospital approval,[8] instead of the entire time to initiation including contract negotiations. In the British phase IV trial SANADII on treatment of epilepsy the median 'opening time' for study sites in 2012 and 2013 was 10.5 months, but this was after ethics approval had already been obtained.[7] The study identified several delaying factors, such as negotiating excess treatment costs, finalising logistics, collecting CVs, and ongoing discussions about participation. The median time of 10.5 months is much shorter than the median time to initiation of almost 25 months for pre-planned trial sites in the UK, but the starting point of VHP submission in the present study is much earlier. In addition, SANADII was a phase IV trial whereas PRECIOUS is phase III, and SANADII was performed only in the UK, whereas PRECIOUS involves nine European countries.

Obviously, we have to declare a mea culpa. Although the study Sponsor and most of the centres of the NCs have ample experience with clinical trials, and all of these are partners in the PRECIOUS project and therefore share responsibilities, they may occasionally have contributed to some delays, for example because of other obligations or priorities. This also applies to local Principal Investigators. Most investigators work on the trial in addition to their everyday clinical work. The trial had no commercial interest and local investigators only receive a small reimbursement for expenses for including a patient in the trial, which could have an impact on the speed of setting up the trial. With the exception of Greece, Hungary, and Poland, the approval process was not supported by a commercial CRO, which could have accelerated the process but at considerable cost. It would be interesting to compare our findings with those in other academic trial with or without the involvement of a CRO, and with those in industry-driven trials. Such a comparison could support the development of best practice examples that could aid future clinical trials.

The current study also has other limitations. First, the time needed for preparation of the submissions to the regulatory authorities is not incorporated in the duration of the approval processes. The submission package consists of multiple forms and other documents, some of which need translation to the national language in some countries. Therefore, the actual time needed for ethics or hospital management approval is longer than reported here. Secondly, we assessed the approval process in just nine countries in Europe. These were however relatively well distributed across Europe.

We observed considerable overlap between the assessments of different regulatory authorities. Whereas the VHP is intended to facilitate and shorten NCA approval and VHP timelines dictate that NCA approval should follow within 10 days after VHP approval,[10] we experienced a median time for NCA review of 105 days in the six countries that participated in the VHP (in addition to the 84 days needed for VHP approval). Therefore, in our experience the VHP was an additional bureaucratic burden that required a separate submission with often little additional value with regard to subsequent approvals. We believe that stricter adherence to VHP timelines should be pursued. Likewise, the EC provides ethical approval for a clinical trial and ensures that a trial is performed according to (inter)national law and regulations. This approval should serve as a proof of warranty for local trial sites to conduct a clinical trial. However, in our experience, institutions at regional or hospital level may repeat a large part of the same approval procedure as the EC. In our opinion, countries should strive for a single regulatory review process that serves as global approval in that country. Any local review afterwards should be limited to issues related to local practicability and should be bound to specific timeframes. In addition, we support proposals to make regulatory requirements proportional to the risk of the study. This is likely to shorten the approval process and to increase patient recruitment.

Moreover, clinical trials could benefit from a universally accepted template for national contracts. In PRECIOUS, we used a local template for the CCAs. The CCA was reviewed by lawyers in each country, who were often not familiar with this format. In addition, there are no established timeframes for legal review of research contracts (both CCA and CTA). Legal departments of hospitals or institutions often have a high work load with limited capacity and the quick opening of a trial site may not be their top priority. This regularly resulted in recurrent discussions between lawyers of both parties, often on details of which the relevance was not immediately clear to the investigators, interrupted by lengthy periods of apparent inactivity. This is illustrated by a delay of 201 days for the CCA and 194 days for the CTA. Moreover, most of the times the CCA and CTA were handled consecutively. We suggest that an international template for clinical trials should be developed, with specific timeframes and deadlines for local lawyers to complete legal review.

In conclusion, ethical and legal review including the evaluation of contracts with study sites lead to serious delays in initiating trial sites, which reduce time available for patient recruitment, and results in substantial increases in efforts and costs, jeopardising the conduct of academic clinical trials.

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SUPPLEMENTAL MATERIAL

Table 1. Time to first included patient

Country	REC	
	Number of sites	Median [IQR]
Estonia	4/4	573 [251-692]
Germany	6/8	63 [14-148]
Greece	5/5	66 [29-132]
Hungary	7/13	72 [7-204]
Italy	9/11	89 [30-216]
Netherlands	11/14	71 [26-162]
Norway	2/4	271
Poland	5/6	88 [19-172]
United Kingdom	18/20	47 [24-108]
Total	67/85	83 [33-154]

Median number of days from trial site initiation to the first included patient for each country Abbreviations: IQR, interquartile range.


5

Chapter 5

Surgical decompression for space-occupying hemispheric infarction: a systematic review and individual patient meta-analysis of randomised clinical trials

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ABSTRACT

Importance
n patients with space-occupying hemispheric infarction, surgical decompression reduces the risk of death and increases the chance of a favourable outcome. Uncertainties, however, still remain about the benefit of this treatment for specific patient groups.

Objective
To assess whether surgical decompression for space-occupying hemispheric infarction is associated with a reduced risk of death and an increased chance of favourable outcomes, as well as whether this association is modified by patient characteristics.

Data sources
MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the Stroke Trials Registry were searched from database inception to October 9, 2019, for English-language articles that reported on the results of randomised clinical trials of surgical decompression vs conservative treatment in patients with space-occupying hemispheric infarction.

Study selection
Published and unpublished randomised clinical trials comparing surgical decompression with medical treatment alone were selected.

Data extraction and synthesis
Patient-level data were extracted from the trial databases according to a predefined protocol and statistical analysis plan. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and the Cochrane Collaboration's tool for assessing risk of bias were used. One-stage, mixed-effect logistic regression modelling was used for all analyses.

Main outcomes and measures
The primary outcome was a favourable outcome (modified Rankin Scale [mRS] score ≤3) at 1 year after stroke. Secondary outcomes included death, reasonable (mRS score ≤4) and excellent (mRS score ≤2) outcomes at 6 months and 1 year, and an ordinal shift analysis across all levels of the mRS. Variables for subgroup analyses were age, sex, presence of aphasia, stroke severity, time to randomisation, and involved vascular territories.

Results
Data from 488 patients from 7 trials from 6 countries were available for analysis. The risk of bias was considered low to moderate for 6 studies. Surgical decompression was associated with a decreased chance of death (adjusted odds ratio, 0.16; 95% CI, 0.10-0.24) and increased chance of a favourable outcome (adjusted odds ratio, 2.95; 95% CI, 1.55-5.60), without evidence of heterogeneity of treatment effect across any of the prespecified subgroups. Too few patients were treated later than 48 hours after stroke

onset to allow reliable conclusions in this subgroup, and the reported proportions of elderly patients reaching a favourable outcome differed considerably among studies.

Conclusions and relevance
The results suggest that the benefit of surgical decompression for space-occupying hemispheric infarction is consistent across a wide range of patients. The benefit of surgery after day 2 and in elderly patients remains uncertain.

INTRODUCTION

Space-occupying brain oedema is a potentially life-threatening complication of ischaemic stroke that has been reported to occur in 2% to 8% of patients with supratentorial infarction[1-4] and that most often manifests in the first 4 days after stroke onset.[5] Randomised clinical trials and intensive care–based series have reported death rates of up to 80% with conservative treatment alone.[5,6] Surgical decompression, consisting of a large hemicraniectomy and duraplasty, consistently reduced the risk of death in randomised clinical trials and increased the chance of a favourable outcome in some meta-analyses of these trials.[7-14] However, because of the small size of the individual trials and of pooled analyses of these trials, uncertainties still remain about the benefit of surgical decompression for specific patient groups,[15,16] including those with aphasia or involvement of an additional vascular territory next to that of the middle cerebral artery (MCA) and those presenting later than 48 hours after stroke onset. Data pooling may provide more precise estimates of treatment effects.[17,18] We therefore aimed to address these uncertainties by analysing pooled individual patient data from randomised clinical trials that compared functional outcomes in patients with space-occupying supratentorial hemispheric infarction treated with surgical decompression with outcomes in patients who received medical treatment alone. We also sought to assess whether patient characteristics modify surgical decompression outcomes for space-occupying hemispheric infarction.

METHODS

Literature search and selection criteria

In this meta-analysis, 2 investigators (H.R. and H.N.) performed a systematic literature search of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Stroke Trials Registry from database inception to October 9, 2019, to identify randomised clinical trials reported in English of surgical decompression vs conservative treatment in patients with space-occupying hemispheric infarction. The full search strategy is described in Appendix 1 in the Supplement. Individual articles were checked for potentially relevant citations. We contacted the investigators of the identified studies and requested coded, individual patient data. Studies were included if (1) patients were randomised to receive surgical decompression or medical treatment alone because of space-occupying hemispheric infarction; (2) functional outcome was assessed at 6 to 12 months after stroke onset using the modified Rankin Scale (mRS), a

7-point functional outcome scale ranging from 0 (no symptoms) to 5 (severe disability) and 6 (death); and (3) the authors provided individual patient data. A predefined protocol and statistical analysis plan were created and agreed on by all collaborating investigators (Appendix 2 in the Supplement). The risk of bias in each trial was independently assessed by 2 investigators (H.R. and H.N.) with the Cochrane Collaboration's tool for assessing risk of bias.[19] In case of disagreement, a consensus meeting was convened. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[20]

Data collection and management

After individual patient data were collected, variables were transformed when possible to create a uniform database. The following baseline patient-level data were extracted from the trial databases: age; sex; presence of aphasia (if unknown, aphasia was considered present if the left hemisphere was affected); score on the National Institutes of Health Stroke Scale (NIHSS) at baseline (if not available because of sedation at randomisation, the patient was regarded comatose and given an NIHSS score of 35)[21]; score on the Glasgow Coma Scale at baseline; time to randomisation; and vascular territory involved (MCA alone vs MCA plus anterior cerebral artery (ACA) or posterior cerebral artery (PCA) territory). If information on the vascular territory was not available, information about the site of occlusion on computed tomographic angiography or magnetic resonance angiography was used, with carotid occlusion being regarded as MCA plus ACA or PCA territory. We also collected the scores on the mRS at 6 months and 1 year after stroke onset. If the outcome at 1 year for an individual patient was missing, the latest recorded mRS score was used for estimating the 1-year outcome provided that the score was not obtained earlier than 6 months (±30 days) after stroke.

Outcomes and statistical analysis

The primary outcome was a favourable outcome, defined as a score of 0 to 3 on the mRS at 1 year (±30 days) after stroke. Secondary outcomes were functional independence (mRS score ≤2), reasonable outcome (mRS score ≤4), and death at 6 months and 1 year after stroke. The analysis was supplemented by a shift analysis to investigate improvement across all levels of the mRS at 1 year after stroke. In addition, we aimed to analyse location of residence (home, rehabilitation service, long-term nursing facility, or hospital) and serious adverse events (limited to surgical complications) in the first year.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. No additional per-protocol analyses were performed because crossovers and major protocol violations were reported in only 16 patients (3.3%).

A 1-stage model was used for the primary and secondary analyses, which pools all data in a single regression model. We used mixed-effect logistic regression modelling, taking treatment and trial as random effects in all mixed models. This approach ensured that between-trial variance is incorporated in the estimation of all effect sizes and their CIs. Binary logistic regression was used to calculate the odds ratios (ORs) and 95% CIs

for dichotomous outcomes (such as the primary outcome), and additional adjusted analyses were performed to account for potential baseline incomparability. Adjustments were planned for the following prespecified covariates: age, sex, baseline stroke severity (NIHSS), presence of aphasia, and time from stroke onset to randomisation. These covariates were incorporated into the mixed models as common effects. Ordinal logistic regression was used for secondary ordinal outcomes, such as improvement on the mRS (shift analysis) at 1 year. Results are reported as absolute risk difference (RD) and crude and adjusted (common) ORs (aORs) with accompanying 95% CIs, with a 2-sided $P < .05$ considered statistically significant.

Prespecified subgroup analyses were performed to assess the potential effect modification of the association between surgical decompression and the primary outcome for age (18-50, 51-60, 61-70, and >70 years), sex (male vs female), presence of aphasia, vascular territory (MCA alone vs MCA and ACA or PCA), time from stroke onset to randomisation (by day), and NIHSS score at baseline (≤20, 21-25, and >25). Because of low numbers of primary outcomes in subgroups with multiple categories, we not only combined age subgroups (≤60 vs >60 years) for visualization in a forest plot but also included the prespecified analysis with 4 age subgroups.

The consistency of the treatment effect between subgroups was assessed by interaction terms, with significant interaction defined a priori as 2-sided $P < .10$, reflecting heterogeneity. Subgroup analyses included the random-effects variables trial and treatment in addition to the multiplicative interaction term treatment × prespecified subgroup variable. To separate within-study and across-study interaction, we centred the covariate of interest (by subtracting the mean in each trial) and used the interaction term of the centred variable and treatment allocation in the model. The regression coefficient and significance level for this interaction term were used as an estimation of the within-trial covariate interaction. Age, time to randomisation, and baseline NIHSS score were used as continuous variables in these analyses. Subgroup analyses were again adjusted, assuming common effects for the prespecified covariates.

In addition, we performed several post hoc analyses, including sensitivity analyses for published trials with low to moderate risk of bias, for trials that reported all 5 prespecified adjustment variables, for patients older than 60 years, and for patients randomised after 48 hours of symptom onset.

All statistical analyses were performed with R, version 3.5.1 (R Foundation for Statistical Computing).

RESULTS

Study and patient characteristics

In this meta-analysis, 8 published randomised clinical trials[7,8,10-12,22-24] and 1 unpublished trial[25] that had assessed the effectiveness of surgical decompression for space-occupying hemispheric infarction were identified (Figure 1 in the Supplement). These trials include 7 completed published trials from 6 countries,[7,8,10-12,23,24] and 1 trial that was completed at the time we performed the meta-analysis, but was published and withdrawn later in 2021.[25] One trial[22] had only published preliminary results for the first 28 of a total of 44 included patients. Research groups of 7 trials[7,8,10-12,22,25] provided full data, 1 research group provided incomplete data (10 of 29 patients) that were excluded from the analysis,[23] and data of 1 other trial[24] that randomised 26 patients were not available. The authors of the trial that was published later[25] provided patient data and a completed manuscript for the meta-analysis. In total, the analysis comprised 488 of all 543 patients (90%) randomised.

The score on the mRS at 1 year was assessed in all studies. In all except 1 study,[8] the mRS was also assessed at 6 months. The location of residence at 1 year was recorded in only 1 study,[8] and systematically collected information about serious adverse events was available in only 1 study,[11] hindering the use of these outcomes in the current meta-analysis. Information on time to randomisation was not available for individual patients in one trial,[25] and NIHSS score at baseline was not available in another trial[10] (Table 1 in the Supplement). Therefore, the variables NIHSS score at baseline and time to randomisation could not be used as adjustment covariates because doing so would lead to exclusion of these trials in the main analyses. Instead, additional sensitivity analyses with exclusion of these 2 trials were performed (Tables 2-4 in the Supplement).

Six studies,[7,8,10-12,25] including 86% of the patients, were judged to have a low to moderate risk of bias (Appendix 3 in the Supplement). Given the nature of treatment, blinding of participants and personnel involved in the trial was not possible. For blinding of the outcome assessment, 2 studies[7,25] used surgical head caps for all patients, 1 study[8] blinded narratives of mRS interviews, and 1 used questionnaires[10] that were completed by patients or family at home.

Of the 488 patients included in the trial, 234 (48%) were randomised to receive surgical decompression and 254 (52%) to receive medical treatment. Baseline characteristics were largely balanced between the populations (Table 1). Baseline characteristics stratified by trial are given in Table 1 in the Supplement. Large differences were found among trials in age at randomisation and time to randomisation caused by differences in the relevant inclusion criteria, but differences in other clinical and radiologic eligibility criteria were small (Table 2 and Appendix 4 in the Supplement).

Table 1. Baseline characteristics in the pooled data

	Medical treatment	Surgical decompression	Total
Number randomised	254	234	488
Time (hours) to randomisation (mean + SD)	29.7 (18.2)	28.1 (14.5)	28.9 (16.5)
NIHSS at baseline (median + IQR)	24 (21-30)	24 (20-28)	24 (21-29)
Age at randomisation (mean + SD)	60.3 (12.8)	59.1 (12.9)	59.7 (12.9)
Age per decade (%)			
18-50 years	68 (26.8)	63 (26.9)	131 (26.8)
51-60 years	49 (19.3)	55 (23.5)	104 (21.3)
61-70 years	72 (28.3)	72 (30.8)	144 (29.5)
>70 years	65 (25.6)	44 (18.8)	109 (22.3)
Male sex (%)	141 (55.5)	138 (59.0)	279 (57.2)
Aphasia present (%)	116 (45.7)	106 (45.3)	222 (45.5)
Vascular territory (%)			
MCA alone	103 (40.6)	97 (41.5)	200 (41.0)
MCA + ACA and/or PCA	89 (35.0)	69 (29.5)	158 (32.4)
Missing	62 (24.4)	68 (29.1)	130 (26.6)
GCS sum score (median + IQR)	10 (8-11)	9 (8-12)	10 (8-12)

SD indicates standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; GCS, Glasgow coma score; NA, not available.

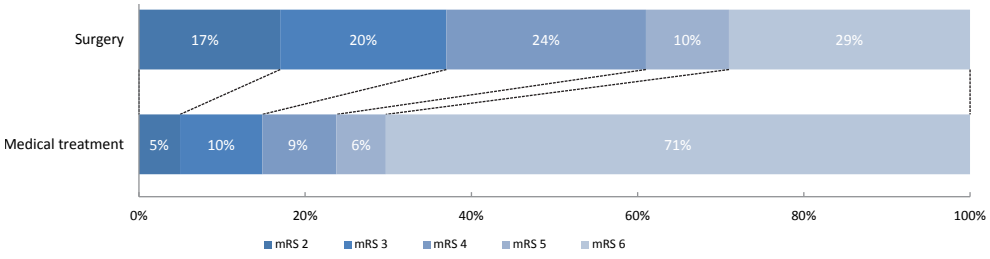

Figure 1. Scores on the modified Rankin Scale at 1 year.

Table 2. Trial eligibility criteria

	DECIMAL[12]	DEMITUR[25]	DESTINY[7]	DESTINY II[11]	HAMLET[8]	Slezins[22]	Zhao[10]
Inclusion criteria							
Age (years)	18-55	40-80	18-60	>60	18-60	>18	18-80
Time stroke onset to randomisation (hours)	≤24	-	-	-	-	-	-
Time stroke onset to treatment (hours)	≤30	12-38	12-36	<48	≤96	≤48	≤48
Time randomisation to surgery (hours)	≤6	<6	≤6	≤6	≤3	-	-
NIHSS (dominant hemisphere)	>15	>18	>20	>19	>20	>15	-
NIHSS (non-dominant hemisphere)	>15	>16	>18	>14	>15	>15	-
NIHSS item 1a	≥1	≥1	≥1	≥1	-	-	-
GCS (Eyes + Motor score)	-	-	-	-	≤9	-	≤9
MCA territory involved on brain CT	>50%	≥2/3	≥2/3	≥2/3	≥2/3	≥50%	≥2/3
Infarct volume (cm^3) on MRI-DWI	>145	>150	NA	NA	NA	>145	NA
Involvement of basal ganglia required	-	Yes	Yes	Yes	-	-	-
Oedema formation required	-	-	-	-	Yes	Yes	Yes
Exclusion criteria							
Pre-stroke mRS	≥2	≥2	≥2	≥2	≥2	≥2	≥2
Contralateral infarction	Yes	Yes	Yes	Yes	-	-	Yes
Severe haemorrhagic transformation of infarct	Yes	Yes	Yes	Yes	-	-	Yes
Life expectancy (years)	<3	<3	<3	<3	<3	-	<3
Known coagulopathy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pregnancy	Yes	Yes	Yes	-	-	-	Yes
MRI contraindication	Yes	-	NA	NA	NA	-	NA
Anaesthesia contraindication	-	Yes	Yes	Yes	-	Yes	Yes
GCS	-	<6	<6	<6	-	<6	<6
Pre-stroke Barthel Index	-	<95	<95	<95	<95	-	-
Fixed and dilated pupils	-	Both	Both	Both	Both	Both	One
Other serious illness that could affect outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Involvement of entire cerebral hemisphere	-	-	-	-	Yes	-	-

* See Supplement for full manuscript. NIHSS indicates National Institute of Health Stroke Scale; MCA, middle cerebral artery; DWI, diffusion-weighted imaging; GCS, Glasgow coma score; mRS, modified Rankin Scale; rt-PA, recombinant tissue plasminogen activator; NA, Not applicable.

Primary and secondary outcomes

Figure 1 shows the distribution of mRS scores at 1 year by treatment population. Pooled analysis found an increased chance of a favourable outcome (mRS score ≤3) at 1 year in patients randomised to surgery vs those randomised to medical treatment (RD, 21%; 95% CI, 9-33; aOR, 2.95; 95% CI, 1.55-5.60) (Table 3). Surgical decompression was also associated with reduced risk of death and increased chance of a reasonable outcome at 1 year and was associated with a shift toward functional improvement. Similar treatment outcomes were observed after 6 months, with improvements after surgical decompression in favourable and reasonable outcomes and a reduced death rate (Table 3). Crude and adjusted ORs were essentially the same for all outcomes. Additional sensitivity analyses that excluded unpublished trials, trials with a high risk of bias, and trials that did not report all prespecified adjustment variables found a comparable reduction in mortality and improvement of acceptable outcome but lower rates of favourable outcome after decompressive surgery than the main analyses (Tables 2-4 in the Supplement).

Table 3. Efficacy outcomes from the pooled data at 1 year and 6 months

Outcome	Surgery Population	Medical Population	RD (%)	Crude (c)OR (%95 CI)	Adjusted (c)OR (%95 CI)
Primary outcome					
mRS ≤ 3 at 1 year	87/234 (37%)	37/254 (15%)	21	3.23 (1.75-5.94) p<.001	2.95 (1.55-5.60) p=.001
Secondary outcomes					
mRS ≤ 2 at 1 year	39/234 (17%)	12/254 (5%)	10	2.91 (1.06-7.99) p=.04	2.77 (0.97-7.88) p=.06
mRS ≤ 4 at 1 year	143/234 (61%)	59/254 (23%)	38	5.55 (3.42-9.00) p<.001	5.34 (3.26-8.74) p<.001
Death at 1 year	68/234 (29%)	180/254 (71%)	-41	0.16 (0.10-0.24) p<.001	0.16 (0.10-0.24) p<.001
mRS ≤ 3 at 6 months	60/202 (30%)	19/222 (9%)	20	4.85 (2.43-9.67) p<.001	4.67 (2.20-9.87) p<.001
mRS ≤ 4 at 6 months	118/202 (58%)	43/222 (19%)	39	6.07 (3.79-9.74) p<.001	5.67 (3.18-10.09) p<.001
Death at 6 months	55/202 (27%)	158/222 (71%)	44	0.14 (0.09-0.22) p<.001	0.13 (0.08-0.22) p<.001
Shift analysis					
mRS at 1 year				5.29 (3.27-8.56) p<.001	4.95 (2.99-8.20) p<.001
mRS at 6 months				6.38 (4.15-9.79) p<.001	6.62 (4.01-10.92) p<.001

Subgroup analysis

In the subgroup analysis for the primary outcome (mRS score ≤3 at 1 year), no evidence of heterogeneity of treatment effect was found across the prespecified variables: age, sex, aphasia, NIHSS score at baseline, time to randomisation, and vascular territories involved (Figure 2 and Figure 2 in the Supplement). Similar results were found in the subgroup

analysis for the secondary outcomes (mRS score ≤4, death, and shift analysis) (Figure 3 and Figures 3 and 4 in the Supplement). Only 32 patients (6.6%) were randomised after the first 48 hours of stroke onset (Table 5 in the Supplement). In post hoc analysis of patients older than 60 years, the proportion of patients who reached a favourable (mRS score ≤3) outcome after surgical decompression differed considerably among studies. In 4 trials,[8,10,11,22] 0% to 12.5% of patients older than 60 years reached a favourable outcome, as opposed to 66% in DEMITUR[25] (Table 6 in the Supplement). Treatment effects in these patients were fairly consistent, but absolute numbers of patients who reached a favourable outcome were small, especially when DEMITUR[25] was excluded (Figure 5 in the Supplement).

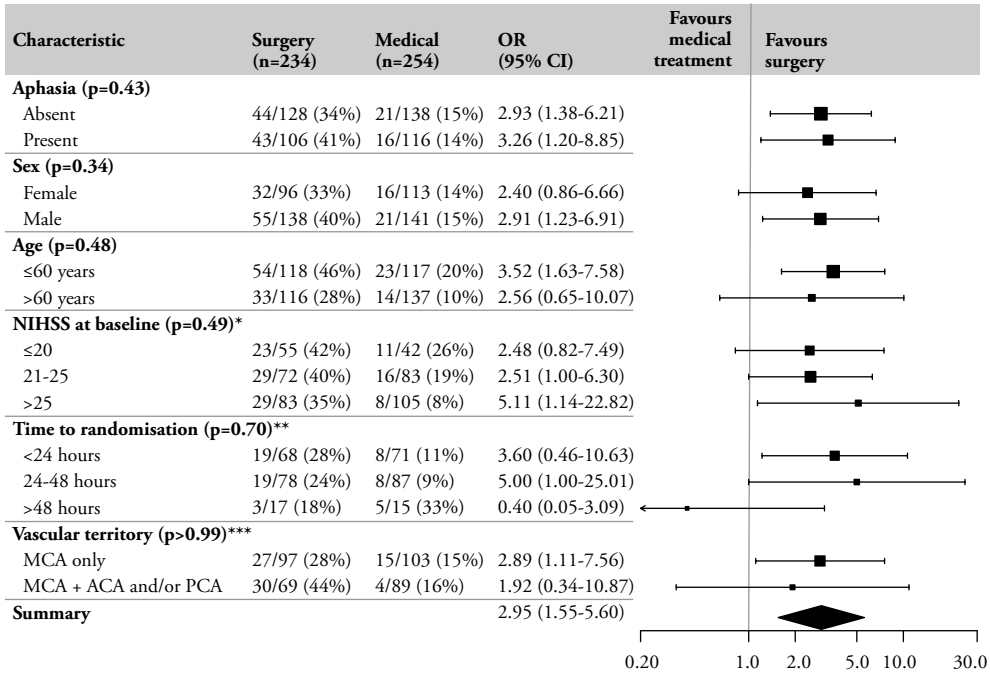

Figure 2. Forest plot of subgroups - mRS ≤ 3 at one year.

P-values for heterogeneity across subgroups are shown (interaction term treatment*subgroup variable). Odds ratios are adjusted for age, sex and presence of aphasia (not NIHSS at baseline and time to randomisation). All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'.

* not recorded in Zhao et al.[10] (n=47) and missing (n=1) in HAMLET[8].

** not recorded in DEMITUR[25] (n=151) and missing (n=1) in DESTINY II[11].

*** not recorded in Slezins et al[22] (n=44), DECIMAL[12] (n=38) and DESTINY[7] (n=32) and missing (n=16) in DEMITUR.[25]

OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

Characteristic	Surgery (n=234)	Medical (n=254)	cOR (95% CI)
Aphasia (p=0.45)			
Absent	128	138	4.96 (2.87-8.58)
Present	106	116	5.06 (2.70-9.49)
Sex (p=0.44)			
Female	96	113	4.35 (2.15-8.81)
Male	138	141	5.21 (2.78-9.77)
Age (p=0.45)			
≤50 years	63	68	5.07 (2.06-12.48)
51-60 years	55	4	9.24 (3.08-27.72)
61-70 years	72	8	2.55 (0.55-11.75)
>70 years	43	65	7.27 (2.97-17.80)
NIHSS at baseline (p=0.65)*			
≤20	55	42	3.16 (0.41-24.10)
21-25	72	83	4.25 (2.04-8.87)
>25	83	105	5.75 (2.53-13.10)
Time to randomisation (p=0.53)**			
<24 hours	68	71	7.70 (3.36-17.65)
24-48 hours	78	87	16.01 (3.12-82.07)
>48 hours	17	15	0.66 (0.17-2.61)
Vascular territory (p=0.52)***			
MCA only	97	103	4.85 (2.34-10.07)
MCA + ACA and/or PCA	69	89	5.77 (2.51-13.27)
Summary			4.95 (2.99-8.20)

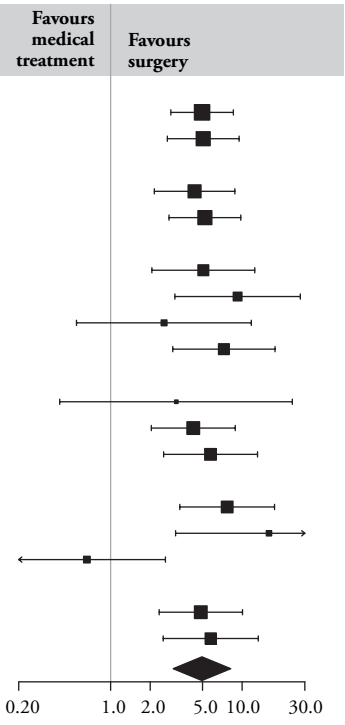

Figure 3. Forest plot of subgroups - shift analysis of the mRS.
P-values for heterogeneity across subgroups are shown (interaction term treatment*subgroup variable). Common Odds ratios are adjusted for age, sex and presence of aphasia (not NIHSS at baseline and time to randomisation). All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'.
* not recorded in Zhao et al.[10] (n=47) and missing (n=1) in HAMLET[8].
** not recorded in DEMITUR[25] (n=151) and missing (n=1) in DESTINY II[11].
*** not recorded in Slezins et al[22] (n=44), DECIMAL[12] (n=38) and DESTINY[7] (n=32) and missing (n=16) in DEMITUR.[25]
OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

DISCUSSION

The results of this meta-analysis of pooled, individual patient–level data suggest that surgical decompression in patients with space-occupying hemispheric infarction strongly reduces the risk of death and increases the chances of a favourable functional outcome (mRS score ≤3) compared with conservative treatment. We found no evidence of heterogeneity of treatment outcome based on the presence of aphasia, stroke severity, age, and involvement of other vascular territories in addition to that of the MCA.

These findings are consistent with the results of the first 2 pooled individual patient–level data analyses of 93 and 109 patients up to 60 years of age treated within 48 hours of stroke onset[8,9] and those of the latest published, aggregated data meta-analyses,

including adult patients of all ages from the same previously published randomised clinical trials.[13,14] However, the sizes of the earlier pooled analyses were too small for reliable subgroup analyses, and meta-analyses of aggregated data cannot properly account for patient-level characteristics that may influence benefit of surgery.[17,18] In the present meta-analysis, individual data of 488 patients from a total of 7 studies[7,8,10-12,22,25] across different continents and health care systems were used, including data from 2 trials[22,25] that had not been reported in full before. As a result of the large sample size of the present study and the use of individual patient data, assessment of the association of surgery with outcomes in the subgroups mentioned was possible.

In clinical practice, aphasia or involvement of an additional vascular territory may be considered a reason to withhold surgical treatment.[26-28] In the current study, however, there was no statistically significant difference in the benefit of treatment across these subgroups. In addition, no evidence of heterogeneity was found in treatment outcomes with increasing time to randomisation when used as a continuous variable. However, only 32 patients were randomised later than 48 hours from symptom onset (Table 5 in the Supplement), and the protocol of only 1 of the included trials[8] allowed treatment of patients beyond this time window. Therefore, treatment outcomes in the first 48 hours should not be extrapolated to patients who present later.

The finding of an apparently consistent benefit of surgical decompression across age groups should be interpreted with caution. These results suggest that treatment is effective in patients up to 60 years, in line with previous meta-analyses.[8,9] In older patients, outcomes were also consistently better in surgically treated patients, and there was no evidence of heterogeneity of treatment outcome with increasing age when used as a continuous variable. However, estimates of treatment outcome in higher age decades were imprecise because of the low numbers of favourable outcomes in the medically treated group (Figure 2 in the Supplement). In absolute terms, only 8% of patients 61 years or older achieved a favourable outcome after surgery in DESTINY II[11] compared with 66% in DEMITUR[25] (Table 6 in the Supplement). This observation cannot be explained on the basis of the available data of this pooled analysis, but it may be a consequence of unreported differences in patient characteristics or differences in adjudication of outcomes on the mRS. For implementation in clinical practice, we suggest consideration of the absolute numbers of patients who reached a favourable outcome in these 2 studies.[11,25]

This study has limitations. Most individual studies were small in terms of number of included patients, and individual patient–level data were not available for 2 previously published small trials,[23,24] which could have added a total of 55 patients and increased the sample size by 11%. In addition, data from some studies could not be used for all subgroup analyses because the relevant variables were missing. It was also not possible to adjust for baseline stroke severity and time to randomisation in the main analyses because each was missing in a single study. Although the sample is large for this specific patient population, the interaction analyses may still have too limited power to detect heterogeneity in treatment outcomes. Finally, the largest study[25] included in the meta-analysis was not registered in a database approved by the International Committee of

Medical Journal Editors and was published after the completion of the meta-analysis, but subsequently withdrawn at the request of the authors. However, a sensitivity analysis in which this trial was excluded did not substantially change the results of the primary and main secondary analyses (Table 2 in the Supplement).

What constitutes a favourable outcome after surgical decompression remains a matter of debate, with some trials[8,12] of surgical decompression for ischaemic stroke defining favourable outcome as an mRS score of 3 or less and other trials[9,10,22] defining it as an mRS score of 4 or less. What is considered acceptable may differ between patients and cultural settings, and the score on the mRS does not fully grasp all dimensions of outcome.[29] Quality-of-life outcomes were not included in this meta-analysis because the use of these instruments was limited in the included trials and the choice of instrument differed. Most importantly, however, such analyses will be strongly affected by survivor bias. Previous systematic reviews[30-32] of randomised clinical trials and nonrandomised studies concluded that most patients surviving surgical decompression experience a reasonable quality of life at long-term follow-up and are satisfied with the treatment received. The choice to perform surgical decompression remains a matter of shared decision-making between the practitioner and the patient and relatives, incorporating information about the treatment and the patient's preferences in each individual case.[29,33]

CONCLUSIONS

In this meta-analysis of patients with space-occupying hemispheric infarction, surgical decompression was associated with a substantial increase in the chance of a favourable outcome. This benefit appeared to be independent of the presence of aphasia, stroke severity, age, and the involvement of other vascular territories in addition to that of the MCA. Data on surgical decompression performed later than 48 hours after stroke onset were too limited for reliable conclusions, and the reported proportions of elderly patients who reached a favourable outcome varied widely between studies.

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SUPPLEMENTAL MATERIAL

Appendices

Supplemental Figures

Supplemental Tables

APPENDIX 1. SEARCH SYNTAXES

MEDLINE (Ovid)

Search performed on: 8-5-2019. Total number of results: 672

1. brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or vertebral artery dissection/ or brain edema/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$ or edema or oedema or edema or swell$ or swollen or herniation)).tw.
4. ((cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 stroke$).tw.
5. 1 or 2 or 3 or 4
6. decompression, surgical/ or decompressive craniectomy/
7. (decompress$ or craniectom$ or hemicraniect$ or hemi-craniect$).tw.
8. 6 or 7
9. Randomized Controlled Trials as Topic/
10. random allocation/
11. Controlled Clinical Trials as Topic/
12. control groups/
13. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
14. (randomized controlled trial or controlled clinical trial).pt.
15. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
16. (random$ or RCT or RCTs).tw.
17. (controlled adj5 (trial$ or stud$)).tw.
18. (clinical$ adj5 trial$).tw.
19. trial.ti.
20. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)).tw.
21. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
22. controls.tw.
23. Meta-Analysis as Topic/ or Meta-Analysis/
24. (meta analy$ or metaanaly$).tw.
25. (systematic adj (review$1 or overview$1)).tw.
26. exp Review Literature as Topic/

27. (cochrane or medline or pubmed or embase or cinahl or science citation index).ab.
28. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
29. (selection criteria or data extraction).ab. and Review/
30. or/9-29
31. 5 and 8 and 30
32. comment/ or letter/ or editorial/
33. exp animals/ not humans.sh.
34. (neonat$ or newborn$ or new born or pediatric or paediatric or birth or infant or infants or perinatal or peri-natal or baby or babies or child or children).ti.
35. decompression sickness/ or decompression sickness.tw.
36. 32 or 33 or 34 or 35
37. 31 not 36

EMBASE (Ovid)
Search performed on 8-5-2019. Total number of results: 1948

1. stroke/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/ or brain edema/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$ or edema or oedema or edema or swell$ or swollen or herniation)).tw.
4. ((cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 stroke$).tw.
5. 1 or 2 or 3 or 4
6. decompression surgery/ or brain decompression/ or decompressive craniectomy/ or craniectomy/
7. (decompress$ or craniectom$ or hemicraniect$ or hemi-craniect$).tw.
8. 6 or 7
9. randomized controlled trial/ or "randomized controlled trial (topic)"/
10. Randomization/
11. Controlled Study/
12. control group/
13. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
14. (random$ or RCT or RCTs).tw.
15. (controlled adj5 (trial$ or stud$)).tw.
16. (clinical$ adj5 trial$).tw.
17. trial.ti.
18. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)).tw.
19. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
20. controls.tw.
21. meta analysis/ or "meta analysis (topic)"/ or "systematic review"/ or "systematic review (topic)"/
22. (meta analy$ or metaanaly$).tw.
23. (systematic adj (review$1 or overview$1)).tw.
24. (cochrane or medline or pubmed or embase or cinahl or science citation index).ab.
25. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search).ab.
26. (selection criteria or data extraction).ab.
27. review.pt. or literature/ or review/
28. 26 and 27

29. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 28
30. 5 and 8 and 29
31. (letter or editorial).pt.
32. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
33. (neonat$ or newborn$ or new born or pediatric or paediatric or birth or infant or infants or perinatal or peri-natal or baby or babies or child or children).ti.
34. decompression sickness/ or decompression sickness.tw.
35. 31 or 32 or 33 or 34
36. 30 not 35

Cochrane Database of Systematic Reviews (CDSR)
Cochrane Central Register of Controlled Trials (CENTRAL)

Database of Reviews of Effects (DARE)
Search performed on 8-5-2019
Total number of results:
6 cochrane reviews
221 clinical trials

#1 [mh ^"brain ischemia"] or [mh "brain infarction"] or [mh ^"hypoxia-ischemia, brain"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh stroke] or [mh ^"vertebral artery dissection"] or [mh ^"brain edema"]

#2 isch*mi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva):ti,ab

#3 (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or "middle cerebral artery" or MCA* or "anterior circulation" or "posterior circulation" or "basilar artery" or "vertebral artery" or "space-occupying") near/5 (isch*mi* or infarct* or thrombo* or emboli* or occlus* or hypoxi* or edema or oedema or edema or swell* or swollen or herniation):ti,ab

#4 ((cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or MCA* or "anterior circulation" or "posterior circulation" or "basilar artery" or "vertebral artery" or "space-occupying") near/5 stroke):ti,ab

#5 #1 or #2 or #3 or #4

#6 [mh ^"decompression, surgical"] or [mh ^"decompressive craniectomy"]

#7 (decompress* or craniectom* or hemicraniect* or hemi-craniect*):ti,ab

#8 #6or#7

#9 #5 and #8

APPENDIX 2. PROTOCOL AND STATISTICAL ANALYSIS PLAN

Surgical decompression for space-occupying hemispheric infarction – an individual-patient meta-analysis
Protocol version 2.3 – 9-10-2019

Background
Individual randomised clinical trials and pooled analyses of data from part of these trials have shown that surgical decompression reduces the risk of death and increases the chance of a favourable outcome in patients with space-occupying hemispheric infarction. However, the individual trials were too small to allow meaningful subgroup analyses based on potentially important prognostic variables. Such prognostic information might be helpful supporting future treatment decisions.

Aim
To assess the effects of surgical decompression in patients with space-occupying hemispheric infarction, and among patient subgroups.

Methods
We will perform an individual-patient meta-analysis of completed randomised trials of surgical decompression for space-occupying hemispheric infarction versus medical treatment. To identify relevant studies, we will perform a systematic review of the literature based on MEDLINE; EMBASE; the Cochrane Central Register of Controlled Trials (CENTRAL); and the Stroke Trials Registry (http://www.strokecenter.org/trials). Investigators of the identified studies will be requested to provide coded individual patient data. By providing these data, investigators will become members of the collaboration to perform and present this meta-analysis. Each study may contribute a maximum of three investigators to the collaboration. This may be added with a maximum of three investigators who will perform the search or statistical analyses.

Eligibility criteria

Patients will be included in the pooled analysis if they were randomised to surgical decompression or medical treatment alone because of space-occupying hemispheric infarction based on the definitions used in the relevant trials. No further in- or exclusion criteria will be used. A sensitivity analysis will be performed in those patients who fulfilled the eligibility criteria of the 2007 pooled analysis of DECIMAL, DESTINY, and HAMLET.

Exploratory analysis and missing data

After collecting individual patient data from all the trials, we will make a uniform database and transform variables to make them as uniform as possible. Subsequently we will perform descriptive and exploratory analyses, prior to the primary analysis. The frequency of missing baseline data and missing outcome data will be assessed. Depending

on the extent of missing data we will choose the most appropriate statistical approach to handle these, for example complete case analysis or multiple imputations. We expect all studies to report the primary outcome, i.e. the score on the modified Rankin Scale (mRS) at 12 months. If this is not the case, we will use the latest recorded mRS score if this is not earlier than 6 months (±30 days) after stroke.

Primary outcome

The primary outcome will be the proportion of patients having a favourable outcome (mRS ≤3) one year after stroke (±30 days).

Secondary outcomes

- Secondary outcomes will include:
- Functional independent outcome defined as mRS ≤2 at one year
- Reasonable outcome defined as mRS ≤4 at one year;
- Death at one year;
- Improvement on the modified Rankin Scale (shift analysis);
- Location of residence at one year (home; rehabilitation service; chronic nursing facility; hospital);
- The above outcomes at 6 months (±30 days);
- Serious adverse events, limited to surgical complications in the first year.

Intention-to-treat (ITT) and on-treatment analyses

The primary analysis will be performed according to the intention-to-treat principle, meaning that all randomised patients will be analysed, regardless of whether they received the intended treatment or not. Also, patients who received another treatment than the treatment they were randomised to ("cross-overs") will be analysed as if they were on the allocated treatment. To complement the ITT analysis, additional on-treatment analyses will be performed.

Primary and secondary analyses

A one-stage approach will be used for primary and secondary analyses, because it offers more flexibility when considering covariates and treatment-covariate interactions. A one-stage IPD meta-analysis pools all data in one regression model. To account for between trial differences, we will use mixed-effects logistic and ordinal logistic regression as appropriate, taking 'trial' and 'treatment' as random effects in all mixed models. Adjustments in all analysis will be made for the following pre-specified covariates: age; sex; baseline stroke severity (NIHSS); the presence of aphasia; and time from stroke onset to randomisation. These covariates will be incorporated into the mixed models as common effects. All results will be reported as crude and adjusted (common) odds ratios (OR) with accompanying 95% confidence intervals. The criterion for statistical significance of the treatment effect will be set at $\alpha = 0.05$ and that for differences between subgroups at $\alpha = 0.10$.

Subgroup analysis

Subgroup analyses will be performed to assess effect modification of the association between surgical decompression and the primary outcome (mRS ±3). The results will also be reported with forest plots.

The following variables will be used for subgroup analyses:

- Age, divided in 4 subgroups: 18-50 years, 51-60 years, 61-70 years and >70 years
- Sex (Male vs. Female)
- Side of the lesion (dominant vs. non-dominant for language). In case it is not known which hemisphere was dominant, the left hemisphere will be considered dominant.
- Vascular territory (MCA alone vs. MCA + ACA/PCA)
- Time to randomisation (per day after stroke onset: days 1 up to day 4 individually and days 5 and later combined)
- NIHSS at baseline (<20, 21-25 and >25)

Subgroup analyses will include the random effect variables 'trial' and 'treatment' terms. In addition, the models will include the interaction term 'treatment*prespecified subgroup variable'. We will use age, time to randomisation and baseline NIHSS as continuous variable. Subgroup analyses will be adjusted, assuming common effects for the pre-specified covariates. The results will be reported visually with forest plots for subgroup-specific treatment effects along with the p-value for the interaction term.

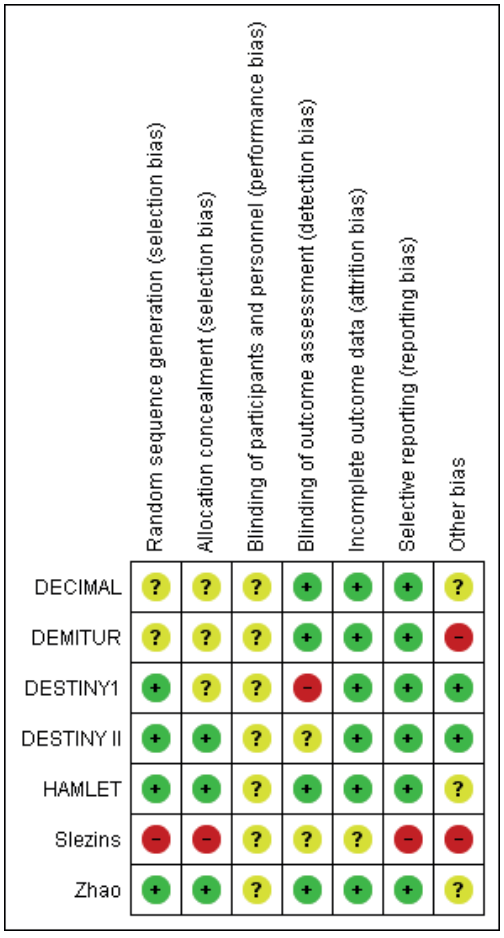
Assessment of risk of bias

Risk of bias will be assessed for all articles with The Cochrane Collaboration's tool for assessing risk of bias. Risk of bias will be assessed by two investigators. In case of disagreement, a consensus meeting will be convened.

Publication

The junior investigators who will perform the search of the literature and statistical analysis and who will write a first draft of the manuscript will be shared first authors. The trial Chief Investigators will be shared last authors.

APPENDIX 3. STUDY CHARACTERISTICS AND RISK OF BIAS ANALYSIS



Summary of risk of bias analysis
+ = low risk of bias; ? = unclear risk of bias; - = high risk of bias

DECIMAL[1]

Study characteristics

Methods	Multicentre, prospective, randomised, open-label trial in France with blinded evaluation of primary end point.
Participants	Patients between 18 and 55 years of age with malignant MCA infarction, within 24 hours and NIHSS of at least 16 with NIHSS item 1a at least 1, MCA territory on CT >50% and DWI infarct volume >145cm^3.
Interventions	Decompressive craniectomy plus standard medical therapy versus standard medical therapy alone.
Outcomes	Primary: mRS 0-3 at 6 months Secondary: survival, mRS 0-3 and Barthel Index >85 at 12 months, NIHSS at 12 months and Stroke Impact Scale (QOL) at 12 months.

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly assigned to receive standard medical therapy alone or standard medical therapy plus decompressive craniectomy and durotomy." Comment: the exact method of sequence generation is not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible patients were randomly assigned to receive standard medical therapy alone or standard medical therapy plus decompressive craniectomy and durotomy." Comment: the exact method of allocation concealment is not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: blinding of participants in this study is virtually impossible, blinding of personnel is not mentioned and therefore probably not performed.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "At all visits after the 12-week visit, a neurologist blinded to the therapeutic arm assignment of the patient assessed the mRS (primary outcome). To keep the investigator neurologist blinded to therapeutic assignment, the head of each patient (in both groups) was covered with a surgical cap" Comment: ensures blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Comment: the study had no drop-outs or withdrawals.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes seem to be reported.
Other bias	Unclear risk	Quote: "On the basis of interim data, the data safety monitoring committee recommended first, to stop the trial, mainly because of slow recruitment and high difference in mortality between the 2 groups, and second, to organize a pooled analysis of the individual data from DECIMAL and the 2 other ongoing European randomised trials of decompressive craniectomy in malignant MCA infarction (DESTINY and HAMLET)." Comment: premature determination based on external reason such as slow recruitment and the intention to organize a pooled analysis do not constitute a high risk of bias, which seems to have been the main reason for trial termination. However, internal factors (high difference in mortality) also seem to have played a role in the decision to stop recruitment, which may constitute a risk of bias.

DEMITUR[2]

Study characteristics

Methods	Prospective, randomised, controlled clinical trial in Turkey.
Participants	Patients between 40 and 80 years of age with a malignant MCA infarct, within 48 hours of onset, NIHSS of at least 16 and NIHSS item 1a at least 1, MCA territory on CT >50% and MRI DWI volume >150cm^3.
Interventions	Decompressive surgery plus conservative treatment or conservative treatment alone.
Outcomes	mRS (primary outcome): mRS 0-3 at 6 and 12 months. Secondary: Mortality at 30 days. Barthel Index 85 or more at 6 and 12 months, NIHSS and Turkish Stroke Impact Scale (SIS) at 12 months.

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information in (non-published) manuscript about sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was performed by a senior neurologist and neurosurgeon (A.S., N.Ö.), and codes were kept in sealed envelopes." Comment: This does not guarantee that the allocation is fully random and non-predictable. In addition, the size of the treatment groups differs considerably (71 vs 80). If envelopes are used, the allocation process should be monitored to preserve concealment of the allocation process, which is not mentioned in the manuscript. In addition to the use of sequentially numbered, opaque, sealed envelopes, investigators should ensure that the envelopes are opened sequentially, and only after the envelope has been irreversibly assigned to the participant. This is not adequately described in the manuscript.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: not described, given the nature of the treatment participants and personnel are very unlikely to be blinded.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "a senior neurologist (E.K or H.S.) who was not involved in screening, randomisation, or patient care, blinded to the therapeutic arm assignment of the patient assessed the mRS (primary outcome) and Barthel Index (secondary outcome). To keep the investigator neurologist blinded to therapeutic assignment, the head of each patient (in both groups) was covered with a surgical cap as described before." Comment: ensures blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Comment: the study had no drop-outs or withdrawals.
Selective reporting (reporting bias)	Low risk	Comment: no protocol available, but it seems as if all outcomes described in method section of the manuscript were reported.
Other bias	High risk	Comment: Since the data were never published in a peer-reviewed journal, there is a risk of publication bias.

DESTINY[3]

Study characteristics

Methods	Prospective, multicentre, randomised, controlled, open, clinical trial in Germany.
Participants	Patients aged 18-60 years, NIHSS >18 (non-dominant hemisphere) and >20 (dominant hemisphere), NIHSS score of at least 1 on item 1a, at least 2/3 MCA territory and at least part of the basal ganglia on CT, with or without ACA/PCA, onset >12 and <36 hours before surgery and <6 hours between randomisation and surgery
Interventions	Surgical plus conservative treatment versus conservative treatment alone (treatment protocol)
Outcomes	Primary outcome: mRS 0-3 at 6 months Secondary outcome: mortality at 30 days. Barthel, NIHSS and mRS at 6 months and 12 months

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Blocked randomisation codes, stratified for centre, were provided by an institute in sealed envelopes." Comment: randomisation codes will probably ensure random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: sealed envelopes (if not transparent) will adequately conceal allocation sequence. If investigators use envelopes, they should develop and monitor the allocation process to preserve concealment. In addition to the use of sequentially numbered, opaque, sealed envelopes, they should ensure that the envelopes are opened sequentially, and only after the envelope has been irreversibly assigned to the participant. It is not described in the article if these conditions were met.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "no blinding was applied" Comment: blinding of participants and personnel is virtually impossible given the nature of the treatment.
Blinding of outcome assessment (detection bias)	High risk	Quote: "no blinding was applied" Quote: "the steering committee also decided to additionally analyse functional outcome, the quality of life as measured by the SF-36 and the Stroke Impact Scale, and aphasia with the Aachen Aphasia Test at 2 and 3 years in a blinded fashion to avoid bias." Comment: outcome assessors for the primary outcome (6 and 12 months) were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Comment: although there were two patients with major protocol violations/crossovers, these are clearly reported and it is stated that the per protocol analysis did not significantly alter the results (the actual per protocol analysis is not published). However, both data from ITT and PP analysis were available for the current IPD meta-analysis and no large differences were observed when comparing ORs for surgery vs medical for all outcomes (mRS 0-3, mRS 0-4 and death). Therefore, risk of bias is probably low.
Selective reporting (reporting bias)	Low risk	Quote: "Because substantial recovery, especially regarding aphasia, activities of daily living, and quality of life, seems to extend into the 3-year period after stroke in patients enrolled in this trial, the steering committee also decided to additionally analyse functional outcome, the quality of life as measured by the SF-36 and the Stroke Impact Scale and aphasia with the Aachen Aphasia Test at 2 and 3 years in a blinded fashion to avoid bias." Comment: the outcomes at 2 and 3 years are not reported in the publication, which could be selective reporting. However, this will not have affected the outcome at 6 months and 1 year. All other outcomes seem to be reported.
Other bias	Low risk	Comment: The trial was interrupted in line with a predefined procedure after reaching significance for the 30-day mortality end point was reached.

DESTINY II[4]

Study characteristics

Methods	Randomised, controlled, open, multicentre trial in Germany.
Participants	Patients 61 years or older, acute unilateral MCA infarction with onset <48 hours, NIHSS>14 (non-dominant hemisphere) or NIHSS>19 (dominant hemisphere) and >2/3 of MCA territory (including the basal ganglia) on brain imaging.
Interventions	Large hemicraniectomy versus conservative treatment with a consensus protocol.
Outcomes	Primary outcome: mRS 0-4 at 6 months. Secondary outcomes: mRS 0-4, survival, NIHSS, Barthel Index, SF 36 (quality of life), EuroQol (quality of life), VAS (quality of life), Hamilton Depression Rating Scale, adverse events and question about agreement to consent in retrospect at 12 months.

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients are randomly assigned to one of the two treatment groups (visit 1): (1) conservative treatment alone or (2) hemicraniectomy plus conservative treatment within 48 h of symptom onset. Randomisation of patients in one of the two treatment groups is carried out online (http://www.randomizer.at). In order to ensure a balanced distribution of both therapies in each participating centre, randomisation is stratified for the centre. In case of failure to randomise a patient online, a 24-h/7-day phone service is provided for alternative randomisation by sealed envelopes." Comment: randomisation by an online randomiser will probably ensure random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "patients are randomly assigned to one of the two treatment groups (visit 1): (1) conservative treatment alone or (2) hemicraniectomy plus conservative treatment within 48 h of symptom onset. Randomisation of patients in one of the two treatment groups is carried out online (http://www.randomizer.at). In order to ensure a balanced distribution of both therapies in each participating centre, randomisation is stratified for the centre. In case of failure to randomise a patient online, a 24-h/7-day phone service is provided for alternative randomisation by sealed envelopes." Comment: Online randomisation service will probably ensure allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Based on the experience of DESTINY, blinding is impossible for treating physicians and patients as well as for most of the investigators." Comment: blinding of participants and personnel was not performed, but is virtually impossible in practice.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "According to the trial protocol, visit 2 is followed by two further visits at six-months (visit 3) and one-year (visit 4) after randomisation. These two visits are part of the trial and are performed by investigators, who were not involved in the patient's treatment. The last follow-up will be after one-year for all arms." Comment: Primary outcome was performed by investigators not involved in the treatment. However, they were not fully blinded, because the scar on the patient's head might still be visible.

Bias	Judgement	Support for judgement
Incomplete outcome data (attrition bias)	Low risk	Quote: "Five DH patients and six control patients were excluded from the per protocol analysis. Reasons for exclusion were crossover to the other treatment in two patients, one from each treatment group. The other patients were excluded because follow-up visits were outside the time frame. For the primary endpoint of the study, the results of the per-protocol population are very similar to the results of the FAS (Whitehead's triangular test, OR = 3.61 in favour of DH, 95% CI: 1.20 to 9.80, P = 0.024, Table S3). Based on the per-protocol population, recruitment would have been stopped for efficacy (Figure S3), as in the primary analysis." Comment: Although there was considerable cross-over and exclusion for the PP analysis, it seems that these are clearly stated and primary outcome was not heavily influenced.
Selective reporting (reporting bias)	Low risk	Comment: All primary and secondary outcomes in the protocol article seem to be reported in the publication of the results.
Other bias	Low risk	Comment: there was no early termination of the study based on interim analysis. A predefined sequential design was used.

HAMLET[5]

Study characteristics

Methods	Multi-centre, open, randomised treatment trial with masked outcome assessment in The Netherlands
Participants	Patients 18-60 years old with acute ischaemic stroke onset within 96 h of start of treatment, start of treatment <3 hours of randomisation, MCA territory on CT >2/3 and oedema, NIHSS at least 16 (right hemisphere) or NIHSS at least 21 (left hemisphere), EMV 13 or less (right hemisphere) or EMV 9 or less (left hemisphere).
Interventions	Decompressive hemicraniectomy within 96 hours of symptom onset and 3 hours of randomisation versus best medical treatment (stroke unit OR intensive care unit with recommendations for best medical treatment).
Outcomes	Primary outcome: mRS score 0-3 at 1 year. Secondary outcomes: Case fatality, Barthel Index, MADRS (depression rating scale) and SF-36 and VAS (quality of life scores) at 1 year.

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to surgical decompression or best medical treatment by use of a computerized randomisation service that was available 24 h a day. Randomisation was based on a published algorithm designed to prevent imbalance between treatment groups." Comment: published algorithm for sequence generation
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to surgical decompression or best medical treatment by use of a computerized randomisation service that was available 24 h a day. Randomisation was based on a published algorithm designed to prevent imbalance between treatment groups." Comment: computerized randomisation service ensures allocation sequence concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: not described, but given the nature of the treatment participants and personnel are very unlikely to be blinded.
Blinding of outcome assessment (detection bias)	Low risk	"To prevent observer bias, patients' scores on the mRS were decided independently by three blinded investigators on the basis of a narrative written by an unblinded and independent study nurse who had visited each patient and their relatives." Comment: blinding of the primary outcome assessor is assured and observer bias is minimalized.
Incomplete outcome data (attrition bias)	Low risk	Quote: "There was no cross-over between the intervention groups, and the follow-up rate was 100%"
Selective reporting (reporting bias)	Low risk	Comment: all outcomes described in the protocol seem to be reported
Other bias	Unclear risk	Comment: inclusion stopped after 64 patients (interim analysis after 50 patients), because it was very unlikely that a statistically significant difference would be seen for the primary outcome measure between the two treatment groups with the planned sample size. Trial termination based on an interim analysis might lead to bias. Although interim analysis after the 30th patient was described in the protocol, the interim analysis after the 50th patient was not.

Slezins et al.[6]

Study characteristics

Methods	A sequential, design-based, prospective, open, randomised, controlled trial in Latvia.
Participants	Patients at least 18 years old, at least 50% of MCA territory on CT and/or MRI, with or without ACA/PCA OR cerebral infarct volume > 145cm3, NIHSS >15, within 48 hours of symptom onset.
Interventions	Decompressive hemicraniectomy versus best medical treatment either stroke unit or intensive care unit, no treatment protocol for conservative treatment.
Outcomes	mRS 0-4 at 1 year.

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients were randomly divided (one-by-one randomisation of patients who fulfilled the inclusion criteria) either into the DCE plus best medical treatment group or the best medical treatment (BMT) alone group." Comment: Sequence generation is not random and predictable if patients are sequentially allocated one-by-one to one of the two treatment groups.
Allocation concealment (selection bias)	High risk	Comment: Sequence generation is not random and predictable if patients are sequentially allocated one-by-one to one of the two treatment groups.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: blinding not mentioned, but probably not performed because this is virtually impossible in practice.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: no information about blinding of outcome assessors is given.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: information about drop-outs and loss to follow-up is not described in the article.
Selective reporting (reporting bias)	High risk	Comment: primary and secondary outcomes are not predefined in the methods section and there is no protocol, so there is risk of selective reporting.
Other bias	High risk	Comments: since only the results of the first 28 patients are published (and 44 patients were treated), there is risk of publication bias.

Zhao et al.[7]

Study characteristics

Methods	Prospective, multicentre, randomised, controlled open trial with blinded evaluation of outcomes.
Participants	Patients aged 18-80 years, <48 hours from symptom onset, GCS (E+M score) 9 or lower, at least 2/3 MCA territory on CT with or without ACA/PCA involvement, development of space-occupying oedema.
Interventions	Early decompressive hemicraniectomy plus standard medical treatment versus standard medical therapies alone.
Outcomes	mRS 0-4 at 6 months. Secondary end points: death at 6 months and 1 year, mRS score at 12 months classified as good (0–4) or poor (5–6), and the 6- and 12-month mRS score dichotomized to 0–3 versus 4–6.

Risk of bias analysis

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "With the adoption of a random number list, eligible patients were centrally randomised to either DHC plus standard medical treatment (the surgical group) or to standard medical treatment alone (the medical group)." Comment: A random number list probably ensures random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The list had been sealed in an envelope before the initiation of the trial and could only be accessed by a single investigator (W. Chen) who was in charge of the randomisation. During the whole course of this trial, the investigator was not involved in patient screening and care, or data gathering and analyses." Comment: investigators who were involved in patient screening were probably concealed to allocation sequence.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: the study was open (e.g., participants and personnel were not blinded). In practice this is virtually impossible given the nature of the therapy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A self-report questionnaire was utilized to collect outcome data, and it was designed with reference to the Barthel Index and a structured system for assigning grades on the mRS. At each follow-up time point, the questionnaires were centrally mailed, emailed, or faxed to the patients. The patients themselves (if possible) or their caregivers (e.g., close relatives or personal nurses), were requested to answer them and reply within 10 days. Non-responders were reminded by telephone. On the basis of the answers, patients' mRS scores were determined independently by two neurophysicians who were unaware of the treatment group assignments (L. Wang and R. Gao)." Comment: outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Comment: there were no crossovers and no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all predefined outcomes seem to be reported, although there is no trial protocol available to compare reported outcomes and planned outcomes.

Bias	Judgement	Support for judgement
Other bias	Unclear risk	Quote: "The trial was designed to enrol up to 110 patients." Quote: "In April 2010, when the 36th patient (about 30 % of the target sample) had reached the 6-month follow-up, the safety monitoring committee did the third interim analysis and found a significant difference between the two treatment groups in the poor outcome of mRS > 4 at this time. Namely, the primary endpoint demonstrated statistical superiority of DHC. Thereafter, on the advice of the safety monitoring committee, the steering board stopped patient enrolment in May 2010 (at that time 47 patients had been recruited)." Comment: Premature termination of the trial is based on internal factors (e.g., superiority at interim analysis), which may constitute risk of bias.

APPENDIX 4. SUMMARY OF TRIAL ELIGIBILITY CRITERIA

See Table 2 in the main text for an overview of trial eligibility criteria. Three trials used upper age limits of 54-60 years,[1,3,5] whereas two others included patients up to the age of 80 years.[2,7] One trial did not define an upper age limit.[6] By contrast, one trial only included patients if they were 61 years of age or older.[4] Time to start of treatment ranged from 30 to 48 hours in six trials[1,2,3,4,6,7] and to 96 hours in one trial.[5] There were small differences in clinical and radiological inclusion criteria. Two trials[1,6] required >50% involvement of the territory of the MCA and five trials[2,3,4,5,7] required at least 2/3 involvement on brain CT. In addition, three trials[1,2,6] required a diffusion-weighted imaging (DWI) lesion volume of at least 145-150 ml. Oedema formation on neuro-imaging was required in three trials.[5-7] All but one trial[7] required a minimum total NIHSS score, ranging from 15 to 19 for non-dominant hemisphere and 16 to 21 for dominant hemisphere infarcts, and a decrease in consciousness, defined as a score of NIHSS item 1a ≥1 in four trials[1,2,3,4] and GCS (Eye + Motor) ≤9 in two trials.[5,7] In one trial a parenchymal intracranial pressure monitoring gauge was implanted in patients randomised to surgery and decompression was only performed if intracranial pressure exceeded 25 mmHg for 1 hour or more, which was applicable to all but one patient.[6]

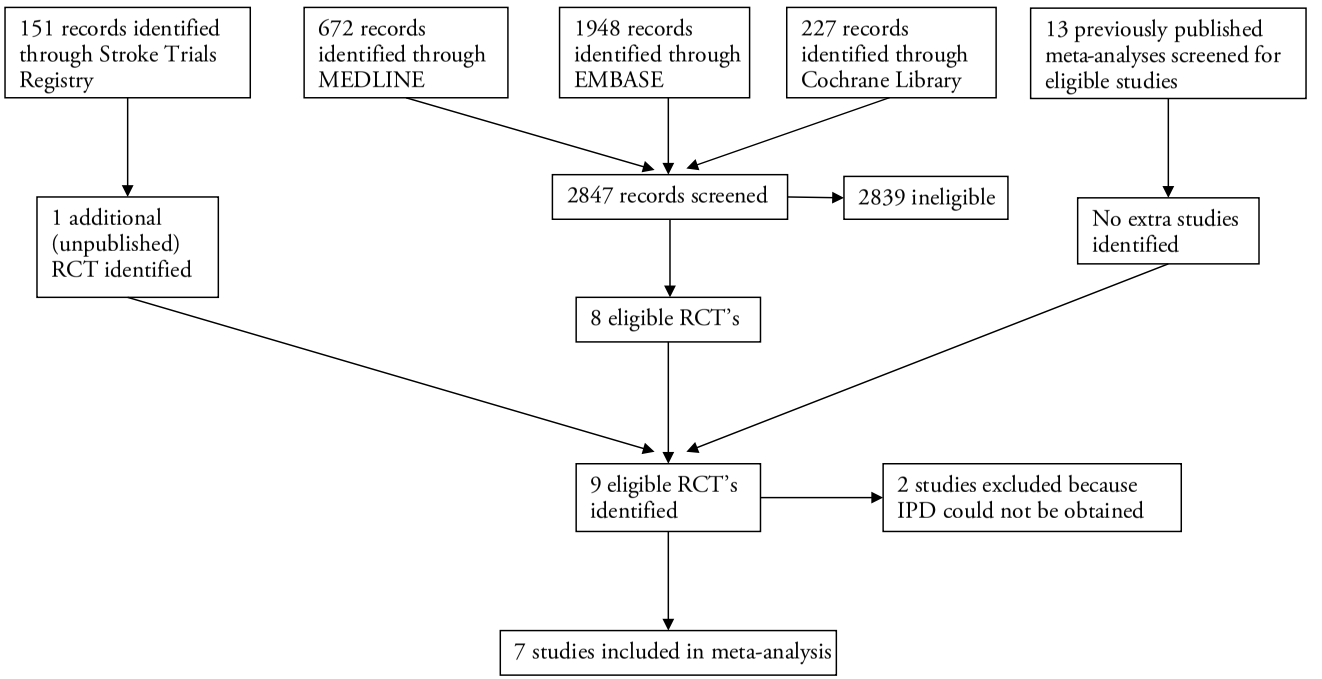


Figure 1. Flowchart of study identification and selection
RCT indicates randomised controlled trial; IPD, individual patient data.

Characteristic	Surgery (n=234)	Medical (n=254)	OR (95%CI)
Aphasia (p=0.43)			
Absent	44/128 (34%)	21/138 (15%)	2.93 (1.38-6.21)
Present	43/106 (41%)	16/116 (14%)	3.26 (1.20-8.85)
Sex (p=0.34)			
Female	32/96 (33%)	16/113 (14%)	2.40 (0.86-6.66)
Male	55/138 (40%)	21/141 (15%)	2.91 (1.23-6.91)
Age (p=0.48)			
≤50 years	33/63 (52%)	19/68 (28%)	3.07 (1.16-8.11)
51-60 years	21/55 (38%)	4/49 (8%)	49.52 (0.21-11480)
61-70 years	19/72 (26%)	8/72 (11%)	1.37 (0.24-7.91)
>70 years	14/44 (32%)	6/65 (9%)	24.29 (0.15-4007)
NIHSS at baseline (p=0.49)*			
≤20	23/55 (42%)	11/42 (26%)	2.48 (0.82-7.49)
21-25	29/72 (40%)	16/83 (19%)	2.51 (1.00-6.30)
>25	29/83 (35%)	8/105 (8%)	5.11 (1.14-22.82)
Time to randomisation (p=0.70)**			
<24 hours	19/68 (28%)	8/71 (11%)	3.60 (0.46-10.63)
24-48 hours	19/78 (24%)	8/87 (9%)	5.00 (1.00-25.01)
>48 hours	3/17 (18%)	5/15 (33%)	0.40 (0.05-3.09)
Vascular territory (p>0.99)***			
MCA only	27/97 (28%)	15/103 (15%)	2.89 (1.11-7.56)
MCA + ACA and/or PCA	30/69 (44%)	14/89 (16%)	1.92 (0.34-10.87)
Summary			2.95 (1.55-5.60)

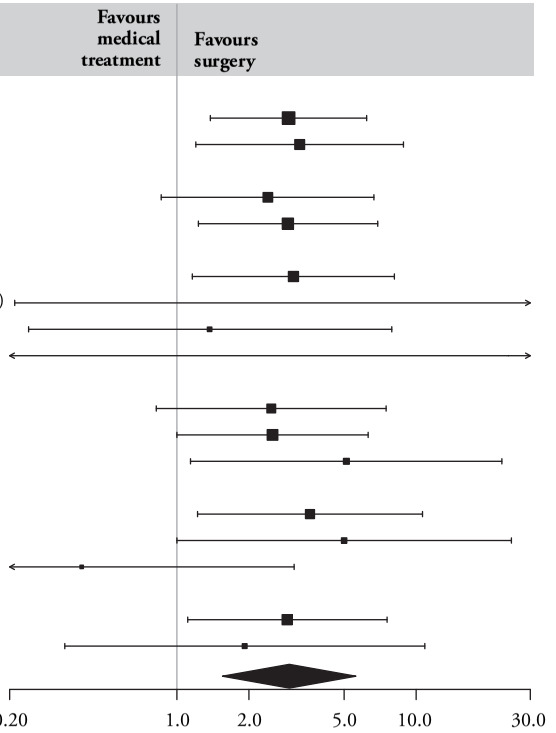


Figure 2. Forest plot of subgroups - mRS ≤ 3 at one year (age subgroup per decade)
P-values for heterogeneity across subgroups are shown (interaction term treatment*subgroup variable). Odds ratios are adjusted for age, sex and presence of aphasia (not NIHSS at baseline and time to randomisation). All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'.
* not recorded in Zhao et al.[7] (n=47) and missing (n=1) in HAMLET.[5]
** not recorded in DEMITUR[2] (n=151) and missing (n=1) in DESTINY II.[4]
*** not recorded in Slezins et al[6] (n=44), DECIMAL[1] (n=38) and DESTINY[3] (n=32) and missing (n=16) in DEMITUR.[2]
OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

Characteristic	Surgery (n=234)	Medical (n=254)	OR (95% CI)
Aphasia (p=0.88)			
Absent	78/128 (61%)	33/138 (24%)	6.09 (3.11-11.91)
Present	65/106 (61%)	26/116 (22%)	5.58 (2.62-11.86)
Sex (p=0.91)			
Female	58/96 (60%)	25/113 (22%)	5.69 (2.54-12.78)
Male	85/138 (62%)	34/141 (24%)	4.98 (2.70-9.17)
Age (p=0.62)			
≤50 years	46/63 (73%)	22/68 (32%)	6.58 (2.17-20.00)
51-60 years	37/55 (67%)	12/49 (25%)	10.83 (2.27-51.68)
61-70 years	38/72 (53%)	15/72 (21%)	2.58 (0.50-13.27)
>70 years	22/44 (50%)	10/65 (15%)	6.57 (2.37-18.21)
NIHSS at baseline (p=0.24)*			
≤20	35/55 (64%)	14/42 (33%)	3.89 (1.31-11.54)
21-25	44/72 (61%)	24/83 (29%)	3.79 (1.70-8.45)
>25	46/83 (55%)	17/105 (16%)	6.25 (2.72-14.09)
Time to randomisation (p=0.78)**			
<24 hours	37/68 (54%)	11/71 (16%)	7.89 (3.05-20.41)
24-48 hours	43/78 (55%)	15/87 (17%)	13.24 (3.13-56.04)
>48 hours	10/17 (59%)	10/15 (67%)	0.54 (0.05-5.93)
Vascular territory (p>0.99)***			
MCA only	58/97 (60%)	28/103 (27%)	5.05 (2.41-10.57)
MCA + ACA and/or PCA	42/69 (61%)	20/89 (23%)	5.97 (2.23-16.02)
Summary			5.34 (3.26-8.74)

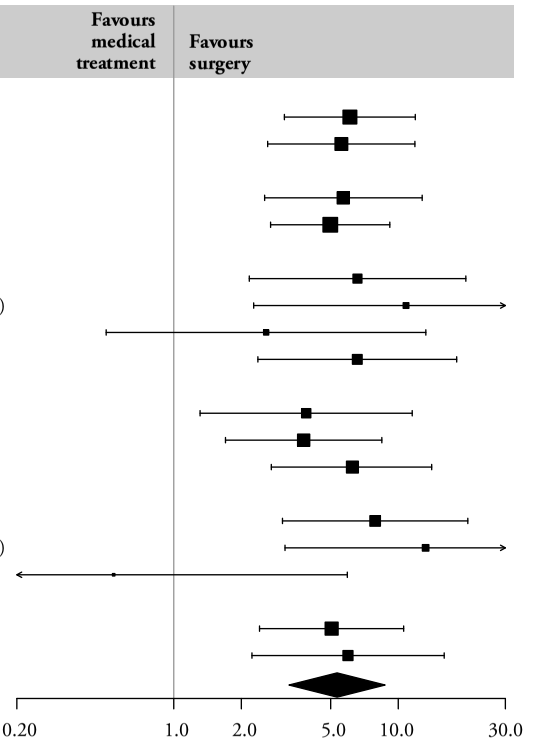


Figure 3. Forest plot of subgroups - mRS ≤ 4 at one year.
P-values for heterogeneity across subgroups are shown (interaction term treatment*subgroup variable). Odds ratios are adjusted for age, sex and presence of aphasia (not NIHSS at baseline and time to randomisation). All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'.
* not recorded in Zhao et al.[7] (n=47) and missing (n=1) in HAMLET.[5]
** not recorded in DEMITUR[2] (n=151) and missing (n=1) in DESTINY II.[4]
*** not recorded in Slezins et al[6] (n=44), DECIMAL1 (n=38) and DESTINY[3] (n=32) and missing (n=16) in DEMITUR.[2]
OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

Characteristic	Surgery (n=234)	Medical (n=254)	OR (95% CI)
Aphasia (p=0.89)			
Absent	36/128 (28%)	96/138 (70%)	0.15 (0.08-0.27)
Present	32/106 (30%)	84/116 (72%)	0.17 (0.08-0.33)
Sex (p=0.91)			
Female	28/96 (29%)	80/113 (71%)	0.16 (0.08-0.34)
Male	40/138 (29%)	100/141 (71%)	0.15 (0.08-0.27)
Age (p=0.68)			
≤50 years	12/63 (19%)	44/68 (65%)	0.12 (0.04-0.33)
51-60 years	14/55 (26%)	35/49 (71%)	0.11 (0.04-0.35)
61-70 years	27/72 (38%)	50/72 (69%)	0.29 (0.08-1.12)
>70 years	15/44 (34%)	51/65 (79%)	0.14 (0.06-0.33)
NIHSS at baseline (p=0.99)*			
≤20	15/55 (27%)	27/42 (64%)	0.18 (0.06-0.51)
21-25	20/72 (28%)	56/83 (68%)	0.18 (0.08-0.38)
>25	29/83 (35%)	81/105 (77%)	0.15 (0.07-0.32)
Time to randomisation (p=0.77)**			
<24 hours	24/68 (35%)	58/71 (82%)	0.11 (0.05-0.26)
24-48 hours	23/78 (30%)	62/87 (71%)	0.06 (0.01-0.43)
>48 hours	6/17 (35%)	5/15 (33%)	1.18 (0.21-5.81)
Vascular territory (p=0.29)***			
MCA only	28/97 (29%)	66/103 (64%)	0.18 (0.09-0.39)
MCA + ACA and/or PCA	18/69 (26%)	65/89 (73%)	0.11 (0.05-0.24)
Summary			0.16 (0.10-0.24)

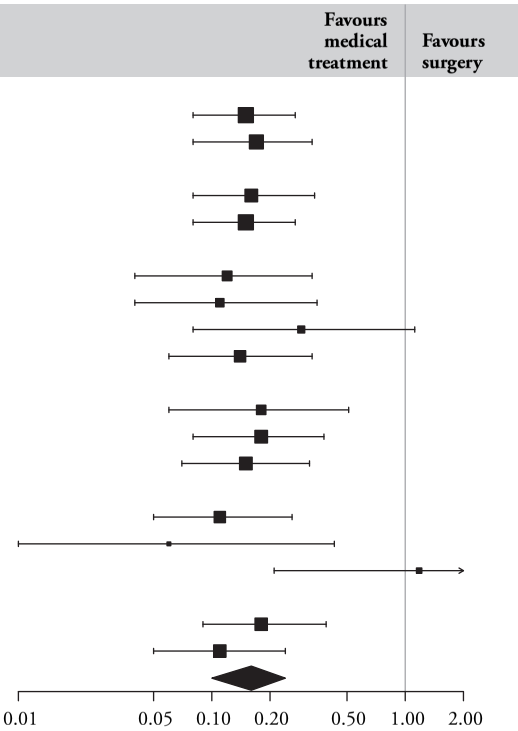


Figure 4. Forest plot of subgroups - death at one year
P-values for heterogeneity across subgroups are shown (interaction term treatment*subgroup variable). Odds ratios are adjusted for age, sex and presence of aphasia (not NIHSS at baseline and time to randomisation). All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'.
* not recorded in Zhao et al.[7] (n=47) and missing (n=1) in HAMLET.[5]
** not recorded in DEMITUR[2] (n=151) and missing (n=1) in DESTINY II.[4]
*** not recorded in Slezins et al[6] (n=44), DECIMAL[1] (n=38) and DESTINY[3] (n=32) and missing (n=16) in DEMITUR.[2]
OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

	Surgery	Medical	OR (95% CI)
All studies (n=488)			
Age ≤60 years	54/118 (46%)	23/117 (20%)	3.52 (1.63-7.58)
Age >60 years	33/116 (28%)	14/137 (10%)	2.56 (0.65-10.07)
DEMITUR excluded (n=377)			
Age ≤60 years	36/89 (40%)	18/83 (21%)	2.55 (1.15-5.65)
Age >60 years	6/75 (8%)	3/90 (3%)	2.28 (0.53-9.80)
Summary			2.95 (1.55-5.60)

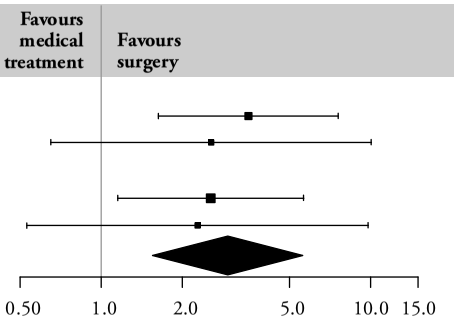


Figure 5. Age subgroups excluding DEMITUR[2] - mRS ≤ 3 at 1 year
Odds ratios are adjusted for sex and presence of aphasia. All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'. OR indicates odds ratio.

Table 1. Baseline characteristics per trial

	DECIMAL[1]	DEMITUR[2]	DESTINY[3]	DESTINY II[4]	HAMLET[5]	Slezins[6]	Zhao[7]
Number of randomised patients	38	151	32	112	64	44	47
Age at randomisation (mean + SD)	43.4 (8.5)	63.7 (11.0)	44.6 (9.1)	70.2 (4.6)	48.7 (9.1)	59.6 (7.6)	61.0 (12.6)
Time to randomisation-hours (mean + SD)	15.6 (6.0)	NA	22.8 (7.3)	29.5 (10.1)	45.1 (24.3)	25.7 (16.5)	23.8 (6.3)
NIHSS at baseline (median + IQR)	21 (18-25)	28 (24-30)	22 (20-24)	23 (20-35)	24 (22-27)	21 (20-24)	NA
Age per decade (%)							
18-50 years	31 (81.6)	22 (14.6)	24 (75.0)	-	38 (59.4)	7 (15.9)	9 (19.1)
51-60 years	7 (18.4)	41 (27.2)	8 (25.0)	-	23 (35.9)	16 (36.4)	9 (19.1)
61-70 years	-	44 (29.1)	1 (3.1)	61 (46.4)	3 (4.7)	18 (40.9)	18 (38.3)
>70 years	-	44 (29.1)	-	51 (53.6)	-	3 (6.8)	11 (23.4)
Male sex (%)	18 (47.4)	94 (62.3)	15 (46.9)	56 (50.0)	38 (59.4)	24 (54.5)	34 (72.3)
Aphasia present (%)	23 (60.5)	74 (49.0)	20 (62.5)	41 (36.6)	24 (37.5)	22 (50.0)	18 (38.3)
Vascular territory (%)							
MCA alone	NA	47 (31.1)	NA	76 (67.9)	46 (71.9)	NA	31 (66.0)
MCA + ACA and/or PCA	NA	88 (58.3)	NA	36 (32.1)	18 (28.1)	NA	16 (34.0)
Missing	38 (100)	16 (10.6)	32 (100)	-	-	44 (100)	-
GCS sum score (median + IQR)	NA	9 (8-11)	10 (8-13)	11 (9-14)	10 (7-12)	9 (7-11)	NA

SD indicates standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; GCS, Glasgow coma score; NA, not available.

Table 2. Sensitivity analysis - published trials only (DEMITUR[2] excluded)

Outcome	Surgery Population	Medical Population	RD (% 95 CI)	Crude OR (% 95 CI)	Adjusted OR (% 95 CI)[a]
mRS ≤ 3 at 1 year	42/164 (26%)	21/173 (12%)	14% (5-24)	2.49 (1.29-4.80); p=.007	2.82 (1.44-5.51); p=.002
mRS ≤ 4 at 1 year	91/164 (56%)	36/173 (21%)	36% (22-51)	5.48 (2.82-10.63); p<.001	5.84 (2.77-12.33); p<.001
Death at 1 year	53/164 (32%)	125/173 (72%)	40% (30-50)	0.17 (0.10-0.27); p<.001	0.16 (0.09-0.27); p<.001

[a] Adjusted for age, sex and presence of aphasia at randomisation. All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'. mRS indicates modified Rankin Scale; RD, absolute risk difference; OR, odds ratio.

Table 3. Sensitivity analysis - published trials with low-moderate risk of bias only (DEMITUR[2] and Slezins et al.[6] excluded)

Outcome	Surgery Population	Medical Population	RD (%95 CI)	Crude OR (%95 CI)	Adjusted OR (%95 CI)[a]
mRS ≤ 3 at 1 year	36 /142 (25%)	21/151 (14%)	12% (2-23)	2.01 (1.08-3.76); p=.03	2.34 (1.17-4.67); p=.02
mRS ≤ 4 at 1 year	84/142 (60%)	35/151 (23%)	39% (22-55)	5.57 (2.67-11.61); p<.001	5.49 (3.29-9.15); p<.001
Death at 1 year	39/142 (28%)	104/151 (69%)	43% (30-56)	0.16 (0.08-0.29); p<.001	0.17 (0.10-0.28); p<.001

[a] Adjusted for age, sex and presence of aphasia at randomisation. All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'. mRS indicates modified Rankin Scale; RD, absolute risk difference; OR, odds ratio.

Table 4. Sensitivity analysis - only trials that reported all five prespecified adjustment variables (DEMITUR[2] and Zhao et al.[7] excluded)

Outcome	Surgery Population	Medical Population	RD (%95 CI)	Crude OR (%95 CI)	Adjusted OR (%95 CI)[a]
mRS ≤ 3 at 1 year	36 /140 (26%)	19/150 (13%)	14% (3-26)	2.40 (1.15-5.01); p=.02	2.32 (1.11-4.86); p=.03
mRS ≤ 4 at 1 year	73/140 (52%)	33/150 (22%)	30% (19-41)	4.06 (2.38-6.91); p<.001	4.73 (2.46-9.09); p<.001
Death at 1 year	39/140 (28%)	104/150 (69%)	37% (27-48)	0.18 (0.11-0.31); p<.001	0.15 (0.08-0.30); p<.001

[a] Adjusted for age, sex, presence of aphasia at randomisation, NIHSS at baseline and time to randomisation. All analyses were performed with a one-stage model with random effects for the variables 'trial' and 'treatment'. mRS indicates modified Rankin Scale; RD, absolute risk difference; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale.

Table 5. Subgroup time to randomisation > 48 hours years per trial - mRS ≤ 3 and mRS ≤ 4 at 1 year

Trial	Outcome mRS≤3		Outcome mRS≤4	
	Surgery	Medical	Surgery	Medical
DESTINY II (n=2)[4]	0/2 (0%)	0/0 (0%)	1/2 (50%)	0/0 (0%)
HAMLET (n=26)[5]	3/11 (27%)	5/15 (33%)	8/11 (73%)	10/15 (67%)
Slezins et al. (n=4)[6]	0/4 (0%)	0/0 (0%)	1/4 (25%)	0/0 (0%)
Total (n=32)	**3/17 (18%)**	**5/15 (33%)**	**10/17 (59%)**	**10/15 (67%)**

Absolute numbers of patients randomised after 48 hours reaching a favourable outcome (mRS ≤ 3) and reasonable outcome (mRS ≤ 4) at 1 year per trial. Randomisation after 48 hours was only covered in the inclusion criteria of HAMLET and the randomisation after this time frame in Slezins et al[6] and DESTINY II[4] should be regarded as protocol violations.

Table 6. Subgroup > 60 years per trial - mRS ≤ 3 at 1 year

Trial	Surgery	Medical
DEMITUR[2]	27/41 (66%)	11/47 (23%)
DESTINY II[4]	4/49 (8%)	3/63 (5%)
HAMLET[5]	0/1 (0%)	0/2 (0%)
Slezins et al.[6]	0/9 (0%)	0/12 (0%)
Zhao et al.[7]	2/16 (12.5%)	0/13 (0%)
Total	**33/116 (28%)**	**14/137 (10%)**

Absolute numbers of patients aged 61 years or older reaching a favourable outcome (mRS ≤ 3) at 1 year per trial.

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6

Chapter 6

Treatment restrictions and the risk of death in patients with ischaemic stroke or intracerebral haemorrhage

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ABSTRACT

Background and purpose
Do-not-resuscitate (DNR) orders in the first 24 hours after intracerebral haemorrhage have been associated with an increased risk of early death. This relationship is less certain for ischaemic stroke. We assessed the relation between treatment restrictions and mortality in patients with ischaemic stroke and in patients with intracerebral haemorrhage. We focused on the timing of treatment restrictions after admission and the type of treatment restriction (DNR order versus more restrictive care).

Methods
We retrospectively assessed demographic and clinical data, timing and type of treatment restrictions, and vital status at 3 months for 622 consecutive stroke patients primarily admitted to a Dutch university hospital. We used a Cox regression model, with adjustment for age, sex, comorbidities, and stroke type and severity

Results
Treatment restrictions were installed in 226 (36%) patients, more frequently after intracerebral haemorrhage (51%) than after ischaemic stroke (32%). In 187 patients (83%), these were installed in the first 24 hours. Treatment restrictions installed within the first 24 hours after hospital admission and those installed later were independently associated with death at 90 days (adjusted hazard ratios, 5.41 [95% CI, 3.17–9.22] and 5.36 [95% CI, 2.20–13.05], respectively). Statistically significant associations were also found in patients with ischaemic stroke and in patients with just an early DNR order. In those who died, the median time between a DNR order and death was 520 hours (interquartile range, 53–737).

Conclusions
The strong relation between treatment restrictions (including DNR orders) and death and the long median time between a DNR order and death suggest that this relation may, in part, be causal, possibly due to an overall lack of aggressive care.

INTRODUCTION

In North American studies, treatment restrictions in the first 24 hours after intracerebral haemorrhage (ICH) have been associated with an increased risk of early death.[1–3] Avoidance of treatment restrictions during the first 5 days after ICH has been associated with a lower 30-day mortality rate than predicted.[4,5] In line with this, American guidelines for the management of ICH advocate aggressive therapy without any treatment restriction in the first days after hospitalization.[6]

However, many uncertainties about the association between treatment restrictions and mortality after stroke remain. First, it is uncertain whether this association is also present in patients with ischaemic stroke. Second, the relation between the timing of treatment restrictions and death remains largely unknown. Few studies have investigated the relation between treatment restrictions installed after the first day and clinical outcomes.[7,8] Third, information on the relation between different types of treatment restriction and clinical outcomes is limited.[8] Furthermore, only a small number of studies have assessed the frequency of treatment restrictions in patients with acute stroke in Europe,[9–12] which may be different from that in North America as a result of demographic or cultural differences.

We assessed the frequency and types of treatment restriction in patients with acute ischaemic stroke or ICH admitted to the stroke unit of a university hospital in The Netherlands. We also assessed whether any association between treatment restrictions and the risk of death at 90 days is dependent on the timing of their instalment.

MATERIALS AND METHODS

We retrospectively studied consecutive patients with acute ischaemic stroke or ICH primarily admitted to the Stroke Unit of the University Medical Center in Utrecht, The Netherlands, between January 2016 and December 2018. Patients were excluded if the final diagnosis was transient ischaemic attack, if they were referred from another hospital, or if they were admitted because of elective treatment (e.g., carotid endarterectomy). In our centre, all stroke patients (including those with ICH) are admitted to the stroke unit, unless mechanical ventilation is required. The study was evaluated by the Medical Ethics Committee of the hospital, and the need for informed consent was waived. To avoid the possibility of unintentionally sharing information that can be used to reidentify private information, individual patient data of this monocentre study will not be made available to other researchers. Methods used in the analysis, such as scripts for statistical packages, are available from the first author upon reasonable request.

Records of eligible patients were manually searched by one investigator (B.K.) and were checked by a second investigator in case of uncertainty (H.R.). Information about patient characteristics (age, sex, ethnicity, and pre-stroke modified Rankin Scale [mRS]), stroke characteristics (type of stroke, score on the National Institutes of Health Stroke Scale, and Glasgow Coma Scale on admission), and functional outcome (score on the mRS

at discharge and at 90 days [±30 days] after stroke onset) was automatically extracted from the patient files and manually complemented with information from the discharge letters. If functional outcome at 90 days was not available, the latest known poststroke mRS score was used. Pre-stroke comorbidity was quantified according to the Charlson Comorbidity Index.[13]

The date and time of presentation in the hospital and date and time of the instalment of treatment restrictions were retrieved from the hospital charts. We coded treatment restrictions as early (installed within 24 hours after hospital admission) or late (installed later). Treatment restrictions were categorized by type on the following ordinal scale: do-not-resuscitate (DNR) order, withhold admission to intensive care unit, withhold curative treatment of complications, and withhold artificial nutrition and hydration (ANH). In principle, treatment restrictions have no effect on patient monitoring, except for no-ANH orders, in which case measurements of vital signs are usually stopped. Whenever possible, the question whether a treatment restriction should be installed is discussed with every patient or the representative on admission to the stroke unit. Treatment restrictions are incremental (e.g., a no-intensive-care-unit order is accompanied by a DNR order) and may be extended by the treating physician at any time during the hospital stay, after consultation with the patient or the representative.

For descriptive analyses, we compared the proportions of patients with a treatment restriction between patients with ischaemic stroke and patients with ICH by the χ^2 test. In addition, we calculated the median and mean times between hospital admission and treatment restrictions and between treatment restrictions and death (if applicable) and used Kaplan-Meier curves to visualize survival.

The primary outcome was death at 90 days (±30 days). We used a time-to-event analysis and compared the survival time between patients with and those without treatment restrictions. To avoid the inclusion of patients who were already moribund on admission in the analyses of the relation between early treatment restrictions and death at 90 days, we used the date and time 24 hours after hospital admission as the start of survival time (t=0). As a consequence, patients who were already moribund at first presentation in the hospital and died within 24 hours were not included in this analysis, and only patients who survived the first 24 hours with a treatment restriction were compared with those who survived without a treatment restriction. We performed separate analyses for patients with ischaemic stroke and for those with ICH and for the 4 types of treatment restriction present at t=0 separately.

To assess the effect of treatment restrictions installed later, we did separate analyses in which t=0 was moved to subsequent days after admission (48 hours, 72 hours, etc.) up to 1 week (168 hours) and compared survival time in patients without treatment restrictions to patients with treatment restrictions present at t=0. In this analysis, the treatment restrictions present at t=0 could be a continuation of early treatment restrictions. In an additional analysis, we selected patients with treatment restrictions installed after 24 hours and compared these with patients without treatment restrictions. For all analysis of late treatment restrictions, we excluded patients who had orders to

withhold artificial fluid and nutrition in place at t=0, as we considered these patients already moribund at this stage.

We used a Cox regression model, with adjustment for the following variables: age, sex, Charlson Comorbidity Index, type of stroke, National Institutes of Health Stroke Scale, and Glasgow Coma Scale (Eye+Motor score) at admission. Survival time was calculated from t=0 to the moment of death (if within 90 days). If patients survived, they were censored at the date of the final follow-up. If follow-up was missing, patients were censored at the latest known moment they were alive. We expressed associations as crude and adjusted hazard ratios (aHRs) with 95% CIs.

RESULTS

Of 1198 patients screened, a total of 576 were excluded from the analysis (Figure I in the Data Supplement). Ninety-four patients were excluded because they were primarily admitted to the intensive care unit. Three-month follow-up was available for 93 of these patients (25 with ischaemic stroke and 68 with ICH). Of the ischaemic stroke patients, 11 (44%) had died and 6 (24%) had reached functional independence (mRS score 0–2). Of the ICH patients, 51 (75%) had died and 2 (3%) had reached a functional independent state.

Six hundred twenty-two patients fulfilled the inclusion criteria and were included in the main analyses. Treatment restrictions were installed in 226 patients (36%), and in 187 of these patients (83%), treatment restrictions were installed in the first 24 hours. In 43 patients, restrictions were extended during the course of the admission. Treatment restrictions were more prevalent in patients with ICH (51%) than in those with ischaemic stroke (32%; P<0.0001). Patients with treatment restrictions were older, more often women, more often had pre-stroke handicap, and had more comorbidity and more severe stroke as illustrated by higher National Institutes of Health Stroke Scale and lower Glasgow Coma Scale scores on admission than patients without treatment restrictions (Table 1). The median time from admission to a DNR order was 3 hours (Table 2). In patients with ICH, 35 of 43 orders (81.4%) to withhold artificial hydration and nutrition were installed within the first 24 hours after hospital admission, versus 8 of 28 orders (28.6%) in patients with ischaemic stroke (Table 2).

Twenty-nine patients (14%) with treatment restrictions reached functional independence (mRS score 0–2) at 90 days versus 248 (64%) patients without treatment restrictions (Figure 1). Patients with more extensive treatment restrictions had a higher risk of death and died earlier than those with a DNR order alone (Figure 2). In those who died after a DNR order, the median time between the order and death was 520 hours (Table 3). After installing a no-ANH order, the mean survival time was 52 hours, with 50% of the patients dying in the first 24 hours.

Thirty patients (5%; 4 with ischaemic stroke and 26 with ICH) died within the first 24 hours after hospital admission. In 26 (87%) of these patients, death or poor prognosis

was perceived imminent after evaluation in the emergency department, and these patients had immediate withdrawal from any curative treatment. They either died in the emergency department or were admitted to the regular ward for end-of-life care. In those who survived the first day, the presence of any treatment restriction at 24 hours was independently associated with increased mortality at 90 days (aHR, 5.41 [95% CI, 3.17–9.22]), even when patients with no-ANH orders were excluded (aHR, 4.57 [95% CI, 2.62–7.99]; Table 4). Hazard ratios for mortality increased with more extensive treatment restrictions.

Table 1. Baseline characteristics.

	Overall (n=622)	**Treatment restriction (n =226)**	**No treatment restriction (n=396)**	**p-value**
Ischaemic stroke	477 (77%)	152 (67%)	325 (82%)	<0.001
Sex (male)	346 (56%)	100 (44%)	246 (62%)	<0.001
Ethnicity				0.225
Caucasian	570 (92%)	208 (92%)	362 (91%)	
Non-Caucasian	52 (8%)	18 (8%)	34 (9%)	
Age (mean + SD)	68.22 (15.78)	79.19 (9.30)	61.96 (15.30)	<0.001
Pre-stroke mRS				<0.001
0	276 (44%)	39 (17%)	237 (60%)	
1	88 (14%)	35 (15%)	53 (13%)	
2	95 (16%)	42 (19%)	53 (13%)	
3	73 (12%)	44 (19%)	29 (7%)	
4	45 (7%)	34 (15%)	11 (3%)	
5	5 (1%)	4 (2%)	1 (0.3%)	
unknown	40 (6%)	28 (12%)	12 (3%)	
Pre-stroke CCI				<0.001
0	232 (37%)	64 (28%)	168 (42%)	
1	174 (28%)	64 (28%)	110 (28%)	
2	82 (13%)	35 (16%)	47 (12%)	
3	65 (10%)	28 (12%)	37 (9%)	
4	22 (4%)	9 (4%)	13 (3%)	
≥5	47 (8%)	26 (12%)	21 (5%)	
GCS (E+M) at admission (median + IQR)	10 [9, 10]	10 [8, 10]	10 [10, 10]	<0.001
NIHSS at admission (median + IQR)	6 [3, 13]	10 [5, 18]	5 [2, 10]	<0.001

SD indicates standard deviation; mRS, modified Rankin Scale; CCI, Charlson Comorbidity Index; IQR, interquartile range; GCS (E+M), eyes and motor score on the Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

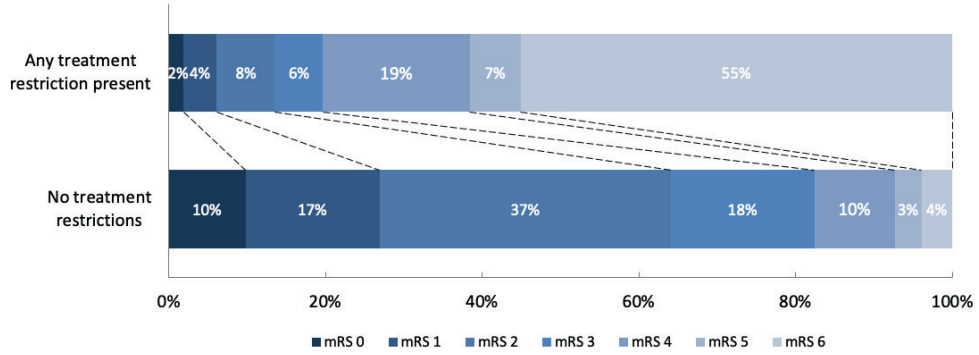

Figure 1. Distribution of score on the modified Rankin Scale (mRS) at 90 days in patients with any treatment restriction present vs no treatment restriction during the entire hospital stay. Patients with orders to withhold artificial fluids and nutrition are excluded.

The presence of just a DNR order at 24 hours after hospital admission was independently associated with death at 90 days (aHR, 2.46 [95% CI, 1.23–4.92]; Table 4). Of the 72 patients with just a DNR order at 24 hours, 20 had died at 90 days follow-up. Of these, 9 were discharged alive, and relevant information about the causes of their deaths was not available. In the 11 patients who died during hospital admission, none of the deaths could realistically have been avoided by cardiopulmonary resuscitation. Rather, their death was preceded by a gradually deteriorating clinical condition (e.g., respiratory insufficiency or progressive loss of consciousness).

Table 2. Number and timing of treatment restrictions.

	N	hours from admission (median, IQR)	<12 hours of hospital admission	<24 hours of hospital admission
All treatment restrictions (n = 278)				
DNR	93	3 (2-17)	68 (73%)	76 (82%)
No ICU	94	6 (2-34)	56 (60%)	67 (71%)
No curative treatment	20	6 (2-220)	11 (55%)	11 (55%)
No ANH	71	4 (2-69)	40 (57%)	43 (61%)
Treatment restrictions in ICH patients (n = 89)				
DNR	18	3 (2-17)	13 (72%)	15 (83%)
No ICU	21	21 (2-66)	9 (43%)	12 (57%)
No curative treatment	7	6 (2-222)	5 (71%)	5 (71%)
No ANH	43	3 (1-6)	35 (81%)	35 (81%)
Treatment restrictions in ischaemic stroke patients (n = 189)				
DNR	75	3 (1-17)	55 (73%)	61 (81%)
No ICU	73	5 (2-24)	47 (64%)	55 (75%)
No curative treatment	13	42 (2-220)	6 (46%)	6 (46%)
No ANH	28	55 (1-138)	5 (18%)	8 (29%)

Treatment restrictions are incremental and only the most extended treatment restriction is shown (e.g., 'no ICU order' also includes a DNR order). IQR indicates interquartile range; DNR, do-not-resuscitate; no ICU, withhold admission to intensive care unit; no curative treatment, no curative treatment of complications; no ANH, no artificial nutrition and hydration.

In patients with ischaemic stroke, all types of early treatment restriction were associated with an increased risk of death at 90 days. In patients with ICH, this association was statistically significant for any treatment restriction after adjusting for baseline confounders but not when no-ANH orders were excluded (Table 4). It should be noted that only 15 patients with ICH had a DNR order only at 24 hours, which is too few to draw conclusions.

We found similar effect sizes when we moved t=0 to subsequent days in the first week after hospital submission (Table 1 in the Data Supplement). Effect sizes were comparable when we only considered patients with treatment restrictions installed later than 24 hours (aHR, 5.36 [95% CI, 2.20–13.05]). For late treatment restrictions, patient numbers were too small to perform subgroup analyses based on the type of stroke.

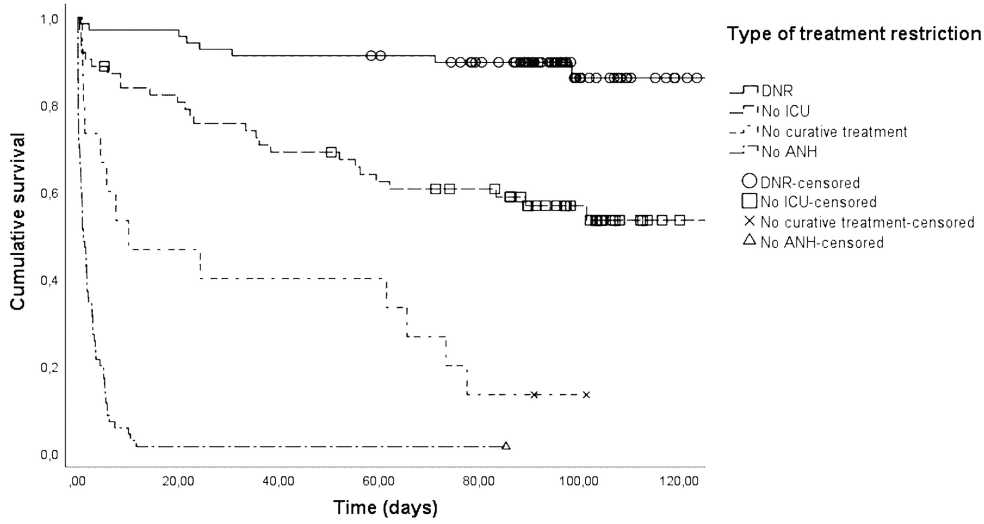

Figure 2. Kaplan Meijer survival curve for patient with different types of treatment restrictions.
t=0 is the moment of instalment of the treatment restriction. In patients with multiple treatment restrictions during hospital admission, only the latest treatment restriction was used. DNR indicates do-not-resuscitate; no ICU, withhold admission to intensive care unit; no curative treatment, withhold curative treatment of complications; no ANH, withhold artificial nutrition and hydration.

Table 3. Survival time (hours) in patients with treatment restrictions who died within 90 days.

	Median (IQR)	Mean (SD)	Minimum	Maximum
All patients				
DNR	520 (53-737)	808 (289)	13	2363
No ICU	537 (66-1327)	741 (138)	8	2435
No curative treatment	182 (33-1477)	618 (208)	21	1862
No ANH	24 (3-78)	52 (8)	0	279

Treatment restrictions are incremental. In patients with multiple treatment restrictions during hospital admission, only the latest treatment restriction was used. IQR indicates interquartile range; SD, standard deviation; DNR, do-not-resuscitate; no ICU, withhold admission to intensive care unit; no curative treatment, no curative treatment of complications; no ANH, no artificial nutrition and hydration.

Table 4. Effect of stroke type and extent of treatment restrictions on the association between early treatment restrictions (<24 hours) and death at 90 days.

	Death at 90 days		Hazard ratio (95% CI)	
	Treatment restriction	No treatment restriction	Crude	Adjusted
Full cohort (n = 592)				
Any treatment restriction	74/158 (47%)	29/434 (7%)	10.14 (6.58-15.61)	5.41 (3.17-9.22)
DNR + no ICU + no curative treatment	56/140 (40%)	29/434 (7%)	8.15 (5.20-12.79)	4.57 (2.62-7.99)
DNR + no ICU	48/130 (37%)	29/434 (7%)	7.26 (4.57-11.52)	4.10 (2.32-7.26)
DNR	20/72 (28%)	29/434 (7%)	5.05 (2.85-8.93)	2.46 (1.23-4.92)
Ischaemic stroke (n = 473)				
Any treatment restriction	49/118 (42%)	22/355 (6%)	9.28 (5.59-15.38)	6.59 (3.55-12.22)
DNR + no ICU + no curative treatment	42/111 (38%)	22/355 (6%)	8.20 (4.89-13.77)	6.01 (3.17-11.39)
DNR + No ICU	39/106 (37%)	22/355 (6%)	7.81 (4.62-13.19)	5.63 (2.95-10.73)
DNR	16/57 (28%)	22/355 (6%)	5.56 (2.91-10.59)	3.93 (1.80-8.59)
Intracerebral haemorrhage (n = 119)				
Any treatment restriction	25/40 (63%)	7/79 (9%)	11.92 (5.12-27.77)	3.79 (1.16-12.34)
DNR + no ICU + no curative treatment	14/29 (48%)	7/79 (9%)	7.92 (3.19-19.71)	1.50 (0.37-6.17)
DNR + No ICU	9/24 (38%)	7/79 (9%)	5.55 (2.06-14.94)	0.71 (0.13-3.77)
DNR	4/15 (27%)	7/79 (9%)	3.48 (1.02-11.91)	0.17 (0.014-2.08)

Patients who died <24 hours are excluded (n = 30 for full cohort). Hazard ratios are adjusted for age, sex, CCI, comorbidity index, NIHSS ad admission, GCS and admission and stroke type (if applicable). DNR indicates do-not-resuscitate; no ICU, withhold admission to intensive care unit; no curative treatment, no curative treatment of complications; no ANH, no artificial nutrition and hydration.

DISCUSSION

In this study, at a stroke unit of a university medical centre in The Netherlands, about one-third of the patients admitted with ischaemic stroke or ICH had a treatment restriction installed during hospital admission. Having any treatment restriction was independently associated with an increased risk of death at 90 days. The large majority of patients with a DNR or no-intensive-care-unit order survived up to 90 days, and in those who died, the median time from their instalment to death was about 3 weeks, demonstrating that these orders were not only placed in patients in whom death was already imminent.

The prevalence of treatment restrictions in our cohort was comparable to that in a study in stroke patients in the United Kingdom (34%),[10] and the prevalence in patients with ICH was comparable to that in an American study (45%)[1] but different from those in Finnish (35.5%)[9] and Chinese studies (8.4%).[14] This may be explained by geographic or cultural differences but also by the use of different definitions of treatment restrictions.

No earlier study has assessed the association between early treatment restrictions and the risk of death in patients with ischaemic stroke alone. In these patients, we found that all types of early treatment restriction (even just the instalment of a DNR order) were associated with an increased risk of death at 90 days. Not surprisingly, the relation appeared to become stronger with more extensive restrictions. Previous studies focused on the association between treatment restrictions and mortality after ICH. In contrast to these studies,[1,2,12] we found no statistically significant relation between treatment restrictions and mortality at 90 days in ICH patients after adjusting for baseline prognostic factors and when patients with an order to withhold artificial administration of fluids and nutrition were excluded. This may be due to the limited number of patients, in part, caused by the exclusion of patients who died within the first 24 hours of admission.

In addition, most previous studies have only assessed the association between treatment restrictions installed in the first day after hospital admission and mortality at 90 days. We found that this association was comparable for treatment restrictions installed later during the first week after hospital admission. One older cohort study reported increasing in-hospital mortality rates for each successive day on which a DNR order was written during the first 7 days after admission.[7] However, this study did not use a time-to-event analysis, and the increasing mortality rates and effect sizes per day suggest that patients who had died on previous days were still included in the analysis of the consecutive days.

As treatment restrictions are likely to serve as a marker for adverse prognostic factors, we were not surprised to find that functional outcome was worse and survival time was shorter in patients with more extensive treatment restrictions. However, the strong and consistent relationship between the presence of treatment restrictions and death found in our and in previous studies after correcting for important prognostic factors, even when considering only a DNR order, remains remarkable.[1–3,7,15] Our finding that

about one-third of patients with a DNR order were functionally independent at 90 days demonstrates that these orders are not exclusively installed in patients with a poor prognosis, and the long survival time in those who died after a DNR order suggests that their instalment is not just a preterminal measure in moribund patients. In addition, a previous study that stratified stroke patients by prognostic factors found that the impact of a DNR order on mortality was greatest among patients with a more favourable outcome.[7] In our view, this suggests that the relationship between a DNR order and death may, in part, be causal.

There are several possible other explanations for higher mortality rates in patients with treatment restrictions. Even though we adjusted for prognostic variables, important but unknown confounders for the relationship between treatment restrictions and death may not have been captured. Moreover, treatment restrictions might be a reflection of patient's advanced wishes or family preference to refrain from life-prolonging interventions after a disabling stroke. Unfortunately, we could not use information about advance directives in our analysis, as this is not systematically collected in our stroke database or specifically documented in the hospital charts. However, advance directives are infrequent in The Netherlands: it has been estimated that around 7% of the general population has an advance directive.[16] In addition, a previous study in The Netherlands reported that around 2% of the patients with severe stroke admitted to the stroke unit had a treatment restriction in place before admission.[17]

It has also been suggested that treatment restrictions might be a proxy for overall lack of optimal care, creating a ripple effect with restrictions leading to an overall milieu of nihilism that may influence attitudes of care for patients beyond the DNR orders themselves.[18] Previous studies have demonstrated that patients with intracerebral hemorrhage[9] or ischaemic stroke[10] who have a DNR order are less likely to be treated on a stroke unit or by specialist teams and, therefore, may indeed receive less optimal care. There is a potential risk of self-fulfilling prophecies if patients predicted to have a poor outcome have early limitations in care or withdrawal of support and subsequently die.[19,20] It has been emphasized that clinicians should be aware of the limited accuracy of models predicting outcomes after ischaemic stroke or ICH and on the potential impact of subsequent early treatment restrictions on the overall aggressiveness of care.[21]

The results of our study should raise further awareness of the potential of an increased risk of death as an undesired side effect of treatment restrictions installed in the early phase after stroke and highlight the importance of avoiding limitations in care beyond that of the treatment restriction itself.

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SUPPLEMENTAL MATERIAL

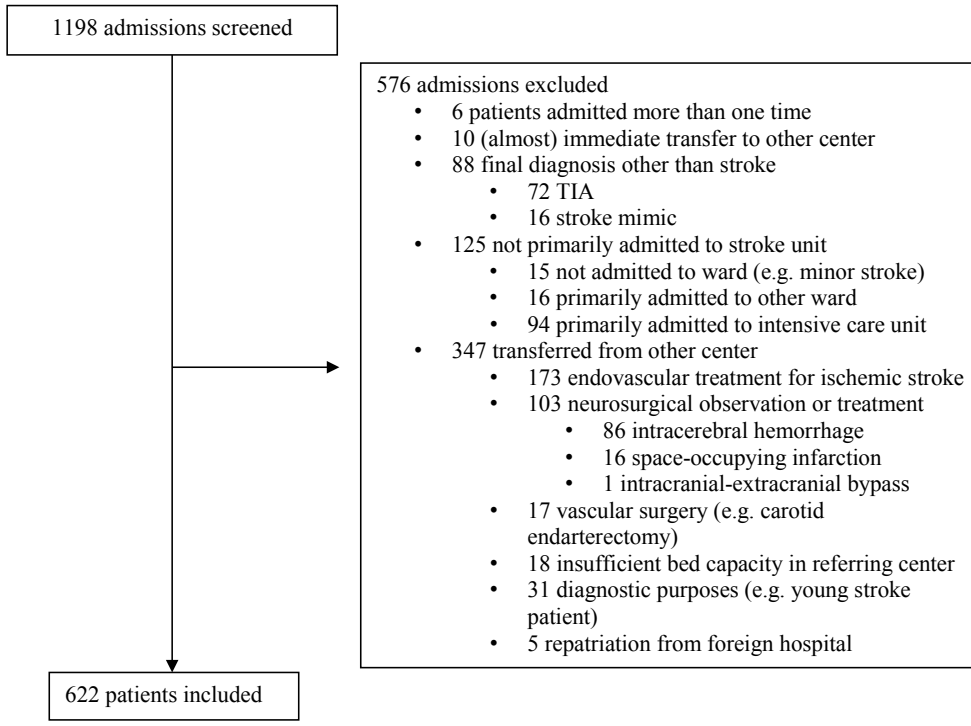

Figure 1. Flowchart showing reasons for exclusion of patients.

Table 1. Effect of timing of treatment restriction on the association between late treatment restrictions (between 24 hours and 1 week) and death at 90 days.

Time after admission (t=0)	Patients excluded		Mortality at 90 days		
	Dead at t=0	No ANH at t=0	Treatment restriction	No treatment restriction	Adjusted HR* (95%CI)
Presence of treatment restrictions (early and late combined)					
24 hours	30	18	56/140 (40%)	29/434 (7%)	4.57 (2.62-7.99)
48 hours	40	17	54/148 (36%)	22/417 (5%)	5.04 (2.78-9.14)
72hours	48	16	50/147 (34%)	19/411 (5%)	4.91 (2.63-9.19)
96 hours	57	14	46/145 (32%)	16/406 (4%)	5.50 (2.82-10.73)
120 hours	61	13	43/143 (30%)	16/405 (4%)	4.89 (2.49-9.61)
144 hours	62	14	42/142 (30%)	15/404 (4%)	5.16 (2.59-10.30)
168 hours	70	10	39/136 (29%)	14/402 (3%)	5.19 (2.53-10.67)

HR's are adjusted for age, sex, Charlson comorbidity index, NIHSS at admission, GCS at admission, stroke type and mRS at discharge (for treatment restrictions at discharge). HR indicates hazard ratio; no ANH, no artificial nutrition and hydration.

Chapter 7

Quality of dying after acute stroke

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ABSTRACT

Introduction
There is a lack of evidence concerning the palliative needs of patients with acute stroke during end-of-life care. We interviewed relatives of patients who deceased in our stroke unit about the quality of dying and compared their experiences with those of nurses.

Patients and methods
Relatives of 59 patients were interviewed approximately 6 weeks after the patient had died. The primary outcome was a score assessing the overall quality of dying on a scale ranging from 0 to 10, with 0 representing the worst quality and 10 the best quality. We investigated the frequency and appreciation of specific aspects of the dying phase with an adapted version of the Quality of Death and Dying Questionnaire. The nurse who was most frequently involved in the end-of-life care of the patient completed a similar questionnaire.

Results
Family members were generally satisfied with the quality of dying (median overall score 8; interquartile range, 6-9) as well as with the care provided by nurses (9; 8-10) and doctors (8; 7-9). Breathing difficulties were frequently reported (by 46% of the relatives), but pain was not. Unsatisfactory experiences were related to feeding (69% unsatisfactory), inability to say goodbye to loved ones (51%), appearing not to have control (47%), and not retaining a sense of dignity (41%). Two thirds of the relatives reported that palliative medication adequately resolved discomfort. There was a good correlation between the experiences of relatives and nurses.

Discussion and Conclusion
Most relatives were satisfied with the overall quality of dying. Negative experiences concerned feeding problems, not being able to say goodbye to loved ones, sense of self control and dignity, and breathing difficulties. Experiences of nurses may be a reasonable and practical option when evaluating the quality of dying in acute stroke patients.

INTRODUCTION

Approximately half of stroke-related deaths occur in hospital,[1] and palliative and end-of-life care are therefore common practice at a stroke unit.[1,2,3] Research on end-of-life care has mainly focused on cancer patients, whereas patients dying as a consequence of stroke may have different palliative needs.[4,5] An American Heart Association statement concluded that there is a striking lack of evidence concerning optimal palliative care practices in patients with acute stroke,[1] including a large knowledge gap regarding specific needs of dying stroke patients and their families.[2,6] Pain, agitation and dyspnoea have been reported as the main symptoms in dying stroke patients,[1] but studies that systematically analysed symptoms in these patients are scarce and are mostly based on review of symptoms reported in hospital charts.[7] Impairments in communication with the patient are a frequent complicating factor in the interpretation of symptoms of dying stroke patients.[2,6] Healthcare professionals therefore often include the experience of family members when assessing if palliative needs have been met.

In the current study, we aimed to assess the experience of family members about symptoms during the terminal phase and the 'quality of dying' in patients who deceased in our stroke unit. We also ascertained the opinion of nurses about the quality of dying in the same patients.

METHODS

We prospectively included consecutive patients with acute ischaemic stroke, intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH) from October 2017 to June 2020 who died after a decision to withdraw life-sustaining measures and to start end-of-life care on the stroke unit of the University Medical Center Utrecht, a tertiary referral centre in The Netherlands. In this stroke unit, patients in whom life-sustaining measures are withdrawn are being cared for in a single room. Palliative care is primarily provided by nurses, residents in neurology and supervising neurologists. A palliative care consultative service is available upon request. Patients in whom no decision to start palliative care was made before death were excluded from this study.

The physician who had overseen the end-of-life care sent the first contact person of the deceased patient a letter of condolence approximately four weeks after the patient had died. This letter included an introduction of the study and a do-not-contact-me return form. Subsequently, relatives who did not return the do-not-contact-me form were contacted by telephone by one of two trained research nurses who asked permission to be interviewed at home approximately two weeks later. Informed consent was obtained from all relatives for the use of the information they provided during the interview. During the COVID-19 outbreak, interviews were performed by telephone. The Medical Ethics Committee of our hospital waived approval of the study under the Dutch Medical Research Involving Human Subjects Act.

The questionnaires that were used during the interviews can be found in the Supplemental Material. The research nurse started the interview by asking relatives the question: 'Overall, how would you rate the quality of dying of your family member on a scale ranging from 0 to 10, with 0 representing the worst quality and 10 the best?' In addition, relatives were asked to rate the care provided by nurses, the care provided by doctors, the quality of communication and support provided by healthcare professionals, as well as to assess the letter of condolence and the interview on the same 0–10 scale. Relatives were also asked to score the length of the end-of-life phase after the decision to stop all curative treatments on the same scale, with 0 representing that the process was 'much too short' and 10 representing that it was 'much too long'. Subsequently, the research nurse and relatives completed the ICU version of the Quality of Death and Dying Questionnaire (QODD-ICU).[8] The QODD is a validated questionnaire developed for palliative research that may be used for interviewing bereaved significant others after death.[9] The QODD-ICU consists of 25 of the original 31 questions that evaluate symptoms, experiences and perceptions about the dying process in the last week of life.[10] Each item of the QODD instrument consists of two parts: a frequency component and a quality component. The first assesses the frequency of a particular symptom or experience. Depending on the item, family members are asked to indicate frequencies across a range from 0 (none of the time) to 5 (all of the time) or dichotomously with yes (event/experience occurred) or no (event/experience did not occur). In the second part, the family members are asked how the particular symptom or experience affected the quality of dying on a 0–10 scale: 0 indicates a terrible experience and 10 an almost perfect experience.[8] Family members can skip questions if they feel that they cannot rate the experience or if an item was not applicable.

To better reflect the situation of our population, we disregarded QODD-ICU items on mechanical ventilation, dialysis and healthcare costs. We added questions about whether the patient was short of breath and whether palliative medication successfully relieved signs of discomfort. Additionally, the nurse who had cared most for the patient in the end-of-life phase was asked to fill out the adapted QODD-ICU for nurses within 7 days after the death of the patient (Supplemental Material).[11]

We collected information from the medical records about patient characteristics (age, sex, pre-stroke functional dependency (modified Rankin Scale)); stroke characteristics (dates and times of onset and hospital admission, stroke type, stroke severity (National Institute of Health Stroke Scale)) and details about end-of-life care (date and time of start of end-of-life care, location where this was started (stroke unit, emergency room or ICU), use of opioids or benzodiazepines, moment of death). The start of the end-of-life phase was defined as the moment the treating physician had made a note in the patient record that life-sustaining measures were withdrawn and that the goal of further care was aimed at optimizing patient comfort.

The primary outcome was the relatives' experience of the quality of dying, defined as the score given in response to the first overall question. Secondary outcomes were (1) the nurses' opinion on the quality of dying, defined as their score on the first overall question; (2) the frequency component of each item of the QODD-ICU scored by either relatives

or nurses; and (3) the quality rating component of individual items of the QODD-ICU scored by either relatives or nurses. For descriptive analysis of symptoms of discomfort, we dichotomized the frequency component of each item of the QODD-ICU to 'never or sometimes' (score 0–2) and 'most or all of the time (score 3–5)' and dichotomized the quality rating component to 'unsatisfactory' (score 0–5) and 'satisfactory' (score 6–10), in line with the general grading system in Dutch schools, where scores of six or higher are considered satisfactory. We disregarded a QODD-ICU item if the quality component was scored by less than half of the relatives, as we considered these items not to be representative for our population. In contrast to previous studies, we therefore decided not to use the QODD-ICU total (average) score as an outcome in our study, which is calculated by adding up the scores of the quality rating components of the individual items and dividing this by the number of items answered.[8] All scores are displayed as median with corresponding IQR. All percentages are displayed as proportion of the number of valid responses to each question.

Differences in scores between relatives and nurses was analysed with the Wilcoxon signed-rank test. If relatives declined to participate or could not be contacted, only the nurses' scores were used. To assess potential selection bias, we compared patient characteristics between participating and non-participating relatives. In addition, we compared the nurses' score on the summary question between patients with a relative who participated and those without using the Mann–Whitney U test.

To analyse the relation of patient and clinical characteristics on the primary outcome, we used a linear regression model. The following independent variables were used for univariate analysis: age, sex, stroke type (ischaemic stroke, ICH or SAH), length of the end-of-life phase (in hours), time between hospital admission and withdrawal of life-sustaining measures (in hours), use of opioids (yes/no), use of benzodiazepines (yes/no) and the level of consciousness at start of palliative phase (assessed with the Glasgow Coma Scale). We hypothesized that symptoms related to uncomfortable breathing would be the most frequently reported sign of discomfort and would be the main target for palliative medication. Therefore, we performed an additional regression analysis with the same independent variables and the score on the quality rating component of the QODD-ICU item about breathing comfort as the dependent variable. Variables were included in multivariate models if $p < 0.10$ in the univariate analysis.

We used Pearson correlation coefficient to analyse the relationship between the length of the end-of-life phase (in hours) and the relatives' opinion of the duration of the end-of-life phase (score 0–10).

The criterion for statistical significance was set at $\alpha = 0.05$. No adjustments were made for multiplicity of testing, as we considered the analyses hypothesis-generating.

RESULTS

During the study period, 105 patients died on the stroke unit after a decision to withdraw life-sustaining measures and to start end-of-life care. Relatives of 59 patients agreed to be interviewed. Relatives of 36 patients declined participation and six relatives could not be contacted (Figure 1). Palliative care consultants were involved in the care of six of the 59 patients (10%). Baseline characteristics were balanced for patients whose relatives were interviewed and those who were not (Table 1). In addition, the nurses' overall scores for quality of dying were not different for participating and non-participating relatives (p = 0.56).

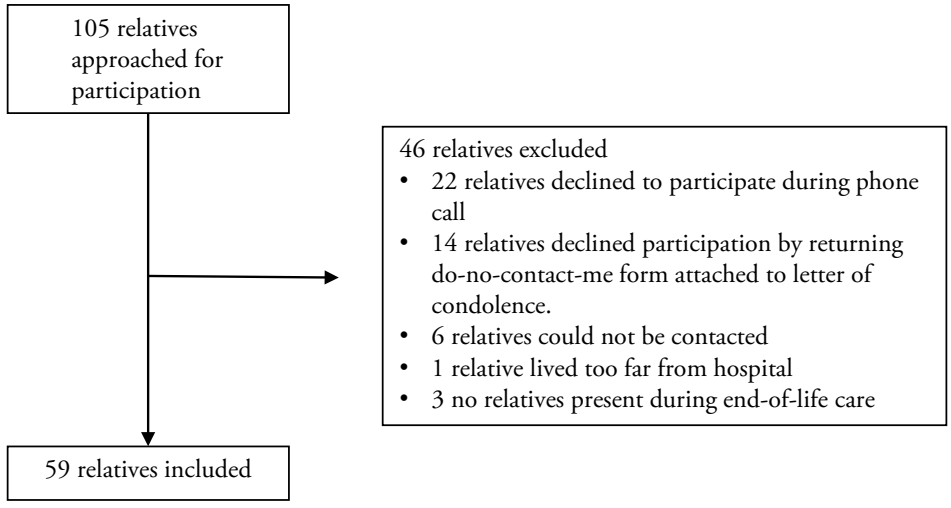

Figure 1. Trial profile

Six QODD-ICU items could not be included in the analysis because they were completed by less than half of the relatives. The deleted QODD items included questions about whether the patient felt at peace with dying; laughed and smiled; cleared up bad feelings with others; had a spiritual ceremony before death; had discussed preferences for end-of-life care or had funeral arrangements in order.

Table 1. Baseline characteristics.

	All patients (n =105)	Relatives interviewed (n =59)	Relatives not interviewed (n =46)	p-value
Age (mean + SD)	75.8 (12.0)	77.0 (12.3)	74.3 (11.6)	0.24
Male sex (%)	48 (46%)	24 (41%)	24 (52%)	0.33
Type of stroke (%)				0.95
Ischaemic stroke	44 (42%)	24 (41%)	20 (44%)	
Intracerebral haemorrhage	44 (42%)	25 (42%)	19 (41%)	
Subarachnoid haemorrhage	17 (16%)	10 (17%)	7 (15%)	
Pre-stroke mRS (%)				0.26
0	23 (22%)	14 (24%)	9 (20%)	
1	11 (11%)	4 (7%)	7 (15%)	
2	19 (18%)	11 (19%)	8 (17%)	
3	19 (18%)	11 (19%)	8 (17%)	
4	11 (11%)	9 (15%)	2 (4%)	
Unknown	22 (21%)	10 (17%)	12 (26%)	
Length EOL-phase (hours; Median + IQR)	24.7 (6.0-45.6)	19.5 (5.5-48.4)	31.4 (6.4-44.4)	0.46
Location start of EOL-care				0.56
Stroke unit	55 (52%)	30 (51%)	25 (54%)	
Intensive Care Unit	22 (21%)	11 (19%)	11 (24%)	
Emergency department	28 (27%)	18 (31%)	10 (22%)	
NIHSS at admission (median + IQR)	21 (16-34)	22 (17-37)	21 (13-29)	0.49
GCS at admission (Median + IQR)	9 (5-13)	9 (4-11)	10 (6-13)	0.27
Latest GCS before EOL-care (median + IQR)	6 (4-9)	6 (4-9)	7 (5-8)	0.66
Use of opioids used (%)	78 (75%)	45 (76%)	33 (73%)	0.91
Use of benzodiazepines (%)	30 (29%)	15 (25%)	15 (33%)	0.56

EOL indicates end-of-life; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale

Experiences of relatives

Overall, the relatives were satisfied with end-of-life care (median overall score 8; IQR, 6–8), with 50 relatives (85%) scoring the overall experience as satisfactory (Figure 2). Both nursing care (9; 8–10) and care provided by doctors (8; 7–9) were highly appreciated, as well as the communication, information and support by the medical personnel (8; 8–9, two relatives (4%) unsatisfactory). Thirty-one (53%) relatives reported that the end-of-life phase was neither too long nor too short (score of 4–6). The median length of the end-of-life phase in these patients was 14 h (IQR 4–31). Five (9%) relatives found the dying phase too short (score of 0–2, median length end-of-life phase 10 h; IQR 4–33), and 16 (27%) found this too long (score of 8–10, median length end-of-life phase 32 h; IQR 14–101). The opinion of relatives concerning the duration of the end-of-life phase correlated with the actual length of this phase in hours (r = 0.363; p = 0.005).

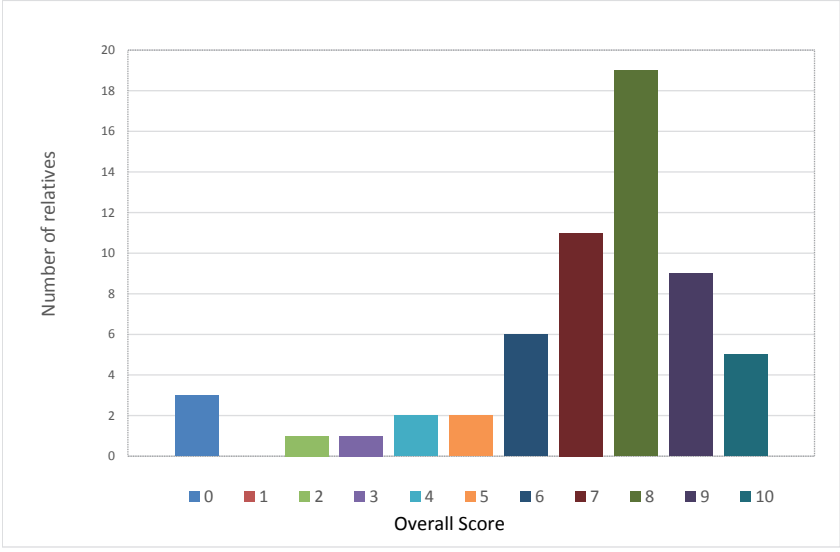

Figure 2.

Table 2. Summary score and scores on the quality rating component of QODD items.

	Relatives (n = 59)			Nurses (n = 59)			
	N	Median (IQR)	Score 0-5 (%)*	N	Median (IQR)	Score 0-5 (%)*	p-value
Overall summary score	59	8 [6,8]	9 (15)	56	7 [6,8]	10 (18)	0.18
QODD items							
Appeared to have pain under control	56	8 [6,9]	10 (18)	55	7 [7,8]	6 (11)	0.56
Appeared to have control over the situation	53	6 [3,7]	25 (47)	48	7 [5,8]	15 (31)	<0.01
Was able to feed him/herself	35	5 [5,6]	24 (69)	43	7 [5,8]	11 (26)	<0.01
Appeared to breath comfortably	56	6 [4,8]	21 (38)	55	6 [4,8]	21 (38)	0.35
Appeared to be short of breath	57	6 [4,8]	18 (32)	54	6 [5,8]	18 (33)	0.74
Medication appeared to relieve symptoms of discomfort	44	8 [6,8]	6 (14)	48	8 [7,8]	9 (19)	0.89
Was unafraid of dying	45	8 [6,9]	11 (24)	44	8 [7,9]	7 (16)	0.53
Appeared to keep dignity and self-respect	32	7 [4,8]	13 (41)	41	7 [5,8]	12 (29)	0.85
Spent time with family/friends	59	9 [8,10]	1 (2)	55	9 [8,10]	8 (15)	0.06
Spent time alone	58	9 [8,10]	3 (5)	54	9 [6,10]	9 (17)	0.16
Was touched/hugged by loved ones	57	9 [8,10]	2 (4)	50	8 [7,9]	4 (8)	0.16
Said goodbye to loved ones	53	5 [2,7]	27 (51)	39	5 [3,6]	28 (72)	0.94
Had visit(s) from spiritual advisor	31	8 [6,9]	3 (10)	33	7 [5,8]	14 (42)	0.15

QODD indicates quality of dying and death. N is the number of valid responses. *Score 0-5 indicates proportion of respondents that scored the item as unsatisfactory. P-values are for differences between scores given by relatives and nurses.

Results for the quality rating components of the QODD-ICU items are shown in Table 2. The items that were most frequently scored as unsatisfactory by relatives were questions about whether or not the patient 'was able to feed him/herself' (69% unsatisfactory), 'said goodbye to loved ones' (51% unsatisfactory), 'appeared to have control over the situation' (47% unsatisfactory), 'appeared to keep dignity and self-respect' (41% unsatisfactory) or 'appeared to breath comfortably' (38% unsatisfactory). Results for the frequency components of the QODD items are shown in Table 1 in the Supplemental Material. All relatives reported that the patient was accompanied by family most to all of the time and 55 (93%) relatives reported physical contact or hugging the patient. The often acute and unexpected occurrence of stroke was also reflected in the answers of the relatives: only 10 (17%) reported that the patient had had the chance to say goodbye to loved ones. Finally, relatives' experiences with the project were positive: both the interview (8; 8–8) and the condolence letter (8; 7–9) were appreciated. An overview of relatives' scores for the quality rating and frequency components of all QODD items is shown in Tables 2 and 3 in the Supplemental Material.

Experiences of nurses

In general, reports of nurses were very much in line with the reports of relatives (Table 2). The only differences were that nurses scored a more positive experience on the quality rating component of the QODD questions about whether the patient 'appeared to be in control over the situation' and 'was able to feed him/herself'. However, as shown by the frequency component of these QODD items (Supplemental Material Table 1), these were rarely applicable to our patients: 48 (84%) relatives and 47 (80%) nurses reported that the patient was never or sometimes (frequency score 0–2) in control of the situation, and 45 (88%) relatives and 56 (95%) nurses reported that the patient was never or sometimes able to feed himself or herself.

Symptoms of discomfort

The most frequently reported signs of discomfort based on the frequency component of the QODD items were related to breathing: 27 (46%) relatives and 19 nurses (36%) reported that breathing was 'never or sometimes' easy. However, 37 (65%) relatives and 41 (71%) nurses reported that symptoms of discomfort were resolved by medication most or all of the time. Pain was not frequently reported: 44 (76%) relatives and 52 (89%) nurses reported that it was under control most or all of the time.

No clinical characteristics were associated with the overall experience of quality of dying in multivariate analysis, but there was a trend towards a more negative experience associated with the use of benzodiazepines (Beta –1.31; p = 0.07; Supplemental Material Table 4). In addition, negative experiences with regard to breathing were associated with the use of morphine after adjustment for age and length of the end-of-life phase (Beta –0.27; p = 0.05; Supplemental Material Table 5).

DISCUSSION

In this single-centre evaluation of patients dying on the stroke unit, we found that the majority of relatives were satisfied with the quality of dying and the quality of care provided by nurses and doctors. The most important negative experiences were related to feeding problems, breathing difficulties, not retaining control and sense of dignity and not being able to say goodbye to loved ones. Pain was not frequently reported as a sign of discomfort and relatives were satisfied with the alleviation of symptoms by palliative medication. Experiences of the nurses correlated well with those of the relatives.

Few previous studies have interviewed relatives with an after-death questionnaire to systematically evaluate quality of dying in the stroke unit. To our knowledge, none have used the QODD-ICU to identify frequent symptoms of dying stroke patients and aspects of the dying process itself, and our study is the first to compare experiences of relatives and nurses. A study from the United Kingdom used the Views of Informal Carers Evaluation of Services postal questionnaire in relatives of stroke patients who died in an institutional setting and reported that individualized end-of-life care increased satisfaction.[12] This study was different from ours because it included also patients who died on hospital wards other than the stroke unit and in nursing homes and used a self-administered questionnaire that had a stronger focus on relatives' satisfaction with the services provided by healthcare professionals. In line with our findings, a Canadian study that used the After–Death Bereaved Family Member Interview in family members of patients in neurology or neurosurgery services reported overall high levels of satisfaction with palliation and more specifically with treatment of pain and dyspnoea.[13] However, conclusions were hampered by the small sample size of 15 patients. By contrast, two retrospective chart reviews on dying stroke patients referred to palliative care consultants did identify pain as an important sign of discomfort,[7,14] which might be explained by the fact that these studies used descriptions of signs of discomfort from the patient charts instead of relatives' reports. The proportion of patients treated with opioids was comparable to that in our study (around 70%), with 81% of patients reported free of pain in the last 48 h before death in one of the studies.[7] This may explain the satisfaction with the alleviation of symptoms by palliative medication observed in our study.

Breathing difficulties are among the most frequent reported signs of discomfort in the last hours or days before death at the stroke unit.[7,14] In our cohort, morphine was used to relieve dyspnoea in 74% of the patients. This is comparable to the use of morphine in 80% of patients who died on a stroke unit in Germany,[15] but less than in one Canadian study (93.6%).[16] Our finding that the use of morphine was negatively associated with an experience of discomfort caused by breathing difficulties is probably a matter of confounding by indication. Also, the assessment of breathing difficulties by family members during the whole end-of-life phase might be influenced by periods with changes in the respiratory pattern associated with the dying process before opioids were started. Opioids will probably have alleviated breathing difficulties in most instances since 65% of the interviewed relatives in our study reported that signs of discomfort were successfully resolved by medication most or all of the time. Unfortunately, the effect of non-pharmacological treatments used on our stroke unit, such as repositioning

of the patients and suctioning to prevent pooling of saliva in the posterior oropharynx, could not be analysed as they were not systematically documented in the hospital charts.

Assessments of quality of dying by nurses correlated well with those of relatives, suggesting that nurses are a reliable surrogate for relatives of stroke patients in future studies. When analysing the quality component of the individual QODD items, we did, however, find a more positive experience of the nurses on items about the patient 'feeding him/herself' and 'appearing in control over the situation'. As indicated by the frequency component of these items (Supplemental Material Table 1), both are rarely applicable to a dying stroke patient, which can be considered common knowledge to an experienced nurse. However, these aspects may be worrisome to family members, particularly with respect to fluid intake. This is supported by our finding that the item about feeding was amongst the most frequent unsatisfactory experiences of family members. In line with this, American Heart Association guidelines state that it is extremely important to counsel families on what to expect in terms of changing and signs and symptoms, including decreased food and fluid intake and decreased levels of consciousness and agitation.[1]

Several limitations to our analysis should be considered. Firstly, results of our single-centre analysis might be heavily influenced by local protocols and caregivers and cannot be directly generalized to stroke units elsewhere. Secondly, the QODD-ICU has not been validated in acute stroke patients and several of its items were not be applicable to dying stroke patients. Thirdly, nurses completed the questionnaire one week after death to prevent recall bias, whereas relatives completed the questionnaire at 6 weeks to respect their grief. Fourthly, the experiences of relatives may not precisely reflect those of the dying patient him- or herself and perspectives may differ between family members depending on their relationship with the deceased.[8] Recall of proxies is prone to bias and bereaved informants' emotions during the dying process may impact their views.[17] However, evidence from a comprehensive review of the literature of studies comparing patient and proxy views suggested that proxies can reliably report on the quality of services and symptoms, especially on the ones that are more observable in nature.[18] Fifthly, we could not analyse the impact of advance directives on the experiences of family members during the dying process, as this information is not systematically recorded in our charts. In a recent study from our centre, just one of 49 patients with severe stroke had a written advance directive at admission,[19] supporting our experience that these are infrequent among stroke patients in The Netherlands. The impact of advance directives, if any, will therefore have been small. Finally, there is a potential for selection bias because just over half of the relatives agreed to be interviewed. Although we found no differences in baseline characteristics and no difference in quality of dying rated by nurses between patients with participating and those with non-participating relatives, we cannot rule out the possibility that relatives who were unsatisfied with the provided end-of-life may been more prone to decline the interview.

CONCLUSION

Bereaved family members were satisfied with the quality of dying of patients on our stroke unit, including pain and symptom control and the role of healthcare professionals. Negative experiences during the dying phase were mainly related to feeding problems, breathing difficulties, not retaining sense of dignity and not being able to say goodbye to loved ones. Our results suggest that nurses can reliably assess the experiences of the family members of dying patients and could be used when evaluating end-of-life care for acute stroke patients in future research.

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SUPPLEMENTAL MATERIAL

Supplemental methods

Supplemental Tables

QUESTIONNAIRE FOR FAMILY MEMBERS

A. General questions

1. Overall, how would you rate the quality of dying of _____?

   Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost perfect

2. What did you think about the length of the dying process?

   Much too short 0 1 2 3 4 5 6 7 8 9 10 Much too long

3. What was the most unpleasant aspect of the dying process?

   .....

4. Was there an aspect that you liked? If yes, what?

   .....

5. How would you rate the care that _____ received in his/her final days from the nurses?

   Worst possible care 0 1 2 3 4 5 6 7 8 9 10 Best possible care

6. How would you rate the care that _____ received in his/her final days from the doctors?

   Worst possible care 0 1 2 3 4 5 6 7 8 9 10 Best possible care

7. a. How would you rate the communication, information and support to you by the medical personnel?

   Worst possible 0 1 2 3 4 5 6 7 8 9 10 Best Possible

   b. Which aspects did you like?

   .....

   c. Which aspects could be improved?

8. a. Did you receive the letter of condolence?

1	2	8
Yes	No	Don't Know

b. How did you experience the letter of condolence?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

c. Please state the reason:

.....

B. Frequency questions

9. a. How often did _____ appear to have her/his pain under control?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

10. a. How often did _____ appear to have control over what was going on around

her/him?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

11. How often was _____ able to feed her/himself?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

12. a. How often did _____ breathe comfortably?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

13. a. How often did _____ seem short of breath?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

14. a. How often did medication resolve symptoms of discomfort?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

15. How often did _____ appear to be unafraid of dying?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

16. How often did _____ appear to feel at peace with dying?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

17. a. How often did _____ laugh and smile?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

18. How often did _____ appear to keep her/his dignity and self-respect?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

19. a. How often did_____ spend time with other family and friends?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

20. a. How often did _____ spend time alone?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

C. Questions about events

21. a. Was _____ touched or hugged by her/his loved ones?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

22. a. Did _____ say goodbye to loved ones?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

23. a. Did _____ clear up any bad feelings with others?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

24. a. Did _____ have one or more visits from a religious or spiritual advisor?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

25. a. Did _____ have a spiritual service or ceremony before his/her death?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

26. a. Did _____ have her/his funeral arrangements in order prior to death or discuss his/her preferences?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

27. Is there anything else you would like to add?

28. How did you experience this interview?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

QUESTIONNAIRE FOR NURSES

1. a. How often did _____ appear to have her/his pain under control?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

2. a. How often did _____ appear to have control over what was going on around her/him?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

3. a. How often was _____ able to feed her/himself?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

4. a. How often did _____ breathe comfortably?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

5. a. How often did _____ seem short of breath?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

6. a. How often did medication resolve symptoms of discomfort?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

7. a. How often did _____ appear to feel at peace with dying?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

8. a. How often did _____ appear to be unafraid of dying?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

9. a. How often did _____ laugh and smile?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

10. a. How often did _____ appear to keep her/his dignity and self-respect?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

11. a. How often did_____ spend time with other family and friends?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

12. a. How often did _____ spend time alone?

0	1	2	3	4	5	8	9
None of the time	A little bit of the time	Some of the time	A good bit of the time	Most of the time	All of the time	Don't know	No response

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

13. a. Was _____ touched or hugged by her/his loved ones?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

14. a. Did _____ say goodbye to loved ones?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

15. a. Did _____ have one or more visits from a religious or spiritual advisor?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

16. a. Did _____ have a spiritual service or ceremony before his/her death?

1	2	8
Yes	No	Don't Know

b. How would you rate this aspect of _____ 's dying experience?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost Perfect

17. What did you think about the length of the dying process?

Much too short 0 1 2 3 4 5 6 7 8 9 10 Much too long

18. What was the most unpleasant aspect of the dying process?

19. Was there an aspect that you liked? If yes, what?

20. Overall, how would you rate the quality of dying of _____?

Terrible experience 0 1 2 3 4 5 6 7 8 9 10 Almost perfect

SUPPLEMENTAL TABLES

Table I. scores on the frequency component of QODD items

	Relatives (n = 59)					Nurses (n = 59)				
	N	**0-2 (%)**	**3-5 (%)**	**Don't know**	**No response**	**N**	**0-2 (%)**	**3-5 (%)**	**Don't know**	**No response**
Frequency QODD items										
Appeared to have pain under control	58	5 (9)	44 (76)	9 (15)	0 (0)	59	5 (8)	52 (89)	2 (3)	0 (0)
Appeared to have control over the situation	57	48 (84)	2 (4)	6 (10)	1 (2)	59	47 (80)	5 (8)	5 (8)	2 (3)
Was able to feed him/herself	51	45 (88)	0 (0)	3 (5)	3 (5)	59	56 (95)	0 (0)	1 (2)	2 (3)
Appeared to breath comfortably	59	27 (46)	31 (53)	1 (2)	0 (0)	59	22 (37)	36 (61)	1 (2)	0 (0)
Appeared to be short of breath	59	47 (80)	10 (17)	2 (3)	0 (0)	59	47 (80)	10 (17)	2 (3)	0 (0)
Medication appeared to relieve symptoms of discomfort	57	6 (11)	37 (65)	14 (24)	0 (0)	58	6 (10)	41 (71)	10 (17)	1 (2)
Was unafraid of dying	59	27 (46)	16 (27)	15 (25)	1 (2)	58	18 (31)	23 (40)	15 (26)	2 (3)
Appeared to keep his/her dignity and self-respect	59	7 (12)	17 (29)	32 (54)	3 (5)	59	9 (15)	26 (44)	23 (39)	1 (2)
Spent time with family/friends	59	0 (0)	59 (100)	0 (0)	0 (0)	56	6 (11)	50 (89)	0 (0)	0 (0)
Spent time alone	59	53 (90)	5 (8)	1 (2)	0 (0)	59	50 (85)	7 (12)	0 (0)	2 (3)
Yes/no QODD items	**N**	**Yes**	**No**	**Don't know**		**N**	**Yes**	**No**	**Don't know**	
Was touched or hugged by loved ones	59	55 (93)	3 (5)	1 (2)		59	50 (85)	2 (3)	7 (12)	
Said goodbye to loved ones	58	10 (17)	44 (76)	4 (7)		59	7 (12)	34 (58)	18 (31)	
Had visit(s) from spiritual advisor	59	9 (15)	24 (41)	26 (44)		59	2 (3)	44 (75)	13 (22)	

N is the number of valid responses. The upper panel shows the proportion of relatives or nurses that scored the frequency component as occurring "never or sometimes (score 0-2)", "most or all of the time" (score 3-5), "don't know" (score 8) or "no response" (score 9). The lower panel shows the answers of relatives and nurses to dichotomous questions that asked whether situations occurred during the end-of-life phase ("yes") or did not occur ("no").

Table II. Distribution of all relatives' scores on the quality rating component of QODD items.

		Relatives' score (%)										
	N	**0 (%)**	**1 (%)**	**2 (%)**	**3 (%)**	**4 (%)**	**5 (%)**	**6 (%)**	**7 (%)**	**8 (%)**	**9 (%)**	**10 (%)**
Overall summary score	59	3 (5.1)	0 (0)	1 (1.7)	1 (1.7)	2 (3.4)	2 (3.4)	6 (10.2)	11 (18.6)	19 (32.2)	9 (15.3)	5 (8.5)
Appeared to have pain under control	56	1 (1.8)	1 (1.8)	2 (3.6)	1 (1.8)	1 (1.8)	4 (7.1)	4 (7.1)	8 (14.3)	17 (30.4)	5 (8.9)	12 (21.4)
Appeared to have control over the situation	53	8 (15.1)	3 (5.7)	2 (3.8)	3 (5.7)	4 (7.5)	5 (9.4)	5 (9.4)	13 (24.5)	8 (15.1)	2 (3.8)	0 (0)
Was able to feed him/herself	35	4 (11.4)	0 (0)	0 (0)	2 (5.7)	1 (2.9)	17 (48.6)	5 (14.3)	3 (8.6)	1 (2.9)	1 (2.9)	1 (2.9)
Appeared to breath comfortably	56	5 (8.9)	2 (3.6)	3 (5.4)	3 (5.4)	4 (7.1)	4 (7.1)	9 (16.1)	8 (14.3)	11 (19.6)	3 (5.4)	4 (7.1)
Appeared to be short of breath	57	4 (7.0)	0 (0)	3 (5.3)	5 (8.8)	3 (5.3)	3 (5.3)	11 (19.3)	4 (7.0)	13 (22.8)	1 (1.8)	10 (17.5)
Medication appeared to relieve symptoms of discomfort	44	1 (2.3)	0 (0)	0 (0)	1 (2.3)	2 (4.5)	2 (4.5)	5 (11.4)	9 (20.5)	17 (38.6)	4 (9.1)	3 (6.8)
Was unafraid of dying	45	3 (6.7)	0 (0)	1 (2.2)	2 (4.4)	3 (6.7)	2 (4.4)	2 (4.4)	2 (4.4)	15 (33.3)	5 (11.1)	10 (22.2)
Appeared to keep dignity and self-respect	32	1 (3.1)	1 (3.1)	2 (6.3)	3 (9.4)	1 (3.1)	5 (15.6)	2 (6.3)	3 (9.4)	8 (25.0)	1 (3.1)	5 (15.6)
Spent time with family/friends	59	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7)	0 (0)	1 (1.7)	2 (3.4)	22 (37.3)	7 (11.9)	26 (44.1)
Spent time alone	58	0 (0)	0 (0)	1 (1.7)	1 (1.7)	1 (1.7)	0 (0)	3 (5.2)	7 (12.1)	15 (25.9)	9 (15.5)	21 (36.2)
Was touched/hugged by loved ones	57	0 (0)	0 (0)	1 (1.8)	0 (0)	1 (1.8)	0 (0)	3 (5.3)	2 (3.5)	21 (36.8)	10 (17.5)	19 (33.3)
Said goodbye to loved ones	53	8 (15.1)	5 (9.4)	2 (3.8)	6 (11.3)	2 (3.8)	4 (7.5)	6 (11.3)	9 (17.0)	5 (9.4)	3 (5.7)	3 (5.7)
Had visit(s) from spiritual advisor	31	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	2 (6.5)	6 (19.4)	6 (19.4)	6 (19.4)	3 (9.7)	7 (22.6)

QODD indicates quality of dying and death. N is the number of valid responses per QODD item.

Table III. Distribution of all relatives' scores on the frequency component of QODD items

	Relatives (n = 59)								
	N	**0 (%)**	**1 (%)**	**2 (%)**	**3 (%)**	**4 (%)**	**5 (%)**	**Don't know (%)**	**No response (%)**
Frequency QODD items									
Appeared to have pain under control	58	1 (1.7)	0 (0)	4 (6.9)	4 (6.9)	10 (17.2)	30 (51.7)	9 (15.5)	0 (0)
Appeared to have control over the situation	57	30 (52.6)	10 (17.5)	8 (14.0)	1 (1.8)	1 (1.8)	0 (0)	6 (10.5)	1 (1.8)
Was able to feed him/herself	51	41 (80.4))	2 (3.9)	2 (3.9)	0 (0)	0 (0)	0 (0)	3 (5.9)	3 (5.9)
Appeared to breath comfortably	59	5 (8.5)	4 (6.8)	18 (30.5)	10 (16.9)	13 (22.0)	8 (13.6)	1 (1.7)	0 (0)
Appeared to be short of breath	59	25 (42.4)	5 (8.5)	17 (28.8)	7 (11.9)	3 (5.1)	0 (0)	2 (3.4)	0 (0)
Medication appeared to relieve symptoms of discomfort	57	0 (0)	3 (5.3)	3 (5.3)	6 (10.5)	15 (26.3)	16 (28.1)	14 (24.6)	0 (0)
Was unafraid of dying	59	20 (33.9)	3 (5.1)	4 (6.8)	1 (1.7)	2 (3.4)	13 (22.0)	15 (25.4)	1 (1.7)
Appeared to keep his/her dignity and self-respect	59	4 (6.8)	2 (3.4)	1 (1.7)	0 (0)	6 (10.2)	11 (18.6)	32 (54.2)	3 (5.1)
Spent time with family/friends	59	0 (0)	0 (0)	0 (0)	8 (13.6)	10 (16.9)	41 (69.5)	0 (0)	0 (0)
Spent time alone	59	35 (59.3)	8 (13.6)	10 (16.9)	4 (6.8)	1 (1.7)	0 (0)	1 (1.7)	0 (0)
Yes/no QODD items	**N**	**Yes (%)**	**No (%)**					**Don't know (%)**	
Was touched or hugged by loved ones	59	55 (93.2)	3 (5.1)					1 (1.7)	
Said goodbye to loved ones	58	10 (17.2)	44 (75.9)					4 (6.9)	
Had visit(s) from spiritual advisor	59	9 (15.3)	24 (40.7)					26 (44.1)	

QODD indicates quality of dying and death. N is the number of valid responses per QODD item.

Table IV. Relationship between clinical characteristics and quality of dying experience.

Variable	Univariate (beta)	p-value	Multivariate (beta)	p-value
Age	0.02	0.52		
Male sex (vs female sex)	0.25	0.69		
SAH (vs ischaemic stroke)	0.96	0.24		
ICH (vs ischaemic stroke)	0.24	0.70		
Latest recorded GCS before end-of-life phase	-0.15	0.19		
Use of morphine (yes vs no)	-0.24	0.74		
Use of benzodiazepines (yes vs no)	-1.57	0.02	-1.31	0.07
Length of end-of-life phase (hours)	-0.01	0.06	-0.01	0.18
Time to end-of-life phase (hours)	-0.21	0.10		
Location ICU (vs stroke unit)	-0.46	0.56		
Location ER (vs stroke unit)	0.41	0.54		

Analyses are performed by univariate and multivariate linear regression models using the relatives score on the single summary score as the independent variable. SAH indicates subarachnoid haemorrhage; ICH, intracerebral haemorrhage; GCS, Glasgow Coma Scale; location, location where end-of-life care was initiated; ICU, intensive care unit; ER, emergency department. Time to end-of-life phase indicates the time between start of hospital treatment and decision to withdraw life-sustaining measures.

Table V. Relationship between clinical characteristics and experience of shortness of breath

Variable	Univariate (beta)	p-value	Multivariate (beta)	p-value
Age	0.05	0.13		
Male sex (vs female sex)	-1.04	0.19		
SAH (vs ischaemic stroke)	0.69	0.50		
ICH (vs ischaemic stroke)	-0.41	0.61		
Latest recorded GCS before end-of-life phase	-0.09	0.52		
Use of morphine (yes vs no)	-2.35	0.01	-0.27	0.05
Use of benzodiazepines (yes vs no)	-0.02	0.98		
Length of end-of-life phase (hours)	-0.01	0.08	-0.13	0.34
Time to end-of-life phase (hours)	-0.24	0.07	-0.14	0.30
Location ICU (vs stroke unit)	-0.06	0.95		
Location ER (vs stroke unit)	1.21	0.15		

Analyses are performed by univariate and multivariate linear regression models using the quality component of the QODD item about shortness of breath as the independent variable. SAH indicates subarachnoid haemorrhage; ICH, intracerebral haemorrhage; GCS, Glasgow Coma Scale; location, location where end-of-life care was initiated; ICU, intensive care unit; ER, emergency department. Time to end-of-life phase indicates the time between start of hospital treatment and decision to withdraw life-sustaining measures.

Chapter 8

General discussion

In this thesis, I focus on strategies for the prevention and treatment of complications after acute stroke, in particular post-stroke infections, dysphagia, fever and space-occupying oedema. In addition, I discuss the challenge and implications of end-of-life care in patients with acute stroke.

PREVENTING COMPLICATIONS AFTER ACUTE STROKE – THE PRECIOUS TRIAL

In **chapters 2 and 3,** I present the study protocol and statistical analysis plan of the PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) trial, a phase III, international, randomised, controlled, open-label clinical trial with blinded outcome assessment. This study is designed to assess whether prevention of aspiration, infections, or fever with (a combination of) metoclopramide, ceftriaxone and paracetamol in the first 4 days after stroke onset improves functional outcome at 90 days in elderly patients with acute stroke. The project was started in 2015 and is currently ongoing.

The rationale and design of PRECIOUS have been guided by the results of previous studies that investigated the preventive use of these drugs in acute stroke patients. The PASS[1] and STROKE-INF[2] trial showed that the preventive use of antibiotics in stroke patients was safe, with a very low prevalence of microbial resistance and clostridium difficile infections.[1,2] Both trials showed a significant decrease in overall rate of post-stroke infections in the treatment group, but not in the occurrence of pneumonia. The trials also did not show an improvement in functional outcome, which was supported by a 2018 Cochrane review.[3] In PASS, adult patients of any age and with relatively mild strokes (median NIHSS of 5) were included, possibly leading to a substantially lower prevalence of infections than in a previous large meta-analysis.[4] STROKE-INF included patients with stroke and dysphagia, but there was considerable heterogeneity in types, doses, and routes of administration of antibiotics and treatment was started within 48 hours of stroke onset, which may be too late for a preventive treatment. In addition, the cluster-randomised design and low recruitment numbers per centre are prone to selection bias. Therefore, PRECIOUS uses an individually randomised design and only elderly patients (>65 years) with a moderately severe to severe stroke (NIHSS>6) are included within 24 hours after stroke onset.

The neutral results of PASS and STROKE-INF suggest that stroke-associated pneumonia is not merely a bacterial infection, but may involve chemical and immunological alterations, that could benefit from the additional effects of metoclopramide. In line with this, the MAPS trial reported a significant decrease in pneumonia in patients with acute stroke and dysphagia who were preventively treated with metoclopramide, but functional outcome was not assessed.[5] The PAIS trial showed a significant decrease in body temperature in patient with acute stroke that were preventively treated with paracetamol and showed better functional outcome in the treatment group, although this difference was just not statistically different.[6] Subsequent confirmation in a larger population in the PAIS 2 trial was unfortunately hampered by lack of funding.[7]

With its large sample size, specific focus on early treatment and focus on patient subgroups that may especially benefit from their prevention, PRECIOUS has the potential to show a significant effect on post-stroke complications and functional outcome. The $2 \times 2 \times 2$ factorial design allows analysis of the effects of ceftriaxone, paracetamol and metoclopramide separately, while simultaneously adjusting for treatment allocation in the other two strata. The pragmatic design of the trial aims to keep the required efforts for local investigators to a minimum and keep motivation for patient recruitment high. Furthermore, the centralised adjudication with three separate video outcome assessments assures blinding and may improve statistical power. Considering the results of previous studies, the effect of the drugs under investigation will likely be small: PRECIOUS is powered to detect a 5% increase in patients with an independent functional outcome. However, given that these are cheap, safe and widely available drugs, I expect that a proven benefit will change clinical practice, also in middle- and low-income countries.[5]

BARRIERS IN THE CONDUCT OF CLINICAL TRIALS

In November 2020 PRECIOUS was extended for two years due to slow patient recruitment, which, unfortunately, did not allow the results to be included in this thesis. Although multiple factors, including the COVID-19 pandemic, have played a role, the process of obtaining regulatory approval in this multicentre international trial was a major delaying factor. In **chapter 4**, I elucidate and quantify these delays. Despite the apparent simple and pragmatic set up and adequate funding of the study, the median overall time to initiate a trial site was over 2 years. With a median time of 201 days and 194 days respectively, the most time-consuming activities were the completion of study contracts between sponsor and coordinating centre in each country (country coordinator agreement, CCA), and between national coordinating centre and individual trials sites (clinical trial agreement, CTA).

In PRECIOUS a median time of 87 days was needed to obtain approval by the ethical committee (EC) and 91 days for National Competent Authority (NCA) approval, which is not longer than in the few previous reports available in the literature. An analysis of an intercontinental study in HIV patients suggested that regulatory approvals may take longer in Europe (median of 218 days) than in other parts of the world.[8] However, a previous study from Australia reported 203 business days needed to obtain EC and NCA approval,[9] whereas in a South African study 122 days were required for NCA approval and 60 days for EC approval.[10] As these timeframes are comparable, the long period to site initiation in PRECIOUS can only partly be attributed to delays in obtaining national regulatory approvals.

The time required for opening a study site in PRECIOUS was, however, substantially longer than in previous studies. A recently published analysis of multiple cardiovascular trials in Northern America reported a median of 171 days of total time from first contacting a site to activation to enrolment, and 143 days needed for contract execution.[11] An analysis of 38 surgical studies conducted in Boston found an average total study start-up time for study sites of 319 days and 131 days needed for budget and contract

negotiations of drug trials.[12] The SANADII trial, that included patients with epilepsy in more than 100 sites in the UK described a mean opening time of 10.5 months.[13] It should be noted that direct comparison is complicated by the fact that the time required to acquire EC and NCA approval was not included in any of these analyses.

The main reasons for delay in PRECIOUS were a consequence of its multinational character. First, this caused the need to execute an international agreement (CCA) before any contracts on a national level could be completed. As lawyers in other countries were not familiar with the template used as the basis for the CCA, the result was lengthy legal discussions and considerable delay. Translation of the documents from English into national languages and the subsequent back-translation of the modified documents into English was additionally time-consuming.[14] This highlights the importance of universally accepted template for international research contracts, which would be very beneficial for multinational trials. Secondly, there was a striking difference between countries in the time needed to complete contracts with the different study sites (CTA). In my experience, the process of contract negotiations is outside the influence of the principal investigator and is largely dependent on institutional lawyers who may have no intrinsic or extrinsic motivation to speed up this process. I believe that formalised and specific deadlines for legal review of trial documents, comparable to the maximum review period for ethical committees, could greatly benefit international trials. It would be helpful to appoint a responsible lawyer at the moment a site expresses interest in participating in a trial, similar to the selection of the principal investigator. In countries like The Netherlands, where a signed site suitability declaration form for each participating site is required before EC submission, both the responsible institutional lawyer and deadline for legal review could be recorded in this document.

The importance of achieving swift regulatory and legal approvals is further emphasised by our finding that slower site initiation was associated with fewer included patients in the first six months. This is in line with previous reports that studies with longer contract finalization periods have a lower probability of enrolling subjects, and, similarly, budget and contract finalization processes take longer in studies which ultimately do not enrol a patient.[12] It is understandable that trials may lose momentum when investigators who were initially motivated must wait for two years before recruiting their first patient. If the time period for a trial is set, delays in site initiation also mean that less time remains for patient recruitment. In PRECIOUS almost half of the 60 months trial duration granted by the European Union was spent on obtaining regulatory approvals, which is one of the reasons a trial extension was needed.

In addition to the often cumbersome and time-consuming start-up phase of a trial, several barriers in the subsequent conduct of a trial have been described, including overly complex regulations producing needlessly complex trial procedures, excessive monitoring and over-restrictive interpretation of privacy laws.[15] Based on my experience in PRECIOUS, I believe the presently effective EU Clinical Trial Directive 2001/20/EC may impede, rather than facilitate trial objectives in very low-risk trials that evaluate well-established and safe drugs with a known side-effect profile. This results in excessive requirements in monitoring and labelling of study medication that pose a large logistical

and financial burden on trials, without any apparent improvement of subject safety.[16] In addition, these requirements lead to unnecessary lengthy multiple-page consent forms, which may intimidate potential participants, rather than truly inform them. Trials need to be easily embedded in clinical practice to be affordable and successful,[15] and participation should take minimal effort for researchers to ensure motivation for patient recruitment. A new Clinical Trial Regulation (EU No 536/2014) was approved in 2014, which aims to simplify procedures and harmonise European regulatory requirements, to ensure that Europe remains an attractive site for future clinical research.[16] However, due to major delays in its implementation the new regulation will come into force in 2022. Unfortunately, it still requires that study medication is labelled in investigator-initiated trials, without differentiating between the use of experimental medication or the use of drugs approved by the European Medicines Agency that are used for a new therapeutic indication. This means that trials using simple, safe and cheap medication such as PRECIOUS are still obliged to spend a significant proportion of their budget on labelling, without conceivable benefit for safety of participants.

SURGICAL DECOMPRESSION FOR SPACE-OCCUPYING SUPRATENTORIAL ISCHAEMIC STROKE

In **chapter 5,** I present the results of an individual patient data (IPD) meta-analysis on the effects of surgical decompression for patients with space-occupying hemispheric infarction, which was the result of an international cooperation of stroke researchers. We show that surgical decompression dramatically improves survival and significantly improves the chance of a favourable outcome, confirming the findings of previous European IPD meta-analyses, but now in a four times larger cohort that also includes non-European trials.[17,18] In addition, we found that surgical decompression increased the number of patients who were functionally independent (mRS≤2) at 1 year after stroke, but sample sizes were just too small to show a significant effect size. In a subgroup analysis there was no evidence that the effect of surgical decompression was heterogeneous across the prespecified variables age, sex, aphasia, NIHSS score at baseline, time to randomisation and vascular territories involved. This analysis is the most comprehensive on this topic to date and, as I consider new trials in the near future unlikely, this may be the final word on this topic for a long time. The results of this analysis served as an important reference for the 2021 European Stroke Organisation guidelines on the management space-occupying brain infarction.[19]

As the sample size of previous IPD meta-analyses was essentially too small to allow reliable subgroup analysis, uncertainty still remained about treatment effect in specific subgroups of patients. Meta-analyses that included more recent trials used aggregated data averaged across all individuals in the study, [20,21] which cannot properly account for patient-level characteristics that may influence treatment effect.[22,23] The combined advantages of a larger data set and individual patient data allowed a more reliable assessment of treatment effect in subgroups of patients in our analysis.

In addition, this is the first IPD meta-analysis on this topic to use a one-stage model. In a two-stage approach, aggregate effect sizes for each study are first calculated and these are subsequently combined in a meta-analysis.[24] It works under the assumption that study treatment effect estimates have normal sampling distribution, with reasonably accurate variance estimation.[24] For a binary outcome, estimations may become inaccurate when sample sizes of individual studies are small and outcomes are rare, or incomputable if a treatment group has a zero count (anyone who has ever used a 2x2 contingency table to calculate effect size will recognise this problem). As medically treated patients with space-occupying ischaemic stroke fare so poorly, favourable outcome (a binary outcome) is rare in this treatment group and zero counts occur, in particular when analysing subgroups. Therefore, I believe that the one-stage approach is the only suitable option for our purposes, as it directly models the actual distribution of the IPD and avoids making any assumptions about the distribution of the treatment effect estimates in each study. It also allowed us to include an ordinal (shift) analysis of the full scale of the modified Rankin Scale (mRS), which is strongly encouraged by the European Stroke Organisation Outcomes Working Group when analysing outcomes in stroke research.[25] Finally, it enabled analysis of treatment effect modification of continuous patient characteristics (e.g., age, time to treatment) on its full scale, obviating the use of artificial binary cut-offs.

Which patient should we treat?

At the moment I believe there is no evidence to suggest that either sex, the involvement of an additional vascular territory next to that of the middle cerebral artery, or higher NIHSS at baseline have a significant influence on the effect of surgical decompression. Most studies in our analysis used a decreased level of consciousness as an inclusion criterion, which is a consequence of tissue shifts, increased intracranial pressure and subsequent impairment of contralateral hemisphere and brain stem function, and may potentially be reversible by surgical decompression.[26,27] The NIHSS score is almost invariably high in patients with a decreased consciousness,[28] and I believe the NIHSS score before surgical decompression does not capture the true severity of the focal brain damage and does not adequately differentiate between patients with or without potential for reversibility of symptoms. Therefore, I believe it should not be used in making a decision about surgical treatment.

Infarction of the language-dominant hemisphere may be used in clinical practice as a reason to exclude a patient from surgical decompression, but our results strongly suggest that treatment effect is not different between aphasic and non-aphasic patients. One could argue that the modified Rankin scale as a functional outcome measure does not adequately capture the burden that language difficulties pose on a patient, as functional dependency may still be preserved. However, previous studies reported that it is possible for patients with space-occupying infarction in the dominant hemisphere to show improvement of aphasic symptoms after treatment.[29] More importantly, quality of life after surgical decompression is reasonable in most patients and does not seem to be affected by the side of the infarction.[30] Therefore, I would argue against the use of aphasia as a criterion to exclude a patient from surgical treatment.

There has been ongoing debate about treatment of elderly patients, especially since the DESTINY II trial, which included only patients over 60 years of age, showed a significant increase in patients reaching an mRS ≤4 after one year, but not mRS ≤3.[31] In our analysis we found no evidence that treatment effect altered with increasing age, when used as a continuous variable. I did, however, find a lower proportion of patients reaching mRS ≤3 and mRS ≤4 with higher age in both treatment groups (Chapter 5 - Figure 2 and 3 in the Supplement). The relative differences between the treatment groups seem more stable, which leads to similar effect size estimates. I believe that these data suggest that surgical decompression is still effective in elderly patients, but the chance of reaching a favourable outcome after surgical treatment is lower in these patients. For clinical practice, I would advise to not only consider treatment effect sizes of surgical decompression in elderly patients, but also incorporate absolute numbers when discussing treatment options with patients or their family members. I would like to point out that 86% of the data on patients >60 years in our meta-analysis was data from the DESTINY II and DEMITUR trials (Chapter 5 - Table 6 in the Supplement), but the reported proportions of elderly patients reaching a favourable outcome (mRS ≤3) after surgical decompression in these trials were strikingly different (66% in DEMITUR versus 8% in DESTINY II). I believe the design of the trials is not sufficiently different to explain such a large discrepancy in outcome and this suggests that other (unreported) factors may have played a role, such as patient characteristics or outcome adjudication (e.g., interpretation of the modified Rankin Scale). It should be noted that the DEMITUR trial was published after the completion of the meta-analysis and was subsequently withdrawn for unknown reason at the request of the authors.

Our meta-analysis also did not show any evidence that treatment effect was altered with increasing time to treatment. In my opinion, the results of this and previous analyses clearly show that surgical decompression within 48 hours after symptom onset is a viable option. However, absolute numbers of treated patients beyond this time window in our analysis were small, which complicates recommendations for late treatment. Interestingly, a recent Dutch cohort study and meta-analysis of randomised and non-randomised trials reported that the outcome of decompressive craniectomy after 48 hours was not worse than in earlier treatment.[32] Treatment decisions in this study were made after discussion between neurologist and neurosurgeon, which may very likely have induced selection bias. In addition, it is conceivable that patients who require more than 48 hours to develop symptoms coherent with the inclusion criteria (e.g., decreased consciousness) have a better outcome, regardless of choice of treatment. Nevertheless, in the absence of sufficient evidence from randomised clinical trials in this subgroup of patients, I believe it is fair not to set a strict restriction of 48 hours after stroke onset in the decision whether to perform surgical decompression. Personally, I would still consider surgical decompression if a patient develops signs of severe space-occupying oedema after 48 hours that I would expect to be fatal if treated conservatively, especially if I reckon the patient "fit for surgery" based on age, pre-stroke functional status and clinical course.

What constitutes a favourable outcome?

Surgical decompression in space-occupying hemispheric infarction decreases midline shift and intracranial pressure and may successfully restore impaired function of non-

infarcted brain tissue, but will not change the fact that the patient still suffered a major stroke. Therefore, expected functional outcome is usually worse than for acute therapies that have the potential to salvage ischaemic brain tissue. As a consequence, studies on surgical decompression still regard mild to moderate dependency as a favourable outcome, with definitions ranging between mRS ≤3 and mRS ≤4. But what is really important, of course, is how the patient reviews the outcome. In this respect, health-related quality of life could be a more relevant outcome and provide a more holistic picture of disease effect.[33] Unfortunately, adequate data on quality of life (QoL) outcomes was not available for our meta-analysis, but previous systematic reviews concluded that most patients surviving surgical decompression experience a reasonable QoL at long-term follow-up.[30,34] Although increasing disability is generally associated with reduction of QoL, this relationship is not true for all patients.[35,36] In addition, patients may adjust their internal standards and values and their appreciation of quality of life in the face of disability, a phenomenon known as "response shift".[37,38]

What should we tell our patients and their families?

The results of our analysis may serve as a good basis for informing patients and their relatives about the expected impact of treatment on functional outcome, including the incorporation of relevant patient and treatment characteristics. In the end, the decision to perform surgical decompression will remain a matter of shared-decision making and should be heavily influenced by the patient's personal preferences and values. In the figure below I have summarized my recommendations for the decision to perform surgical decompression in clinical practice.

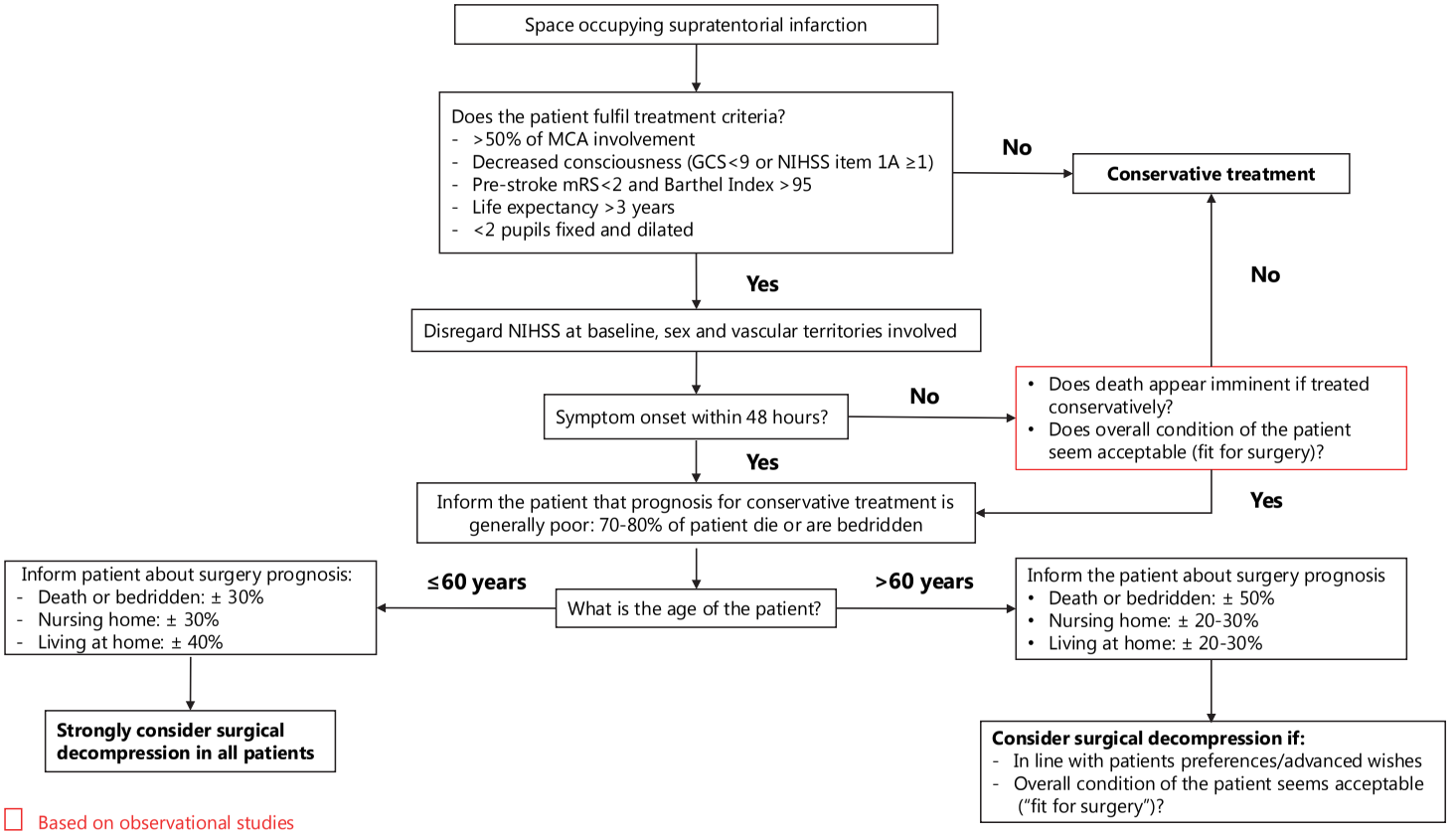

Figure 1. recommendations for the decision to perform surgical decompression for space-occupying ischaemie in clinical practice.
MCA: Middle cerebral artery, GCS: Glasgow Coma Scale, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale.

TREATMENT RESTRICTIONS IN ACUTE STROKE

In **chapter 6,** I describe the results of a retrospective analysis of the prevalence of treatment restrictions in patient with ischaemic stroke and intracerebral haemorrhage and their relationship with the risk of death. Treatment restrictions were installed in 36% of all patients on our stroke unit, more frequently after intracerebral haemorrhage (51%) than after ischaemic stroke (32%) and 83% were early treatment restrictions (installed within first 24 hours).

Discussions about limitation of life-sustaining therapy usually occur in a clinical setting in which the expected outcome of treatment would allow patients to continue living, but would result in a state of disability that might be against their wishes.[36] As treatment outcome is presumed to be poorer in patients with adverse prognostic characteristics, it is not remarkable that restrictions were installed in patients who were older, had more pre-stroke handicap and comorbidity, and a more severe stroke and a lower level of consciousness on hospital admission. Treatment restrictions were also more prevalent in women, which in line with an American nationwide database survey into hospital admissions for intracerebral haemorrhage that reported more do-not-resuscitate orders in women. This has been attributed to the idea that, compared to men, women seek less heroic resuscitative measures upon cardiopulmonary arrest and may be more likely to have already expressed their wishes to the families/surrogate decision-maker on how to handle this type of situation.[39,40] Unsurprisingly, differences in functional outcome were large, with 14% of patients with treatment restrictions reaching a functional independent state after 90 days, versus 64% of patients without treatment restrictions.

A treatment restriction often means refraining from therapy that could be potentially life-saving. As expected, we found higher death rates at 90 days in patients with treatment restrictions than in those without (55% vs 4%). If care limitations include withdrawing artificial nutrition and fluids, death may be regarded as inevitable. In other cases, death should, in essence, only occur in a setting that requires care that has previously been limited (such as ICU care). Interestingly, I found that the presence of an early treatment restriction was strongly associated with the risk of death, even after adjusting for important prognostic factors. When restrictions that encompassed stopping artificial nutrition and fluids were excluded from the analysis, the association was still very strong. Even the presence of an early do-not-resuscitate (DNR) order *alone* was significantly associated with death at 90 days. None of the deceased patients with a DNR order died from a cause that could have been prevented by cardiopulmonary resuscitation. Moreover, these DNR orders were not merely a preterminal measure in dying patients, as evidenced by the median time of three weeks between DNR order and death.

Despite the limitations of the retrospective design of our analysis, in which important (unknown) confounders may not be accounted for, I believe the consistent findings of our and previous analyses suggest that there is a genuine relationship between treatment restrictions and death.[41,42] It is probably not the treatment restrictions themselves that are leading to the patient's death, but they may serve as marker for an, unwanted, nihilistic milieu of care in which treatment restrictions may influence attitudes of care for patients

beyond the restrictions themselves.[43] It has been reported that patients with intracerebral haemorrhage admitted to hospitals with a higher rate of early DNR orders have a higher risk or death, even after adjusting for relevant patient and hospital characteristics.[44] Importantly, the relationship between individual DNR status and mortality is influenced by hospital DNR rate,[44] suggesting that some additional aspect, possibly overall aggressiveness or care, is at least partly responsible.[43] Other studies demonstrated that patients with intracerebral haemorrhage or ischaemic stroke who have a DNR order are less likely to be treated on a stroke unit or by specialist teams and, therefore, may indeed receive less optimal care.[45,46]

The decision to limit or withdraw curative care is usually made under the assumption of a known and accurate prognosis. However, prediction models are not sufficiently accurate to be the exclusive foundation of decisions to limit treatment and were usually not developed with the specific aim of informing end-of-life decisions.[36] In addition, the association between treatment restrictions and mortality may suggest a "self-fulfilling prophecy", as patients who are predicted to have a poor outcome are withdrawn from curative treatments and subsequently die.[47] This may substantially bias and impact the performance of prognostic models that do not consider treatment restrictions as a predictive factor.[48,49] Unfortunately, physician estimates of prognosis are no more reliable: previous studies in acute stroke reported superior performance of a simple prognostic model including only age and early NIHSS as predictors over physician's expectations of functional recovery and death.[50] Physician's predictions of quality of life in patients with a major disabling stroke are even less accurate: a previous study found that only 63% of patients with unsatisfactory quality of life were correctly identified in advance.[51] Although more severe handicap usually leads to a poorer quality of life,[52] prediction of the future perspective of a patient is further complicated by the fact that patients may adapt internal values and standards to their situation and may even report a better quality of life than healthy people, a phenomenon referred to as "the disability paradox".[53,54]

As this information was not available in my analysis, some treatment restrictions may have been reflections of advanced wishes expressed prior to hospital admission. In this case the relationship between the presence of treatment restrictions is easily understood and acceptable. However, advanced directives are rare in the Dutch general population,[55] and in patients with acute stroke.[56] Yet, if present, I believe they should play an essential role in the decision to install treatment restrictions. This is particularly true for stroke patients, as the vast majority will suffer additional disability compared to the pre-stroke functional status as a consequence of the disease and most patient will not be capacitated to actively participate in discussions when the time comes to discuss treatment limitations.[36]

Implications for clinical practice

The decision to install treatment restrictions remains a complex issue and the challenge lies in determining for which patients this is the most appropriate plan of care. I would advise clinicians to use prognostic information to support shared decision making, but be aware of and transparent about the uncertainty of prognostic models. I would suggest to avoid a paternalistic approach and be modest about the ability of physicians

to predict long-term quality of life. I believe much weight should be given to (previously expressed) patient wishes and directives, while acknowledging the limitations that the response shift and disability paradox may pose upon predicting future quality of life. I think all clinicians should be aware of the potential effect of early treatment restrictions on mortality and should consider aggressive full care in the first (few) day(s) after stroke, provided that this in in line with the patient's wishes.[57]

END-OF-LIFE CARE FOR PATIENTS WITH ACUTE STROKE

With approximately one-third of patients dying in the first month after acute stroke,[58] and half of stroke-related deaths occurring in hospital, it is clear that the palliative care and end-of-life needs of patients with stroke are enormous.[59] Most of the available evidence on end-of-life care has been obtained in patients with more slowly progressive disease, such as cancer, but the specific palliative care needs of dying stroke patients are likely to be different. Stroke patients are more often incapacitated at the time of palliative care than patients dying from other diseases and models of palliative care developed in the context of cancer may not be applicable or appropriate for patients with stroke.[60-62] At the moment there is a striking lack of evidence regarding optimal palliative care in stroke.[59] In **chapter 7,** I describe the results of an observational study with the aim to evaluate treatment of symptoms in the end-of-life phase of dying stroke patients, as well as satisfaction of bereaved family members with the quality of dying. In addition, I compare their answers to those of nurses involved in end-of-life care.

Symptoms related to breathing were among the most frequently reported during the end-of-life phase. When asked if the patient appeared to breathe comfortably, 46% of relatives and 36% of nurses answered that this was rarely the case. This is in line with previous studies that identified respiratory secretions and dyspnoea as the most frequently recorded symptoms in the dying phase after stroke,[63,64] as well as with a recently published systematic review on palliative care after acute stroke.[65] In an analysis of a nationwide palliative care registration in Sweden, dying stroke patients were more likely to have death rattles and more likely to be prescribed medication for the relief of death rattles compared to patients dying of cancer.[66] Both symptoms of pain, as well as prescription medication for pain relief were less frequent in stroke patients, which corresponds to my finding that 76% of patients and 89% of nurses reported that pain was under control for most of the dying phase. In accordance with AHA guidelines, symptoms of discomfort are successfully managed in our stroke unit with drugs such as morphine and midazolam,[59] as indicated by the high number of relatives that reported satisfactory relief of symptoms of discomfort.

I was pleased to learn that family members were satisfied with the patient's quality of dying, as well as with the care provided by nurses and doctors. Nevertheless, a substantial portion of relatives reported negative experiences, which were mostly related to self-feeding, retaining sense of dignity and control. At the same time, the answers of relatives on the frequency component of these items show that that these situations rarely occurred in our patients. Interestingly, nurses were in agreement that these situations

were rare, but were significantly less negative about these aspects of care. I believe this is probably a consequence of the clinical experience of nurses, who may view these as inevitable and non-distressing consequences of the dying process of a stroke patient. Several previous studies reported that most conflicts between health care providers and family members in end-of-life decisions pertain to artificial nutrition and feeding.[67-69] Better counselling of families to prepare them for these aspects of the end-of-life phase and assuring them that terminally ill patients are for the most part unaware of hunger or thirst may enhance understanding and improve satisfaction.[67,70]

The story behind the numbers

The results of my analysis give valuable insights into a largely unknown field and provide us with evidence of the quality of end-of-life care we currently provide, but I believe one of the major limitations is that the use of a quantitative questionnaire is not able to capture all emotional and psychosocial aspects that influence experiences of the dying phase. When asked to rate an experience on a 0 to 10 scale during the interview, family members in our study regularly replied that it was "too complex to put into a single number". In an effort to overcome this we supplemented the quantitative questionnaire with additional open questions about which aspects of the dying phase family members and nurses liked and disliked most, and which aspects of care they thought should be improved. As this part of the interviews was not systematically recorded or transcribed it was not suited for formal (qualitative) analysis, but it does provide an interesting basis for recommendations for end-of-life care in clinical practice and future research.

The importance of a break-point dialogue

Although most family members were satisfied about communication with medical personnel, some reported that no caregiver had formally expressed the fact that their loved one was going to die and some felt that the doctor was unclear and somewhat ambiguous when informing them about the terminal prognosis. A previous qualitative study identified honesty and clarity of information as a central element in the experience of end-of-life care of acute stroke patients and their family members, even when prognosis is poor.[71] Denoting a terminal prognosis may be especially important, as the diagnosis of stroke appears not to immediately trigger fears about dying, unlike that of cancer.[71] This highlights the importance of a "break point dialogue", a clear communication between the physician, patient and family members about the transition to palliative end-of-life care.[66]

Preparing the family for the end-of-life phase

If family members have accepted the fact that death is inevitable, their major concern is that the patient is not in any form of distress and that death is peaceful and dignified.[71] Several family members in my analysis indicated that they wished that they would have received more information about symptoms in the terminal phase. This highlights the importance to counsel family members about anticipated signs and symptoms, including changes in breathing, decreased food and fluid intake and decreased levels of consciousness, and prepare family members for the fact that death may or may not occur in the short term. The family should be assured that their loved one's pain or other discomfort will be treated aggressively and that clinical care will be continued

throughout the dying process.[59] Preferably, patients should be transferred to a single room; the importance of calm and privacy that a personal space offers was highlighted both in our and previously conducted interviews.[71] I personally believe that it is essential to monitor the patient's physical wellbeing and adequately treat symptoms of discomfort to ensure patients and their families that death is dignified and without struggle. At the same time, I think we should be cautious not to overly medicate the end-of-life phase and leave ample room for the psychological needs of family members, by encouraging relatives to use this period to say goodbye to their loved one in the way that they want.

Offering follow-up contact

The often unexpected death of a stroke patient may primarily direct attention to the needs of the dying person, causing family members to forget their own needs and lead to difficulties in information intake.[72] Nevertheless, families of patients who die of stroke have a significantly lower prevalence of being offered bereavement follow-up contact than the families of dying cancer patients.[66] The after-death interviews in our study served as an extra opportunity for relatives to ask outstanding questions regarding the dying phase to an experienced nurse and this was indicated as one of the reasons this interview was appreciated. For clinical practice, I would suggest to offer potential follow-up contact to all family members of deceased stroke patients.

A standardized approach to end-of-life care

One of the most voiced complaints by nurses in our analysis was that palliative medication was started or increased in dose too late, due to lengthy discussions with the attending physician or the physician being occupied with other duties. I believe the results of my analysis support the idea that nurses are a good judge of the palliative needs of dying stroke patients. I think they should have a central position in coordinating care and should have a certain bandwidth in which they can administer palliative medication. For future studies, I would suggest to focus on developing and evaluating a formalised approach to end-of-life care in acute stoke patients, including standardised palliative orders that deal with all aspects of patient care. The use of palliative checklist has been described as a successful way to enhance teamwork and reduce conflict between healthcare professionals involved in end-of-life care on the stroke unit.[73] Previous small studies that reported promising results in improvement of end-of-life care with standardised approaches may serve as a starting point.[66,73,]

The role of palliative care consultants

In my analysis, palliative care consultants were involved in end-of-life care in the minority of stroke patients, which is in line with previous reports.[60] I believe that their specialised knowledge has the potential to improve holistic views on the palliative needs of patients and their families and that stroke neurologists should reach out to them in the development of end-of-life care pathways. A randomised controlled trial in patients with lung cancer showed that early intervention by a palliative care consultant leads to improved quality of life and less healthcare resource use.[75] If and under what circumstances stroke patients may equally benefit is unknown at the moment and deserves further study.[59]

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A

Appendices

Summary

Acute stroke is a devastating disorder and one of the major causes of death and disability worldwide. The two main causes of stroke are a blockade of an artery by a blood clot, which results in deprivation of blood to a brain region (ischaemic stroke) and rupture of a blood vessel, which causes blood to leak into the brain tissue and damage it (haemorrhagic stroke). The clinical syndrome of ischaemic and haemorrhagic is very similar and is characterised by the sudden onset of focal neurological deficits, such as aphasia, paresis, dysarthria and hypaesthesia. Treatment of acute stroke is challenging, but at the moment several treatment options are available. All ischaemic stroke patients receive secondary preventive treatment such as anticoagulants and are treated in specialized stroke units, but the effects of these treatments are modest. In addition, intravenous thrombolysis and endovascular thrombectomy can be used in the acute phase of ischaemic stroke, but can only be used in a selected number of patients. For haemorrhagic stroke no treatment options other than care in specialized stroke units are currently available.

PREVENTION OF COMPLICATIONS IN ACUTE STROKE

The long-term outcome after acute stroke is determined by many factors, including the severity of the stroke and its symptoms at onset. However, after the acute phase, patients also frequently develop secondary complications, such as dysphagia, aspiration pneumonia, urinary tract infections and fever. All of these complications have a negative impact on outcome. In current clinical practice, these complications are monitored and, if present, are treated by medication such as metoclopramide, antibiotics and paracetamol. At the moment it is unknown if the use of these medications in the acute phase of stroke may prevent secondary complications and improve functional outcome. In chapter 2 and 3, I present the study protocol and statistical analysis plan of the PRECIOUS trial, which aims to answer this question. I discuss the rationale of the trial and conclude that I believe that the trial may show effectiveness, particularly because of its very early treatment and focus on a specific patient group that is most prone to develop complications: elderly patients with severe stroke. I also highlight several strengths of the trial, including the 2*2*2 factorial design, which allows separate analysis of the effects of metoclopramide, paracetamol and ceftriaxone and the use of three video outcome assessments, which reduces bias and improves the reliability of study outcome data.

DELAYS IN CLINICAL TRIALS

When I completed this thesis, the PRECIOUS trial was still ongoing and its results could, unfortunately, not be reported. This is a consequence of a two-year extension of the trial in November 2020, which was necessary because an insufficient number of patients were included at the original end point. There are many reasons for slow patient recruitment in PRECIOUS and in chapter 4, I discuss one of the major delaying factors. Before any participating centre in a clinical trial may include patients, all necessary approvals by regulatory authorities must be in order, including approval by the Ethics Committee and National Competent Authority. Furthermore, approval by the board of the participating hospital and a legal agreement must be completed. In chapter 4, I quantify the time that was needed to start up over 80 participating centres in PRECIOUS and specify the required period for each individual step in the approval process. I conclude that the median time required to open a study site in PRECIOUS was over 2 years. The most time-consuming step was the execution of legal agreements with each study site. In addition, I show that centres that were opened later were less likely to recruit patients in the first 6 months, which may reflect declining motivation of participating investigators and loss of momentum of the trial. Therefore, I suggest that future large, multinational trials such as PRECIOUS may strongly benefit from internationally accepted templates for research contracts and formal deadlines for review of legal documents, which may restrict the time institutional lawyers require for legal review.

SURGICAL DECOMPRESSION FOR SPACE-OCCUPYING ISCHAEMIC STROKE

One of the most life-threatening complications of acute ischaemic stroke is space-occupying oedema, which is a result of swelling of the infarcted brain tissue. This leads to increased intracranial pressure, which further hampers brain function and, if untreated, leads to death in most patients. Surgical decompression has been shown to strongly reduce mortality in patients that develop this complication. However, many surgically treated patients have residual disability and may remain dependent on others, leading to controversy if this treatment should be used. In addition, uncertainty remains if certain patient groups may specifically benefit from this treatment. In chapter 5, I discuss the results of a meta-analysis that used individual patient data from virtually all clinical trials on this topic. I conclude that surgical decompression in patients with space occupying oedema not only strongly reduces mortality, but also significantly improves the chance of a favourable functional outcome. In subgroup analysis, I found no evidence that treatment effect was modified by the presence of aphasia, stroke severity, affected vascular territories, or age of sex of the patient. I conclude that treatment within 48 hours after stroke onset is a feasible treatment option, but acknowledge the limitation that few patients were treated beyond this time frame, which complicates extrapolation of the effect of early treatment to treatment after 48 hours. In addition, the trials that were included in the meta-analysis reported very different proportions of favourable outcome in elderly patients (>60 years), which complicates consistent conclusions about treatment effect in this patient group.

TREATMENT RESTRICTIONS IN ACUTE STROKE

Unfortunately, stroke is still one of the leading causes of death worldwide. About one third of patient die within the first month after stroke onset. Approximately half of stroke-related deaths occur in-hospital and most die after a decision to withhold or withdraw life-sustaining treatments, such as cardiopulmonary resuscitation or treatment in the Intensive Care Unit (ICU). These treatment restrictions are usually installed when it is expected that allowing the patient to continue living would result in a state of disability that is against his or her wishes ('a fate worse than death'). As most patients with severe stroke are incapacitated as a result of the disease, they usually cannot participate in these discussions and physicians rely upon family members to communicate the patient's wishes and preferences.

The decision to install treatment restrictions usually implies that prognosis is accurate and indisputably poor. To estimate outcome for a patient, physicians may use prognostic markers, including patient characteristics (e.g., age, pre-stroke morbidity), stroke severity and treatment success. However, previous studies have suggested that treatment restrictions itself may also influence the risk of death, independent of prognostic factors related to the patient or the stroke. In chapter 6, I analyse if a relationship between treatment restrictions and mortality may be present in patients treated in the stroke unit in het University Medical Center in Utrecht. I conclude that the presence of a treatment restriction is strongly associated with mortality, even when adjustments are made for important prognostic factors such as age, sex, pre-stroke comorbidity, stroke type, and stroke severity. The association is stronger in ischaemic stroke patients than in patients with intracerebral haemorrhage. Remarkably, the presence of only a do-not-resuscitate (DNR) increases the change of death in stroke patients. In essence, a treatment restriction should only affect outcome in a setting that requires care that has been limited, but none the deceased patients in the DNR group died of a cause that could have been prevented by cardiopulmonary resuscitation. I suggest that that treatment restriction may lead to an overall milieu of nihilism that influences attitudes of care for patients beyond the DNR orders themselves and recommend that physicians are aware that the relationship between treatment restrictions and mortality may have the potential of a "self-fulfilling prophecy" when estimating prognosis for stroke patients.

END-OF-LIFE CARE IN STROKE

When death is regarded as inevitable, a transition from curative to palliative treatment is made in many stroke patients. This means that all life-sustaining treatment are suspended and the focus of care is shifted to keeping the patient's remaining life as comfortable as possible. Since death frequently occurs after acute stroke, palliative end-of-life care is common practice on a stroke unit, but evidence to guide optimal practices is very scarce. In chapter 7, I present the results of an observational study in patients that died on the stroke unit in the University Medical Center. Relatives of the patients, as well as the nurses that treated them during end-of-life care, were asked to rate the patient's overall "quality of dying", as well as their experience with several components of the dying

phase. I conclude that most relatives were satisfied with the overall "quality of dying" and with the care provided by doctors and nurses. Negative experiences were mostly related to feeding, inability to say goodbye to loved ones, appearing not to have control and not retaining a sense of dignity. Breathing difficulties were reported as a frequently occurring symptom in the dying phase, but palliative medication adequately resolved discomfort in most patients. I conclude that these findings highlight the importance of counselling family members on what to expect in terms of signs and symptoms during the end-of-life phase. There was a generally good correlation between the experiences of nurses and relatives. Therefore, I suggest that nurses can reliably assess the experiences of the family members and could be used when evaluating end-of-life care for acute stroke patients in future research.

Nederlandse samenvatting (summary in Dutch)

Een acute beroerte is een ernstige aandoening en is wereldwijd één van de belangrijkste oorzaken van handicap en overlijden. De meest voorkomende vormen van beroerte zijn een herseninfarct en een hersenbloeding. Bij een herseninfarct is er sprake van een bloedprop die de bloedtoevoer naar een gedeelte van de hersenen blokkeert en daardoor leidt tot schade aan het hersenweefsel. Bij een hersenbloeding scheurt een bloedvat, waardoor bloed de hersenen in stroomt en het hersenweefsel beschadigt. Beide vormen van beroerte geven vergelijkbare symptomen, die bestaan uit plots optredende uitvalsverschijnselen. Voorbeelden zijn een eenzijdige verlamming van het aangezicht, arm of been, taalproblemen (afasie) of problemen met spreken en articuleren (dysartrie).

Op dit moment zijn er verschillende behandelopties voor patiënten met een beroerte in het acute stadium. Alle patiënten met een herseninfarct krijgen bloedverdunners om een recidief te voorkomen en worden behandeld op gespecialiseerde afdeling voor patiënten met een beroerte (zogenaamde stroke units). Deze behandelingen kunnen bij vrijwel alle patiënten worden gegeven, maar het effect is bescheiden. In de acute fase van een herseninfarct kan een sterke bloedverdunner via een infuus worden toegediend in een poging de bloedprop op te lossen (intraveneuze trombolyse). Ook kan de bloedprop mechanisch worden verwijderd met een katheter in het bloedvat (endovasculaire behandeling). Deze behandelingen zijn vaak effectief, maar slechts een beperkt aantal patiënten komt hiervoor in aanmerking. Voor patiënten met een hersenbloeding zijn er geen andere bewezen behandelopties dan behandeling op gespecialiseerde stroke units.

COMPLICATIES NA EEN BEROERTE

De prognose na een beroerte wordt in de eerste plaats bepaald door de ernst van de beroerte en de bijbehorende symptomen. Daarnaast ontwikkelen patiënten vaak secundaire complicaties in de dagen na de beroerte. Een voorbeeld is slikstoornissen, waardoor speeksel, voeding en vocht de longen bereiken en kunnen leiden tot een longontsteking (aspiratiepneumonie). Ook zijn patiënten met een beroerte gevoeliger voor het ontwikkelen van een urineweginfectie. Infecties leiden vervolgens vaak tot koorts, wat op zich ook weer gepaard gaat met een slechtere prognose. Van al deze complicaties is bekend dat ze een negatief effect hebben op de uitkomst op de langere termijn. Op de stroke unit wordt er nauwkeurig gelet op deze complicaties en als ze optreden worden ze behandeld met antibiotica (zoals ceftriaxon), paracetamol (om koorts te verlagen) en metoclopramide (om maaglediging te bevorderen). Op dit moment is het echter onduidelijk of het mogelijk en zinvol is om deze veelvoorkomende complicaties te voorkomen door deze middelen al vroeg na het ontstaan van de beroerte preventief in te zetten. In hoofdstukken 2 en 3 van dit proefschrift presenteer ik de rationale en de opzet van de PRECIOUS-studie, die is ontworpen met het doel om deze vraag te beantwoorden. In mijn ogen heeft deze studie potentie om de effectiviteit

van deze behandeling aan te tonen, voornamelijk omdat het zich specifiek richt op een patiëntengroep die extra gevoelig is voor het ontwikkelen van complicaties: ouderen met een ernstige beroerte. Daarnaast benoem ik een aantal sterke punten in het ontwerp van de studie, die bijdragen aan het genereren van bruikbare en betrouwbare data. Een voorbeeld hiervan is het gebruik van drie videobeoordelingen om het primaire uitkomstpunt van de studie te bepalen.

Omdat er bij het originele eindpunt van de PRECIOUS-studie in november 2020 te weinig patiënten waren geïncludeerd, was een verlenging van het project met twee jaar noodzakelijk. Daardoor was het bij het schrijven van dit proefschrift helaas niet mogelijk om de resultaten van de studie op te nemen. Er zijn meerdere redenen voor deze vertraging te geven, maar één van de belangrijkste was het tijdsverlies bij het aanvragen en verkrijgen van de verplichte goedkeuringen voor een wetenschappelijk studie in de verschillende centra. In hoofdstuk 4 geef ik een overzicht van de tijd die het verkrijgen van deze goedkeuringen kostte voor de meer dan 80 centra die deelnemen aan PRECIOUS. Samen met mijn collega's heb ik de verschillende tussenstappen in dit proces geanalyseerd en heb ik geconcludeerd dat het sluiten van een contract met de studiecentra het meest tijdrovende onderdeel was. In de resultaten valt op dat de centra die meer tijd nodig hadden voor het afronden van het onderzoekscontract, in de eerste zes maanden na opening minder patiënten voor de studie rekruteerden. Dit zou een gevolg kunnen zijn van verlies van enthousiasme en momentum. We doen een aantal suggesties hoe dit proces in de toekomst verbeterd zou kunnen worden, waarbij we de nadruk leggen op het belang van internationaal geaccepteerde templates voor onderzoekcontracten en op het instellen van deadlines voor juridische toetsing van deze overeenkomsten. Dit zou de tijd die juristen van onderzoekscentra krijgen voor contractonderhandelingen aanzienlijk verkorten en daarmee de kans vergroten dat wetenschappelijke onderzoeken het beoogde aantal patiënten includeren.

CHIRURGISCHE DECOMPRESSIE VOOR EEN HERSENINFARCT MET MASSAWERKING

Na een herseninfarct kan zwelling optreden van het beschadigde hersenweefsel. Doordat de hersenen door de starre schedel worden omvat, leidt deze massawerking tot verhoging van de druk in de schedel (intracraniële druk). Verplaatsing van hersenweefsel en een verhoogde druk in het hoofd kunnen functiebeperkingen geven van andere hersengebieden dan die van het infarct alleen en kunnen, indien onbehandeld, leiden tot het overlijden van de patiënt. Chirurgische decompressie, waarbij zowel de schedel als de hersenvliezen worden geopend, kan de intracraniële druk verlagen en daarmee het overlijden voorkomen. De meeste patiënten houden echter een ernstige handicap over na deze behandeling en daardoor is het gebruik ervan controversieel. Ook is onbekend of bepaalde kenmerken van de patiënt of kenmerken van de beroerte invloed hebben op de uitkomst van de behandeling en welke kenmerken kunnen worden gebruikt om het succes van de behandeling te voorspellen. In hoofdstuk 5 presenteer ik de resultaten van een meta-analyse over dit onderwerp, waarvoor ik samenwerkte met een groep internationale onderzoekers. Voor deze meta-analyse combineerden we

individuele patiëntdata van vrijwel alle klinische studies die op dit gebied zijn verricht. We concluderen dat chirurgische decompressie niet alleen de kans op overlijden sterk verkleint, maar ook de kans op een gunstige functionele uitkomst significant vergroot. In een subgroepanalyse vonden we geen aanwijzingen dat de uitkomst van de behandeling wordt beïnvloed door geslacht of leeftijd van de patiënt, de ernst of omvang van de beroerte of de tijd tussen de behandeling en het ontstaan van de beroerte. Wel moet worden opgemerkt dat weinig patiënten langer dan 48 uur na het ontstaan van de beroerte werden behandeld. Hierdoor zijn de beschikbare gegevens over het effect van deze late behandeling zeer beperkt en worden aanbevelingen voor de klinische praktijk bemoeilijkt. Ook valt op dat de individuele studies waarvan we data gebruikten voor deze meta-analyse zeer verschillende percentages rapporteren van oudere patiënten (>65 jaar) met een gunstige uitkomst, ondanks het gebruik van een vergelijkbare studieopzet. Dit verschil is voor ons niet goed te verklaren en dit maakt het lastig om een consistente conclusie over het behandeleffect in deze patiëntengroep te trekken.

BEHANDELBEPERKINGEN NA EEN BEROERTE

Ongeveer een derde van de patiënten overlijdt in de eerste maand na een beroerte. Veel van deze patiënten overlijden in het ziekenhuis nadat een beslissing is genomen om af te zien van een levensreddende handeling, zoals reanimatie, opname op de Intensive Care afdeling of het niet behandelen van een infectie. Deze behandelbeperkingen worden vaak afgesproken vanwege de verwachting dat de situatie waarin de patiënt verder zal leven niet in lijn is met hoe de patiënt het gewild zou hebben. De meeste patiënten met een beroerte zijn door de gevolgen van de ziekte niet in staat om zelf deel te nemen aan de gesprekken over behandelbeperkingen en zorgverleners zijn daarom vaak aangewezen op familieleden om de wensen en voorkeuren van de patiënt te verwoorden.

Bij de beslissing om een behandelbeperking in te stellen wordt uitgegaan van een betrouwbare en onmiskenbaar slechte prognose van de patiënt. Bij het inschatten van de prognose na een beroerte kunnen artsen gebruik maken van patiëntkenmerken (zoals leeftijd en voorgeschiedenis) en kenmerken van de beroerte (zoals type en ernst). Eerder onderzoek bij mensen met hersenbloeding toonde echter dat ook de behandelbeperkingen zelf een onafhankelijke rol spelen bij het risico op overlijden van de patiënt. In hoofdstuk 6 presenteer ik de resultaten van een analyse naar het effect van behandelbeperkingen bij patiënten die werden behandeld na een beroerte op de stroke unit van het Universitair Medisch Centrum in Utrecht. Ik concludeer dat de aanwezigheid van een behandelbeperking sterk geassocieerd is met overlijden binnen 90 dagen na het ontstaan van de beroerte, zelfs na correctie voor belangrijke prognostische factoren zoals leeftijd en voorgeschiedenis van de patiënt en ernst en type van de beroerte. Deze relatie lijkt sterker bij patiënten met een herseninfarct dan bij patiënten met een hersenbloeding. Opvallend is dat de aanwezigheid van slechts een niet-reanimeren afspraak onafhankelijk geassocieerd is met mortaliteit, terwijl geen van de patiënten met deze behandelbeperking overleden is door een oorzaak die door reanimatie voorkomen had kunnen worden. Dit suggereert dat de behandelbeperkingen in de praktijk kunnen leiden tot een attitude van nihilisme ten aanzien van de zorg voor de patiënt en ook de

onderdelen van zorg kunnen beïnvloeden die buiten de omvang van de afgesproken behandelbeperking liggen. Ik benadruk dat er sprake is van een potentiële "self fulfilling prophecy" als patiënten van wie verwacht wordt dat de prognose slecht is, door het instellen van een behandelbeperking ook daadwerkelijk een slechtere uitkomst bereiken. Artsen zouden zich bewust moeten zijn van de relatie tussen behandelbeperkingen en mortaliteit en ervoor moeten waken dat een behandelbeperking effect heeft op het gedeelte van de zorg dat niet is opgenomen in de behandelbeperking.

ZORG IN DE TERMINALE FASE NA EEN BEROERTE

Als het overlijden van een patiënt met een beroerte onvermijdelijk lijkt, wordt in veel gevallen gekozen voor palliatieve zorg. Dit betekent dat het doel van de behandeling niet langer gericht is op het verlengen van het leven van de patiënt, maar dat ernaar wordt gestreefd om het resterende deel van het leven zo comfortabel mogelijk te maken. Aangezien overlijden vaak voorkomt na een beroerte, is dit een situatie waar vasculaire neurologen in de praktijk vaak mee geconfronteerd worden. Desalniettemin is er een gebruik aan wetenschappelijk bewijs om te dienen als leidraad voor dit type zorg. In hoofdstuk 7 bespreek ik de resultaten van een observationele studie die we hebben verricht bij patiënten met een beroerte die overleden op de stroke unit van het UMC Utrecht. In deze studie hebben we de ervaringen van nabestaanden en behandelend verpleegkundigen met betrekking tot de kwaliteit van sterven geanalyseerd, waarbij we ook navraag hebben gedaan naar de ervaringen met specifieke onderdelen van het stervensproces. Hieruit komt naar voren dat nabestaanden over het algemeen tevreden zijn met de kwaliteit van sterven, als ook met de kwaliteit van de zorg die geleverd wordt door artsen en verpleegkundigen. Negatieve ervaringen hadden voornamelijk te maken met voeding, geen afscheid kunnen nemen, geen controle lijken te hebben over de situatie, of het verlies van waardigheid. Moeilijkheden met ademhalen werden door de nabestaanden benoemd als vaak voorkomende symptoom tijdens de stervensfase, maar in de meeste gevallen werden de symptomen effectief behandeld door de palliatieve medicatie. Deze resultaten benadrukken dat het belangrijk is om familieleden goed te begeleiden en voor te bereiden over wat ze kunnen verwachten met betrekking tot symptomen tijdens de terminale fase. We concluderen daarnaast dat de ervaringen van nabestaanden en behandelende verpleegkundigen goed met elkaar overeenkwamen, wat suggereert dat verpleegkundigen betrouwbaar de ervaringen van nabestaanden kunnen inschatten. Dit betekent naar mijn mening dat de ervaringen van verpleegkundige in toekomstig onderzoek gebruikt zouden kunnen worden bij het evalueren van terminale zorg voor patiënten met een beroerte.

Curriculum Vitae

Hendrik (Rik) Reinink was born on December 29th 1988, in Wageningen, the Netherlands as the son of Kees Reinink and Ina van Trijp. He grew up in Wageningen and Delft with his brother Frank.

In 2006, he graduated from secondary school (Christelijk Lyceum Delft) and started medical school at Utrecht University. During medical school he performed a scientific project at the department of Neurology and Neurosurgery on perivascular spaces on 7T MRI under supervision of dr. Willem Bouvy and prof. dr. Geert Jan Biessels.

He started the Neurology Residency program at the University Medical Center in Utrecht in 2014 (supervisors: prof. dr. John Wokke, prof. dr. Tatjana Seute and prof. dr. Geert Jan Biessels). In 2021 and 2022, he completed internships in movement disorders at the Radboud University Medical Center in Nijmegen (supervisors: prof. dr. Bas Bloem and dr. Bart Post) and in Multiple Sclerosis at the St Antonius Hospital (supervisors: dr. Erwin Hoogervorst and dr. Stephan Frequin) and the Amsterdam UMC, location VUmc (supervisor: dr. Bob van Oosten).

In 2015, he started his PhD on complications, treatment restrictions and end-of-life care in patients with acute stroke at the department of Neurology and Neurosurgery of the UMC Utrecht (promotors: prof. dr. Bart van der Worp and prof. dr. Jaap Kappelle; copromotor: dr. Marjolein Geurts). During this period, he was study coordinator of the PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) trial and the Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR-ASAP) trial.

He was a member of the board of the Dutch Association of Neurology Residents (Vereniging Arts-Assistenten in opleiding tot Neuroloog, VAAN) and advisor to the board of the Dutch Society for Neurology (Nederlandse Verenging voor Neurologie, NVN) from 2018 to 2022.

Currently, Rik is still working as a neurology resident at the UMC Utrecht and is expected to finish his program in the summer of 2023. Rik lives in Utrecht together with his wife Merel. His hobbies include football, going out for drinks, cooking and hosting dinner parties, wine tasting and collecting, and karaoke.

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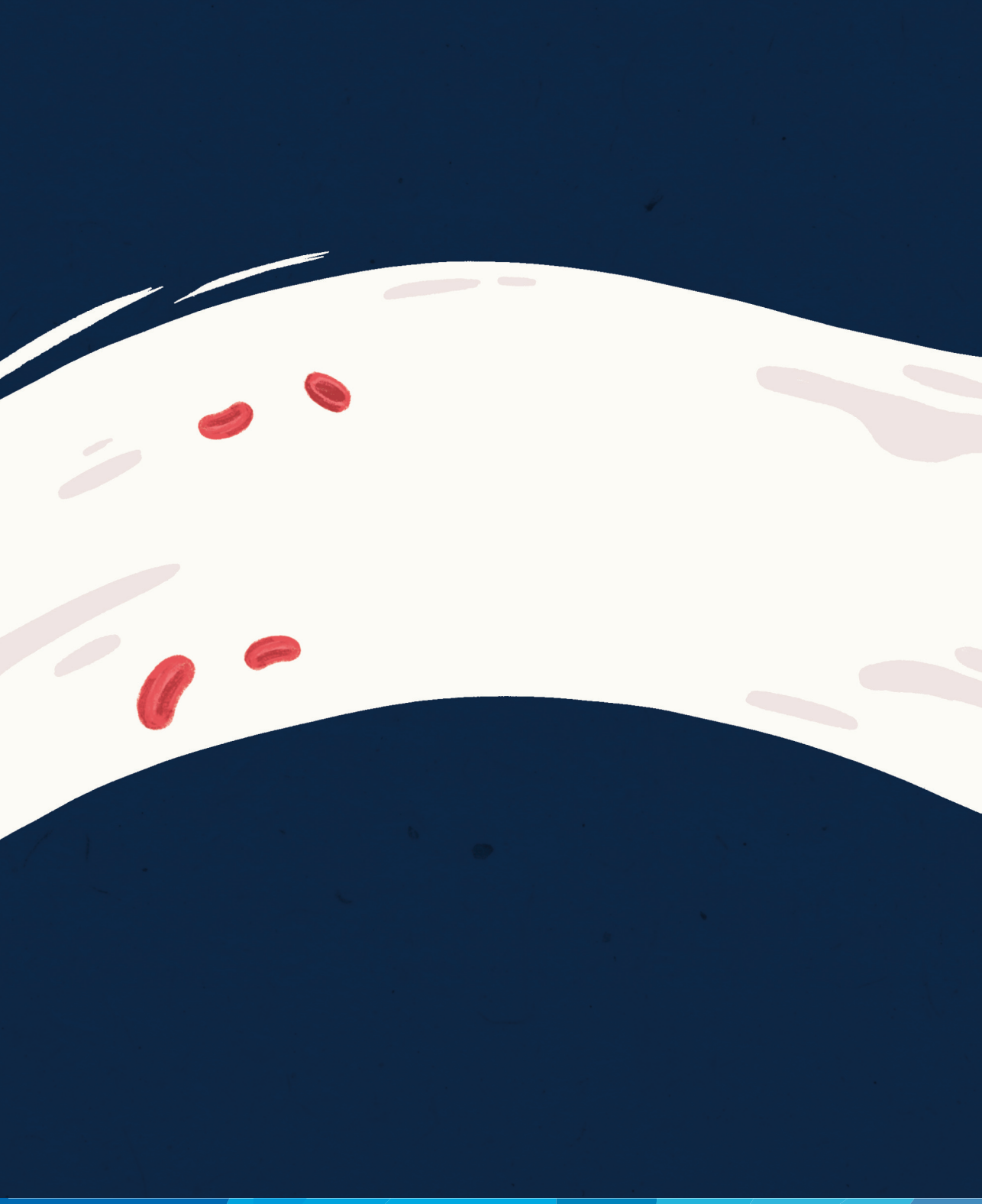

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