TREATMENT AND TREATMENT RESTRICTIONS IN PATIENTS WITH ACUTE ISCHAEMIC STROKE

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TREATMENT AND TREATMENT RESTRICTIONS IN PATIENTS WITH ACUTE ISCHAEMIC STROKE

Behandeling en behandelbeperkingen na een herseninfarct

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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te Tilburg

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Kunst

Wat we willen:
Momenten
Van helderheid
Of beter nog: van grote
Klaarheid

Schaars zijn die momenten
En ook nog goed verborgen

Zoeken heeft dus
Nauwelijks zin, maar
Vinden wel

De kunst is zo te leven
Dat het je overkomt

Die klaarheid, af en toe

Martin Bril

CONTENTS

Chapter 1

General introduction

BACKGROUND

Acute stroke is often a devastating condition. Five years after the event, 70% of patients with stroke are either dead or disabled.[1] Stroke is the fourth common cause of death in the Netherlands, after lung cancer, myocardial infarction and dementia[2] and the second cause of death worldwide.[3] Every year about 45000 patients in the Netherlands have their first stroke.[4] In Western communities, about 80% of strokes are ischaemic; the other strokes are haemorrhagic.[5]

Ischaemic stroke is caused by an occlusion of a cerebral artery or arteriole. More than any other organ, the brain depends on a continuous supply of oxygenated blood. Brain tissue deprived of blood for a sufficient period of time will be damaged irreversibly. The clinical syndrome associated with brain tissue deprived of blood is characterised by the sudden onset of a focal neurological deficit. Common deficits include dysphasia, dysarthria, hemianopia, weakness, ataxia, and sensory loss.

Common causes of an occlusion of a cerebral artery or arteriole are an embolism from the heart, large artery atherosclerosis or small artery disease.

CURRENT TREATMENT STRATEGIES

Over the last two decades, stroke has changed from an untreatable disease, to a condition with options for acute interventions. Current treatment strategies include aspirin, intravenous thrombolysis, endovascular treatment and decompressive hemicraniectomy.

In the acute stage, aspirin can prevent a poor functional outcome. The benefit of aspirin is small: 79 patients have to be treated to prevent poor outcome in one patient.[6] However, aspirin is widely available and can be given to a broad range of patients with acute ischaemic stroke. Intravenous thrombolysis with alteplase can prevent a poor functional outcome in a substantial number of patients, when treated within 4.5 hours after symptom onset. However, even in a densely populated country with short distances to hospitals such as the Netherlands, only 6 to 22% of the patients receive this therapy.[7] In other high-income countries, intravenous thrombolysis rates are usually below 10%.[8] Endovascular treatment of an occlusion of a proximal intracranial artery improves clinical outcome when initiated within 6 hours of symptom onset.[9,10] Seven patients have to be treated to prevent poor outcome in a single patient,[11] and the number of patients eligible for endovascular treatment is small.

In patients with a space-occupying ischaemic stroke up to 60 years, decompressive hemicraniectomy within 48 hours after stroke onset increases survival and improves functional outcome, with absolute risk reductions compared with conservative treatment of 50 and 51%, respectively.[12] The same is true for older patients with a space-occupying ischaemic stroke, although the treatment effects are smaller than in younger patients.[13]

Finally, stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke.[14]

Despite the current treatment strategies, about half of patients have a poor functional outcome after acute ischaemic stroke. New treatments strategies are clearly needed.

Hypothermia as a new treatment strategy for acute ischaemic stroke

Therapeutic hypothermia, the intentional reduction of body temperature, is a promising new treatment for acute ischaemic stroke. Animal models show that hypothermia affects multiple pathways in the cascade that leads from ischaemia to cell death. These include energy depletion, disruption of the blood-brain barrier, free radical formation, excitotoxicity, and inflammation.[15,16]

In a systematic review and meta-analysis of animal studies of focal cerebral ischaemia, including data from a total of 3353 animals, hypothermia reduced infarct size by 44% (95% confidence interval (CI), 40 to 47%).[17] In these studies, even modest cooling considerably decreased infarct size.

Therapeutic hypothermia is well established in the management of acute global cerebral ischaemia such as anoxic encephalopathy after cardiac arrest and perinatal asphyxia.[18,19]

So far, clinical trials of therapeutic hypothermia in patients with acute ischaemic stroke have been too few and too small to allow any conclusions. Four randomized phase II clinical trials have assessed the feasibility of therapeutic hypothermia in awake patients with acute ischaemic stroke,[20-23] including a total of 176 patients. Cooling methods, target temperatures, duration of cooling, and time from stroke onset to initiating of cooling varied considerably across these studies. The feasibility of different target temperatures has not been investigated.

In part I of this thesis, I focus on the feasibility and safety of therapeutic hypothermia as a new treatment strategy for acute ischaemic stroke.

END-OF-LIFE DECISIONS IN STROKE

Despite the advances of acute stroke treatment in recent decades, the current lack of curative treatments means that many patients with stroke have a poor outcome. Around 14% of patients with ischaemic stroke[1] and 50% of patients with intracerebral haemorrhage[24] die within 30 days of their stroke. A substantial part of stroke survivors are left dependent on others for everyday activities.[1,25]

Most in-hospital deaths of patients with acute stroke follow a decision to withhold or withdraw life-sustaining treatments.[26,27] These treatment restrictions usually evolve from complex discussions that encompass prognosis, patient preferences, and institutional and societal norms

and values. Treatment restrictions in patients with stroke differ from those in patients in the terminal phase of most other diseases, because continuation of treatment often allows patients to live for months or years, but at the cost of being left in a state of disability that might be against their wishes.[26,28]

The end-of-life decision-making process in stroke patients is fraught with difficulty for several reasons.

First, outcomes after stroke are hard to predict, and prognostic models are not sufficiently accurate to serve as the sole basis of decisions to limit treatment. Second, what constitutes an acceptable outcome after stroke differs per individual patient. A poor functional outcome is associated with a reduced quality of life,[29,30] but exceptions to this rule exist.[31,32] Moreover, patients who have always considered dependency a fate worse than death might change their opinion once they find themselves in that situation. This can be explained by the response shift phenomenon: the change of internal standards, values and the conceptualization of quality of life after an important life event.[33]

Most stroke patients in whom treatment restrictions are considered have lost their capacity to participate in the end-of-life decision making process, which further complicates this process. The instalment of treatment restrictions in the acute phase after stroke has been associated with an increased risk of death, thereby making self-fulfilling prophecies a serious threat in the end-of-life decision making process.[27,34,35]

Although the process of making end-of-life decisions in patients with stroke is routine in clinical practice, it has received little attention in the medical literature, especially when compared with similar decisions in patients with a more gradually progressive severe illness such as cancer or amyotrophic lateral sclerosis (ALS). Many neurologists receive little training in how or when to address end-of-life issues in stroke patients.

In part II of this thesis, I focus on the challenges that accompany the end-of-life decision making process in patients with acute stroke.

OUTLINE OF THIS THESIS

PART I Hypothermia as a new treatment strategy for acute ischaemic stroke

In **chapter 2** I assess the temporal profile of the relation between body temperatures during the first three days after ischaemic stroke on the one hand, and infarct size and functional outcome on the other. In **chapter 3** I study the relation between body temperature and recanalization in patients with acute ischaemic stroke, treated with or without intravenous alteplase. In **chapter 4** I present the results of a phase II randomized clinical trial assessing the feasibility and safety of surface cooling to 34.0°C, 34.5°C, and 35.0°C for 24 hours in awake patients with acute ischaemic stroke on a stroke unit. In **chapter 5** I present the results of a systematic review and meta-analysis of all randomized trials of therapeutic hypothermia, irrespective of indication, to assess whether therapeutic hypothermia is associated with an increased risk of infections.

PART II Challenges in the end-of-life decision making process after acute stroke

Chapter 6 provides a review of the evidence to guide end-of-life decisions in patients with severe acute brain injury. I address the judgement of prognosis, the possibilities to respect the patient's autonomy despite incapacity, and the adaptation of patients to life with severe disability. In **chapter 7** I assess the relation between the instalment of treatment restrictions and mortality in patients who had survived the first four days after severe ischaemic stroke or intracerebral haemorrhage. In **chapter 8** I assess the predictive accuracy of treating physicians' estimates on mortality, functional outcome and quality of life at six months after severe ischaemic stroke or intracerebral haemorrhage. In **chapter 9** I present functional outcome and quality of life three years after severe stroke and inclusion in the randomized Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET). **Chapter 10** describes the role of advanced directives and proxy opinions in end-of-life decisions after severe stroke.

Finally, in **chapter 11** I review the main findings of this thesis and its implications for clinical practice and future research.

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PART I

Hypothermia as a new treatment strategy for acute ischaemic stroke

Chapter 2

Temporal profile of body temperature in acute ischaemic stroke: relation to infarct size and outcome

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BMC Neurol. 2016;16:233

ABSTRACT

Background: High body temperatures after ischaemic stroke have been associated with larger infarct size, but the temporal profile of this relation is unknown. We assess the relation between temporal profile of body temperature and infarct size and functional outcome in patients with acute ischaemic stroke.

Methods: In 419 patients with acute ischaemic stroke we assessed the relation between body temperature on admission and during the first three days with both infarct size and functional outcome. Infarct size was measured in milliliters on CT or MRI after three days. Poor functional outcome was defined as a modified Rankin Scale score ≥3 at three months.

Results: Body temperature on admission was not associated with infarct size or poor outcome in adjusted analyses. By contrast, each additional 1.0°C in body temperature on day 1 was associated with 0.31 ml larger infarct size (95% confidence interval (CI) 0.04–0.59), on day 2 with 1.13 ml larger infarct size (95% CI, 0.83–1.43), and on day 3 with 0.80 ml larger infarct size (95% CI, 0.48–1.12), in adjusted linear regression analyses. Higher peak body temperatures on days two and three were also associated with poor outcome (adjusted relative risks per additional 1.0°C in body temperature, 1.52 (95% CI, 1.17–1.99) and 1.47 (95% CI, 1.22–1.77), respectively).

Conclusions: Higher peak body temperatures during the first days after ischaemic stroke, rather than on admission, are associated with larger infarct size and poor functional outcome. This suggests that prevention of high temperatures may improve outcome if continued for at least three days.

BACKGROUND

Acute ischaemic stroke is a devastating disease, leaving more than half of patients with a poor functional outcome.[1] High body temperatures in the early stage after ischaemic stroke have consistently been associated with poor functional outcome.[2-13] Preclinical studies suggest that hyperthermia increases metabolic demands, release of neurotransmitters, free-radical production and breakdown of the blood–brain barrier after cerebral ischaemia, hereby increasing cell death and infarct volume.[14]

The association between body temperature and infarct size in patients with ischaemic stroke is however still controversial, mainly when it comes to the temporal profile of this association. Two studies did not find a relation with body temperatures on admission[4] or after 6–12 hours.[15] One study did show an association between infarct size and body temperature on admission,[11] and two between infarct size and body temperature at 24 hours.[3,6] Temperature assessment in all studies was limited to the first 24 hours after stroke onset.

The temporal profile of the association between body temperature and functional outcome or death also show inconsistent results. Several studies have suggested that this is limited to body temperatures on admission or during the first day,[3,5,6,10,11,13] whereas others have found that this relation persists for up to one week[2,7-9,12] These inconsistencies may be attributed to differences in study designs and populations,[8] for example related to the time of admission,[13] the definition of a poor outcome outcome,[11] and selection of patient populations.[3,10]

In this study, we assessed the temporal profile of the relation between body temperatures during the first three days after ischaemic stroke and infarct size and functional outcome.

METHODS

This is a substudy of the Dutch acute Stroke study (DUST). Patients older than 18 years were included between May 2009 and August 2013 if they had symptoms suspected to be caused by ischaemic stroke. Inclusion criteria were symptom duration <9 hours, and National Institutes of Health Stroke Scale (NIHSS) ≥2, or ≥1 if intravenous thrombolysis with recombinant tissue type plasminogen activator (IV-rtPA) was indicated. Patients were not eligible if another diagnosis on non contrast CT (NCCT) such as intracranial haemorrhage explained the symptoms. Patients with an unknown onset time were included if the elapsed time between the time they were last seen without symptoms and imaging was <9 hours.[16]

We selected patients enrolled at the five of 14 DUST study centers that had included over 100 patients. Tympanic or rectal temperatures over the first 72 hours after stroke onset were retrospectively collected from patients' charts by one single investigator (FEVS), who was blinded for outcome measures. For each patient, we recorded the mean body temperature and the peak body temperature (highest body temperature) on days one to three after admission. Body temperature on admission was defined as the first recorded body temperature within six hours after admission; day one as the first 24 hours after stoke onset, day two as 24 to 48 hours, and day three as 48 to 72 hours after stroke onset. Patients were included if at least one body temperature was recorded.

Infarct size was measured three (± two) days after symptom onset. The default follow-up imaging modality was non contrast CT (NCCT) after 3 days or at the time of clinical deterioration or earlier discharge. Follow-up MRI was used if this had been performed for clinical reasons instead of NCCT. Infarct volume was obtained by manually delineating the hypodense infarcted area(s) on axial NCCT slices and hyper-intense area(s) on axial DWI slices on MRI. The surface of these area(s) was subsequently multiplied by the slice thickness to obtain the infarct volume.[16] Patients with no visible infarct on follow-up scan were included in the analyses with an infarct volume of 0 milliliter. Functional outcome was measured with the modified Rankin Scale (mRS) at 90 days by a trained research nurse or neurologist. Poor outcome was defined as mRS ≥3.

The primary outcome measure was infarct volume (ml) at three days. The relation between each additional 1.0°Celsius in body temperature and infarct size was calculated by means of linear regression, and the relation between body temperatures and functional outcome with Poisson regression analysis with a robust error. The relation was expressed as regression coefficient (B) or relative risk (RR) with corresponding 95% confidence interval (CI), respectively. We adjusted for age, sex, previous stroke, hypertension, diabetes mellitus, current smoking, treatment with intravenous alteplase, intra-arterial treatment, and National Institutes of Health Stroke Scale (NIHSS) score on admission, with backward stepwise regression with 0.10 alpha levels of removal. Potential confounders were selected on basis of known associations with the outcome. We considered a p-value ≤0.05 significant.

The study was approved by institutional review board of the initiating center (University Medical Center Utrecht), and written informed consent was obtained for each patient.

RESULTS

Of 1393 patients included in DUST, 696 were included in the five selected centers. We included 419 of these patients for the present study, after excluding 173 patients without follow-up imaging, 66 without a recorded body temperature available and 38 with an other diagnosis than ischaemic stroke (Figure 2.1).

The mean age of the patients was 66 years (SD 13); 256 (61%) were male. Additional patient characteristics are presented in Table 2.1. Follow-up imaging was performed with CT (95%) or MRI (5%). Patients without follow-up imaging were older (70 vs 66 years, p=0.001), were more often men, and had a higher median NIHSS score on admission (7 vs 6, p=0.02; Table 2.1).

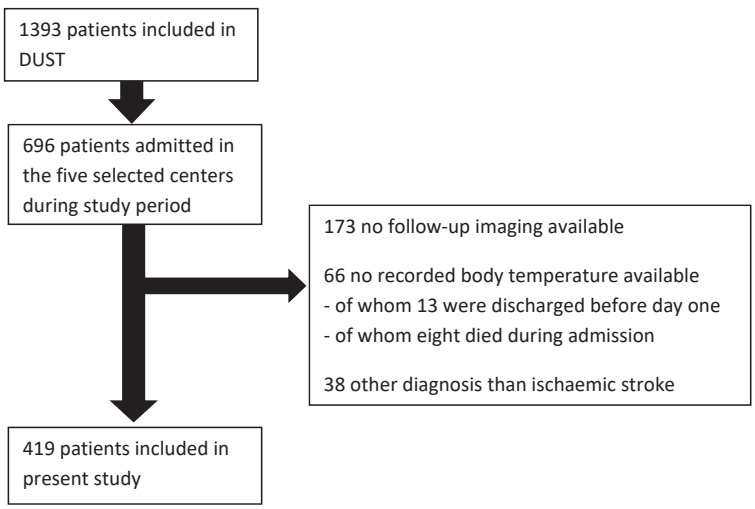

Figure 2.1. Flow of patients through this study.

Table 2.1. Patient characteristics

	Included patients (n=419)	Patients without follow-up imaging (n=173)	p
Age (years)	66 (13)	70 (15)	0.001
Men	256 (61)	84 (49)	0.01
Body temperature on admission (°C)	36.7 (0.6)	36.7 (0.8)	0.94
NIHSS on admission	6 (10)	7 (10)	0.02
Hypertension	206 (49)	102 (59)	0.25
Diabetes mellitus	65 (16)	23 (13)	0.49
Current smoking	122 (29)	38 (22)	0.39
Previous stroke	88 (21)	43 (25)	0.38
TOAST			0.66
Large-artery atherosclerosis	130 (31)	51 (30)	
Cardioembolism	79 (19)	33 (19)	
Small vessel disease	49 (12)	16 (9)	
Other	24 (6)	4 (9)	
Unknown	137 (32)	58 (33)	
Posterior circulation stroke	14 (3)	2 (3)	0.67
Treatment with intravenous alteplase	249 (59)	112 (65)	0.29
Intra-arterial treatment	26 (6)	11 (6)	0.94
Poor outcome (mRS ≥3)	144 (34)	71 (41)	0.11

Data are n (%), median (range), median (interquartile range (IQR)) or mean (standard deviation (SD)) where appropriate. NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification; mRS, modified Rankin Scale.

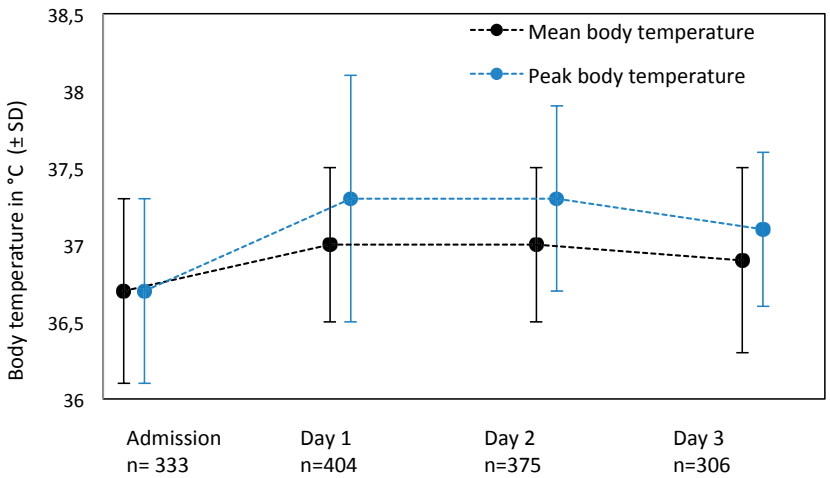

Figure 2.2. Course of body temperatures in the first three days after stroke onset.

At follow-up, median infarct volume was 1.5 ml (range, 0–500 ml) in the total study population of 419 patients. There were 131 (31%) patients without a visible infarct on follow up imaging, i.e. an infarct volume of 0 ml. The mean body temperatures during the first three days are presented in Figure 2.2.

A total number of 406 patients had at least one body temperature recorded at day one, 376 patients at day two, and 308 patients at day three. The mean peak body temperature on day one was 37.3°C (SD 0.8), on day two 37.3°C (SD 0.6), and on day three 37.1°C (SD 0.5; Figure 2.1). Mean and peak body temperatures were higher at days one, two and three than on admission ($p<0.001$ for all days).

Higher peak body temperatures on days one, two and three after stroke onset were associated with larger infarct size. In adjusted linear regression analyses, each additional 1.0°C in body temperature on day 1 was associated with 0.31 ml larger infarct size (95% CI, 0.04–0.59), on day 2 with 1.13 ml larger infarct size (95% CI, 0.83–1.43), and on day 3 with 0.80 ml larger infarct size (95% CI, 0.48–1.12) (Figure 2.3, Table 2.2). Peak body temperatures on days two and three were also associated with a poor outcome (Figure 2.4, Table 2.2). With every additional 1.0°C in peak body temperature on days two and three, the risk of a poor outcome was 52% (95% CI, 17–99%) and 47% (95% CI, 22–77%) larger, respectively. Body temperature on admission was neither related to infarct size nor to functional outcome. Mean body temperatures at days one, two and three were, after adjustment, neither associated with infarct size nor with poor functional outcome.

Subgroup analyses

In a post-hoc subgroup analysis of 288 patients with a visible infarct on follow-up imaging, median infarct volume was 9.6 ml (range, 0.2–500). Results were essentially the same (Table 2.3). In a post-hoc subgroup analysis of 398 patients with CT as follow-up imaging modality, results were essentially the same (data not shown).

DISCUSSION

This study shows that in patients with acute ischaemic stroke, higher peak body temperatures on days one, two and three after stroke onset are associated with larger infarct size. Peak body temperatures on days two and three were also associated with poor functional outcome after three months. Body temperature at admission was neither related to infarct size nor to functional outcome. This is the first study that assesses the temporal profile of the association between body temperature and infarct size in the first days after stroke.

High body temperature after stroke may be the result of infections, which are frequent and have also been associated with poor functional outcome. However, no source of infection could

Table 2.2. The relation between body temperature and infarct size

	Infarct size at day 3 (±2)			Functional outcome at 90 days		
	After adjustment*			After adjustment*		
	B	95% CI	p	RR	95% CI	p
Body temperature on admission (n=333)	-0.15	-0.49–0.18	0.38	0.99	0.77–1.26	0.90
Peak body temperature on day 1 (n=404)	0.31	0.04–0.59	0.02	1.20	0.99–1.46	0.06
Mean body temperature on day 1 (n=404)	0.09	-0.41–0.60	0.71	1.38	0.84–2.28	0.21
Peak body temperature on day 2 (n=375)	1.13	0.83–1.43	<0.001	1.52	1.17–1.99	0.002
Mean body temperature on day 2 (n=375)	-0.27	-0.78–0.26	0.33	0.74	0.33–1.64	0.46
Peak body temperature on day 3 (n=306)	0.80	0.48–1.12	<0.001	1.47	1.22–1.77	<0.001
Mean body temperature on day 3 (n=306)	0.40	-0.18–0.97	0.17	1.64	0.83–3.25	0.16

B, regression coefficient in ml per additional 1.0°C in body temperature; CI, confidence interval.
*Adjusted for age, sex, previous stroke, hypertension, diabetes mellitus, current smoking, treatment with intravenous alteplase, intra-arterial treatment and National Institutes of Health Stroke Scale score on admission.

Table 2.3. Relation between body temperature and infarct size in patients with an infarct of >0 ml

	Infarct size at day 3 (±2)			Functional outcome at 90 days		
	After adjustment*			After adjustment*		
	B	95% CI	p	RR	95% CI	p
Body temperature on admission n=202	0.04	-0.32–0.40	0.83	1.10	0.83–1.48	0.53
Peak body temperature on day 1 n=273	0.26	-0.04–0.57	0.09	1.19	0.95–1.48	0.13
Mean body temperature on day 1 n=273	0.28	-0.43–0.99	0.44	1.23	0.50–3.03	0.65
Peak body temperature on day 2 n=244	0.87	0.53–1.22	<0.001	1.43	1.07–1.91	0.02
Mean body temperature on day 2 n=244	0.06	-0.59–0.72	0.85	0.64	0.27–1.05	0.31
Peak body temperature on day 3 n=175	0.62	0.27–0.97	0.001	1.45	1.14–1.84	0.002
Mean body temperature on day 3 n=175	0.90	0.22–1.60	0.01	1.49	0.73–3.10	0.28

B, regression coefficient in ml per additional 1.0°C in body temperature; CI, confidence interval.
*Adjusted for age, sex, previous stroke, hypertension, diabetes mellitus, current smoking, treatment with intravenous alteplase, intra-arterial treatment and National Institutes of Health Stroke Scale score on admission.

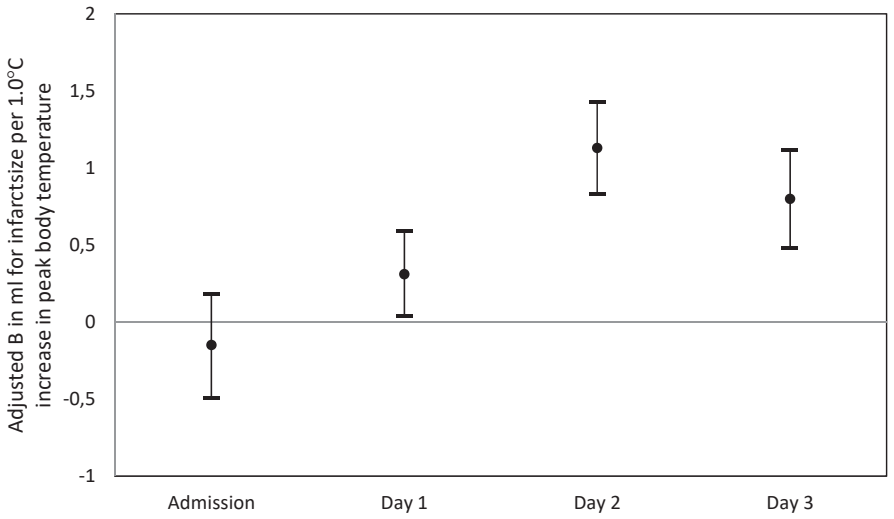

Figure 2.3. Relation between infarct size and peak body temperature.

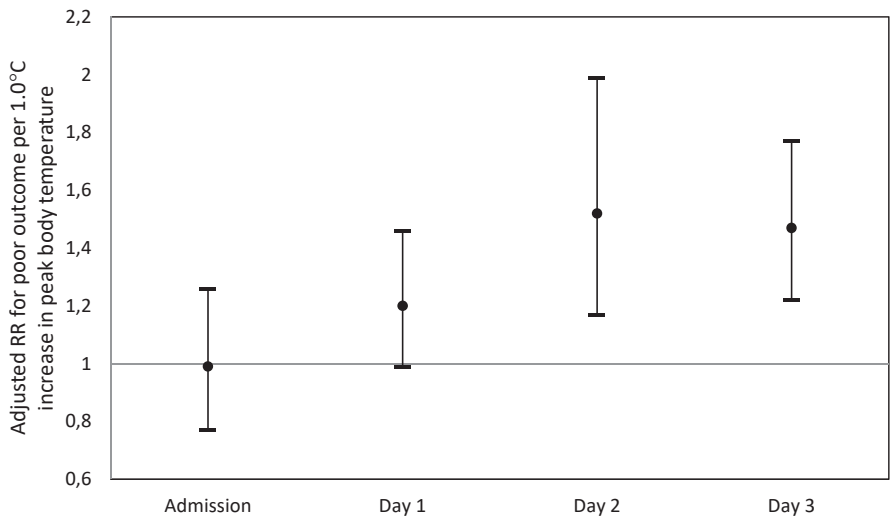

Figure 2.4. Relation between poor functional outcome and peak body temperature.

be found in almost half of the hyperthermic patients in a previous study.[8] Fever could also be the result of an inflammatory response of the body to the infarcted tissue. Additionally, in the first days after stroke temperature-dependent processes which lead to increased extracellular edema, infarct swelling, and restricted capillary flow in the ischaemic tissue, can increase ischaemic damage.[8] Although increased body temperature is often thought to be a reflection of extensive cerebral damage, we found an association between increased body temperature and poor functional outcome that was independent of baseline stroke severity.

If the relation between higher body temperatures and larger infarct volumes and poor functional outcome is at least partially causal, our findings suggest that a reduction in body temperature up to three days after stroke may reduce infarct size and improve functional outcome. In a post-hoc subgroup analysis of the randomized Paracetamol (Acetaminophen) In Stroke (PAIS) trial, treatment with paracetamol for three days was associated with an improvement in functional outcome at three months in patients with a baseline body temperature of 37.0°C or above,[17] supporting the causal relationship between body temperature and functional outcome.

Our study has limitations. First, we had to exclude 173 patients because of lack of follow-up scans, and of the remaining patients we excluded 10% without any recorded temperature. Up to 27% of included patients did not have temperature measurements on one of the three days. We used tympanic and rectal temperatures interchangeably, whereas values may differ between those methods. In addition, patients in our study may have been treated with antipyretics, which could have affected temperature measurements and would underestimate the number of patients with high body temperatures. However, by assessing the peak body temperatures rather than mean temperatures, we aimed to assess body temperatures before administration of antipyretics. This may also explain our finding that mean body temperatures were not related to infarct size or functional outcomes. Of the included patients, one third had no visible infarct on follow-up CT. One could argue that these patients did not suffer from cerebral ischaemia. However, in subgroup analysis including patients with a visible infarct results were essentially the same. We included patients without a visible infarct on follow-up imaging in this substudy to ensure the association we assess applies to all patients with the clinical diagnosis of stroke, including the small strokes and patients that recover completely. Infarct size was measured on either CT or MRI. As the default follow-up modality was CT, it is possible that some smaller infarcts were not detected. However, in subgroup analysis including only patients with CT as follow-up modality, results were essentially the same. With a median NIHSS of 6 on admission, included patients had relatively milder strokes than excluded patients (median NIHSS of 7). Our data may differ in a selection of patients with severe stroke. The time between stroke onset and first measurement of temperature was not predefined in the DUST study protocol. Therefore, the variation between time from stroke onset to first recorded body temperature might have affected our results. We did not have data on the occurrence of infections in our population and could therefore not analyze their relationship with hyperthermia. We present results per 1.0°C, which results in wide confidence intervals. As a result of small patient numbers in extreme body temperature categories, this study is insufficient to detect associations at body temperatures lower than 35.5°C or higher than 38.5°C.

CONCLUSIONS

In conclusion, we found that higher body temperatures in the first days after ischaemic stroke, rather than on admission, are associated with larger infarct size and poor functional outcome. Our findings suggest that prevention of high temperatures in clinical trials may improve outcome if continued for at least three days.

Guidelines recommend the use of antipyretics for febrile patients with stroke, but do not provide a time window.[18] In the randomised Paracetamol (Acetaminophen) In Stroke (PAIS) trial, treatment of patients with a baseline body temperature of 37°C or above with high-dose paracetamol, started within 12 hours of stroke onset and continued for three days, resulted in a temperature reduction of just 0.3°C at 24 hours, but also in an improved outcome at three months.[17] A large phase III trial on the effect of induced hypothermia after stroke is ongoing, cooling patients 12 to 24 hours after their stroke.[19] Future clinical trials should further assess the effect of preventing fever or inducing hypothermia up to at least three days after stroke.

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Chapter 3

No relation between body temperature and arterial recanalization at three days in patients with acute ischaemic stroke

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ABSTRACT

Background: Recanalization of an occluded intracranial artery is influenced by temperature-dependent enzymes, including alteplase. We assessed the relation between body temperature on admission and recanalization.

Methods: We included 278 patients with acute ischaemic stroke within nine hours after symptom onset, who had an intracranial arterial occlusion on admission CT angiography, in 13 participating centres. We calculated the relation per every 0.1°Celsius increase in admission body temperature and recanalization at three days.

Results: Recanalization occurred in 80% of occluded arteries. There was no relation between body temperature and recanalization at three days after adjustments for age, NIHSS score on admission and treatment with alteplase (adjusted odds ratio per 0.1°Celsius, 0.99; 95% confidence interval, 0.94–1.05; p=0.70). Results for patients treated or not treated with alteplase were essentially the same.

Conclusions: Our findings suggest that in patients with acute ischaemic stroke there is no relation between body temperature on admission and recanalization of an occluded intracranial artery three days later, irrespective of treatment with alteplase.

INTRODUCTION

In patients with acute ischaemic stroke, recanalization of the occluded cerebral artery is strongly associated with improved functional outcome.[1] Spontaneous recanalization is influenced by temperature-dependent enzymes,[2] and the *in vitro* activity of alteplase reduces with lower temperatures.[3] Whether body temperature also affects *in vivo* recanalization with or without alteplase is uncertain. This might be important, because guidelines recommend the use of antipyretics in stroke patients with fever[4,5] and two phase III trials of therapeutic hypothermia for ischaemic stroke are in progress.[6,7] We assessed the relation between body temperature and recanalization in patients with acute ischaemic stroke, treated with or without intravenous alteplase.

METHODS

This is a substudy of the Dutch acute Stroke study (DUST), a prospective multi-centre cohort study including adult patients with acute ischaemic stroke within nine hours after symptom onset between May 2009 and July 2013. The design, eligibility criteria, and neuroimaging protocol have been reported previously.[8] All patients underwent non-contrast CT, CT perfusion, and CT angiography (CTA) within 9 hours after symptom onset. In this substudy, we included

patients with visible intracranial arterial occlusion on admission CTA, and follow-up vascular imaging at 3 (±2) days. Patients who received intra-arterial treatment were excluded. Body temperature was recorded on admission.

Stroke severity at admission was assessed with the National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was recorded according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Recanalization was assessed on follow-up vascular imaging and classified as no recanalization on the one hand, or partial or complete recanalization on the other. All scans were centrally evaluated by one of three experienced observers, who were blinded for the clinical data except for the side of symptoms. Poor functional outcome was defined as a modified Rankin Scale (mRS) score ≥3 at 90 days.

Temperature data were retrospectively collected from patients' charts by one investigator, blinded for outcome measures. Body temperature on admission was defined as first recorded body temperature within twelve hours after admission, measured either tympanic or rectal.

The medical ethics committee of the University Medical Center Utrecht approved the DUST study, and written informed consent was obtained from each patient or a legal representative.

Statistical analyses

The relation per 0.1°Celsius increase in admission body temperature and recanalization or functional outcome was calculated by means of logistic regression with a generalized estimating equations model, and expressed as an odds ratio (OR) with a corresponding 95% confidence interval (CI). We adjusted for age, NIHSS score on admission and treatment with alteplase.

Pre-defined subgroup analyses were performed with regard to treatment with alteplase and etiology of stroke. In a separate analysis patients were stratified according to the time of the second CT angiography.

Finally, we performed two additional analyses assuming that either none or all of the patients excluded because of no follow up imaging had recanalization.

RESULTS

Of the 1393 patients in DUST, 643 had an occluded intracranial artery on admission CTA. Reasons for exclusion for the present study were: no follow-up vascular imaging (n=289), no admission body temperature recorded (n=30), or intra-arterial treatment (n=46). We included 278 patients, with 288 occluded intracranial arteries. Patient characteristics are presented in Table 3.1.

Table 3.1. Patient characteristics

	Baseline characteristics n=278
Body temperature on admission (°C)	36.7 (0.6)
Age (years)	66 (14)
Female sex	122 (44)
NIHSS score on admission	11 (7)
Previous stroke	52 (19)
Hypertension	143 (51)
Stroke etiology (TOAST)	
Large-artery atherosclerosis	118 (42)
Cardioembolism	69 (25)
Small vessel disease	0 (0)
Other	20 (7)
Unknown	71 (26)
Current smoking	90 (32)
Diabetes mellitus	28 (10)
Treatment with alteplase	187 (67)

Data are n (%), median (range), median (interquartile range (IQR)) or mean (standard deviation (SD)) where appropriate. NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification.

Location of the most proximal part of the intracranial occlusion was middle cerebral artery in 215 (75%) arteries, posterior cerebral artery in 30 (10%), the intracranial part of the internal carotid artery in 18 (6%), anterior cerebral artery in 10 (4%), basilar artery in 8 (3%), and another artery in 7 (2%) patients. Ten patients had more than one occluded intracranial arteries.

Patients without follow-up imaging were older than patients with follow-up imaging (68 versus 65, p=0.01), had higher NIHSS scores on admission (13 versus 11, p=0.01), and had worse outcomes (median mRS 3 versus 2, p<0.001).

Follow-up imaging was performed at a median of 3 days (IQR 2 days) after admission. Follow-up imaging was CTA (95%) or MR angiography (5%). Recanalization occurred in 229 (80%) of occluded arteries. Partial or complete recanalization was associated with a better outcome compared to no recanalization (median mRS 2 (IQR 3) versus 3 (IQR2), respectively; p=0.01).

Body temperature on admission was not associated with recanalization (OR per 0.1°C, 0.98; 95% CI, 0.93–1.03; p=0.39; adjusted OR (aOR) per 0.1°C, 0.99; 95% CI, 0.94–1.05; p=0.70) (Table 3.2, Figure 3.1), nor with poor outcome (OR per 0.1°C, 0.97; 95% CI, 0.93–1.01; p=0.09).

Because follow-up imaging was missing in a substantial proportion of patients who were otherwise eligible for our study, we performed post-hoc analyses that modelled several scenarios in these patients. In these post-hoc analyses, we included all patients with a visible intracranial

Table 3.2. Results of unadjusted and adjusted logistic regression on the relation between body temperature and recanalization

	Unadjusted			Adjusted for age, NIHSS, and treatment with alteplase			Test of interaction
	OR	95% CI	p	OR	95% CI	p	p
Overall analysis (n=278)	0.98	0.93–1.03	0.39	0.99	0.94–1.05	0.70	NA
Subgroup analyses							
Treatment with alteplase (n=187)	1.02	0.94–1.11	0.66	1.03	0.93–1.13	0.60	
No treatment with alteplase (n=91)	0.96	0.90–1.04	0.32	0.97	0.90–1.04	0.33	0.20
Large artery atherosclerosis (n=118)	0.94	0.87–1.01	0.10	0.95	0.87–1.03	0.22	
Cardio-embolic (n=69)	1.01	0.90–1.13	0.91	1.02	0.88–1.19	0.76	0.42

NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval; NA, not applicable.

arterial occlusion on admission CTA, with or without follow up imaging. Patients who received intra-arterial treatment were excluded.

In a best case scenario assuming that all patients without follow-up imaging had recanalization, body temperature on admission was not associated with recanalization (aOR per 0.1°C, 0.99; 95% CI, 0.95–1.04; p=0.67). The same was found in a worst case scenario assuming that none of the patients without follow-up imaging had recanalization (aOR per 0.1°C, 1.01; 95% CI, 0.98–1.04; p=0.50).

Results stratified by time of the second (follow-up) CT angiography are shown in Table S3.3 (Supplementary data).

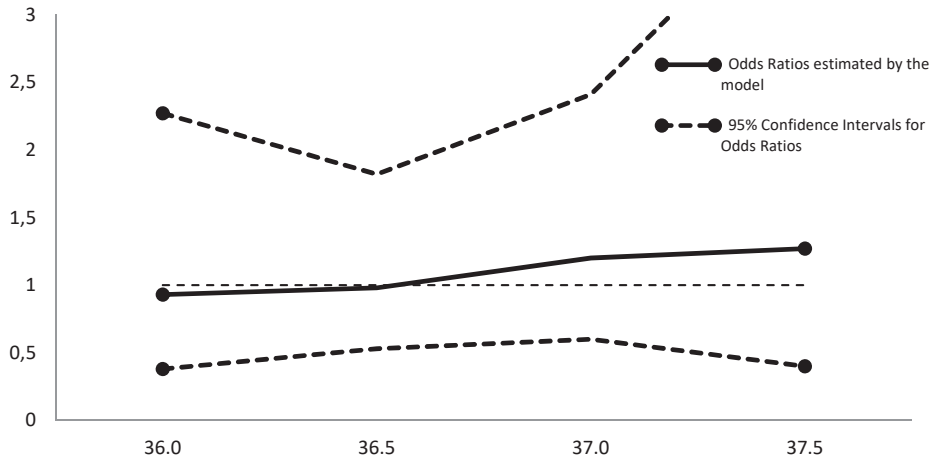

Figure 3.1. Odds ratios for the relation between body temperature on admission and recanalization.

Subgroup analyses

Characteristics of patients in subgroups are presented in Tables S3.1 and S3.2 (Supplementary data). Treatment with iv alteplase was related to recanalization (aOR, 2.44; 95% CI, 1.33–4.28; p=0.004). There was neither difference in the relation between body temperature and recanalization between patients treated or not treated with alteplase, nor between patients with large-artery atherosclerosis and patients with cardioembolic stroke (Table 3.2).

DISCUSSION

Our findings suggest that in patients with acute ischaemic stroke, there is no relation between body temperature on admission and recanalization of an occluded intracranial artery three days later, irrespective of treatment with alteplase.

Most reports on the relation between body temperature and clot lysis concern *in vitro* studies. These have shown a reduced rate of fibrinolysis by alteplase at lower temperatures.[3] However, *in vitro* studies may not adequately reflect the *in vivo* setting of an acute arterial occlusion. Data from animal and human studies are limited. Some clinical studies found an association between higher admission body temperatures and a favourable outcome after thrombolysis with alteplase,[9,10] but others did not.[11] No studies have investigated whether this was related to higher recanalization rates.

We did not find a relation between body temperature on admission and recanalization or functional outcome. Other studies have suggested that increased body temperatures in the first few days, rather than on admission, are related to poor outcome.[12,13]

This study has limitations. Body temperature was assessed at admission and recanalization at three (±2) days. Recanalization occurring after several hours may be of little or no benefit to ischaemic tissue, and clinical consequences of delayed recanalization are therefore limited.[1] Previous studies suggest that body temperatures during the first three days may also have affected recanalization rates.[14,15] However, in this study recanalization was strongly related to alteplase treatment within 4.5 hours, suggesting that most recanalization occurs in the first hours after stroke, and recanalization was associated with improved clinical outcome. The generalizability of our findings is hampered because in numerous patients missed follow-up imaging, but this is unlikely to have a major effect on the findings in this explanatory rather than prognostic study. We did not have data on the occurrence of infections in our population. The inter- or intra-observer variability in the measurement of recanalization was also not determined. Finally, the vast majority of our study population had normal body temperatures. Due to the limited variability in body temperatures, we could not assess associations between recanalization and body temperatures below 36.0°C or above 37.5°C.

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SUPPLEMENTARY DATA

Table S3.1. Baseline characteristics of patients treated and not treated with intravenous alteplase

	Treated with iv alteplase (n=187)	Not treated with iv alteplase (n=91)	p
Age (years)	66 (14)	67 (16)	0.31
Men	107(57)	49 (54)	0.60
Body temperature on admission (°C)	36.6 (0.9)	36.8 (0.5)	0.06
NIHSS on admission	12 (7)	9 (7)	0.01
Hypertension	84 (45)	59 (65)	0.01
Diabetes mellitus	16 (9)	12 (13)	0.23
Current smoking	61 (33)	29 (32)	0.67
Previous stroke	24 (13)	28 (31)	<0.001
TOAST			0.69
Large-artery atherosclerosis	83 (44)	35 (38)	
Cardioembolism	47 (25)	22 (24)	
Small vessel disease	0 (0)	0 (0)	
Other	13 (7)	7 (8)	
Unknown	44 (24)	27 (30)	

Data are n (%), median (range), median (interquartile range (IQR)) or mean (standard deviation (SD)) where appropriate. NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification.

Table S3.2. Baseline characteristics of patients large-artery atherosclerosis and cardio-embolism etiology of stroke

	Large-artery atherosclerosis (n=118)	Cardioembolism (n=69)	p
Age (years)	67 (13)	70 (11)	0.17
Men	70 (59)	44 (64)	0.55
Body temperature on admission (°C)	36.7 (0.6)	36.6 (1.3)	0.63
NIHSS on admission	11 (12)	11 (10)	0.87
Hypertension	63 (53)	40 (58)	0.64
Diabetes mellitus	15 (13)	9 (13)	0.95
Current smoking	37 (31)	21 (30)	0.85
Previous stroke	24 (20)	16 (23)	0.65
Treatment with alteplase	83 (70)	47 (68)	0.75

Data are n (%), median (range), median (interquartile range (IQR)) or mean (standard deviation (SD)) where appropriate. NIHSS, National Institutes of Health Stroke Scale.

Table S3.3. Results of unadjusted and adjusted logistic regression on the relation between body temperature and recanalization, stratified by time of the second CT angiography

	Unadjusted			Adjusted for age, NIHSS, and treatment with alteplase		
	OR	95% CI	p	OR	95% CI	p
Day 0 (n=0)	NA			NA		
Day 1 (n=29)	1.00	0.91-1.11	0.96	1.01	0.91-1.12	0.82
Day 2 (n=50)	0.94	0.73-1.22	0.66	0.97	0.81-1.15	0.69
Day 3 (n=114)	0.99	0.91-1.06	0.70	0.99	0.91-1.08	0.72
Day 4 (n=51)	1.00	0.98-1.12	0.99	1.14	0.98-1.32	0.08
Day 5 (n=34)	0.91	0.76-1.09	0.30	0.89	0.72-1.10	0.29

NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval; NA, not applicable.

Chapter 4

COOLIST: COOLing for Ischaemic Stroke Trial. A multi-center, open, randomized, phase II, clinical trial

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ABSTRACT

Background and purpose: Animal studies suggest that cooling improves outcome after ischaemic stroke. We assessed the feasibility and safety of surface cooling to different target temperatures in awake patients with acute ischaemic stroke.

Methods: A multi-center, randomized, open, phase II clinical trial, comparing standard treatment with surface cooling to 34.0°C, 34.5°C or 35.0°C in awake patients with acute ischaemic stroke and a score on the NIHSS≥6, initiated within 4.5 hours after symptom onset and maintained for 24 hours. The primary outcome was feasibility, defined as the proportion of patients that had successfully completed the assigned treatment. Safety was a secondary outcome.

Results: Inclusion was terminated after 22 patients because of slow recruitment. Five patients were randomized to 34.0°C, six to 34.5°C, five to 35.0°C (cooling was initiated in four) and six to standard care. No (0%), one (17%) and three (75%) patients, respectively, completed the assigned treatment (p=0.03). No (0%), two (33%) and four (100%) patients reached the target temperature (p=0.01). Pneumonia occurred in eight cooled patients but not in controls (absolute risk increase, 53%; 95% confidence interval (CI), 28–79%; p=0.002).

Conclusions: In awake patients with acute ischaemic stroke, surface cooling is feasible to 35.0°C, but not to 34.5°C and 34.0°C. Cooling is associated with an increased risk of pneumonia.

Clinical Trial Registration-URL: http://www.trialregister.nl.
Unique identifier: NTR2616.

INTRODUCTION

Cooling is a promising new treatment for patients with acute ischaemic stroke.[1] In animal studies of acute ischaemic stroke, the benefit of hypothermia was inversely related to the temperature reduction achieved, but infarct size was still reduced by 30% with cooling to 35.0°C.[2]

Few randomized phase II clinical trials have assessed the feasibility of cooling in awake patients with acute ischaemic stroke,[3-6] and cooling strategies varied considerably across these studies. The feasibility of different target temperatures has not been compared.

We assessed the feasibility and safety of surface cooling to 34.0°C, 34.5°C, and 35.0°C for 24 hours in awake patients with acute ischaemic stroke on a stroke unit. The surface cooling protocol was comparable to that in the ongoing phase III study EuroHYP-1.[7]

METHODS

This was a prospective, randomized, open, phase II, clinical trial with blinded end point assessment, registered as NTR2616. The study design and complete eligibility criteria are included in the Supplementary data. In brief, adult patients with a clinical diagnosis of acute ischaemic stroke, a possibility to initiate cooling within 4.5 hours after stroke onset, and a National Institutes of Health Stroke Scale (NIHSS) score ≥6 were randomized to standard care or to cooling to 34.0°C, 34.5°C, or 35.0°C in a 1:1:1:1 ratio.

Cooling was started as soon as possible and within 4.5 hours after stroke onset by means of intravenous infusion of 20 ml/kg cooled normal saline (4°C) over 30 to 60 minutes. Surface cooling was initiated immediately after the start of the infusion and continued for 24 hours. The detailed cooling and rewarming strategies are included in the Supplementary data.

Shivering was assessed with the 4-point Columbia Shivering Scale. The anti-shivering regime is included in the Supplementary data.

The primary outcome measure was feasibility of cooling, defined as the proportion of patients who completed the 24 hours of cooling on the assigned target temperature. Secondary outcome measures included time to target temperature and safety. Tertiary outcome measures were functional outcome at three months and tolerability.

The chi square test, independent t-test, ANOVA, Mann Whitney U test or Kruskal Wallis were used to compare continuous data between the treatment groups where appropriate. Analyses were by intention to treat (baseline, functional outcome), or per protocol (cooling parameters, adverse events).

RESULTS

We included 22 patients in three centers (Supplemental Table S4.1); mean age, 63 years (SD, 12); 19 (86%) male; median score on the NIHSS, 13 (range, 7–23). Five patients were randomized to 34.0°C, six to 34.5°C, five to 35.0°C, and six to standard care. Baseline characteristics are shown in Supplemental Table S4.2. Patients randomized to 35.0°C had a higher median score on the NIHSS than other cooled patients. One patient who was allocated to cooling to 35.0°C completely recovered after randomization but before initiation of cooling. Cooling was therefore not started. All patients were followed-up until 90 days. The trial was stopped in January 2015 because of slow recruitment.

No (0%) patients randomized to 34.0°C, one (17%) to 34.5°C, and three (75%) to 35.0°C in whom cooling was initiated, successfully completed the assigned treatment (p=0.03) (Table 4.1). Completeness of assigned treatment was different between 35.0°C on the one hand and 34.5°C or 34.0°C on the other (p=0.04 and p=0.003, respectively) (Figure 4.1).

No (0%) patients randomized to 34.0°C, two (33%) to 34.5°C, and four (100%) to 35.0°C in whom cooling was initiated, reached their respective target temperatures (p=0.01) (Table 4.1). Reaching target temperature was different between 35.0 and 34.0 (p=0.02) (Figure 4.1).

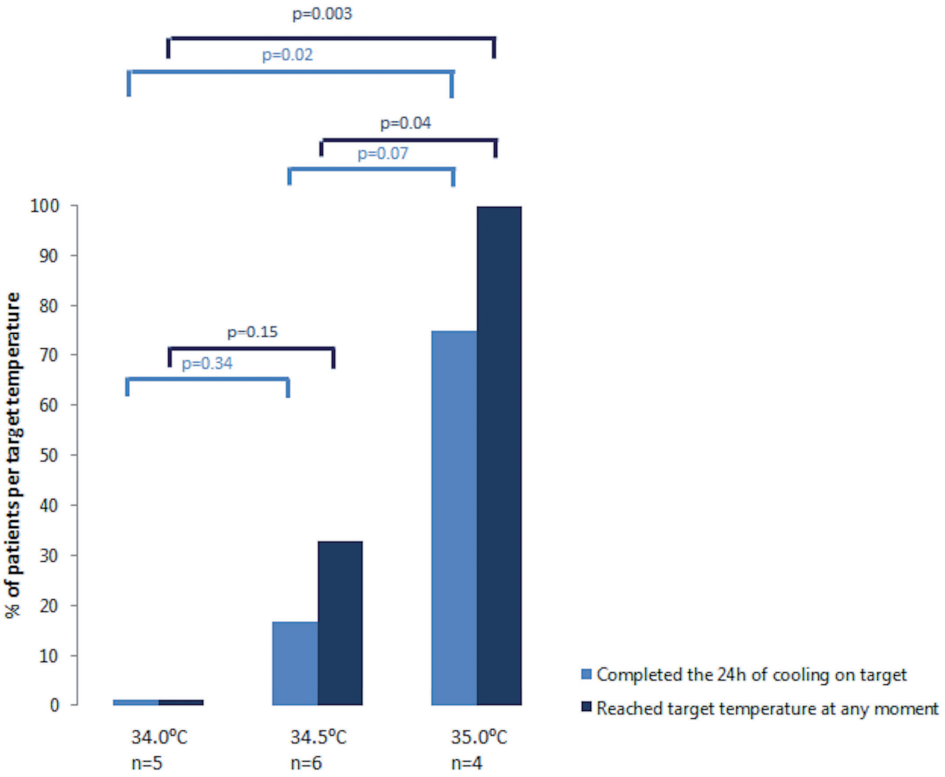

Figure 4.1. Cooling outcomes.

Median times to target temperature varied widely between patients, and did not differ between groups (Table 4.1).

Adverse events are presented in Supplemental Table S4.3. Shivering occurred in all cooled patients, mainly between 2 and 6 hours after initiating of cooling (Supplemental Figure S4.1). Pneumonia occurred in eight cooled patients and in none of the patients with standard treatment (absolute risk increase, 53%; 95% confidence interval, 28–79%), and was diagnosed at a mean interval of 43 hours (SD 37) after stroke onset. The occurrence of pneumonia was not associated with NIHSS at admission.

There was no difference in functional outcome or mortality at three months between the groups (Supplemental Table S4.4 and Supplemental Figure S4.2). Tolerability results are presented in Supplemental Table S4.5.

Table 4.1. Cooling parameters

	34.0°C (n=5)	34.5°C (n=6)	35.0°C (n=4)*	p
Time from stroke onset to start of cooling (min)	229 (52)	216 (39)	214 (60)	0.89†
Reach of target temperature at any moment	0 (0)	2 (33)	4 (100)	0.01
Time from start cooling to target temperature (hh:mm)	NA	6:52 (1:45–12:00)	7:22 (3:30–12:00)	1.00‡
Completion of the 24h of cooling	2 (40)	4(67)	4 (100)	0.17
Completion of the 24h of cooling on target	0 (0)	1 (17)	3 (75)	0.03
Completion of 12h of cooling on target	0 (0)	2 (33)	4 (100)	0.01
Duration of cooling (hours)	11 (10–24)	24 (8–24)	24 (24–25)	0.21†
Change of target temperature	5 (100)	2 (33)	1 (25)	0.04
Total dose pethidine (mg)	682 (426–1746)	771 (149–1075)	740 (650–1085)	0.80§

Data are number (%), mean (SD), or median (range). * Analyses per protocol. † ANOVA; ‡ Mann Whitney U test; § Kruskal-Wallis test; others chi square.

DISCUSSION

This study suggests that surface cooling to 35.0°C for 24 hours is feasible in awake patients with acute ischaemic stroke, whereas cooling to 34.0°C or 34.5°C is not. Cooling is associated with an increased risk of pneumonia. Our results may have implications for the ongoing phase III trial EuroHYP-1.[7]

COOLIST is the only study that has compared different target temperatures in a randomized fashion. Previous studies have shown the feasibility of surface cooling in awake patients with acute ischaemic stroke with target temperatures to 35.5°C for 6 hours[3] and to 35.0°C for 12 hours.[6]

Shivering occurred in all our patients and was a common side effect in all previous cooling trials involving awake patients,[3-6] despite anti-shivering regimes. Shivering could be the most important reason for not reaching target temperature, and might partially explain the differences between the treatment groups.

Pneumonia is a common side effect in patients treated with hypothermia for any indication,[8] possibly due to a detrimental effect on inflammatory mechanisms such as secretion of pro-inflammatory cytokines, leucocyte migration and phagocytosis. Further, awake stroke patients treated with hypothermia might be prone to pneumonia because the anti-shivering regime entails nausea and mild sedation, leading to an increased risk of dysphagia and (micro-)

aspiration. Although pneumonia did not affect functional outcome after three months in our series, infections in stroke have been associated with a poor functional outcome.[9] Therefore, therapeutic benefits of hypothermia might be decreased by the increased risk on pneumonia.

Our analyses are limited by the premature termination of the study and by the small number of patients recruited. One reason for slow recruitment was a competing trial in all but one of the participating centers. Second, the institutional review board of the initiating center (University Medical Center Utrecht), had significant concerns before approval, mostly regarding presumed risks of arrhythmia and respiratory insufficiency. Therefore, the approval of the trial was granted under specific conditions, including the continuous presence of a trial physician in the hospital during the 24 hours of cooling, and one-on-two nursing. These conditions could often not be met.

Since we included patients with an NIHSS≥6, our results do not apply to patients with a less severe stroke. The study was not designed to assess efficacy outcomes, and the results of the ongoing large phase III trial EuroHYP-1[7] have to be awaited.

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SUPPLEMENTARY DATA

Supplemental methods

Eligibility criteria

Inclusion criteria

1. A clinical diagnosis of acute ischaemic stroke;
2. A possibility to initiate cooling within 4.5 hours of stroke onset. Onset time for patients who awoke with symptoms is defined as the last time the patient was awake without symptoms of stroke;
3. Score on the National Institutes of Health Stroke Scale (NIHSS)[1] ≥6;
4. Age ≥18 years;
5. Written informed consent by the patient or a legal representative.

Exclusion criteria

1. Evidence from a CT or MRI scan or from other pre-randomisation investigations of an intracranial haemorrhage, a brain tumour, encephalitis, or any diagnosis other than acute ischaemic stroke likely to be the cause of the symptoms. Haemorrhagic transformation of the infarct is **not** an exclusion criterion, except when there is a parenchymal hematoma covering more than 30% of the infarcted area, with significant space-occupying effect, or when there is a bleeding remote from the infarcted area (PH2 on Fiorelli's scale);[2]
2. Conditions that may be complicated by hypothermia, such as hematological dyscrasias (including oral anticoagulant treatment with INR ≥1.7 or a platelet count <100.10^9/L), severe pulmonary disease, severe heart failure (defined as a NYHA score of III or IV),[3] myocardial infarction within the previous 3 months, angina pectoris in the previous three months, severe infection with a CRP >50 mg/L, or a clinical diagnosis of sepsis;
3. Blood oxygen saturation below 92% without use of oxygen therapy or below 94% with a maximum of 2 L/min oxygen delivered nasally;
4. Bradycardia (<40 beats/min);
5. Body weight >120 kg;
6. Pre-stroke score on the modified Rankin Scale (mRS)[4] >2;
7. Allergy to pethidine, buspirone, or ondansetron, use of a monoamine oxidase inhibitor in the previous 14 days, hepatic or severe renal dysfunction, or asthma. Severe hepatic dysfunction is defined as liver enzymes increased above two times above the upper limit of normal, and severe renal dysfunction as a glomerular filtration rate ≤30 ml/min;
8. Pregnancy. Women of childbearing potential are excluded unless a negative test for pregnancy has been obtained prior to randomization;
9. Other serious illness that may confound treatment assessment;
10. Previous participation in this trial.

NB: The choice to perform intravenous thrombolysis or intra-arterial treatment was left to the discretion of the treating physician and was not an exclusion criterion.

Subjects

Patients were enrolled between October 2011 and October 2014 at three centers in the Netherlands and one in Sweden.

Randomization

Patients were randomized to standard care or to cooling to 34.0°C, 34.5°C, or 35.0°C in a 1:1:1:1 ratio through a web-based randomisation service hosted at the University of Edinburgh. Randomisation was stratified for (the intention to perform) intravenous thrombolysis with alteplase.

Hypothermia and rewarming

Cooling was started as soon as possible and within 4.5 hours after stroke onset by means of intravenous infusion of 20 ml/kg cooled normal saline (4°C) over 30 to 60 minutes. Surface cooling was started immediately after the start of the infusion with Arctic Sun Energy Transfer Pads (Medivance, Inc) applied to the thighs and chest and connected to an Arctic Sun 2000 temperature control module with integrated chiller (Medivance, Inc). Inlet water temperature was automatically controlled to achieve the assigned target rectal temperature. Active cooling was continued for 24 hours, after which patients were passively rewarmed at a rate of 0.3°C per hour to a rectal temperature of 36.0°C.

Anti-shivering management

Shivering was assessed using the 4-point Columbia Shivering Scale,[5] which rates shivering as absent, mild, moderate, or severe.

In order to prevent shivering, cooled patients received a loading dose of pethidine 0.75 mg/kg intravenously over 5 minutes before the start of cooling, followed by a pethidine dose of 0.25 mg/kg/h intravenously. In case of shivering, the patient was given a bolus of 10 to 25 mg pethidine intravenously, followed by an increase in the continuous infusion of 5 mg/h. If the shivering could not be controlled with intravenous pethidine, or if additional pethidine was contra-indicated, the target temperature was increased to a 0.5°C higher level at a rate of 0.3°C per hour. Additionally, patients received 30 mg buspirone orally or per nasogastric tube just before start of cooling and 15 mg at 8, 16, and 24h.

To mitigate drug-related emesis, 8 mg ondansetron was given intravenously before the first dose of pethidine. Administration of ondansetron was repeated at a dose of 4 mg every 4 hours if necessary.

Outcome measures

The primary outcome measure was feasibility of cooling, defined as the proportion of patients who completed the 24 hours of cooling on the assigned target temperature.

Secondary outcomes included time to target temperature and safety. We recorded all serious adverse events. Infections were defined as diagnosed by the clinician.

Functional outcome as measured with the modified Rankin Scale (mRS) score at 90 (±14 days) days was a tertiary outcome. To prevent observer bias, patients' scores on the mRS were assessed independently by three blinded investigators on the basis of a narrative written by an unblinded research nurse after a telephone interview. In case of disagreement, the final mRS score was decided by consensus.

An unblinded member of the study team interviewed the patient and a legal representative on tolerability of cooling at day 7 (or discharge, if earlier).

Temperature measurement

In patients randomized to hypothermia, rectal temperature was measured at baseline and continuously thereafter for at least the time of cooling and rewarming. In all patients, tympanic temperature was recorded with a standard tympanic thermometer at baseline and subsequently at four-hour intervals during the first 36 hours of treatment.

Other measurements

Prerandomization procedures included medical history and physical examination (including stroke severity by means of NIHSS, rectal and bilateral tympanic temperatures, blood pressure, and heart rate), pre-stroke scores on the modified Rankin Scale (mRS) and Barthel Index[6] (BI), CT-brain, 12-lead electrocardiogram, and routine blood tests.

The level of consciousness, presence or absence of shivering, non-invasive blood pressure, heart rate, oxygen saturation, and breathing frequency were recorded – in part with use of telemetry – for the entire cooling and rewarming phase.

Laboratory measurements were repeated 90 minutes, 24 hours and 72 hours after start of cooling. ECG was repeated 12, 24 and 48 hours after randomisation. NIHSS was repeated at 24 and 48 hours and at 7 days (or discharge, if earlier). mRS and BI were taken at day 7 (or discharge, if earlier) Imaging of the brain could be performed with CT of MRI at day 3 ± 2 days.

Respiration

The patient's respiration was monitored continuously in all patients with Capnostream® monitors (Capnostream TM 20, Oridion Medical 1987 ltd) with integrated Nellcor® pulse oximeter. The Nellcor OxiMax™ adult oxygen sensor MAX-A and the Microstream Filterline® were used as sampling lines.

Supplemental results

Supplemental Tables

Table S4.1. Randomization per center

Study center	Patients randomized
University Medical Center Utrecht	10
Skåne University Hospital	10
University Medical Center Groningen	2
Erasmus Medical Center	0

Table S4.2. Baseline characteristics

	34.0°C (n=5)	34.5°C (n=6)	35.0°C (n=5)	Cooling (n=16)	Standard (n=6)
Demographics					
Women	0 (0)	1 (17)	1 (20)	2 (13)	1 (17)
Age (years)	63 (12)	64 (12)	63 (12)	63 (11)	63 (14)
Vital parameters					
Blood pressure systolic (mmHg)	144 (15)	152 (22)	165 (25)	154 (21)	150 (27)
Blood pressure diastolic (mmHg)	85 (7)	85 (9)	87 (10)	86 (9)	82 (13)
Heart rate (beats per minute)	69 (17)	79 (12)	73 (11)	74 (13)	73 (12)
Respiratory rate (per minute)	17 (4)	16 (4)	15 (1)	16 (3)	15 (2)
Rectal temperature (°C)	36.4 (0.3)	36.6 (0.4)	36.4 (0.5)	36.5 (0.4)	36.6 (0.6)
Left tympanic temperature (°C)	36.8 (0.5)	36.4 (0.7)	36.0 (0.6)	36.4 (0.7)	36.4 (0.4)
Right tympanic temperature (°C)	36.9 (0.1)	36.5 (0.9)	35.9 (0.7)	36.4 (0.7)	36.5 (0.3)
NIHSS	11 (7–13)	10 (8–23)	17 (13–23)	13 (7–23)	13 (7–19)
Weight (kg)	78 (6)	83 (21)	90 (7)	84 (14)	80 (9)
History					
Ischaemic stroke	0 (0)	2 (33)	1 (20)	3 (19)	1 (17)
TIA	0 (0)	2 (33)	0 (0)	2 (13)	0 (0)
Diabetes mellitus	0 (0)	0 (0)	1 (20)	1 (6)	1 (17)
Hypertension	2 (40)	3 (50)	4 (80)	9 (56)	3 (50)
Ischaemic heart disease	0 (0)	2 (33)	0 (0)	2 (13)	1 (17)
Heart failure	0 (0)	1 (17)	0 (0)	1 (6)	0 (0)
Atrial fibrillation	1 (20)	0 (0)	0 (0)	1 (6)	1 (17)
Current smoking	1 (20)	0 (0)	2 (40)	3 (19)	2 (33)
Treatment					
Treatment with iv alteplase	5 (100)	5 (83)	5 (100)	15 (94)	6 (100)
Intra-arterial treatment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Time from stroke onset to alteplase (min)	75 (27)*	67 (14)	81 (23)	83 (39)	68 (16)

Data are number (%), mean (SD), or median (range). NIHSS: National Institutes of Health stroke scale. * One outlier (205 min) excluded.

Table S4.3. Side effects and adverse events

	34.0°C (n=5)	34.5°C (n=6)	35.0°C (n=4)*	Cooling (n=15)*	Standard (n=6)	Absolute risk increase (95% CI)†	p
Shivering	5 (100)	6 (100)	4 (100)	15 (100)	0 (0)	100% (100 to 100)	<0.001
Infections (any)	4 (80)	3 (50)	3 (50)	10 (67)	0 (0)	67% (43 to 91)	<0.001
Pneumonia	3 (60)	3 (50)	2 (75)	8 (53)	0 (0)	53% (28 to 79)	0.002
Urinary tract infection	1 (20)	0 (0)	0 (0)	1 (7)	0 (0)	7% (-6 to 19)	0.44
Other infections	0 (0)	0 (0)	1 (25)	1 (7)	0 (0)	7% (-6 to 19)	0.68
Neurologic‡							
Symptomatic haemorrhage	0 (0)	1 (17)	0 (0)	1 (7)	0 (0)	7% (-33 to 30)	0.68
Asymptomatic haemorrhage	0(0)	0 (0)	1 (25)	1 (7)	0 (0)	7% (-33 to 30)	0.68
Recurrent ischaemia	0 (0)	0(0)	0 (0)	0 (0)	1 (17)	-17% (-56 to 8)	0.30
Increase NIHSS ≥4 points	2 (40)	0(0)	0(0)	2 (13)	0 (0)	13% (-27 to 38)	0.44
Cardiovascular							
Hypertension RR>185/105 mmHg	4 (80)	4 (67)	4 (100)	12 (80)	4 (67)	13% (-21 to 52)	0.49
Hypotension RR<100/50 mmHg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	
Bradycardia <50 bpm	3 (60)	2 (33)	1 (25)	6 (40)	1 (17)	23% (- 21 to 51)	0.21
Tachycardia >100 bpm	4 (80)	0 (0)	4 (100)	8 (53)	3 (50)	3% (-36 to 42)	0.89
Cardiogenic shock	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Ventricular arrhythmia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Atrial fibrillation	2 (40)	0 (0)	1 (25)	3 (20)	0 (0)	20% (-21 to 45)	0.24
Myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Other cardiac events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Deep venous thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Pulmonary							
Respiratory insufficiency	1 (20)	1 (17)	1 (25)	3 (20)	0 (0)	20% (-21 to 45)	0.24
Other pulmonary events	0 (0)	0 (0)	0(0)	0 (0)	0 (0)	NA	NA

Electrolyte disturbances							
Hypokalemia	2 (40)	4 (67)	1 (25)	7 (47)	3 (50)	-3% (-42 to 36)	0.89
Hyponatremia	0 (0)	0 (0)	1 (25)	1 (7)	0 (0)	7% (-33 to 30)	0.68
Other							
Elevated liver enzymes	1 (20)	1 (17)	0 (0)	3 (20)	1 (17)	3% (-38 to 32)	0.88
Constipation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Bleeding elsewhere	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Temperature >37.5°C							
During total admission	4 (80)	6 (100)	4(100)	14 (93)	6 (100)	7% (-6 to 19)	0.13
In first 36 hours	4 (80)	4 (67)	4(100)	12 (80)	6 (100)	20% (-45 to 21)	0.24
Between 36 hours and 7 days	4 (80)	5 (83)	4(100)	13 (87)	4 (67)	20% (-14 to 58)	0.28
Medication							
Acetaminophen administered during admission	3 (60)	4 (67)	1 (25)	9 (60)	2 (33)	27 (-17 to 58)	0.16

Data are number (%). CI: confidence interval; NIHSS: National Institutes of Health stroke scale. * Analyses per protocol. † Cooling vs standard treatment. ‡ Intracranial neurological complications only.

Table S4.4. Functional and neurological outcomes at 3 months

	34.0°C (n=5)	34.5°C (n=6)	35.0°C (n=5)	Standard (n=6)	Cooling (n=16)	ARR (95% CI) cooling vs control	p
Poor outcome (mRS 4–6)	2 (40)	3 (50)	2 (40)	2 (33)	7 (44)	-11% (-55 to 35)	0.97
Death	1 (20)	0 (0)	1 (20)	1 (17)	2 (12)	5 (-30 to 38)	0.95
NIHSS	8 (0–15)	8 (1–18)	6 (0–20)	4 (2–19)	8 (0–20)		0.50*
Barthel Index	85 (35–100)	68 (0–100)	98 (70–100)	100 (50–100)	83 (0–100)		0.24*

Data are number (%), mean (SD), or median (range). NIHSS: National Institutes of Health stroke scale; mRS: modified Rankin Scale; ARR: absolute Risk Reduction; CI: confidence interval. * Mann Whitney U test.

Table S4.5. Results from interview on tolerability at 7 days, or at discharge if earlier. We interviewed all 9 patients cooled in one of the Dutch study centers and their caregivers. Two patients could not answer the questions because of severe aphasia.

	34.0°C		34.5°C		35.0°C		Cooling		
	Patient (n=2)	Caregiver (n=3)	Patient (n=3)	Caregiver (n=3)	Patient (n=2)	Caregiver (n=3)	Patient (n=7)	Caregiver (n=9)	p
Accept cooling if proven effective (yes)	2 (100)	3 (100)	1 (33)	3 (100)	2 (100)	3 (100)	5 (71)	9 (100)	0.20
Cooling*	7.5 (7–8)	2 (1–8)	6 (2–7)	2 (1–5)	5 (3–7)	8 (2–10)	6.5 (2–8)	2 (1–10)	0.43†
Stroke unit care*	7.5 (7–8)	8 (8–9)	7 (6–9)	7 (1–7)	7 (7–7)	8 (7–10)	7 (6–9)	8 (1–10)	0.53†
Nausea*	9 (8–10)	NA	10 (7–10)	NA	10 (10–10)	NA	10 (7–10)	NA	
Shivering*	6 (4–8)	NA	4 (2–6)	NA	6 (4–8)	NA	4 (2–8)	NA	
Cold*	6 (4–8)	NA	5 (2–6)	NA	3 (3–3)	NA	4 (2–8)	NA	

Data are n (%) or median (range). * Patients were asked to rate their experience on these items from 1 (very bad) to 10 (very good/no complaints). † Mann Whitney U test.

Supplemental Figures

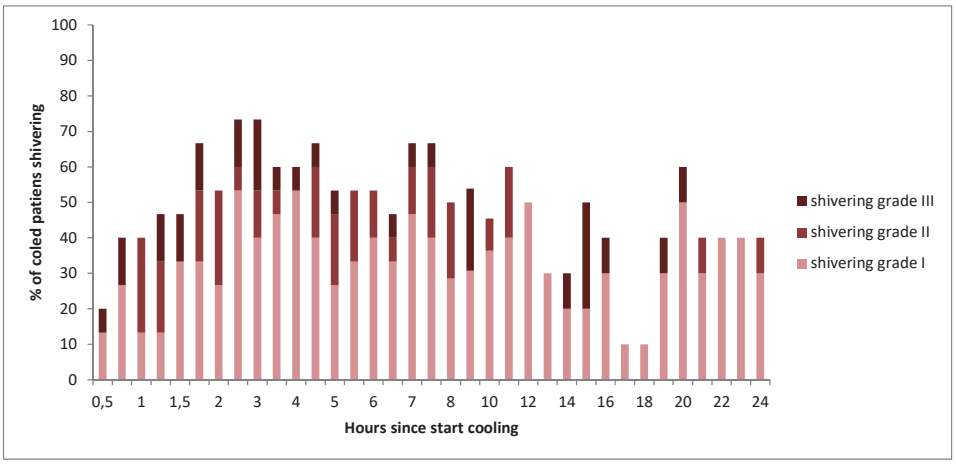

Figure S4.1. Temporal profile of shivering.

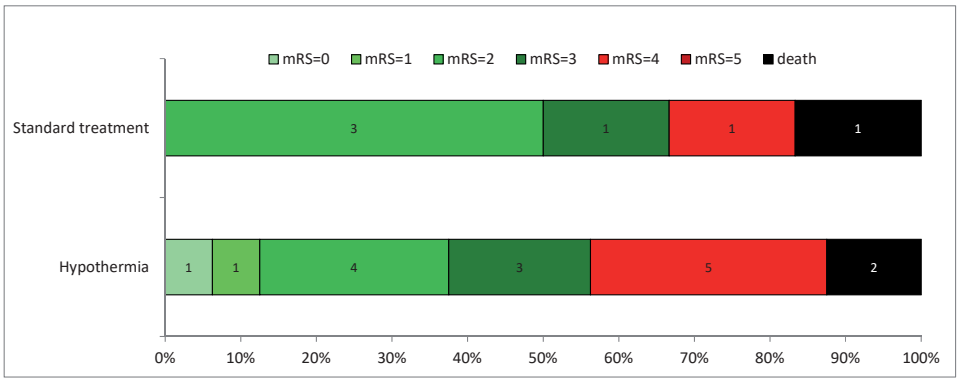

Figure S4.2. Modified Rankin Scale Score at three months.

Supplemental references

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Chapter 5

Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis

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ABSTRACT

Objective: Observational studies suggest that infections are a common complication of therapeutic hypothermia. We performed a systematic review and meta-analysis of randomized trials to examine the risk of infections in patients treated with hypothermia.

Data sources: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched for eligible studies up to October 1st, 2012.

Study selection: We included randomized controlled clinical trials of therapeutic hypothermia induced in adults for any indication, which reported the incidence of infection in each treatment group.

Data extraction: For each study we collected information about the baseline characteristics of patients, cooling strategy, and infections.

Data synthesis: Twenty-three studies were identified, which included 2820 patients, of whom 1398 (49.6%) were randomized to hypothermia. Data from another 31 randomized trials, involving 4004 patients, could not be included because the occurrence of infection was not reported with sufficient detail, or not at all. The risk of bias in the included studies was high because information on the method of randomization and definitions of infections lacked in most cases, and assessment of infections was not blinded. In patients treated with hypothermia, the incidence of all infections was not increased (Rate Ratio, 1.21; 95% confidence interval (CI), 0.95–1.54), but there was an increased risk of pneumonia and of sepsis (Risk Ratios, 1.44; 95% CI, 1.10–1.90 and 1.80; 95% CI, 1.04–3.10, respectively).

Conclusion: The available evidence, subject to its limitations, strongly suggests an association between therapeutic hypothermia and the risk of pneumonia and sepsis, whereas no increase in the overall risk of infection was observed. All future randomized trials of hypothermia should report on this important complication.

INTRODUCTION

Therapeutic hypothermia, the intentional reduction of body temperature, is increasingly used as a treatment for acute brain injury. In randomized trials hypothermia reduced mortality and improved neurological outcomes in adults with hypoxic-ischaemic brain damage after cardiac arrest,[1] in newborns with hypoxic ischaemic encephalopathy,[2] but not in patients with traumatic brain injury[3,4] or during surgery for intracranial aneurysms.[5] Furthermore, hypothermia is a promising treatment for ischaemic stroke.[6,7] One large phase III trial of cooling for ischaemic

stroke is in progress (Unique identifier: NCT01123161) and another will start shortly (Unique identifier: NCT01833312).

Infections are frequent complications in patients hospitalized for cardiac arrest, traumatic brain injury, or stroke, and have been associated with poor outcomes.[8-10] Recent observational studies suggest that cooling increases the risk of infection after cardiac arrest.[11] By contrast, randomized trials have reported no evidence that therapeutic hypothermia in adults is associated with an increased infection rate.[1,2,12-14] However, these trials, and meta-analyses of trials limited to a single indication for hypothermia, may be too small to detect a relation between hypothermia and infection. This is important because if infections do occur more often in patients treated with hypothermia and if this is associated with a poorer outcome, then the therapeutic benefits of hypothermia might be increased through the use of prophylactic antibiotics.

We therefore performed a systematic review and meta-analysis of all randomized trials of therapeutic hypothermia, irrespective of indication, to assess whether cooling is associated with an increased risk of infections.

MATERIAL AND METHODS

Literature search

Randomized controlled trials of therapeutic hypothermia were identified from PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to October 1st, 2012, with the search terms ("cooling" OR "hypothermia") AND ("randomised" OR "randomized" OR "randomly"). We searched reference lists of the identified relevant studies for additional citations and compared the results of our search with those of published Cochrane reviews.

Eligibility criteria

We included all randomized and pseudorandomized clinical trials of therapeutic hypothermia versus control in adult patients. Studies with hypothermia as part of a procedure (e.g., clipping of an intracranial aneurysm) were included, as were studies in which the control group was actively managed to normothermia. We excluded studies with no full text available; in languages other than English, Dutch, or German; using temperature modulation with antipyretics as the active treatment; involving local cooling without lowering of total body temperature; and those which did not report the number of infections or the number of patients with an infection. Infections could be reported as 'infection' in general or more specifically as pneumonia, urinary tract infection, sepsis, or any other specific infection.

Outcome definition

The primary outcome measure of this meta-analysis is 'any infection.' Pancreatitis was not considered an infection, because the etiology of pancreatitis is not necessarily infectious. The occurrence of fever alone, without other evidence of an infection, was not considered an infection. Secondary outcomes of this meta-analysis are the occurrence of pneumonia, urinary tract infection, or sepsis.

Study selection and data extraction

Two reviewers (MG, PHCK) independently applied the eligibility criteria to all titles and abstracts, and if necessary full-text articles, extracted the data using a standardized form, and resolved discrepancies by discussion. For each study we collected information about the baseline characteristics of patients (type of injury), cooling strategy (whether hypothermia was used as procedural treatment, mode and duration of hypothermia, target temperature, whether the patient was mechanically ventilated, and time until start of treatment), and infections (incidence, definition as reported in the original article).

Assessment of risk of bias

The risk of bias was estimated independently by two reviewers (MG, PHCK) using the Cochrane Risk of Bias Methods.[15] Publication bias was assessed by constructing a funnel plot based on the primary outcome and with Egger's regression test.[16]

Data analyses

We used RevMan 5.1 (Nordic Cochrane Centre) for data analysis. We calculated rate ratios (the ratio of the incidence rate of infections in the hypothermia groups to that in the control groups) and 95% confidence intervals (CI) for the primary outcome, unadjusted for baseline variables, with a random effects model. We calculated rate ratios rather than risk ratios because most articles just reported the total number of infections and did not mention whether some patients had more than a single infection (Table 5.1). We therefore interpreted the data as count data, with number of infections as numerators and patient years (defined as the total duration of follow-up for all patients combined, unless it was stated that the occurrence of infections was assessed during a different, measurable, time period) as denominators. Forest plots are based on total number of infectious events. For the secondary outcomes (pneumonia, urinary tract infection or sepsis), we considered it most likely that the majority of patients had only a single infectious event. We therefore calculated risk ratios (the ratio of the risk of infections in the hypothermia groups to that in the control groups) and 95% CIs for the secondary outcomes with a random effects model. We assessed statistical heterogeneity with the I-squared (I^2) index both in overall analyses and in subgroup analyses.[17]

Subgroup analyses

We analyzed the risk of infections in subgroups of studies, based on the type of injury, duration of cooling, whether hypothermia was applied as part of a procedure, the mode of hypothermia, and the use of mechanical ventilation. These subgroup analyses were prespecified in the protocol. A prespecified subgroup analysis based on the target temperature could not be performed because most studies used a range of target temperatures instead of a single one. We therefore performed a post-hoc analysis based on the temperature achieved. Because some studies have suggested that even active management to normothermia increases the risk of infection, a post-hoc subgroup analysis exploring the impact of prophylactic normothermia in the control group was undertaken after the results had been compiled. Subgroup differences were analyzed with the I^2 index.

RESULTS

We identified 4351 unique articles of which 144 were read in full. One additional article was identified from a published Cochrane meta-analysis. Twenty-three articles were included in this meta-analysis (Figure 5.1). Thirty-one articles on randomized controlled trials of hypothermia, involving 4004 patients, were excluded because they did not report the rate of infections with sufficient detail (n=8), or not at all (n=23). There were no significant differences in the effects of hypothermia on mortality or functional outcomes between studies included and excluded from our meta-analysis.

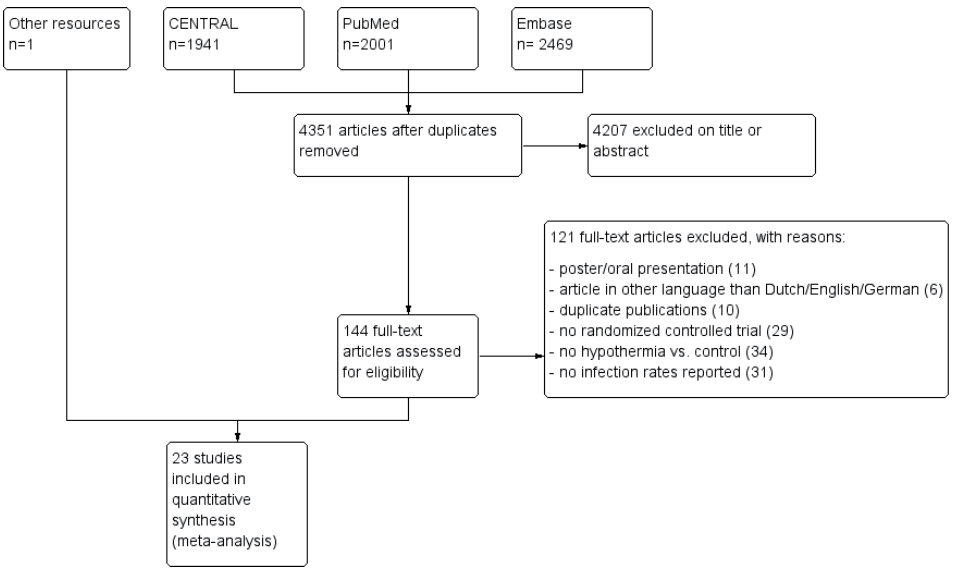

Figure 5.1. Flow chart of the systematic search.

The 23 included studies involved 2820 patients, of whom 1398 (49.6%) had been randomized to hypothermia. Of these 23 studies, eight used hypothermia during a procedure only. Of the other 15 studies, ten involved patients with traumatic brain injury, four with ischaemic stroke, and one with cardiac arrest. Surface cooling was used in 17 studies, endovascular cooling in five, and one article did not specify the mode of cooling. The duration of cooling ranged from several hours for procedural hypothermia to several days for traumatic brain injury. One non-procedural hypothermia study did not specify the duration of cooling. In 18 studies, patients were intubated and mechanically ventilated. All articles reported at least one type of infection. Sixteen reported on the occurrence of pneumonia, six on urinary tract infection, and six on sepsis. One article reported only on all infectious complications together, not specified per type of infection. A definition of infections was given in four articles (Table 5.2). None of the articles mentioned that the occurrence of infections was assessed blinded to treatment allocation, and the exact mode of randomization was reported in 11 articles.

An evaluation of the risk of bias is presented in Table 5.3. Given the lack of uniform and explicit definitions of infections, the open assessment of infections, and the lack of information on the methods of randomization in the large majority of studies, there was a high risk of bias. The funnel plot did not show major asymmetry, suggesting no major effect of bias on the results (Figure 5.2). In addition, no statistically significant effect of publication bias was found with Egger's regression (p=0.47).

A total of 579 infectious events were reported, of which 316 occurred in patients treated with hypothermia and 263 in controls (Rate Ratio, 1.21; 95% CI, 0.95–1.54) The degree of heterogeneity (I^2) was 33% in the overall analysis (Figure 5.3), suggesting moderate heterogeneity between studies in the incidence of infection, perhaps reflecting the different clinical settings.[17]

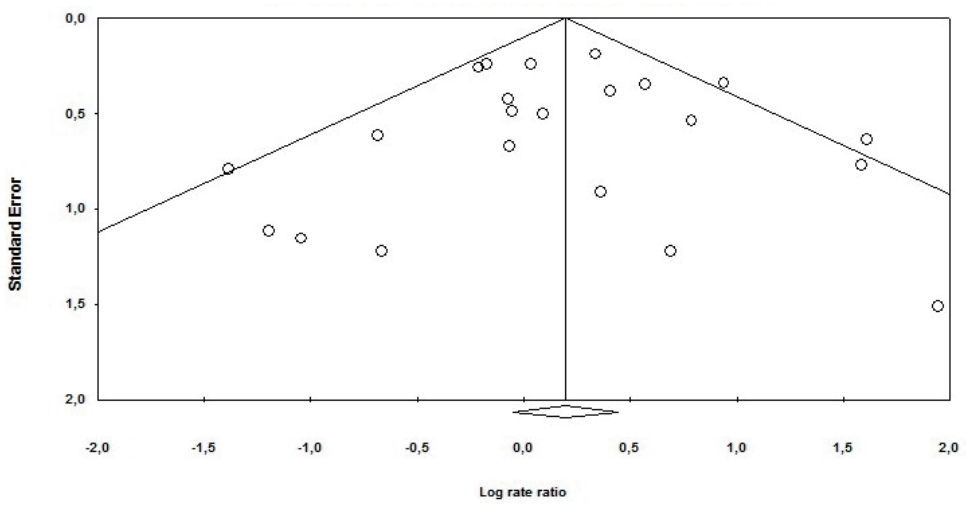

Figure 5.2. Funnel plot of study precision against the log rate ratio of infections. In the absence of publication bias the pattern of points should resemble an inverted funnel.

Table 5.1. Study characteristics

	n	Type of injury	Mechanical ventilation	Mode of cooling	Target body temperature (°C)	Achieved body temperature (°C)	Duration of cooling	Time until start of hypother-mia	Types of infection reported	Definition of infection
Clifton 1993[21]	46	TBI	Yes	Surface	33	33	48 hours	<6 hours	Pneumonia, sepsis	Unclear
Shiozaki[a] 1993[35]	22	TBI	Yes	Surface	33.5–34.5	Unknown	24–48 hours	Unclear	Pneumonia, central nervous system infection	Unclear
Hindman[a] 1999[36]	109	IA surgery	Yes	Surface	33.5	33.7	Procedural: duration unclear	NA	Pneumonia	Unclear
Grimm 2000[37]	144	CPB	Yes	Unclear	32	Unknown	Procedural: duration unclear	NA	Wound infection	Unclear
Shiozaki 1999[38]	16	TBI	Yes	Surface	34	Unknown	48 hours	Unclear	Pneumonia, meningitis	Unclear
Jiang 2000[39]	87	TBI	Yes	Surface	33-35	Unknown	3–14 days	Mean: 15 hours	Pneumonia, UTI	Unclear
Shiozaki[a] 2001[22]	83	TBI	Yes	Surface	34.5–35.5	34.0	48 hours	Unclear	Pneumonia, meningitis	Unclear
HACA[a] 2002[40]	273	Cardiac arrest	Yes	Surface	32–34	33	24 hours	Median: 105 minutes	Pneumonia, sepsis	Unclear

Table 5.1 continues on next page

Table 5.1. ***Continued***

	n	Type of injury	Mechanical ventilation	Mode of cooling	Target body temperature (°C)	Achieved body temperature (°C)	Duration of cooling	Time until start of hypothermia	Types of infection reported	Definition of infection
Hashiguchi 2003[23]	17	TBI	Yes	Surface	34	Unknown	48 hours	Unclear	Pneumonia, meningitis	Pneumonia: at least three of the following criteria: new infiltrates on chest x-ray, purulent tracheobronchial secretions, positive pathogenic bacterial culture from tracheobronchial secretions, and impaired pulmonary gas exchange. Meningitis: white blood cell counts in cerebrospinal fluid greater than 100 cells/liter.
Nathan 2004[41]	144	CPB	Yes	Surface	34	34.1	Procedural: duration unclear	NA	Chest and leg wound infections	Wound infection: documented by using established definitions
De Georgia[a] 2004[42]	39	Ischaemic stroke	No	Endo-vascular	33	Unknown	24 hours	<12 hours	Pneumonia, UTI, sepsis	Unclear

Todd 2005[43]	1001	IA surgery	Yes	Surface	33	33.3	Procedural: duration unclear	NA	Pneumonia, incision or bone-flap infection, meningitis or ventriculitis, bacteremia, UTI	Unclear
Els 2006[44]	25	Ischaemic stroke and hemicrani-ectomy	Yes	Endo-vascular	35	Unknown	48 hours	NA	Sepsis	Sepsis criteria of the American College of Chest Physicians
Liu[a] 2006[45]	44	TBI	Yes	Surface	33–35	37	3 days	Mean: 8.6 hours	Pneumonia	Unclear
Chouhan 2006[46]	47	IA surgery	Yes	Surface	33–34.5	33.7	Procedural: duration unclear	NA	Meningitis	Unclear
Boodhwani 2007[47]	267	CPB	Yes	Surface	34	34	Procedural: duration unclear	NA	Wound infection	Unclear
Qiu 2007[48]	80	TBI	Yes	Surface	33–35	34.5–36	72 hours	NA	Pneumonia	Unclear
Weber 2008[49]	44	Ischaemic stroke	No	Surface	35	35.4	9 hours	<6 hours	Pneumonia, UTI	Unclear
Hemmen[a] 2010[50]	58	Ischaemic stroke	No	Endo-vascular	33	33.4	24 hours	<6 hours	Pneumonia	Unclear
Lee[a] 2010[51]	31	TBI	Yes	Surface	33–35	Unknown	Procedural: duration unclear	Unclear	Pulmonary infection, UTI, sepsis	Unclear

Table 5.1 continues on next page

Table 5.1. ***Continued***

	n	Type of injury	Mechanical ventilation	Mode of cooling	Target body temperature (°C)	Achieved body temperature (°C)	Duration of cooling	Time until start of hypothermia	Types of infection reported	Definition of infection
Gotberg[a] 2010[52]	18	PCI	No	Endovascular	<35	34.7	Procedural: duration 3 hours	NA	Fever and CRP ≥100 mg/L	Pneumonia: fever, cough, focal crepitations on auscultation
Stone 2011[53]	128	Contrast nephropathy	No	Endovascular	33–34	33.6	Procedural: duration 3 hours	NA	UTI, sepsis	Unclear
Clifton 2011[3]	97	TBI	Yes	Surface	33	33	48 hours	Mean: 1.6 hours	Pneumonia, UTI, bloodstream infections, sinusitis, surgical site infections, ventriculitis, meningitis, asymptomatic bacteriuria, positive culture of catheter tip, fever of unknown origin, and soft tissue infections *together*	Unclear

[a]: not all included patients could be assessed for infections; n: total number of patients assessed for infections; TBI: traumatic brain injury; PCI: percutaneous coronary intervention; CPB: cardiopulmonary bypass; IA: intracranial aneurysm; NA: not applicable; UTI: urinary tract infection; CRP: C-reactive protein.

Table 5.2. Raw data of included studies

	n (cooled patients)	Number of infectious events (cooled patients)	Number of infectious events (controls)	Number of events versus number of patients with events	Duration of follow-up for infections	Total duration of follow-up (months)
Clifton 1993[21]	46 (24)	18	11	Unclear	During hospitalization	3
Shiozaki 1993[35]	22 (9)	9	14	Events	Unclear	6
Hindman 1999[36]	109 (53)	1	3	Patients	During hospitalization	3
Grimm 2000[37]	144 (72)	2	1	Patients	Unclear	4
Shiozaki 1999[38]	16 (8)	11	5	Events	Unclear	6
Jiang 2000[39]	87 (43)	32	39	Events	14 days	12
Shiozaki 2001[22]	83 (43)	33	12	Events	14 days	3
HACA 2002[40]	273 (135)	67	49	Unclear	7 days	6
Hashiguchi 2003[23]	17 (9)	11	2	Events	1 week	6
Nathan 2004[41]	144 (71)	1	2	patients	1 month	1
De Georgia 2004[42]	39 (18)	4	5	Events	1 month	1

Table 5.2 continues on next page

Table 5.2. ***Continued***

	n (cooled patients)	Number of infectious events (cooled patients)	Number of infectious events (controls)	Number of events versus number of patients with events	Duration of follow-up for infections	Total duration of follow-up (months)
Todd 2005[43]	1001 (499)	35	34	Unclear	3 months	3
Els 2006[44]	25 (12)	0	0	Unclear	Unclear	6
Liu 2006[45]	44 (21)	8	8	Patients	Unclear	24
Chouhan 2006[46]	47 (24)	3	2	Patients	Death or discharge	0.5
Boodhwani 2007[47]	267 (133)	4	8	Patients	Unclear	3
Qiu 2007[48]	80 (40)	23	13	Patients	Unclear	12
Weber 2008[49]	44 (22)	2	8	Events	7 days	3
Hemmen 2010[50]	58 (28)	14	3	Patients	Unclear	3
Lee 2010[51]	31 (15)	8	9	Unclear	Unclear	6
Gotberg 2010[52]	18 (9)	3	0	Patients	Unclear	1
Stone 2011[53]	128 (58)	1	4	Unclear	30 days	1
Clifton 2011[3]	97 (52)	29	31	Events	Death or discharge	6

Table 5.3. Risk of bias

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Clifton 1993[21]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low risk
Shiozaki 1993[35]	Unclear	Unclear	High	Unclear	Low	Low	Low
Hindman 1999[36]	Low	Low	High	High	Unclear	Low	Low
Grimm 2000[37]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low
Shiozaki 1999[38]	Unclear	Unclear	High	Unclear	Low	Low	Low
Jiang 2000[39]	Unclear	Unclear	High	High	Low	Unclear	Low
Shiozaki 2001[22]	Unclear	Unclear	Unclear	Unclear	High	Low	Low
HACA 2002[40]	Low	Low	High	Low	Low	Low	Low
Hashiguchi 2003[23]	Unclear	Unclear	High	Unclear	Low	Low	Low

Table 5.3 continues on next page

Table 5.3. ***Continued***

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Nathan 2004[41]	Low	Low	High	Unclear	Unclear	Low	Low
De Georgia 2004[42]	Low	Low	High	Unclear	Low	Low	Low
Todd 2005[43]	Low	Low	High	Low	Low	Low	Low
Els 2006[44]	Unclear	Unclear	High	Low	Low	Low	Low
Liu 2006[45]	Low	High	High	Unclear	Low	Unclear	Low
Chouhan 2006[46]	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Boodhwani 2007[47]	Low	Low	High	Unclear	Low	Low	Low
Qiu 2007[48]	Low	Low	High	Low	Low	Low	Low

Weber 2008[49]	Low	Low	Unclear	Unclear	Unclear	Low	Low
Hemmen 2010[50]	Low	Unclear	High	Unclear	Low	Unclear	Low
Lee 2010[51]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Gotberg 2010[52]	Low	Low	Unclear	Unclear	Low	Unclear	Low
Stone 2011[53]	Unclear	Unclear	High	Unclear	High	High	Low
Clifton 2011[3]	Low	Low	High	Low	Low	Low	Low

The terms 'low,' 'unclear,' and 'high' refer to the risk of bias according to the Cochrane Risk of Bias Methods.[15]

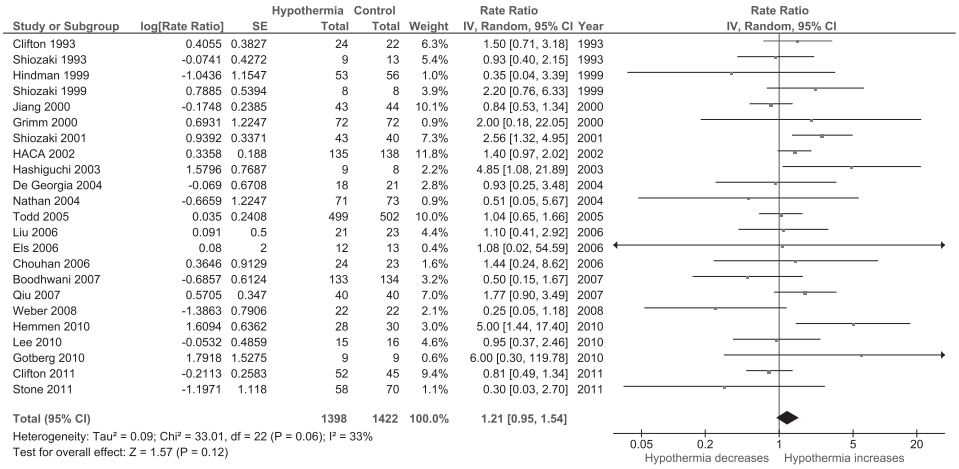

Figure 5.3. Effect of hypothermia on the occurrence of any infection (Rate Ratio).

Pneumonia comprised 295 of 579 (51%) infections identified, and occurred more frequently in patients treated with hypothermia than in controls (Risk Ratio, 1.44; 95% CI 1.10–1.90). Hypothermia was also associated with an almost two-fold increase in the risk of sepsis, (Risk Ratio, 1.80; 95% CI 1.04–3.10). Urinary tract infection occurred 36 times in patients treated with hypothermia and 48 times in controls (Risk Ratio, 0.86; 95% CI 0.58–1.28) (Figure 5.4).

In meta-analyses limited to studies of ischaemic stroke or traumatic brain injury, no differences were found in the risk of infections between both groups (Figure 5.5). In the only study of cardiac arrest providing sufficient data, the risk of infections was not significantly higher in patients treated with hypothermia than in controls (Figure 5.5). A trend towards a higher overall infection rate was observed only in patients cooled for more than 12 hours (Figure 5.6). Where hypothermia was induced as part of a procedure and only for the duration of that procedure, there was no increased incidence of infection (Rate Ratio, 1.02; 95% CI, 0.69–1.50 in patients cooled during a procedure, Rate Ratio, 1.28; 95% CI, 0.94–1.75 in patients cooled for other indications; Figure S5.1 Supplementary data).

Both surface cooling and endovascular cooling were associated with a trend towards more infections (Rate Ratio, 1.17; 95% CI, 0.92–1.49 and Rate Ratio, 1.64; 0.52–5.16 respectively; Figure S5.2 Supplementary data). There was a statistically significant increase in the risk of pneumonia in surface-cooled patients (Risk Ratio, 1.32; 95% CI, 1.04–1.69) and in patients treated with endovascular cooling (Risk Ratio, 4.56; 95% CI, 1.75–11.90; Figure S5.3 Supplementary data). Mechanical ventilation did just not significantly affect the rate ratio of infections (Rate Ratio, 1.21; 95% CI, 0.97–1.49 in mechanically ventilated patients and Rate Ratio, 1.09; 95% CI, 0.30–4.03 in patients who are not mechanically ventilated; Figure S5.4 Supplementary data).

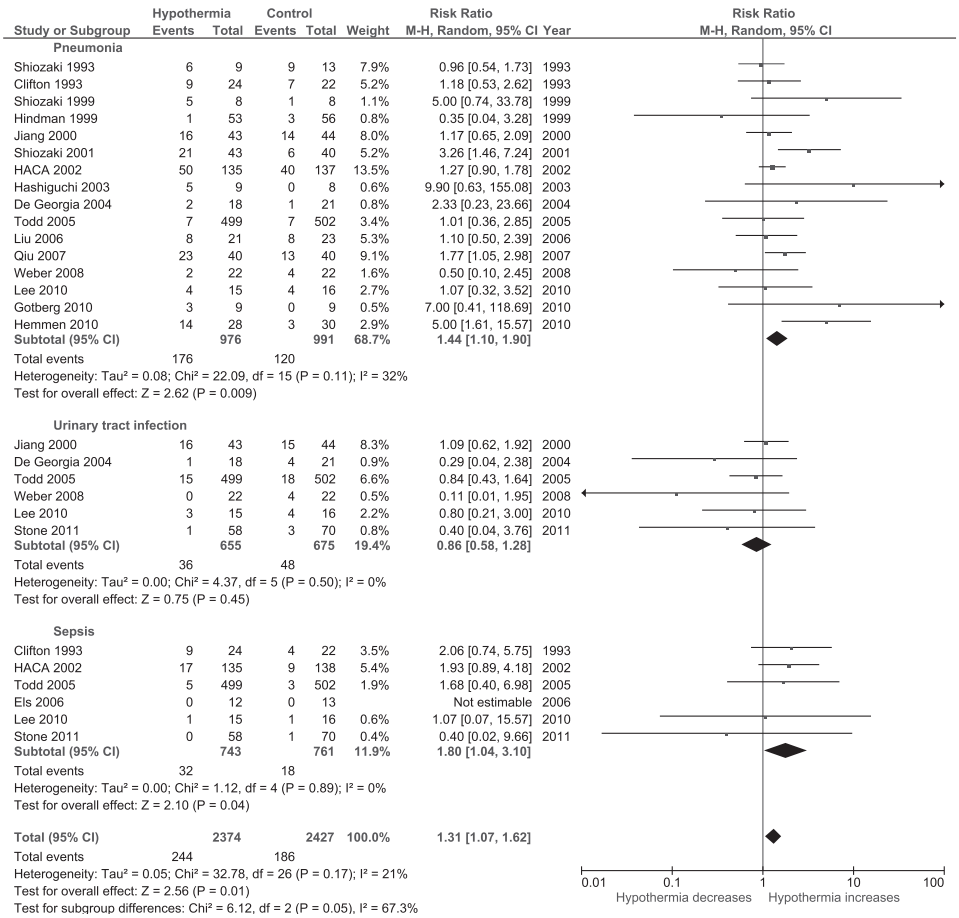

Figure 5.4. Effect of hypothermia on the occurrence of pneumonia, urinary tract infection, and sepsis (Risk Ratio).

The achieved temperature did not significantly affect the rate ratio of infections, but nine studies had to be excluded from this analysis as the achieved temperature was not reported (Figure S5.5 Supplementary data).

Excluding the three studies using prophylactic normothermia in the control group did not change the overall results (Rate Ratio, 1.08; 95% CI, 0.86–1.35; forest plot not shown).

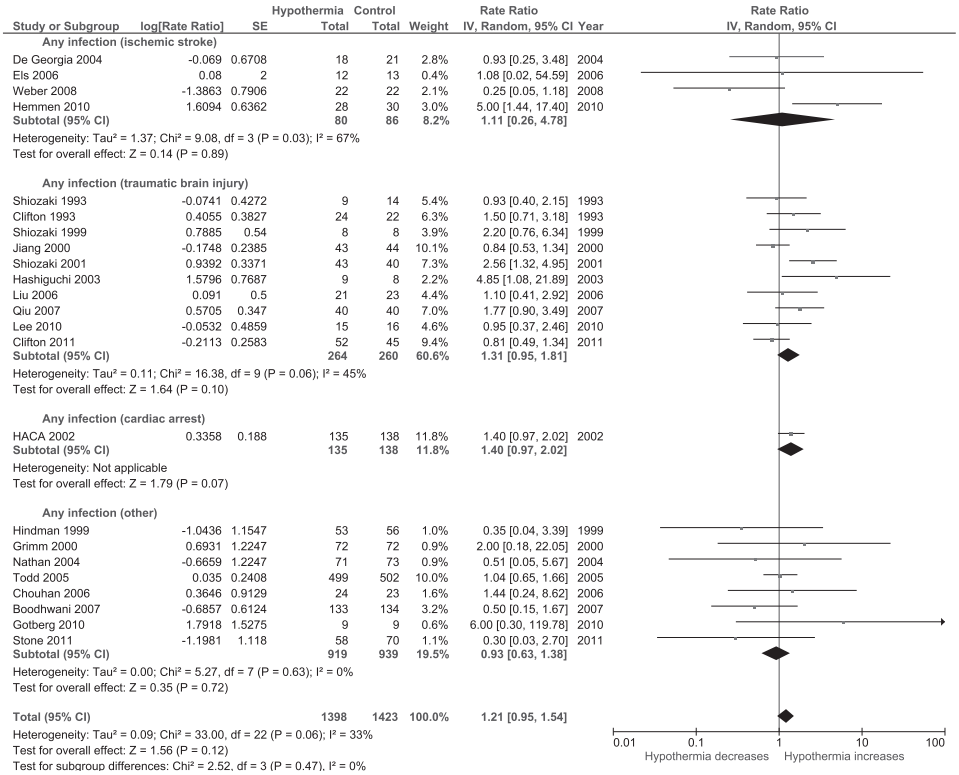

Figure 5.5. Effect of hypothermia on the occurrence of infections by type of disease or procedure (Rate Ratio).

DISCUSSION

In this systematic review and meta-analysis, we found an increased risk of both pneumonia and sepsis in patients treated with hypothermia, although the incidence of sepsis was low. No convincing evidence of an increased risk of all infections in patients treated with hypothermia compared with controls was found. Cooling limited to the duration of an invasive procedure, e.g. the clipping of an intracranial aneurysm, did not increase the rate ratio of all infections.

An increased risk of infection in patients treated with hypothermia might be expected because hypothermia decreases the secretion of proinflammatory cytokines and also inhibits leukocyte migration and phagocytosis. Suppression of neuroinflammation is one of the presumed neuroprotective mechanisms of therapeutic hypothermia, but this may come at the cost of an increased risk of infection.[18] This is supported by the observation that unintentional hypothermia during surgery has convincingly been associated with an increased risk of wound infections.[19]

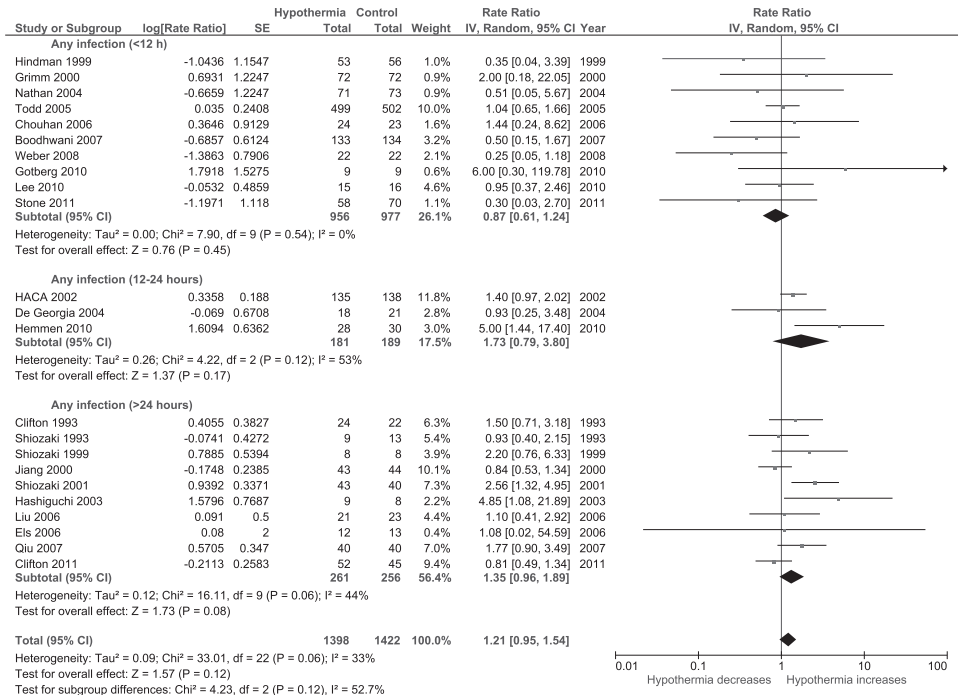

Figure 5.6. Effect of hypothermia on the occurrence of infections by duration of cooling (Rate Ratio).

In a previous meta-analysis[20] of therapeutic hypothermia in traumatic brain injury, a twofold increased risk of pneumonia in patients treated with hypothermia was reported. However, in a later Cochrane review on the same topic, this finding was not confirmed.[4] One reason for this discrepancy may be under-reporting of infections in randomized trials, but differences between studies in patient selection and in the definition of infections may also play a role. A recent meta-analysis on complications of hypothermia after cardiac arrest showed a trend towards an increased pneumonia rate, which was just not statistically significant, possibly because of the relatively small number of trials (8) and patients (795) included.[12]

It has been suggested that a longer duration of cooling increases the risk of infection.[18] In our meta-analysis we indeed found a trend towards a higher risk of infections when cooling was maintained for more than 12 hours than for shorter periods. However, cooling durations of more than 24 hours all involved patients with traumatic brain injury, and cooling durations of 12 hours involved procedural cooling in all but one of the studies. We therefore cannot rule out that the association between the risk of infection and the duration of cooling is caused by confounding factors.

The present systematic review and meta-analysis is the first to specifically evaluate the risk of infection in a large number of patients treated with hypothermia for different indications. Because the review was limited to randomized and pseudorandomized trials, the risk of bias was reduced.

Our review draws attention to important limitations of published reports of randomized trials of hypothermia, and therefore may support the design and reporting of future studies. Subject to these limitations, the available evidence summarized in this review strongly suggests an association between therapeutic hypothermia and the risk of pneumonia and sepsis, whereas no increase in the overall risk of infection was observed.

Certain limitations of our study have to be considered. First, there was a moderate heterogeneity in effect size across the studies. We included studies of various types of injury and thus various patient populations. Moreover, there was a large variation in the mode, duration, and depth of cooling. This should be considered when interpreting the results of the overall analysis. We therefore analyzed subgroups in which there was more homogeneity, and analyzed our data with a random effects model rather than with a fixed effects model.

Secondly, we included three studies in our meta-analysis in which the patients in the control group received prophylactic normothermia. These patients were actively managed to a body temperature of <37.5°C.[21-23] Some studies suggest that even with active normothermia, the risk of infections is increased.[24,25] Excluding these studies from our meta-analysis did however not change the results.

Thirdly, we did not assess the effects of therapeutic hypothermia on mortality and neurological outcomes. These have already been reported in earlier systematic reviews and meta-analyses,[1,2,4-6] and repeating these analyses would not have added to the existing literature on hypothermia.

Our results are limited by the quality and availability of the existing literature. We had to exclude 31 articles involving 4004 patients. Eight of these 31 articles[26-33] described "no significant differences in infection rate between both groups," but because no numbers were reported, we could not add these to the meta-analysis. The other 23 articles just did not report on the occurrence of infections. According to the CONSORT statement, all adverse events occurring in a trial should be reported.[34] We consider the occurrence of an infection as important, also because this has been related to increased mortality and poorer neurological outcomes.[8-10] Although we can only speculate on the reasons for not reporting numbers of infections in a very substantial part of the trials, we think that the main reason is poor reporting. Theoretically, infections could not have been reported because they simply did not occur, but this appears highly unlikely in the relevant patient populations.

The definition of infection was not clear in most articles. In many cases, this is likely to have been a clinical diagnosis, based on clinical symptoms such as fever and elevated infection parameters in the blood. However, it has been suggested that infection parameters such as

CRP and leukocytes have a limited predictive value in hypothermic patients.[25] In the presence of infection, these parameters can be normal or only slightly elevated in cooled patients. However, because of the short duration of hypothermia, any infection left untreated will have been detected shortly after termination of active cooling. We therefore think that there is no reason to assume underreporting of infections in patients treated with hypothermia.

The open assessment of infections may have resulted in detection bias, but even in ongoing and future trials of hypothermia this limitation is almost unavoidable.

In the majority of articles it was not clear whether infections occurred more than once in a single patient. For this reason, we used the rate ratio for the primary outcome of all infections combined. Because we considered it most likely that in the large majority of patients with a specific infection such as pneumonia this did not recur, we used the more common risk ratio for the analyses of the secondary outcomes.

The follow-up period varied considerably between studies, but given the fact that infections related to hypothermia are likely to occur during or early after the termination of cooling, we do not think this will have had an important effect on the results of our study.

A separate analysis based on target temperature was not possible, because most studies used a range of target temperatures instead of a single one. The analysis based on the achieved temperature was limited by the fact that the achieved temperature was not reported in all studies.

Future randomized trials of hypothermia should prospectively assess and report the occurrence of infections, also based on established definitions. Further research should focus on identifying high-risk patients, and on the effect of prophylactic treatment with antibiotics.

CONCLUSIONS

Cooling increased the risk of pneumonia and sepsis, but no convincing evidence of an increased overall rate of infections was observed. Clinicians treating patients with hypothermia should be aware of this common side effect so that treatment can start early.

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SUPPLEMENTARY DATA

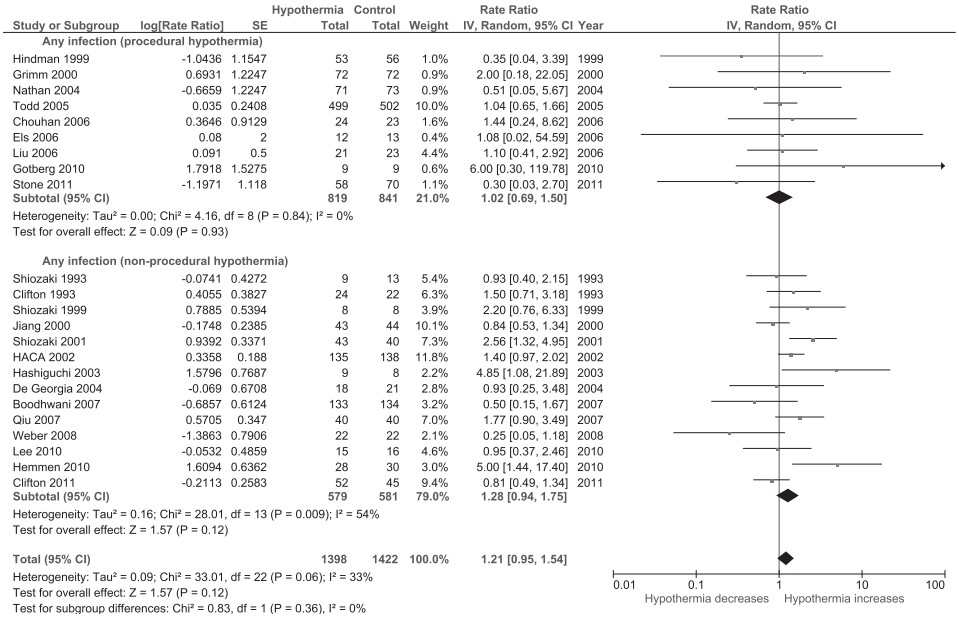

Figure S5.1. Effect of hypothermia on the occurrence of infections by context: procedural versus non-procedural hypothermia (Rate Ratio).

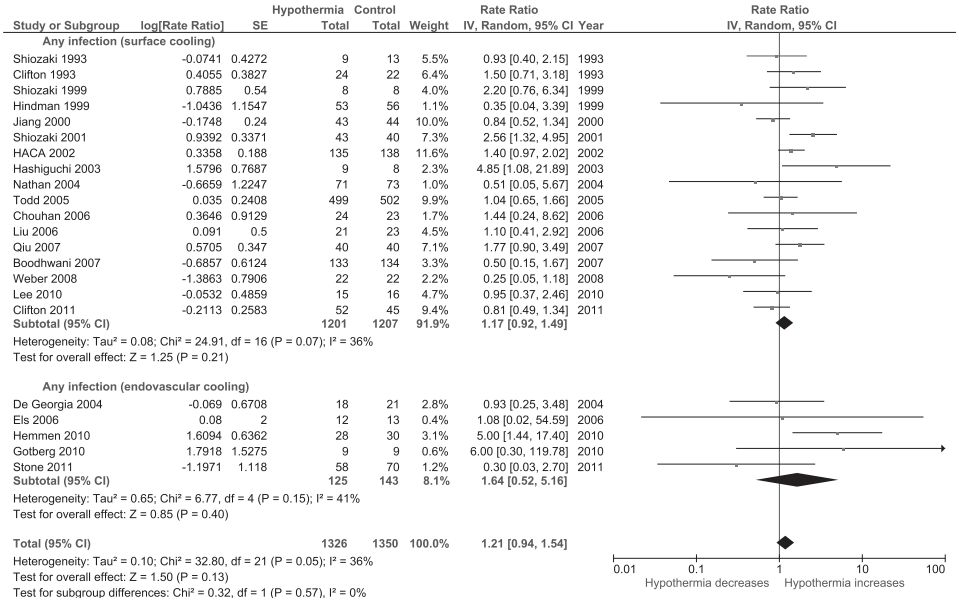

Figure S5.2. Effect of hypothermia on the occurrence of infections by context: mode of cooling (Rate Ratio).

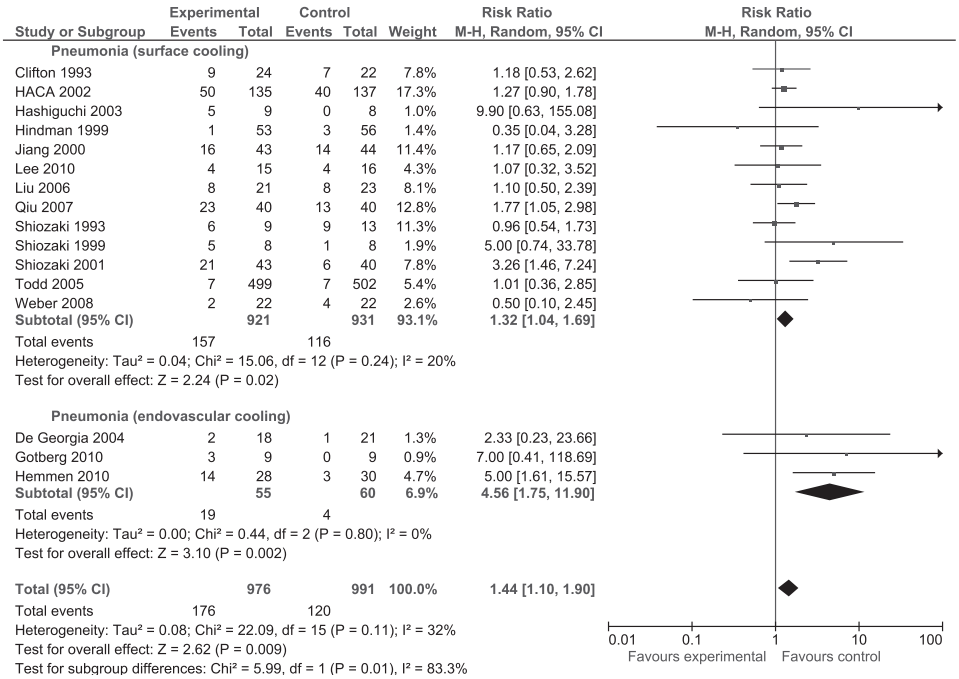

Figure S5.3. Effect of hypothermia on the occurrence of pneumonia by context: endovascular versus surface cooling (Risk Ratio).

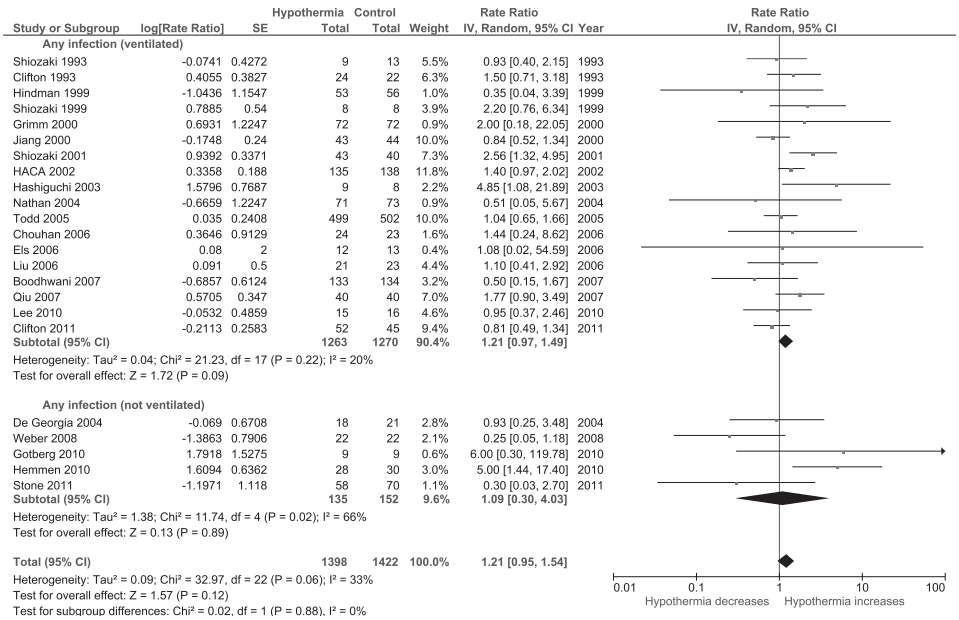

Figure S5.4. Effect of hypothermia on the occurrence of infections by context: mechanical ventilation versus no mechanical ventilation (Rate Ratio).

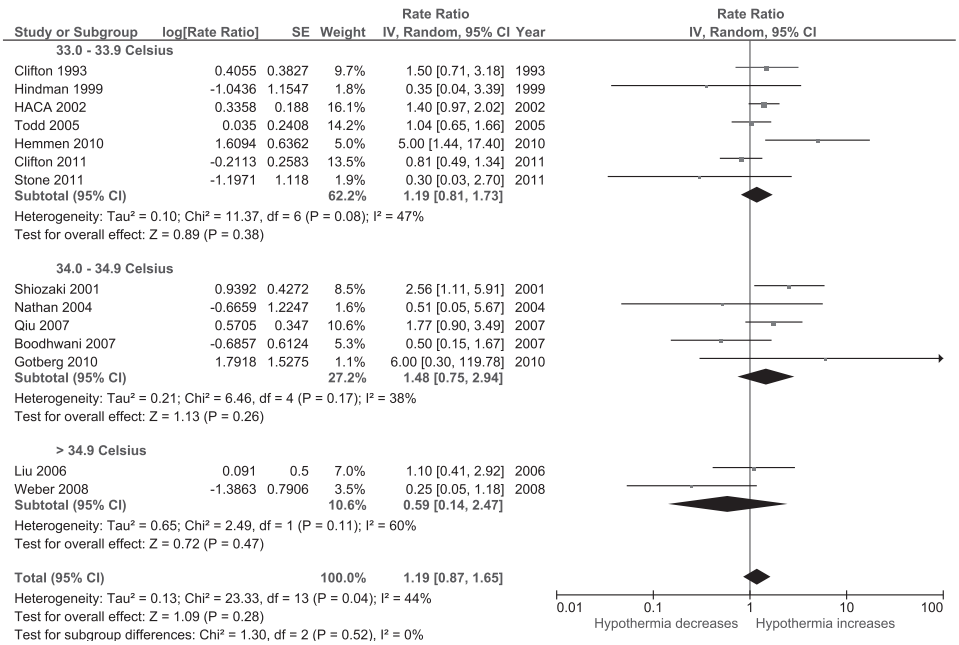

Figure S5.5. Effect of hypothermia on the occurrence of infections by context: achieved temperature (Rate Ratio).

PART II

Challenges in the end-of-life decision making process after acute stroke

Chapter 6

End-of-life decisions in patients with severe acute brain injury

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SUMMARY

Most in-hospital deaths of patients with stroke, traumatic brain injury, or postanoxic encephalopathy after cardiac arrest occur after a decision to withhold or withdraw life-sustaining treatments. Decisions on treatment restrictions in these patients are generally complex and are based only in part on evidence from published work. Prognostic models to be used in this decision making process should have a strong discriminative power. However, for most causes of acute brain injury, prognostic models are not sufficiently accurate to serve as the sole basis of decisions to limit treatment. These decisions are also complicated because patients often do not have the capacity to communicate their preferences. Additionally, surrogate decision makers might not accurately represent the patient's preferences. Finally, in the acute stage it is difficult to predict how a patient would adapt to a life with major disability.

INTRODUCTION

Most in-hospital deaths of patients with acute stroke, traumatic brain injury, or post-anoxic encephalopathy after cardiac arrest occur after a decision to withhold or withdraw life-sustaining therapies.[1-5] These decisions usually evolve from complex discussions that involve prognosis, physician's instinct, patient preferences, and institutional and societal norms and values. Treatment restrictions in patients with severe acute brain injury differ from those in patients in the terminal phase of most other diseases, because continuation of treatment often allows patients to live for months or years, but at the cost of being left in a state of disability that might be against their wishes.[5,6] In patients with severe acute brain injury an additional problem in reaching end-of-life decisions is the difficulty in predicting outcome at an early stage. Furthermore, patients mostly lack the capacity to make medical decisions and therefore cannot be involved with these discussions themselves, and other informants such as family members may not be able to reliably predict which course the patient would prefer.[7] Finally, in the acute stage it is also difficult to predict how a patient would adapt to a life with major disability; patients who have always considered dependency a fate worse than death may change their opinion once they find themselves in that situation.

Although the process of making end-of-life decisions in patients with severe acute brain injury is routine in clinical practice, this has received relatively little attention in the medical literature, especially when compared with similar decisions in patients with a more gradually progressive severe illness. We aim to provide a narrative review of the evidence to guide end-of-life decisions in patients with severe acute brain injury as a consequence of ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, trauma, or postanoxic encephalopathy after cardiac arrest. We address the judgement of prognosis, the possibilities to respect the patient's autonomy despite incapacity, and the adaptation of patients to life with severe disability. Finally, we suggest how clinicians might better integrate the available evidence and the patient's preferences in the decision-making process.

Search strategy and selection criteria

References for the main text of this Review were identified by searches of PubMed and Embase up to 1 January 2014, and references from relevant articles. We used the following search terms and their synonyms or related terms: "end-of-life decisions", "palliative care", "withholding treatment", "withdrawal of treatment", "proxy opinion", "surrogate decision", "response shift", "adaptation", in combination with "ischaemic stroke", "intracerebral haemorrhage", "subarachnoid haemorrhage", "traumatic brain injury", or "post-anoxic encephalopathy." If for important themes studies on acute brain injury were not available, studies in a more general population were selected for illustration. Only articles published in English, German or Dutch were evaluated. We focused on publications from the past 10 years and on original research papers rather than reviews. The final reference list was generated on the basis of relevance to the topics covered in this Review.

For Table 6.1 on prediction models, we searched Thomson Reuters' Web of Science on 31 December 2013, with a combination of the search terms "prognostic model", "prediction model" in combination with "ischaemic stroke", "intracerebral haemorrhage", "subarachnoid haemorrhage", or "traumatic brain injury", or "post-anoxic encephalopathy" and for each condition included two models reported in articles with the highest number of citations (but three for post-anoxic encephalopathy after cardiac arrest to include a model for patients treated with hypothermia).

DEFINITION OF END-OF-LIFE DECISIONS

We define end-of-life decisions as those related to 1. withdrawal or withholding of potentially life-sustaining treatments, including artificial hydration and nutrition; 2. starting medication to alleviate symptoms, with hastening death as a possible or certain side effect; and 3. euthanasia or physician-assisted suicide.[8] Euthanasia (ending life on a patient's own insistence) is legal or legally pardoned in only a minority of countries or states, and generally requires the patient to be fully competent.[9] For this reason, euthanasia is not an option in the large majority of patients with acute brain injury and will not be discussed in this review. *Withholding* treatment is defined as a decision not to start or increase a life-sustaining intervention. An order not to resuscitate is usually classified as withholding therapy. *Withdrawing* treatment is defined as an active decision to stop a life-sustaining intervention presently being given.[10] Although clinicians often are more comfortable with withholding treatments than withdrawing them, most authors consider that there is no ethical or legal distinction between the two.[11,12]

For patients in whom curative treatment is stopped, adequate palliative care to control pain, provide comfort, improve quality of life, and manage the patients' and families' physical, social, psychological, or spiritual needs is essential.[13] In patients who are dying, appropriate action should be taken whenever possible to ensure that death is peaceful and dignified.[14] A full discussion about the elements of palliative care is beyond the scope of this article.

FREQUENCY AND IMPACT OF TREATMENT RESTRICTIONS

Considerable differences in end-of-life practices have been reported, influenced by region, nationality, culture, and religion.[15] In a study of end-of-life practices in intensive care units throughout Europe, treatment restrictions were applied more often in northern than in southern countries, and withdrawal of life-sustaining treatment occurred more often if the physician was Catholic, Protestant, or had no religious affiliation than if s/he was Jewish, Greek Orthodox, or Muslim.[16] A similar association between end-of-life practices and patients' religious affiliation has been observed.[17] Attempts have been made to summarize the views of the largest religions on treatment restrictions and on euthanasia,[17] but these more general views may not necessarily apply to the individual patient. This is in part because the many smaller and larger denominations within the various religions may have different views on these issues, and because views among people of the same religion may differ based on the region where they live. In addition, the interpretation of religious teachings may vary per individual.

In American and Canadian studies in patients with ischaemic stroke,[5] intracerebral haemorrhage,[1] traumatic brain injury,[4] or coma after cardiac arrest,[2] 70–97% of the early deaths have been reported to occur after decisions to withdraw or withhold life-sustaining treatments. Because these studies were small and performed in academic or tertiary referral centres, it is unclear whether these data can be extrapolated to a more general population of patients with acute brain injury.

Since information on the timing and type of the restrictions and the reasons for their institution is limited, the exact influence of treatment restrictions on case fatality in patients with acute brain injury is uncertain. For example, withdrawal of care in a 90-year-old patient with a large intracerebral haemorrhage at a stage in which he is in a deep coma and has two fixed and dilated pupils is unlikely to have a material effect on outcome. By contrast, withholding of care will strongly increase the risk of death in a young patient with a large space-occupying hemispheric infarction who is eligible for a potentially life-saving surgical decompression.[18] A retrospective assessment of patients with ischaemic stroke who had died after a decision to withdraw or withhold potentially life-sustaining interventions suggested that 41% of early deaths might have been delayed beyond 30 days if those potentially life-saving measures had been taken.[5] In a study of patients with intracerebral haemorrhage, the observed prevalence of favourable functional outcome was lower than predicted in patients with "do-not-attempt-resuscitation" orders, and higher than predicted in patients who did not have these orders.[19] Based on these data, it was estimated that in the United States alone each year over 7000 patients with intracerebral haemorrhage lose their chance of a favourable outcome as a result of prognostic pessimism.[19] Despite the considerable limitations surrounding these estimates, it is possible that treatment restrictions will indeed affect case fatality in a substantial number of patients with acute brain injury.

MEDICAL FUTILITY

Decisions to withhold or withdraw life-sustaining treatment are often justified by a claim of 'medical futility.' However, this term is ill-defined, and therefore of limited usefulness. For example, treatments have variously been classified as futile if they had less than 1% chance of success; if they did not lead to an acceptable quality of life; or if they would not prevent death within weeks or months.[20] Treatments might also simply be perceived as futile if they are unlikely to achieve an effect that the patient would appreciate as benefit.[21]

PROGNOSTICATION

Accurate information about the expected outcome of the disease is required to guide physicians and other professionals, patients, and their relatives in making decisions related to withdrawal or withholding of life-sustaining treatments. Overoptimistic expectations may lead to aggressive management where this is not appropriate, and leave patients in severely disabled states that might be against their wishes. Conversely, unfounded pessimism may lead to early withdrawal of treatment and thereby prevent the opportunity for some degree of recovery and adaptation of patients and families to disability.[5]

Prognostic models

Except for postanoxic encephalopathy after cardiac arrest,[22] individual risk prediction based on a single factor is usually poor. This has led to the development of prognostic models based on multiple factors in combination to predict outcome in individual patients.[23-26] Systematic reviews on prognostic models are available for intracerebral haemorrhage,[24,27] subarachnoid haemorrhage,[25] and traumatic brain injury.[28] The majority of these models are limited to use in the first hours or days after the brain injury. Table 6.1 lists examples of such models; an example of a case of traumatic brain injury where a prediction model was applied is presented in Box 6.1. The large majority of prediction models in patients with acute brain injury were not developed with the specific aim of informing end-of-life decisions.

Accuracy

Good prognostic models to be used in decisions concerning life or death should clearly have a strong discriminative power. More specifically, the false positive rate of a predicted poor outcome should preferably be zero, with a narrow confidence interval. At present, such models only exist for comatose patients after cardiopulmonary resuscitation for cardiac arrest.[22] In these patients, the false positive rate for poor outcome is indeed zero (with narrow confidence intervals) for several separate predictors (absent pupillary light response or corneal reflexes

Box 6.1. Case*

An 80-year-old woman is taken to the emergency room of our tertiary trauma centre after having been hit by a car while she was taking a walk. Except for treated hypertension, her medical history is unremarkable. She was fully independent, and still enjoyed her annual hiking holidays. Within minutes after the accident, emergency medical service responders found her comatose (Glasgow Coma Scale, E1M4V2). They sedated and intubated her at the scene, also using muscle relaxants. On examination in the emergency department, she has an oxygen saturation of 100% and a normal blood pressure and pulse. She is still sedated and paralysed; her pupils are 2 mm in diameter and minimally reactive. There is a large wound on the back of her head.

CT scans of her spine and trunk show multiple rib fractures, and CT of her head a right-sided frontotemporoparietal subdural hematoma, subarachnoid blood over both hemispheres, and signs of bilateral occipital contusions (Figure 6.1).

Because there is no relevant mass effect of the subdural haematoma, this is not evacuated. She is transferred to an intensive care unit (ICU) for mechanical ventilation and monitoring of intracranial pressure. Immediately after admission to the ICU, the sedation is temporarily stopped to allow neurological examination; this still shows a persistently reduced level of consciousness (E1M4Vtube) and reactive pupils.

According to the prognostic CRASH model,[32] assessed at http://www.trialscoordinatingcentre.lshtm.ac.uk/Risk%20calculator/index.html, her risk of dying within 14 days is 68·6% (95% confidence intervals (CI), 57·1 to 78·2) and the risk of an 'unfavourable outcome' 93·4% (95% CI 89·9 to 95·8). It should be noted, however, that the validity of the model is debatable at this high age range because of the small number of representative patients in the population in which the model was developed.

The very small chance of recovery to functional independence is discussed with her husband, who emphasizes that his wife would always fight for her life, even with the prospect of functional dependence. There are no written advance directives.

As a consequence of this discussion, treatment on the ICU is continued without restrictions except for an order not to resuscitate. Over the next week, there is no improvement of her consciousness. Repeated CT scans of the brain show marked contusions of the right frontal and temporal lobes, and of both occipital lobes. The patient's family members gradually accept that the chance of a reasonable functional recovery is too small to continue treatment. The patient is extubated and transferred to the regular neurology ward for comfort care. She dies within 24 hours because of respiratory failure. The family members later report they were happy that treatment was not stopped on the first day, and that the week on the ICU has given them the time to come to terms with the expected poor outcome.

* Identifying patient characteristics have been altered to protect anonymity.

after three days, extensor or no motor response to pain after three days, or bilateral absence of the N20 component of the somatosensory evoked potential (SSEP) on days 1 to 3). These predictors are based on findings in patients not cooled after cardiac arrest, and it has long remained uncertain whether they also apply to patients treated with hypothermia. A recent study

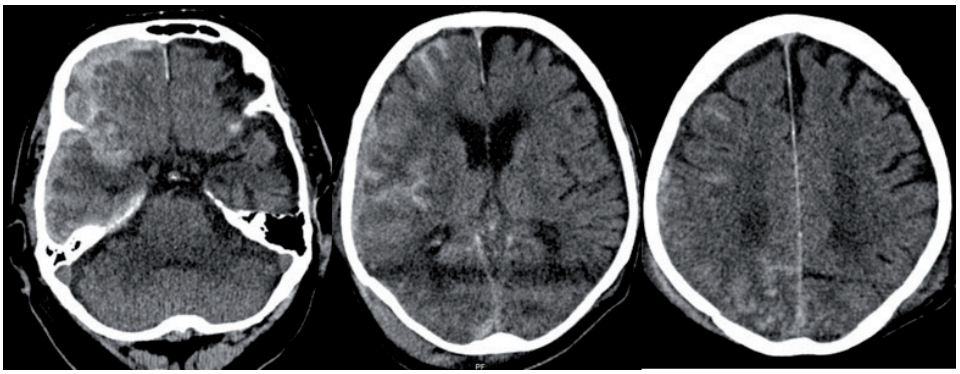

Figure 6.1. First CT-scan of presented case.

suggested that in patients treated with hypothermia, absent pupillary light responses or absent corneal reflexes at 72 hours, or absent SSEPs after one day are also reliable predictors of poor outcome, although with slightly higher false positive rates and wider confidence intervals.[29] For other causes of acute brain injury prognostic models are generally not sufficiently accurate to be the exclusive foundation of decisions to limit treatment. This is the case even for models developed with data from thousands of patients and validated in independent cohorts, such as the CRASH and IMPACT models for patients with traumatic brain injury.[30-32]

Other limitations

The use of many prognostic models is also limited by intrinsic methodological shortcomings and by a lack of external validation.[25,26] A major concern is that treatment restrictions may have affected the outcomes in populations where the prognostic models have been developed, and as such have reduced the validity of these models. In a study assessing the predictive value of SSEP recordings in comatose patients after cardiac arrest, treatment had already been restricted in about a quarter of the patients during the first day.[33] The risk that treatment restrictions may lead to self-fulfilling prophecies has also been acknowledged for patients with other types of acute brain injury.[1,19,34-37] In addition, the sensitivity of the models may be limited even if specificity is not. For example, in a large study in patients with postanoxic encephalopathy cooled after cardiac arrest, the specificity of an absent SSEP after rewarming to predict a poor outcome was 100% (95% confidence interval (CI), 82–100), but the sensitivity just 38% (95% CI, 30–48).[29] In other words, 62% of the patients with a normal test result still had a poor outcome.

Table 6.1. Examples of models to predict outcome after acute brain injury

	Factors included in model	Time of assessment	Predicted outcome	Predictive values
ischaemic stroke[87]	Age, stroke severity (NIHSS), lacunar infarct; history of stroke; history of diabetes; pre-stroke disability*	First 6 hours	very poor outcome at three months (NIHSS ≥20 or death; BI <60 or death; GOS 1 to 3)†	AUC = 0·75–0·89[88]
ischaemic stroke[48]	Age, stroke severity (NIHSS)	First 6 hours	• incomplete functional recovery (BI <95) or death; • case fatality after 100 days	AUC = 0·81[89] AUC = 0·71[89]
intracerebral haemorrhage[90]	"ICH score": level of consciousness (GCS); ICH volume; intraventricular haemorrhage; location (supratentorial vs. infratentorial); age	Initial evaluation	case fatality at 30 days	AUC = 0·88[91]
Intracerebral haemorrhage[92]	"FUNC score": ICH volume, age, ICH location (supratentorial vs. Infratentorial) level of consciousness (GCS), pre-ICH cognitive impairment	Initial evaluation	Poor outcome (GOS 1 to 3) at 90 days	AUC = 0·82[92]
subarachnoid haemorrhage[93,94]	"WFNS Scale‡": level of consciousness (GCS); presence of motor deficit	Admission	Unfavourable outcome (GOS 1–3) at three months	AUC = 0·82[95]
subarachnoid haemorrhage[96]	"Hunt and Hess Scale": Clinical symptoms; level of consciousness (GCS); presence of motor deficit	Admission	In hospital case fatality	AUC = 0·77[97]

traumatic brain injury[32]	"CRASH CT model": age, level of consciousness (GCS), pupil reactivity, presence of major extracranial injury, findings on cranial CT	First 8 hours	• death at 14 days; • unfavourable outcome at six months (GOS 1–3)	AUC = 0·71–0·87[98] AUC = 0·71[98]
traumatic brain injury[30]	"IMPACT extended model": age, motor score, pupillary reactivity; hypoxia, hypotension; CT characteristics glucose and hemoglobin	First few hours	• unfavourable outcome (GOS 1-3) at six months; • mortality at six months	AUC = 0·71–0·86[98] AUC = 0·71[98]
postanoxic encephalopathy[33]	Absence of pupillary and corneal reflexes	At 72 hours	death or persisting unconsciousness at one month	False positive rate 0% (0–9)
postanoxic encephalopathy[33]	Bilateral absence of the N20 component of the SSEP	At 24 hours	death or persisting unconsciousness at one month	False positive rate 0% (0–4)
postanoxic encephalopathy, treated with hypothermia[29]	Bilateral absence of the N20 component of the SSEP	After rewarming to normothermia (≤72 hours)	poor outcome: (GOS 1–3) at six months	False positive rate 0% (0–18)

This table includes the two models or predictors reported in articles most frequently cited according to Thomson Reuters' Web of Science, but three for post-anoxic encephalopathy after cardiac arrest to include a model for patients treated with hypothermia.
NIHSS indicates National Institutes of Health Stroke Scale; BI, Barthel Index; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; mRS, modified Rankin Scale; ICH, intracerebral haemorrhage; SSEP, somatosensory evoked potential; AUC, area under the receiver operating characteristic curve. * With infarct volume at 7 to 10 days included, AUCs are slightly higher. ‡ As assessed by Rosen and Macdonald.[94] † The publication uses a different grading of the GOS.
AUC is based on external validation, unless stated otherwise. References refer to the external validation article.

Predicted outcomes

The choice of the predicted outcome measure is particularly relevant for the use of prognostic models in end-of-life decisions. Usually the predicted measure is either death or 'poor functional outcome,' or both combined in a single endpoint. Death is clearly a valid outcome measure, but there is limited consensus what constitutes a poor functional outcome. Models that use the Glasgow Outcome Scale (Table 6.2) to assess outcome often define poor outcome as a grade between 1 and 3.[30,32] The best outcome in this range (a score of 3, 'severe disability') occurs where the patient is "able to follow commands, but is unable to live independently".[38] Several stroke studies dichotomise the outcome according to whether or not a patient is dependent on the help from others, and do this by defining a poor or unfavourable outcome as a grade of ≥3 on the modified Rankin Scale (mRS) (Table 6.2).[39] As thus defined, dependency and even 'severe disability' do not preclude a quality of life which many might prefer to death. For this reason we think that prognostic models based on such broad definitions of poor outcome are often of little help to aid decisions on treatment restrictions.

Table 6.2. Outcome measures after acute brain injury[38,99,100]

Score	Modified Rankin Scale[99]	Oxford Handicap Scale[100]	Glasgow Outcome Scale[38]
0	No symptoms at all	No change	
1	No significant disability and able to carry out all duties	No interference	Death
2	Slight disability. Unable to carry out some previous activities but able to look after own affairs without assistance	Some restrictions but able to look after self	Persistent vegetative state
3	Moderate disability. Requiring some help but able to walk without assistance	Significant restriction; unable to lead a totally independent existence (requires some assistance)	Severe disability (conscious but disabled)
4	Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance	Unable to live independently but does not require constant attention	Moderate disability (disabled but independent)
5	Severe disability. Bedridden, incontinent and requiring constant nursing care and attention	Totally dependent; requires constant attention day and night	Good recovery

Generalizability

Prognostic models for stroke and postanoxic encephalopathy were generally developed in elderly populations. In recent prognostic studies in survivors after cardiopulmonary resuscitation the mean age of the patients was over 60 years.[29,40] It is uncertain whether the results of these models can be generalised to younger patients, in whom the prognosis may be better.

Uncertainty

Because of these limitations, prognostic models should not be used as the only basis for decisions on treatment restrictions. However, well-developed and well-validated models with well-defined and relevant endpoints can be used to support such decisions as long as the physician is aware of the limitations, takes account of the definition of 'poor outcome' in the prediction model, and shares these shortcomings with family members.

Given that the best estimates of prognosis will carry a large margin of uncertainty in most cases, this very uncertainty may give hope to some patients and their families, or an escape from the need to make a decision at all for others.[41] In a US survey of the general public, more than half of the respondents believed that divine intervention could save a patient with severe traumatic injury when physicians consider treatment futile.[42]

Despite uncertainty, frank discussions about prognosis with the patient's representatives should not be avoided. Unrealistic expectations about the prognosis of gravely ill patients in intensive care units have been associated with increased resource utilization without substantial survival benefit.[43] In an American study, most surrogates of critically ill and incapacitated patients (not only as a consequence of acute brain injury) wanted physicians to disclose prognostic estimates even if they could not be sure these were correct. From structured interviews it emerged that surrogates tend to perceive uncertainty as an unavoidable part of estimating the prognosis for critically ill patients, and most accepted this uncertainty.[44] Because these observations were made in a more general population, it is uncertain whether these also apply to surrogates of patients with acute brain injury.

Physician's estimates

Doctors often tend to be too optimistic in their intuitive survival predictions for terminally ill patients.[45] The prognostic accuracy generally increases with the physician's experience, whereas some found that a stronger doctorpatient relationship was associated with lower prognostic accuracy.[45] In selected patients with acute stroke admitted in tertiary care centres, early prediction of a poor functional outcome or death by the attending physician was correct in about 90% of the cases.[46,47] However, the ability to predict quality of life was substantially lower.[47] The advantage of prognostication based on the physician's estimate is that other

factors not included in prognostic models can be taken into account. However, few clinicians will have systematically followed up patients in whom they made intuitive predictions, and recall bias is likely to play a role. In patients with ischaemic stroke, even simple prognostic models performed better than the attending physicians' impromptu predictions of the risk of death or handicap.[48] In most patients with acute brain injury, physicians will therefore not be able to predict a poor functional outcome or death with sufficient certainty to be the exclusive basis of end-of-life decisions. However, when clinical judgement is used in combination with formal prognostic models, it may reduce prognostic uncertainty.

Other factors

In practice, factors additional to prognostic information influence physicians in making decisions at the end of a patient's life. For example, physicians more often tend to withhold life-sustaining treatment if the patient is aged and has serious comorbidity than if the patient is young and previously healthy, even after adjustment for the patients' condition and preference.[49] Physicians are also influenced by their own personal values and professional characteristics,[50] by institutional and national norms, for example about the application of orders not to resuscitate,[34] by financial incentives,[51] by their religion,[16] and possibly even by audits on which the quality of their care will be judged if these involve case fatality.[5]

WHAT CONSTITUTES AN ACCEPTABLE OUTCOME?

Outcomes predicted with the available prognostic models may not be the most relevant to the patient. Most models predict the risk of death or dependency, or the risk of death alone (Table 6.1). Health-related quality of life (QoL) could be a more relevant outcome measure because this is designed to reflect the impact of the disease from the perspective of the patient; it is therefore likely to provide a more holistic picture of disease impact.[52] Although increasing disability is generally associated with a reduction in QoL,[52,53] there are many exceptions to this rule, with some reporting fair to good QoL or "happiness" despite serious disability.[54,55] Such adjustment to illness may in part be caused by 'response shift,' which includes a change in the internal standards and values in the self-evaluation of QoL.[56] This is important, because this demonstrates that some patients with a poor functional outcome after acute brain injury regain a good QoL. Unfortunately, in the early phase of the illness it is unclear how to identify patients who will adapt well to their new situation and recapture a good QoL.

INCAPACITY TO MAKE MEDICAL DECISIONS

A vital criterion for valid consent to medical treatment is the patient's decision making capacity. The criteria for assessing decision making capacity vary from country to country and from state to state, but generally include four interrelated capacities: to understand relevant information, to appreciate the current situation and consequences of decisions, to use sufficient reasoning to make decisions, and to communicate a choice.[57,58] The notion of *capacity* should be distinguished from the related term *competence*, which is typically used in a legal sense and refers to the mental ability and cognitive capabilities required to execute a legally recognized act.[59,60] Most patients with serious brain injury in whom end-of-life decisions are considered have diminished capacity for treatment decision because of a reduced level of consciousness, aphasia, or another cognitive disorder. In case of incapacity, the patient's autonomy should be respected as much as possible by considering the patient's previously expressed wishes, for example in advance directives, or by appointing a surrogate decision maker (Box 6.2).[61]

Box 6.2. Hierarchy of surrogates based on Health Care Surrogate Act[101]

Surrogates are selected in this order:

1. The appointed guardian of the patient, if any;
2. The individual, if any, to whom the patient has given a durable power of attorney that includes the authority to make health care decisions;
3. The patient's spouse or registered domestic partner;
4. Children of the patient who are at least eighteen years of age;
5. Parents of the patient;
6. Adult brothers and sisters of the patient.

Advance directives

Advance directives document a patient's wishes with respect to life-sustaining treatment (in a living will), their choice of a surrogate decision maker, or both.[62] In patients with severe brain injury in whom withholding or withdrawal of life-sustaining treatments is considered they may give an insight in patient preferences and so provide guidance to medical decisions. The availability and legal recognition of advance directives widely differ per country and reflect the balance between the ethos of patient autonomy and that of paternalism in medical care.[63] In a survey of US citizens of 60 years of age or older who had died of any cause between 2000 and 2006, an advance directive was available in two thirds of those who lacked the capacity to make decisions themselves in the period near death. Most advance directives requested limited care or comfort care, and only a very small minority asked for all care possible. More than 80% of those who requested limited care, and more than 95% of those who requested

comfort care received care consistent with their preferences.[62] Because these observations were made in a more general population, it is uncertain whether these also apply to patients with acute brain injury.

Still, the value of advance directives may be less than optimal. They often represent the patient's wishes in specific conditions (for example coma), and it may not be appropriate to extrapolate these wishes to a different situation (for example aphasia and hemiplegia after a stroke). This also applies to informally expressed preferences, such as "I would never want to spend the rest of my life in a nursing home."

In discussing previously expressed treatment preferences, especially when these are not clearly documented, the physician should point out that patients often report greater happiness and QoL than healthy people predict they would feel under the same circumstances. This phenomenon has been referred to as the 'disability paradox,' and is explained in part by the capacity of patients with chronic illness or disability to adapt to their circumstances.[64,65] In other words, dependency may become acceptable when the alternative is death.

In a German population-based survey that assessed the attitude towards surgical decompression for space-occupying hemispheric infarction, only a minority favoured this potentially life-saving intervention if survival would be associated with severe or moderately severe disability.66 By contrast, the large majority of patients treated with surgical decompression in randomised trials were satisfied with the treatment received at one year after the procedure, even though most had remained dependent in their activities of daily living.[18,67] This may be explained by the fact that most patients experienced their QoL at one year as acceptable, with further improvement in QoL up to the end of year three.[68]

Despite these difficulties, physicians should carefully consider available advance directives or less formally expressed treatment preferences and assess their relevance to the current clinical situation. These directives may improve understanding of patient's preferences, even if the condition described is not exactly similar to the present or predicted circumstances.

Decision making by representatives

When the patient is unable to participate in decision making, caregivers should turn to surrogate decision makers, usually close family members (Box 6.2).[69] They may be asked what the patient would have chosen or – if such information is not available – which decision they consider to be in the patient's best interest.[70] Discussions with family members are often relevant even in the presence of an advance directive, especially if the circumstances described in directives do not reflect the current medical situation. Surrogates can have been designated by the patient while competent. If no surrogate was designated, a next of kin may be appointed. Most countries and states have laws defining the specific order of next of kin to be appointed. A frequently used hierarchy is listed in Box 6.2.[62]

An essential condition for adequate involvement of surrogates in decision making is that the physician provides unbiased information on possible medical scenarios and the risks and benefits of proposed treatment strategies.

There are several limitations to surrogate decision making. First, families are often stressed and distracted, and may therefore have a reduced ability to make any decision. Secondly, family and social factors that are largely undetectable to healthcare providers may influence the decision making process. These include dysfunctional relationships, the wish or preparedness to act as a caregiver, and future inheritance. Decisions may also be affected by recall bias, because families are likely to remember the patient as healthier, more active, and less dependent than he or she really was.[71] Thirdly, surrogates of critically ill patients may have optimistic biases that interfere with their interpretation of negative or dire prognostic information.[72] Finally, the accuracy with which surrogates predict patients' treatment preferences is limited. In a review of 17 studies with 151 hypothetical scenarios describing severe diseases of different kinds, surrogates incorrectly predicted the patients' end-of life treatment preferences in one third of the cases.[7] The accuracy of prediction by surrogates was not higher if patients had designated the surrogates, if there had been prior discussion of patients' treatment preferences,[7] or if advance directives were available.[73] For the patients with acute brain injury included in these studies, the surrogates gave a decision with which the patient agreed in 70% of coma scenarios and 58% of stroke scenarios. However, surrogates still predicted patients' preferences better than physicians.[7] Further information about the expressed wishes of a patient may be available from the patient's primary care physician or from other professionals. In some jurisdictions there are clear arrangements for the appointment of professionals to act as the representative of the patient, and in some the procedure for seeking judicial review is well established.[74]

RECOMMENDATIONS IN GUIDELINES

Given the limitations of prognostic models and limitations of surrogate decision making, relevant American guidelines for patients with intracerebral haemorrhage recommend – if there is no advance directive – aggressive full care early after intracerebral haemorrhage and postponement of new 'do not resuscitate' orders until at least the second full day of hospitalization.[75] A practice parameter of the American Academy of Neurology provides a helpful decision algorithm for use in the prognostication of comatose survivors after cardiopulmonary resuscitation who have not been treated with hypothermia.[22] International recommendations for patients who have been cooled are not available yet.

European and American guidelines for the treatment of patients with ischaemic stroke,[76,77] subarachnoid haemorrhage,[78,79] or traumatic brain injury[80,81] do not provide specific recommendations related to end-of-life decisions.

IMPLICATIONS FOR CLINICAL PRACTICE

Decisions to withdraw or withhold life-sustaining treatments are generally complex and can rely only in part on evidence from the literature. Prognostic models can be used to predict outcomes, but both physicians and surrogate decision makers should be aware that the value of these models in discussions on treatment restrictions is limited because of inaccuracies and a potential bias caused by failure to account for limitations of care in the patient population in which the models were developed. In addition, physicians should be aware that definitions of 'poor outcome' vary across models, and may include a state that is acceptable to the patient.

Despite uncertainty, discussions about prognosis with the patient or his representatives cannot be avoided. If adequately explained, most patients and families will be able to understand uncertainty as an unavoidable reality, and will accept this.

To reduce the risk of prematurely forgoing treatments that could provide benefit, a time-limited trial of a management strategy may be considered,[82] as has been done in the case presented (Box 6.1). With such a trial, physicians and the patient's family agree to use certain medical therapies over a defined period of time. These therapies will be continued if the patient reaches a pre-specified outcome, and are withdrawn if this is not reached. A time-limited trial may also increase the chance that families who initially want 'everything' done to keep the patient alive will come to accept limitations in treatment if the patient shows no sign of recovery.[82] A major disadvantage of this approach is that patients may be denied the chance to die in an early phase, but instead survive in a condition they always considered unacceptable. As well as the private costs which this entails, the resource and opportunity costs of such an approach (preventing access for other patients who may have more to gain) are important considerations.

For an adequate implementation of the patient's preferences in the decision-making process, a five-step approach may be used (Box 6.3). This is based on the notion that physicians are experts on prognosis, treatment options, and their implications, whereas families are experts on the patient's values and preferences.[83] Of course, this approach does not solve the problems related to inaccuracies in prognostication and in the surrogates' view on the patient's preferences.

Finally, residents (as well as more experienced physicians) should be trained in end-of-life discussions with patients and their families.[84] Most of these discussions are held by residents, but only a minority feels comfortable with this aspect of clinical care.[85]

CONCLUSIONS AND FUTURE DIRECTIONS

Decisions on treatment restrictions in patients with severe acute brain injury are often complex and are based only in part on evidence. Except for patients with post-anoxic encephalopathy after cardiac arrest, no prognostic model has the accuracy to be the exclusive foundation of decisions to limit treatment. Furthermore, the availability and usefulness of advance directives

are limited and surrogates too often do not accurately represent the patients' preferences. However, better alternatives to extend the patients' autonomy are not available. Finally, what is a fate worse than death for one patient, can be a life worth living for another.

IMPLICATIONS FOR RESEARCH

Future prediction models should use more explicit outcomes than a broad range on a functional outcome scale and should include an assessment of QoL. For the development of these models, it is a challenge to avoid confounding by treatment restrictions in the population in which they have been developed. An option to control this potential confounder to some extent is the adoption of a protocol for withdrawal of life-sustaining treatment in all centres participating in the development of the model. This will allow future users of the model to assess the criteria used for withdrawal of life-sustaining treatment. Such an approach was used in a recent randomised trial to compare two target temperatures for hypothermia after out-of-hospital cardiac arrest.[86] Finally, future research should focus on factors that predict or improve the capacity of patients to cope with disability and have an acceptable quality of life despite a poor functional outcome.

Box 6.3. Five-step approach to make end-of-life decisions (based on[83])

1. **Collecting evidence:** The physician gathers evidence about prognosis and about the benefits and burdens of a specific treatment, and of not choosing the treatment in question.
2. **Sharing information:** The physician informs the family about the disease, treatment options, and prognosis with and without treatment. The family informs the clinicians about the patient's values and preferences. Building up rapport with the relatives and demonstrating empathy is essential.
3. **Critical appraisal:** Clinicians and the patient's family should critically appraise the evidence and information provided and identify potential biases that might influence decision making. These include uncertainties about prognosis and about the patient's preferences.
4. **Recommendations and decisions:** The clinician must integrate the information and make a recommendation. Shared decision-making is recommended.
5. **Evaluation and follow-up after decision-making:** Evaluate the clinician's performance and assure adequate follow-up.

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Chapter 7

Treatment restrictions in patients with severe stroke are associated with an increased risk of death

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ABSTRACT

Introduction: Treatment restrictions in the first two days after intracerebral haemorrhage have been independently associated with an increased risk of early death. It is unknown whether these restrictions also affect mortality if these are installed several days after stroke onset.

Patients and methods: Sixty patients with severe functional dependence at day four after ischaemic stroke or intracerebral haemorrhage were included in this prospective two-center cohort study. The presence of treatment restrictions was assessed at the day of inclusion. Information about mortality, functional outcome (modified Rankin scale (mRS)) score, and quality of life (visual analogue scale (VAS)) was recorded six months after stroke onset. Poor outcome was defined as mRS >3. Satisfactory quality of life was defined as VAS ≥60.

Results: At six months, 30 patients had died, 19 survivors had a poor functional outcome and 9 patients had a poor quality of life. Treatment restrictions were independently associated with mortality at six months (adjusted relative risk, 1.30; 95% confidence interval, 1.06–1.59; p=0.01), but not with functional outcome.

Discussion: Our findings were observed in sixty selected patients with severe stroke.

Conclusion: The installment of treatment restrictions by itself may increase the risk of death after stroke, even if the first four days have passed. In future stroke studies this potential confounder should be taken into account. Quality of life was satisfactory in the majority of the survivors, despite considerable disability.

INTRODUCTION

Most in-hospital deaths of patients with acute stroke occur after a decision to withhold or withdraw life-sustaining therapies.[1,2] The process to make decisions about treatment restrictions in patients with acute stroke differs from that in patients with progressive disease such as cancer because stroke patients often cannot fully participate in this process and because continuation of treatment potentially allows patients to live for months or years at the cost of being left in a state of disability that might be against their wishes.[3]

Treatment restrictions in the first two days after intracerebral haemorrhage have been independently associated with an increased risk of early death,[2,4,5] and avoidance of new do-not-resuscitate (DNR) orders during the first 5 days after intracerebral haemorrhage has been associated with a substantially lower 30-day mortality rate than predicted.[7] Treatment restrictions are also frequently installed in a later stage,[6] but it has not been investigated whether these are also associated with early mortality. Postponing the instalment of treatment restrictions increases the window of opportunity for patients to express their wishes regarding life-sustaining treatments.

In this prospective observational study, we assessed the relation between the placement of treatment restrictions and mortality in patients who had survived the first four days after severe ischaemic stroke or intracerebral haemorrhage. We also assessed functional outcome and quality of life in survivors.

METHODS

This is a prospective two-center cohort study. Consecutive patients admitted at the stroke unit with an acute severe ischaemic or haemorrhagic stroke with a very small chance of functional independency after 6 months (defined as Barthel Index (BI) ≤6 out of 20 at day 4)[8] were included. Patients with a subarachnoid haemorrhage and incompetent patients without an available legal representative were excluded from the study. Patients were included between September 2012 and December 2013 in the University Medical Center Utrecht, and between January and December 2013 in the St. Elisabeth hospital in Tilburg, a large regional teaching hospital in the Netherlands.

We collected information on patient characteristics, type of stroke (ischaemic or haemorrhagic), stroke severity on admission (by means of National Institutes of Health Stroke Scale (NIHSS) and pre-stroke comorbidity (by means of the Charlson Comorbidity Index (CCI)).[9] Treatment restrictions were assessed by a semi-structured questionnaire administered to the treating physician at the day of inclusion.

Treatment restrictions were coded for the following categories: 1) DNR order; 2) Withhold admission to intensive care unit (ICU); 3) Withhold curative treatment of complications; and 4) Withhold artificial nutrition and hydration. These are incremental steps: each treatment restriction is added up to the before-mentioned treatment restrictions. We assessed all in-hospital treatment restrictions that were installed at study inclusion.

One trained investigator (FASdK) visited each patient and his/her caregiver at six months (+/- six weeks) after stroke to assess functional outcome and quality of life. Functional outcome was assessed with the modified Rankin Scale (mRS); poor outcome was defined as mRS>3. Patients' quality of life was measured with a visual analogue scale (VAS).[10] The VAS was a vertical line of 10 centimeters with a '☺' at the top demarcating the best possible quality of life and a '☹' at the lower end for the worst possible quality of life. Scores were calculated as the indicated level in (centimeters/10)*100. Quality of life was considered acceptable if VAS ≥60.

The primary outcome measure was mortality at six months. Secondary outcome measures were functional outcome (mRS) and quality of life (VAS) at six months. The association between treatment restrictions and these outcomes was calculated with Poisson regression analysis with a robust error after adjustment for age, sex, NIHSS on admission, BI at day 4, CCI, and type of stroke (ischaemic or haemorrhagic). We expressed associations as adjusted relative risk (aRR) with 95% CI.

We performed post-hoc subgroup analyses in patients with acute ischaemic stroke and intracerebral haemorrhage separately. In this subgroup analyses, we adjusted for age, sex, NIHSS on admission, BI at day 4 and CCI.

The study was approved by the institutional review board of each center, and written informed consent was obtained from each patient or a legal representative.

RESULTS

Of 874 stroke patients admitted during the course of the study, 127 fulfilled the inclusion criteria and 60 were included. Eight patients were excluded because they had no legal representative available, 48 patients declined participation, and 11 were missed (Figure 7.1).

The median time between stroke onset and inclusion was 6 days (range, 4–10). The mean age of the patients was 72 years (SD 15); 30 (50%) were male; the median NIHSS on admission was 16 (3–28), and the median BI at day 4 was 2 (0–6). Additional patient characteristics are presented in Table 7.1.

Forty-two patients (70%) had one or more treatment restrictions. Patients without treatment restrictions were younger than patients with treatment restrictions (56 vs 79 years, $p<0.001$), and were more often men (72 vs 41%, $p=0.02$) (Table 7.1).

At six months, 30 (50%) patients had died, of whom 12 during admission. The median time from stroke onset to in-hospital death was 9 days (range, 3–18). Twenty-eight of the patients who died (93%) had a treatment restriction.

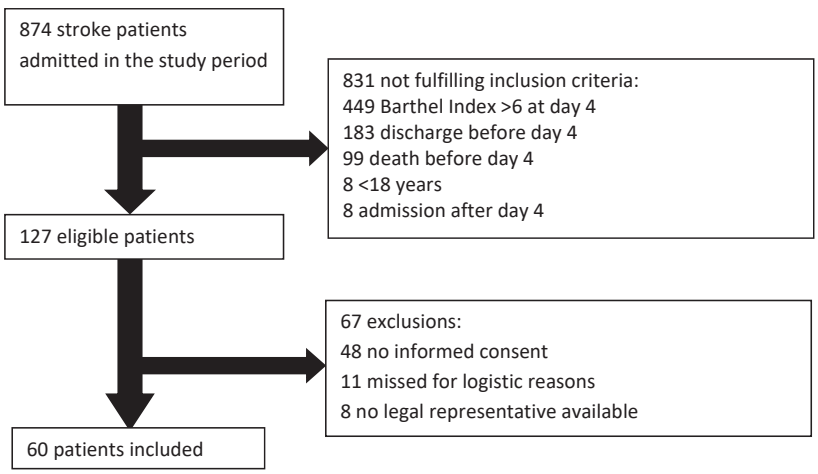

Figure 7.1. Flow of patients through this study.

Table 7.1. Baseline characteristics

	All patients n=60	Full care n=18	DNR-order* n=42	Difference between full care and DNR-order	Withhold admission at ICU n=30	No curative treatment of complications n=12	Withhold artificial nutrition and hydration n=10
Age (years)	72 (15)	56 (11)	79 (11)	p<0.001	80 (12)	78 (15)	80 (8)
Men	30 (50)	13 (72)	17 (41)	p=0.02	11 (37)	4 (33)	3 (30)
Ischaemic stroke	36 (60)	10 (56)	26 (62)	p=0.65	19 (63)	5 (42)	4 (40)
NIHSS on admission	16 (6)	16 (6)	16 (6)	p=0.82	16 (7)	19 (7)	19 (7)
CCI	1 (0–6)	0 (0–4)	1 (0–6)	p=0.22	1 (0–6)	1 (0–4)	1 (0–4)
Barthel Index at day 4	0 (0–6)	2 (0–3)	0 (0–6)	p=0.37	0 (0–6)	0 (0–0)	0 (0–0)

Data are n (%), median (range) or mean (standard deviation (SD)) where appropriate. DNR, Do not resuscitate; ICU, Intensive Care Unit; NIHSS, National Institutes of Health Stroke Scale; CCI, Charlson Comorbidity Index. * DNR-order represents all treatment restrictions.

The presence of any treatment restriction at study inclusion was independently associated with mortality at six months (aRR, 1.30; 95% confidence interval, 1.06–1.59; p=0.01). Each individual type of treatment restriction was also associated with mortality at six months (Table 7.2).

At six months, 19 of 30 survivors (63%) had a poor functional outcome (Table 7.3, Figure 7.2). Quality of life could be assessed in 26 survivors. Mean score on the VAS was 60 (SD 17). Quality of life was considered satisfactory in 11 of 16 (69%) survivors with a poor functional outcome, and in 6 of 10 (60%) patients with a good functional outcome (Table 7.3).

Treatment restrictions were not associated with a poor functional outcome in survivors (Table 7.4), but patient numbers were small.

Table 7.2. Results on adjusted Poisson regression analysis on the relation between type of treatment restrictions and mortality

	aRR*	95% CI	p
DNR-order†	1.30	1.06–1.59	0.01
Withhold admission at ICU	1.41	1.20–1.65	<0.001
No curative treatment of complications	1.26	1.11–1.44	0.001
Withhold artificial nutrition and hydration	1.19	1.05–1.34	0.01

aRR, adjusted relative risk; CI, confidence interval; DNR, Do not resuscitate; ICU, Intensive Care Unit.
* Adjusted for age, sex, National Institutes of Health Stroke Scale score on admission, Barthel Index at day 4, Charlson Comorbidity Index and type of stroke.
† DNR-order represents all treatment restrictions.

Subgroup analyses

In a post-hoc subgroup analysis in the 36 patients with ischaemic stroke, results were essentially the same. The presence of any treatment restriction at study inclusion was independently associated with mortality at six months (aRR, 1.33; 95% confidence interval, 1.01–1.76; p=0.04). Each individual type of treatment restriction was also associated with mortality at six months (Supplemental Table S7.1).

In 24 patients with intracerebral haemorrhage, results were comparable but did not reach statistical significance (aRR, 1.15; 95% confidence interval, 0.97–1.36; p=0.11) (Supplemental Table S7.2).

Table 7.3. Outcome of survivors at six months

	All patients n=60	Full care n=18	DNR-order* n=42	Withhold admission at ICU n=30	No curative treatment of complications n=12	Withhold artificial nutrition and hydration n=10
Alive at six months	30 (50)	16 (89)	14 (33)	5 (17)	0 (0)	0 (0)
Good functional outcome†	10 (34)	7 (44)	3 (23)	1 (20)	0 (0)	0 (0)
Satisfactory quality of life‡	17 (65)	10 (63)	7 (70)	2 (66)	0 (0)	0 (0)

Data are n (%), median (range) or mean (standard deviation (SD)) where appropriate. DNR, Do not resuscitate; ICU, Intensive Care Unit; NIHSS, National Institutes of Health Stroke Scale; CCI, Charlson Comorbidity Index. * DNR represents all treatment restrictions. † n=29 survivors, 1 patient declined follow-up. ‡ n=26 survivors, 3 patients declined follow-up and one was aphasic

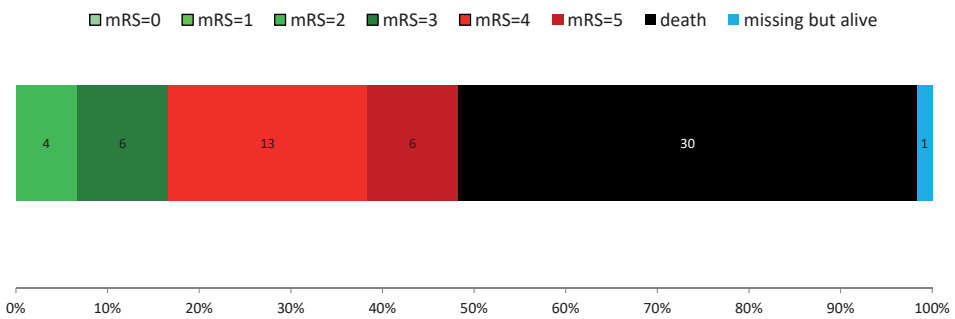

Figure 7.2. Functional outcome at 6 months.

Table 7.4. Results on adjusted Poisson regression analysis on the relation between treatment restrictions and poor functional outcome in survivors

	aRR*	95% CI	p
DNR-order†	0.78	0.49–1.23	0.28
Withhold admission at ICU	0.87	0.64–1.17	0.34
No curative treatment of complications	0.96	0.81–1.15	0.68
Withhold artificial nutrition and hydration	1.02	0.87–1.18	0.84

aRR, adjusted relative risk; CI, confidence interval; DNR, Do not resuscitate; ICU, Intensive Care Unit.
* Adjusted for age, sex, National Institutes of Health Stroke Scale score on admission, Barthel Index at day 4, Charlson Comorbidity Index and type of stroke.
† DNR-order represents all treatment restrictions.

DISCUSSION

This study shows that in patients with severely disabling ischaemic stroke or intracerebral haemorrhage, treatment restrictions installed several days after stroke onset are associated with mortality at six months, independent of age, sex, stroke severity, or pre-stroke comorbidity.

This association between treatment restrictions and mortality is probably at least partially causal, because the aim of these restrictions is to withhold potentially life-prolonging treatments when future quality of life expected to be insufficient, prioritizing comfort care. The associations persist after adjustment for other factors that might affect survival such as age, pre-stroke comorbidity, and stroke severity. Therefore, our findings suggest that treatment restrictions after the first four days increases the risk of death.

Previous studies have also shown that treatment restrictions are associated with mortality in patients with intracerebral haemorrhage[2,4,11,12] and in study populations with both ischaemic

and haemorrhagic stroke patients.[13,14] Avoidance of early DNR orders has been associated with a substantially lower risk of death,[7] supporting a causal relationship between treatment restrictions and early mortality. Whether this relation is causal indeed can only be tested in randomized trials of full medical support during a prespecified time period vs. 'standard' care which includes the placement of treatment restrictions, but this design will likely be considered unethical.

Our findings have important consequences. In clinical practice, physicians should realize that treatment restrictions on their own may increase the risk of death, and that a poor functional outcome does not necessarily implicate an unsatisfactory quality of life. Therefore, physicians should be cautious to withhold their patients a chance on recovery by installing treatment restrictions too early. With respect to intervention trials and prognostic studies, confounding by treatment restrictions should also be avoided, and where this is not possible, the placement of treatment restrictions should be assessed. Confounding by treatment restrictions could be controlled by the adoption of a standard for withdrawal of life-sustaining treatment in the study protocol.

Treatment restrictions can be appropriate after severe stroke to prevent a patient for staying alive at the cost of being left in a state of disability that might be against his or her wishes. What constitutes a poor outcome is however difficult to adequately define. Although the majority of patients in our study had a poor functional outcome, the majority of the survivors had a satisfactory quality of life. While increasing disability is generally associated with a reduction in quality of life, this is not the first time that quality of life has been reported satisfactory in patients with a disabling stroke.[15,16] Assessment of quality of life by these patients is probably influenced by a response shift, which includes a change in the internal standards and values in the self-assessment of quality of life,[17] and by the capacity of patients with chronic illness or disability to adapt to their circumstances, a phenomenon often referred to as the disability paradox.[18,19] Unfortunately, in the early phase after stroke it is still unclear how to identify patients who will adapt well to their new situation and recapture a good quality of life.

We aimed to include patients with a very small chance on regaining functional independence, because treatment restrictions are probably most often installed in this patient group. The BI is an easy accessible and widely used scale to measure ADL dependency. A cut-off point of six on the BI at day five has previously been shown to be an accurate predictor of ADL independency at six months.[8] We measured the BI on day four as part of routine clinical practice in both participating centers. According to the high rate of patients with poor outcome, the cut-off point of 6 on the BI at day four was appropriate.

This study has limitations. We could not include half of the eligible patients, because the majority of these patients declined participation. In addition, patients with more severe strokes or their relatives might have been more likely to decline consent, which may have led to selection bias. Our primary outcome was mortality at six months, and 60% of deaths occurred after discharge. We have no data on mortality at an earlier time point after discharge

and noton treatment restrictions after discharge. We consider it likely that most restrictions already installed were not changed. Moreover, our findings were observed in sixty highly selected patients with severe stroke, and our findings do not apply to patients who are not severely disabled at day four. We included both patients with severe ischaemic stroke or intracerebral haemorrhage, whereas patients who survive intracerebral haemorrhage to the point of rehabilitation have greater improvement in functional abilities than similarly affected patients with ischaemic stroke[12] However, our findings were independent of stroke type. We adjusted for pre-stroke comorbidities but did not collect data on the presence of complications that occurred after stroke, which may have had on impact on prognosis. Finally, quality of life data should be interpreted with caution because patients could have given desired answers during the home visit.

In conclusion, both clinicians and researchers should realize that placement of treatment restrictions by itself may increase the risk of death after stroke. "Our results need further confirmation. Randomized controlled trials on this topic will not be feasible for ethical reasons. Larger multi-center cohort studies, prospectively assessing the relation between treatment limitations and mortality should further confirm our findings." Future research should clarify the clinical practices in end-of-life decisions in stroke patients and focus on identifying patients who will recapture a good quality of life a severely disabling stroke.

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SUPPLEMENTARY DATA

Table S7.1. Results on adjusted Poisson regression analysis on the relation between type of treatment restrictions and mortality in patients with ischaemic stroke

	aRR*	95% CI	p
DNR-order†	1.33	1.01–1.76	0.04
Withhold admission at ICU	1.55	1.22–1.85	<0.001
No curative treatment of complications	1.40	1.14–1.71	0.01
Withhold artificial nutrition and hydration	1.33	1.11–1.59	0.002

aRR, adjusted relative risk; CI, confidence interval; DNR, Do not resuscitate; ICU, Intensive Care Unit.
* Adjusted for age, sex, National Institutes of Health Stroke Scale score on admission, Barthel Index at day 4 and Charlson Comorbidity Index.
† DNR-order represents all treatment restrictions.

Table S7.2. Results on adjusted Poisson regression analysis on the relation between type of treatment restrictions and mortality in patients with intracerebral haemorrhage

	aRR*	95% CI	p
DNR-order†	1.15	0.97–1.36	0.11
Withhold admission at ICU	1.16	0.98–1.37	0.08
No curative treatment of complications	1.15	1.04–1.28	0.01
Withhold artificial nutrition and hydration	1.09	0.98–1.22	0.12

aRR, adjusted relative risk; CI, confidence interval; DNR, Do not resuscitate; ICU, Intensive Care Unit.
* Adjusted for age, sex, National Institutes of Health Stroke Scale score on admission, Barthel Index at day 4 and Charlson Comorbidity Index.
† DNR-order represents all treatment restrictions.

Chapter 8

Accuracy of physicians' estimates of outcome after severe stroke

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ABSTRACT

Objective: End-of-life decisions after stroke should be guided by accurate estimates of the patient's prognosis. We assessed the accuracy of physicians' estimates regarding mortality, functional outcome, and quality of life in patients with severe stroke.

Methods: Treating physicians predicted mortality, functional outcome (modified Rankin scale (mRS)), and quality of life (visual analogue scale (VAS)) at six months in patients with major disabling stroke who had a Barthel Index ≤6 (of 20) at day four. Unfavorable functional outcome was defined as mRS >3, non-satisfactory quality of life as VAS <60. Patients were followed-up at six months after stroke. We compared physicians' estimates with actual outcomes.

Results: 60 patients were included, with a mean age of 72 years. Of 15 patients who were predicted to die, 1 actually survived at six months (positive predictive value (PPV), 0.93; 95% confidence interval (CI), 0.66–0.99). Of 30 patients who survived, 1 was predicted to die (false positive rate (FPR), 0.03; 95% CI 0.00–0.20). Of 46 patients who were predicted to have an unfavorable outcome, four had a favorable outcome (PPV, 0.93; 95% CI, 0.81–0.98; FPR, 0.30; 95% CI; 0.08–0.65). Prediction of non-satisfactory quality of life was less accurate (PPV, 0.63; 95% CI, 0.26–0.90).

Conclusions: In patients with severe stroke, treating physicians could estimate the risk of death or unfavorable functional outcome at six months well, but the accuracy of their estimates is not sufficient to serve as the sole basis of decisions to withdraw or withhold life-sustaining treatments. Prediction of quality of life is even more challenging.

INTRODUCTION

More than half of the patients with acute stroke are dead or disabled after two years.[1] In US studies, most in-hospital deaths of these patients occurred after a decision to withhold or withdraw life-sustaining therapies.[2,3] These decisions usually evolve from complex discussions, in which accurate predictions of prognosis are crucial.

A wide range of prognostic models have been developed to aid prognostication after stroke, but none of these models is sufficiently accurate in the prediction of mortality or poor functional outcome to serve as the sole basis of decisions to limit treatment. In addition, the large majority of these models are based on factors collected in the first hours after stroke onset, whereas treatment restrictions are often considered when there is no meaningful improvement during the first days or weeks.[4] Prognostication based on a physician's estimate rather than on prognostic models can take into account factors that are usually not included in prognostic models, such as complications of stroke, previous comorbidities, changes in functional status over the course of hospitalization and estimated quality of life. However, the

accuracy of prognostic estimates regarding mortality, functional outcome, and quality of life is uncertain.

In this study, we assessed the accuracy of treating physicians' estimates in predicting mortality, functional outcome, and quality of life at six months in patients with severe disability at four days after stroke.

METHODS

Patient selection

We studied patients included in the Advance Directive And Proxy opinions in acute sTroke (ADAPT) cohort, a prospective, two-center cohort study.[5] Consecutive patients admitted at the stroke unit with major disability, defined as Barthel Index (BI)[6] ≤6 (out of 20) at day four after ischaemic stroke or intracerebral haemorrhage were eligible for participation. We restricted ourselves to this population because these are the patients in whom treatment restrictions are most often considered. Patients were included as soon as possible from four days after stroke and could be included until discharge.

Patients with a subarachnoid haemorrhage and patients without an available legal representative were excluded from the study. Patients were included between September 2012 and December 2013 in the University Medical Center Utrecht, and between January and December 2013 in the St. Elisabeth hospital in Tilburg, a large regional teaching hospital, both in The Netherlands.

The study was approved by the institutional review board of the University Medical Center Utrecht and of the St. Elisabeth hospital. Written informed consent was obtained from each patient or a legal representative.

Data collection

We collected information on patient characteristics, type of stroke (ischaemic stroke or intracerebral haemorrhage), stroke severity on admission (by means of National Institutes of Health Stroke Scale (NIHSS))[7] and pre-stroke comorbidity with use of the Charlson Comorbidity Index (CCI).[8]

Physicians' estimates

The treating physicians were neurology residents assigned to the daily care of patients, supervised by stroke neurologists. The treating physicians predicted outcome after six months immediately after patient inclusion by a questionnaire regarding the prediction of mortality,

functional outcome (as measured with the modified Rankin Scale (mRS)),[9] and quality of life (as measured with a visual analogue scale (VAS)).[10] Scores on the mRS range from 0 (no symptoms) through to 5 (severe disability); for statistical purposes, death was given a score of 6. The VAS was a vertical line of 10 centimeters with a '☺' at the top demarcating the best possible quality of life and a '☹' at the lower end for the worst possible quality of life. Scores were calculated as the indicated level in (centimeters/10)*100. Quality of life was considered acceptable if VAS ≥60.[11] No formal prediction models were used in the daily care of the patients, nor in the estimation of outcomes.

Follow-up

A single trained investigator (FASdK) visited each patient and caregiver at six months (+/- six weeks) after stroke to assess functional outcome (as measured with the mRS and BI) and quality of life (as measured with a VAS and with the Medical Outcomes Study 36-item short-form health survey (SF-36)). For the SF-36, two summary scores were calculated as a representation of physical or mental health.[12]

Statistical analyses

The primary outcomes were the physicians' accuracies regarding the prediction of mortality, functional outcome, and quality of life at six months. Predictions of functional outcome were considered correct if the prediction of either favorable (mRS 0–3) or unfavorable (mRS 4–6) functional outcome was correct. Prediction of quality of life was considered correct if the prediction of satisfactory quality of life (VAS ≥60) or non-satisfactory quality of life (VAS <60) was correct.

In a secondary analysis, prediction of functional outcome was considered correct if there was an exact agreement on the mRS.

Accuracy results for mortality and the dichotomized mRS and VAS outcomes were measured by calculating the positive predictive values (PPV), negative predictive values (NPV), and false positive rate (FPR) with corresponding 95% confidence intervals (CI). We used χ^2-test to compare PPVs between groups.

Predefined subgroup analyses were done with regard to type of stroke and, to assess self-fulfilling prophecies, in patients who had no treatment restrictions, including do-not-resuscitate (DNR) orders. The relation between treatment restrictions and predicted outcomes was calculated with Poisson regression analysis with a robust error, and expressed as relative risk (RR) with corresponding 95% CI.

RESULTS

We included 60 patients with a mean age of 72 years (SD, 15) and a median Barthel Index of 0 (range, 0–6). Thirty-six (60%) patients had an ischaemic stroke. The median time from admission to inclusion was six days (range, 4–10). Baseline characteristics are presented in Table 8.1.

Twenty-one neurology residents, supervised by 14 stroke neurologists filled out the questionnaires.

Table 8.1. Demographic characteristics of included patients

	All patients n=60
Age (years)	72 (15)
Men	30 (50)
Ischaemic stroke	36 (60)
NIHSS on admission	16 (6)
CCI	1 (0–6)
Barthel Index at day 4	0 (0–6)

Data are n (%), median (range), or mean (standard deviation (SD)) where appropriate. CCI, comorbidity by the ICD-9-CM version of the Charlson Comorbidity Index; NIHSS, National Institutes of Health Stroke Scale.

Mortality

At six months, 30 patients (50%) had died. Of 30 surviving patients, one patient had been predicted to die (FPR, 0.03; 95% CI, 0.00–0.20). Directly after inclusion, physicians predicted 15 patients to die; fourteen of them actually died (PPV, 0.93; 95% CI, 0.66–0.99) (Table 8.3, Figure 8.1).

Functional outcome

Functional outcome at six months could be assessed in 59 patients; one patient declined follow-up. Thirty patients died, of the survivors 19 (65%) had an unfavorable outcome. The median mRS in survivors was 4 (range, 2–5) (Table 8.2 and Figure 8.1).

Of 45 patients who were predicted to have an unfavorable outcome, fourty-two had an unfavorable outcome (PPV, 0.93; 95% CI, 0.81–0.98). Of the 14 patients who were predicted to have a favorable outcome seven had a favorable outcome (NPV, 0.50; 95% CI, 0.24–0.76) (Table 8.3).

In 26 of 59 patients (44%), the exact prediction of mRS score was correct. The majority (73%) of incorrect predictions on functional outcome were too optimistic (Figure 8.2).

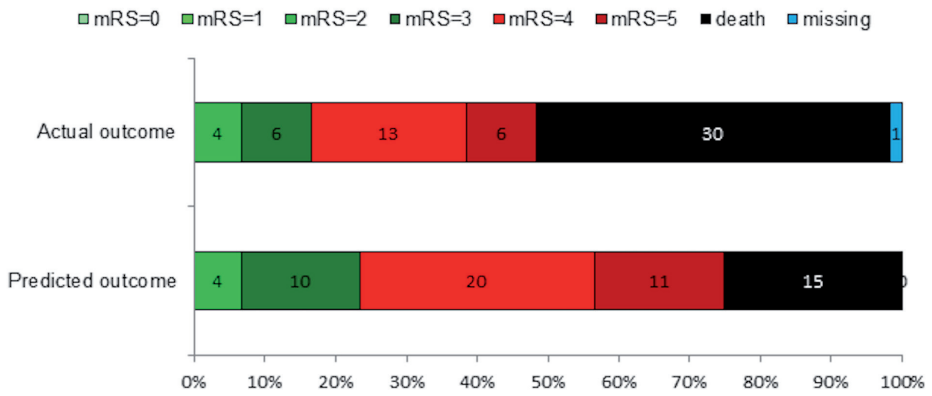

Figure 8.1. Distribution of predicted and actual modified Rankin Scale (mRS) grades at 6 months.

Table 8.2. Outcomes at six months

	All patients (n=60)
Death	30 (50%)
Poor outcome (mRS 4–6)*	49 (83%)
Poor outcome in survivors (mRS 4–5)*	19 (65%)
Barthel Index*	11 (12)
Quality of life (VAS)†	60 (17)
Non-satisfactory QoL	9 (35%)
Quality of life (SF-36)‡	
Physical summary	19 (17)
Mental summary	83 (20)

Data are n (%), median (range), median (interquartile range (IQR)) or mean (standard deviation (SD)) where appropriate. mRS, modified Rankin scale; VAS, visual analogue scale; SF-36, short form 36 questionnaire.
* n=29; † n=26; ‡ n=26.

Quality of life

Data on quality of life were available in 26 of 30 surviving patients. Two patients declined follow-up on quality of life, one patient was moribund at the time of follow-up, one patient could not answer the questions because of severe aphasia. Seventeen (61%) of the 26 survivors had a satisfactory quality of life. The mean score on the VAS was 60 (SD 17). Of eight surviving patients who were predicted to have a non-satisfactory quality of life, 5 had a non-satisfactory quality of life at six months (PPV, 0.63; 95% CI, 0.26–0.90). Of the 18 surviving patients who were predicted to have a satisfactory quality of life, 14 actually had a satisfactory quality of life at six months (NPV, 0.78; 95% CI, 0.52–0.93) (Table 8.3).

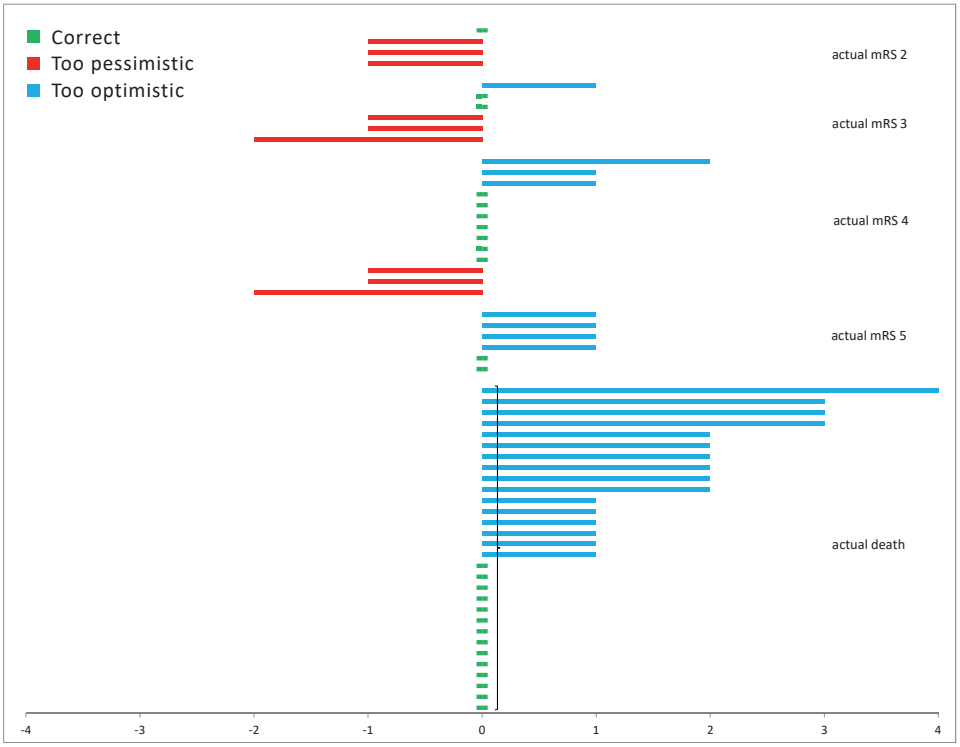

Figure 8.2. Predicted and observed 6 month functional outcome (mRS score, range 0–6) per patient (n=59).

Table 8.3. Accuracy of prognostic estimates

	Predicted outcome	Actual outcome		Predictive value	95% CI
Mortality		Death	Alive		
	Death	14	1	PPV 0.93	0.66–0.99
	Alive	16	29	NPV 0.64	0.49–0.78
				FPR 0.03	0.00–0.20
Functional outcome		Unfavorable	Favorable		
	Unfavorable	42	3	PPV 0.93	0.81–0.98
	Favorable	7	7	NPV 0.50	0.24–0.76
				FPR 0.30	0.08–0.65
Quality of life		Non-satisfactory	Satisfactory		
	Non-satisfactory	5	3	PPV 0.63	0.26–0.90
	Satisfactory	4	14	NPV 0.78	0.52–0.93
				FPR 0.18	0.05–0.44

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate.

Subgroup analyses

There were no differences between patients with ischaemic stroke and intracerebral haemorrhage concerning the predictive accuracy of mortality (p=0.27), unfavorable functional outcome (p=0.11), or unsatisfactory quality of life (p=0.69) (Supplemental Table S8.1 and S8.2).

18 of 60 patients had no treatment restrictions. In these patients, predictive accuracy of unfavorable functional outcome was essentially the same as in the total group (PPV, 0.88; 95% CI, 0.47–0.99), but prognostic errors were more optimistic (Supplemental Table S8.3).

The installment of treatment restrictions was strongly associated with a predicted unfavorable outcome and a predicted unsatisfactory quality of life (Relative Risk (RR), 11.9; 95% CI, 3.0–47.6; p<0.001 and RR, 8.8; 95% CI, 3.6–21.2; p<0.001 respectively).

DISCUSSION

This study shows that in patients with severely disabling stroke, defined as a Barthel Index ≤6 after four days, treating physicians estimate the risk of death or unfavorable functional outcome at six months reasonably well, but not sufficiently accurate to serve as the sole basis of decisions to limit treatment. Prediction of quality of life at six months proves to be much more difficult.

Accurate information about the expected outcome of disease is required to guide physicians and other professionals, patients, and their relatives in making decisions related to the withdrawal or withholding of life-sustaining treatments. If an expected negative outcome (death, unfavorable functional outcome or a non-satisfactory quality of life) is used as a basis for treatment restrictions, the predictive accuracy should be very high to prevent unfounded pessimism which can lead to early withdrawal of treatment in a patient that otherwise could have recovered. The false positive rate of a predicted poor outcome should preferably be zero, with a narrow confidence interval. At present, such predictive accuracy only exists for prognostic models in comatose patients after cardiopulmonary resuscitation for cardiac arrest,[13] and not for stroke patients. Physicians should be aware of prognostic uncertainties and their consequences when discussing end-of-life decisions.

In this study, physicians predicted unfavorable functional outcome better than a non-satisfactory quality of life, probably because quality of life is not only related to the severity of disability, but also to factors such as the presence or absence of meaningful activities and social or emotional support,[14] which are often not identified during admission. Moreover, patients often report greater happiness and quality of life than healthy people predict they would feel under the same circumstances, a phenomenon often referred to as a 'disability paradox', which is explained in part by the capacity of patients with chronic illness or disability to adapt to their circumstances.[15]

The accuracy of the physician's prognostic estimates in this study is in the same range as in a previous study where neurovascular fellows predicted functional outcome at six months in patients with subarachnoid haemorrhage,[16] and in a study where junior neurointensivists predicted functional outcome and quality of life at six months in patients requiring mechanical ventilation in any neurological disease.[17] One previous study compared the accuracy of two prediction models (one predicting complete functional outcome (BI ≥19) at six months and one predicting mortality at six months using age and NIHSS at admission) compared to physicians' estimates, and found the two prediction models to be more accurate.[18] The frequently used iScore for ischaemic stroke and ICH score for intracerebral haemorrhage have areas under the curve for case fatality at 30 days of 0.79 and 0.88, respectively, in validation studies.[19,20] This means that both prognostic models and physicians' prognostic estimates lack the discriminative power to serve as sole base for end-of-life decisions. The predictive accuracy might increase when using a combination of 'mathematical' prediction models and physicians' prognostic estimates, but this requires confirmation in a future study.

Outcomes predicted with the available prognostic models, consisting of death or poor functional outcome, may not be the most relevant to the patient. What constitutes a good outcome differs per individual patient. Patients with a poor functional outcome after acute brain injury can regain a satisfactory quality of life.[5,11] Such adjustment to illness may in part be caused by 'response shift,' which includes a change in the internal standards and values in the self-evaluation of quality of life.[21] Unfortunately, in the early phase after acute stroke it is unclear how to identify patients who will adapt well to their new situation and recapture a good quality of life.

This study has limitations. First, we included patients who were alive but severely dependent on day four, because treatment restrictions are probably most often installed in this patient group. Our results can therefore not be extrapolated to predictions in the first days after stroke or in patients who are less severely disabled at day four. Quality of life predictions were assessed in an even more selected group, because only survivors could be evaluated. Second, quality of life data should be interpreted with caution because patients could have given desired answers during the home visit. Third, self-fulfilling prophecies are a major concern when assessing prognostic accuracy. In the present study, patients with a predicted poor prognosis more frequently had treatment restrictions, which have been associated with an actual poor outcome in previous studies.[2,5,22,23] Only 18 patients received full supportive care, a number too small to draw firm conclusions. Finally, improvement of functional outcome and quality of life may still occur after six months[11] and our results therefore do not represent a completed recovery.

In conclusion, physician's predictions of death or unfavorable functional outcome at six months in patients with severely disabling stroke are not sufficiently accurate to serve as a sole basis of decisions to limit treatment. Prediction of quality of life is even more challenging.

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SUPPLEMENTARY DATA

Supplemental Tables

Table S8.1. Outcome measures in subgroup analysis patients with ischaemic stroke

	Predicted outcome	Actual outcome		Predictive value	95% CI
Mortality		Death	Alive		
	Death	6	1	PPV 0.86	0.42–0.99
	Alive	9	20	NPV 0.69	0.49–0.84
				FPR 0.05	0.02–0.26
Functional outcome		Unfavorable	Favorable		
	Unfavorable	25	3	PPV 0.89	0.71–0.97
	Favorable	4	4	NPV 0.50	0.17–0.83
				FPR 0.53	0.12–0.80
Quality of life		Non-satisfactory	Satisfactory		
	Non-satisfactory	4	1	PPV 0.80	0.30–0.99
	Satisfactory	3	9	NPV 0.75	0.43–0.93
				FPR 0.10	0.01–0.46

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate.

Table S8.2. Outcome measures in subgroup analysis patients with intracerebral haemorrhage

	Predicted outcome	Actual outcome		Predictive value	95% CI
Mortality		Death	Alive		
	Death	8	0	PPV 1.00	0.60–1.00
	Alive	7	9	NPV 0.56	0.31–0.79
				FPR 0.00	0.00–0.37
Functional outcome		Unfavorable	Favorable		
	Unfavorable	17	0	PPV 1.00	0.77–1.00
	Favorable	4	3	NPV 0.43	0.12–0.80
				FPR 0.00	0.00–0.69
Quality of life		Non-satisfactory	Satisfactory		
	Non-satisfactory	1	2	PPV 0.33	0.09–0.69
	Satisfactory	1	5	NPV 0.83	0.36–0.99
				FPR 0.29	0.05–0.70

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate.

Table S8.3. Outcome measures in subgroup analysis patients without treatment restrictions

	Predicted outcome	Actual outcome		Predictive value	95% CI
Mortality		Death	Alive		
	Death	0	0	NA	NA
	Alive	2	16	NPV 0.89	0.64–0.98
				FPR 1.00	0.20–1.00
Functional outcome		Unfavorable	Favorable		
	Unfavorable	7	1	PPV 0.88	0.47–0.99
	Favorable	4	6	NPV 0.60	0.27–0.86
				FPR 0.14	0.01–0.58
Quality of life		Non-satisfactory	Satisfactory		
	Non-satisfactory	3	1	PPV 0.75	0.22–0.99
	Satisfactory	3	9	NPV 0.75	0.43–0.93
				FPR 0.10	0.01–0.46

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate.

Chapter 9

Surgical decompression for space-occupying cerebral infarction: outcomes at three years in the randomized HAMLET trial

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Stroke. 2013;44:2506-2508

ABSTRACT

Background and purpose: We assessed whether the effects of surgical decompression for space-occupying hemispheric infarction, observed at one year, are sustained at three years.

Methods: Patients with space-occupying hemispheric infarction enrolled in the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) within four days after stroke onset were followed-up at three years. Outcome measures included functional outcome (modified Rankin scale (mRS)), death, quality of life, and place of residence. Poor functional outcome was defined as mRS >3.

Results: Of 64 included patients, 32 were randomized to decompressive surgery and 32 to best medical treatment. Just as at one year, surgery had no effect on the risk of poor functional outcome at three years (absolute risk reduction (ARR), 1%; 95% confidence interval (CI), -21 to 22), but reduced case fatality (ARR, 37%; 95% CI, 14 to 60). Sixteen surgically treated patients and eight controls lived at home (ARR, 27%; 95% CI, 4 to 50). Quality of life improved between one and three years in patients treated with surgery.

Conclusions: In patients with space-occupying hemispheric infarction, the effects of decompressive surgery on case fatality and functional outcome observed at one year are sustained at three years.

Clinical Trial Registration-URL: http://www.controlled-trials.com.
Unique identifier: ISRCTN94237756.

INTRODUCTION

A pooled analysis of three European randomized trials has shown that in patients with space-occupying hemispheric infarction, surgical decompression initiated within 48 hours of stroke onset strongly reduces the risk of death, and increases the chance of a favorable functional outcome at one year. However, this large reduction in case fatality comes at the expense of an increased risk of moderately severe or severe disability at one year,[1] and the majority of survivors have global cognitive impairment.[2] Some authors have therefore expressed concerns about the effect of decompressive surgery on long-term quality of life.[3] It is unknown whether the effects of surgery at one year are sustained over a longer follow-up period. We assessed outcomes three years after inclusion in the randomized Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET).

METHODS

The design of HAMLET (ISRCTN94237756) has been reported previously.[1] In brief, adult patients ≤60 years of age with space-occupying hemispheric infarction were randomly assigned to surgical decompression or to best medical treatment. The trial was approved by institutional review boards, and written informed consent was obtained for each patient.

The primary outcome measure was functional outcome as measured with the mRS at one year, dichotomized between good (mRS 0–3) and poor (mRS 4, 5, or death). Predefined secondary outcome measures included functional outcome at three years, and case fatality, functional dependence assessed with the Barthel Index (BI), quality of life assessed with the Medical Outcomes Study 36-item short-form health survey (SF-36) and a visual analogue scale (VAS), symptoms of depression measured by the Montgomery and Åsberg Depression Rating Scale (MADRS), and caregiver strain assessed with the caregiver strain index (CSI) at one and at three years.

A study nurse visited each patient and their caregivers to assess all outcome measures at one and three years follow-up, open to treatment allocation. Predefined subgroup analyses were done with regard to the interval from stroke onset to treatment (≤48 hours versus >48 hours).

Mean differences, absolute risk reductions (ARR), and corresponding 95% confidence intervals (CI) were calculated. The independent t-test, Mann-Whitney test, χ^2-test, paired t-test, or McNemar test were performed where appropriate. Comparisons between one and three years were performed only in patients with outcome data at both time points.

RESULTS

Sixty-four patients were included, of whom 32 were randomized to decompressive surgery. All patients received the treatment they were assigned to. Baseline characteristics and outcomes at one year have been published previously.[1]

The mean duration of follow-up was 3.1 years (SD, 0.1). After three years, eight patients in the surgical group and 20 in the medical group had died, one more than at one year in each group. One patient in the surgical group was lost to follow-up (Figure 9.1).

The table shows all outcomes at three years. Surgical patients had a lower case fatality rate than controls. The risk of a poor outcome did not differ between groups. Quality of life was acceptable for the majority of survivors in both groups.

Figure 9.2 shows the distribution of scores on the mRS after one and three years. Differences between one and three years for other outcome measures are presented in supplemental Table 9.1. Surgical patients had a statistically significant improvement in the physical summary score of the SF-36 and on the VAS, an effect not observed in medical patients. Results of subgroup analyses were comparable to the overall analysis: see Supplementary data Figure S9.1 and Tables S9.2 and S9.3.

Table 9.1. Outcomes at 3 years follow-up

	Surgical	Best medical only	Mean difference (95% CI)	ARR (95% CI)	p
Poor outcome (mRS 4–6)	23 (74%)	24 (75%)		1% (-21 to 22)	0.94
Death	8 (26%)	20(63%)		37% (14 to 60)	0.002
Barthel Index	70 (10–100)	93 (15–100)			0.16
Quality of life (SF-36)					
Physical summary	32 (10)	35 (12)	-3 (-12 to 6)		0.48
Mental summary	56 (10)	53 (9)	3 (-4 to 11)		0.36
Quality of life (VAS)					
Mean VAS	67 (20)	61 (29)	6 (-16 to 28)		0.56
VAS ≥60	19 (83%)	8 (73%)		-10 % (-40 to 21)	0.42
Symptoms of depression					
MADRS ≥7	13 (57%)	7 (70%)		14% (-21 to 48)	0.69
MADRS ≥19	2 (9%)	2 (20%)		11% (-16 to 39)	0.83
CSI >6	14 (70%)	6 (86%)		16% (-17 to 49)	0.41
Living at home	16 (52%)	8 (25%)		-27% (-50 to -4)	0.051

Data are n (%), median (range), or mean (standard deviation (SD)) where appropriate. ARR indicates absolute risk reduction; CI, confidence interval; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; MADRS, Montgomery and Åsberg Depression Rating Scale; CSI, Caregiver Strain Index; mRS: modified Rankin Scale. mRS, death, living at home: n=63 (31/32); SF-36: n=32 (22/10); VAS, MADRS, BI: n=33 (23/10); CSI: n=27 (20/7).

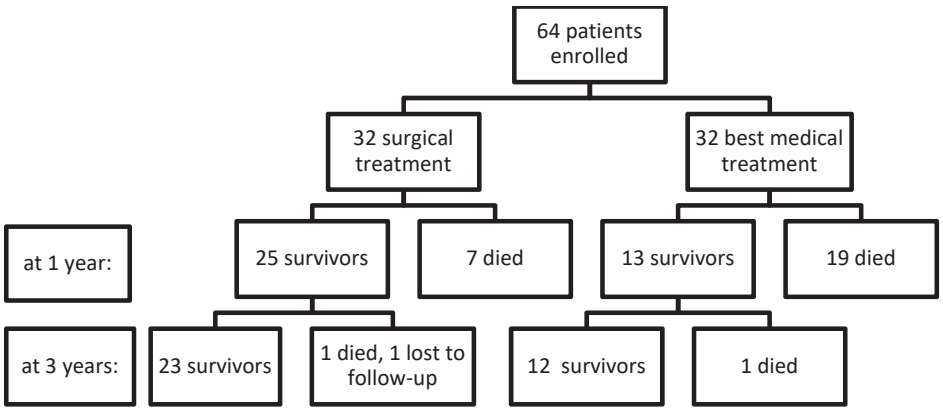

Figure 9.1. Flow of patients through this study.

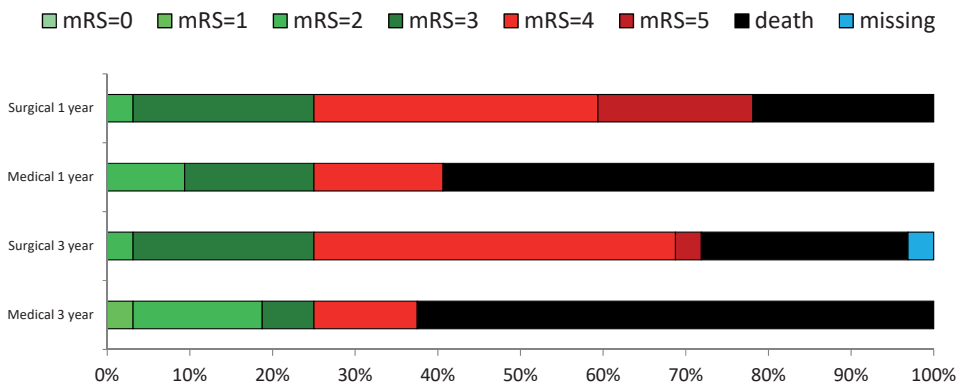

Figure 9.2. Distribution of mRS grades at 1 and 3 years.

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DISCUSSION

This study shows that the effects of decompressive surgery on case fatality and functional outcome in patients with space-occupying hemispheric infarction are sustained up to three years. In HAMLET, decompressive surgery reduced the risk of death at one and three years, but had no effect on the chance of a good functional outcome. Quality of life improved between one and three years in patients treated with surgery.

Previous reports on outcome in randomized trials of decompressive surgery for space-occupying hemispheric infarction were limited to the first year after stroke.[1,4] Observational studies have been limited by a short period of follow-up[5] or the use of short and long periods combined.[6]

Meta-analyses that have demonstrated a benefit of decompressive surgery were limited to treatment in the first 48 hours.[1] In HAMLET, patients could be enrolled within 96 hours after stroke onset. Subgroup analyses in patients enrolled in HAMLET within 48 hours were limited by smaller patient numbers, but are consistent with the overall findings of our study.

Recovery after ischaemic stroke generally follows a non-linear pattern, with the highest rate of recovery in the first weeks, and little improvement after six months.[7] We found improvement in activities of daily living and quality of life after surgical decompression between one and three years after the infarct. A similar improvement was observed in medically treated patients, but this did not reach statistical significance, possibly because of the smaller sample size. Recovery in young patients surviving a severe stroke apparently may take a long time, and outcome assessments in these patients should probably not be limited to the first year.

This study has limitations. Although HAMLET was the largest randomized trial in this field, its sample size was insufficient to detect small differences between groups and small changes over time. In addition, comparisons between treatment groups other than those with regard to case fatality or functional outcome should be interpreted with caution, because of the large differences in case fatality between the groups. Finally, outcome assessment at three years was unblinded.

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SUPPLEMENTARY DATA

Table S9.1. Comparison between 1 and 3 year follow up

	Surgical				Best medical			
	1 year	3 year	Difference	p	1 year	3 year	Difference	p
Barthel Index	55 (5 to 100)	70 (10 to 100)		0.016	80 (35 to 100)	100 (15 to 100)		0.89
Quality of life (SF-36)								
Physical summary	29 (8)	32 (10)	MD 3 (0.1 to 6)	0.042	35 (12)	35 (12)	MD 0 (-5 to 5)	0.97
Mental summary	55 (11)	56 (10)	MD 1 (-3 to 6)	0.52	52 (12)	53 (9)	MD 0.5 (-7 to 8)	0.88
Quality of life (VAS)								
Mean VAS	55 (29)	67 (20)	MD 12 (1 to 23)	0.036	62 (26)	61 (29)	MD -1 (-8 to 6)	0.78
VAS ≥60	9 (41%)	18 (82%)	ARR 41% (15 to 67)	0.012	6 (60%)	7 (70%)	ARR 10% (-32 to 52)	1.00
Symptoms of depression								
MADRS ≥7	17 (77%)	13 (59%)	ARR -18% (-45 to 9)	0.22	7 (70%)	7 (70%)	ARR 0% (-40 to 40)	1.00
MADRS ≥19	2 (9%)	2 (9%)	ARR 0% (-16 to 17)	1.00	1 (10%)	2(20%)	ARR 10% (-21 to 41)	1.00
CSI >6	14 (74%)	14 (74%)	ARR 0% (-28 to 28)	1.00	6 (86%)	6 (86%)	ARR 0% (-37 to 37)	1.00
Living at home	14(45%)	16 (50%)	ARR 5% (-20 to 29)	0.63	9 (28%)	8 (25%)	ARR -3% (-25 to 19)	1.00

Data are n (%), median (range), or mean (standard deviation (SD)) where appropriate. ARR indicates absolute risk reduction; CI, confidence interval; VAS, visual analogue scale; SF-36, short form 36 questionnaire; MADRS, Montgomery and Åsberg Depression Rating Scale; CSI, Caregiver Strain Index. SF-36, MADRS, VAS: n=32 (22/10); BI: n=33 (23/10); CSI: n=26 (19/7); Living at home: n=63 (31/32).

Table S9.2. Subgroup analysis of patients enrolled within 48 hours

			Difference		
	Surgical (n=21)	Best medical only (n=18)	Mean difference (95% CI)	ARR (95% CI)	p
Poor outcome (mRS 4–6)	16 (76%)	14 (78%)		-2% (-28 to 25)	0.91
Death	5 (24%)	14 (78%)		54% (28 to 80)	0.001
Barthel Index	67.5 (10–95)	100 (100–100)			0.002
Quality of life (SF-36)					
Physical summary	32 (10)	45 (4)	13 (-2 to 27)		0.07
Mental summary	54 (10)	51 (6)	-3 (-28 to 27)		0.68
Quality of life (VAS)					
Mean VAS	63 (21)	75 (6)	11 (-7 to 29)		0.17
VAS ≥60	12 (75%)	2 (100%)		25% (4 to 47)	0.42
Symptoms of depression					
MADRS ≥7	10 (63%)	1 (50%)		-13% (–61 to 86)	0.73
MADRS ≥19	2 (13%)	0 (0%)		-13% (-4 to 29)	0.60
CSI >6	11 (85%)	1(100%)		15% (-4 to 35)	0.67
Living at home	9 (43%)	3 (17%)		-26% (-53 to -1)	0.08

Data are n (%), median (range), or mean (standard deviation (SD)) where appropriate. ARR indicates absolute risk reduction; CI, confidence interval; VAS, visual analogue scale; SF-36, short form 36 questionnaire; MADRS, Montgomery and Åsberg Depression Rating Scale; CSI, Caregiver Strain Index; mRS: modified Rankin Scale. mRS, death, living at home: n=39 (21/18); BI, VAS, MADRS: n=18 (16/2); SF36: n=17 (15/2) CSI: n=14 (13/1).

Table S9.3. Comparison between 1 and 3 year follow up in patients enrolled within 48 hours

	Surgical				Best medical			
	1 year	3 year	Difference	p	1 year	3 year	Difference	p
Barthel Index	55 (5 to 90)	67.5 (10 to 95)		0.068	95 (80 to 100)	100		0.11
Quality of life (SF-36)								
Physical summary	29 (8)	33 (10)	MD 4 (0.4 to 8)	0.032	43 (6)	45 (5)	MD -3 (-12 to 7)	0.18
Mental summary	55 (12)	54 (10)	MD -1 (-6 to 5)	0.78	43 (6)	51 (6)	MD 8 (-103 to 120)	0.51
Quality of life (VAS)								
Mean VAS	50 (31)	63 (22)	MD 12 (-3 to 28)	0.12	78 (1)	75 (6)	MD -4 (-48 to 41)	0.50
VAS ≥60	5 (33%)	11 (73%)	ARR 40% (7 to 73)	0.07	2 (100%)	2 (100%)	ARR 0%	*
Symptoms of depression								
MADRS ≥7	12 (80%)	10 (67%)	ARR -13% (-45 to 18)	1.00	2 (100%)	1 (50%)	ARR 50% (-120 to 19)	*
MADRS ≥19	2 (13%)	2 (13%)	ARR 0% (-24 to 24)	1.00	0 (0%)	0 (0%)	ARR 0%	*
CSI >6	10 (77%)	11 (85%)	ARR 8% (-22 to 38)	1.00	1 (100%)	1 (100%)	ARR 0%	1.00
Living at home	10 (48%)	9 (43%)	ARR -5% (-35 to 25)	1.00	3 (17%)	3 (17%)	ARR 0 % (-24 to 24)	1.00

Data are n (%), median (range), or mean (standard deviation (SD)) where appropriate. ARR indicates absolute risk reduction; CI, confidence interval; VAS, visual analogue scale; SF-36, short form 36 questionnaire; MADRS, Montgomery and Åsberg Depression Rating Scale; CSI, Caregiver Strain Index. BI, SF-36, VAS, MADRS: n=17 (15/2); CSI: n=14 (13/1); Living at home: n=39 (21/18). * McNemar test not computed because of constant variables.

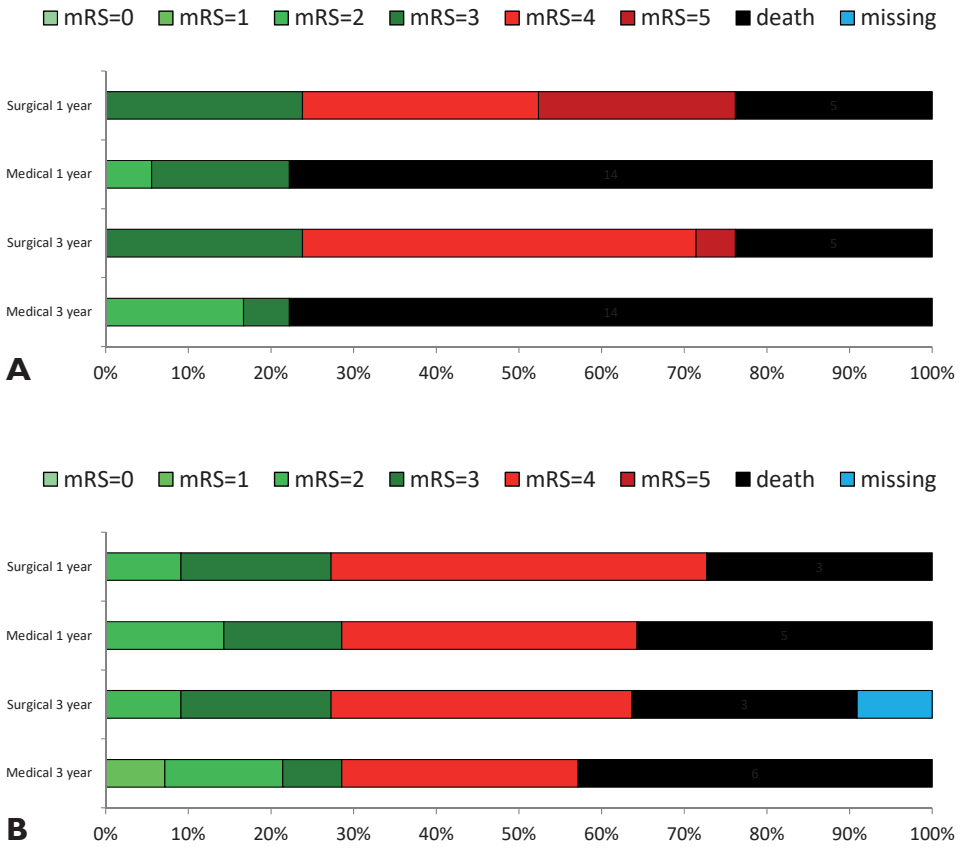

Figure S9.1.
A: Functional outcome at one and three years for patients randomized within 48 hours.
B: Idem for patients randomized between 48 and 96 hours.

Chapter 10

Advance directives, proxy opinions, and treatment restrictions in patients with severe stroke

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ABSTRACT

Background: Patients with severe stroke often do not have the capacity to participate in discussions on treatment restrictions because of a reduced level of consciousness, aphasia, or another cognitive disorder. We assessed the role of advance directives and proxy opinions in the decision-making process of incapacitated patients.

Methods: Sixty patients with severe functional dependence (Barthel Index ≤6) at day four after ischaemic stroke or intracerebral haemorrhage were included in a prospective two-center cohort study. The decision-making process with respect to treatment restrictions was assessed by means of a semi-structured questionnaire administered to the treating physician at the day of inclusion.

Results: Forty-nine patients (82%) did not have the capacity to participate in the decision-making process. In eight patients, there was no discussion on treatment restrictions and full care was installed. One patient had a written advance directive. In the remaining 40 patients (82%), the decision whether to install treatment restrictions was discussed with a proxy. Proxies based their opinion on previously expressed wishes of the patient (18 patients) or decided in the best interest of the patient (22 patients). At six months, 23 of 49 patients had survived. In only three of them the decision on treatment restrictions was based on previously expressed wishes. Remarkably, two of these survivors could not recall any of their alleged previously expressed wishes.

Conclusions: Treatment restrictions were installed in the majority of incapacitated patients after stroke. Proxy opinions frequently served as the best way to respect the patients' autonomy, but their accuracy remains unclear.

INTRODUCTION

Most in-hospital deaths of patients with severe stroke occur after a decision to withhold or withdraw life-sustaining treatments.[1,2] Patients with severe stroke often do not have the capacity to participate in the decision-making process on treatment restrictions because of a reduced level of consciousness, aphasia, or another cognitive disorder.

The principle of autonomy is considered one of the fundamental principles of Western societies.[3] In case of incapacity, the patient's autonomy should be respected as much as possible by considering their previously expressed wishes in advance directives or by appointing a proxy as decision maker.[4] In practice, the value of advance directives and proxy opinions is limited.[5] Although discussions about treatment restrictions are routine in the care for patients with severe stroke in many countries, it is unclear how physicians implement advance directives and proxy opinions in these discussions. In this study, we assessed current practices in the decision whether or not to install treatment restrictions in incapacitated patients with severe stroke.

METHODS

We selected patients from the 'Advance Directives And Proxy opinions in acute sTroke' (ADAPT) cohort,[6] a prospective two-center cohort study which included consecutive patients admitted at the stroke unit with acute severe ischaemic stroke or intracerebral haemorrhage and a very small chance of functional independency after 6 months, defined as Barthel Index (BI) ≤6 out of 20 at day 4.[7] Patients with subarachnoid haemorrhage and patients without an available legal representative were excluded from the study. Patients were included between September 2012 and December 2013 in the University Medical Center Utrecht, and between January and December 2013 in the St. Elisabeth hospital in Tilburg, a large regional teaching hospital in The Netherlands.

The study was approved by institutional review board of the initiating center (University Medical Center Utrecht), and written informed consent was obtained for each patient.

For the present study, we selected patients whom their treating physicians considered incapacitated to participate in discussions on treatment restrictions. The judgment of the patient's decision-making capacity was based on the patient's ability to understand his or her medical condition and on the ability to understand information provided by the physician and to make a reasoned decision based on that information.

The study was approved by the institutional review board of each center and written informed consent was obtained from each patient or a legal representative.

Data collection

Demographic and stroke characteristics were collected from the patients' charts. The decision-making process concerning the instalment of treatment restrictions was assessed by a semi-structured questionnaire administered to the treating physician at the day of the patient's inclusion. The questionnaire included the physician's judgement of the decision-making capacity of the patient, the presence of advance directives, and the role of proxies in the decision-making process.

Follow-up

One investigator (FASdK) visited each patient that had survived and their caregiver at six months (+/- six weeks) after stroke. Their reflection on the decision-making process, including the presence of advance directives, was assessed by a semi-structured questionnaire.

RESULTS

Of 60 patients included in ADAPT,[6] 49 (82%) patients were, according to their physician, incapacitated to decide whether or not to install treatment restrictions. The reasons for incapacity were a reduced level of consciousness in 14 (29%), aphasia in 10 (20%), cognitive impairment in 6 (12%), or a combination of two or more of these conditions in 19 (39%) cases.

The median time between stroke onset and inclusion was 6 days (range, 4–10). The mean age of the patients was 72 years (SD 15); 26 (53%) were male; 27 (55%) had an ischaemic stroke; the median National Institutes of Health Stroke Scale (NIHSS) score on admission was 18 (range, 12–21), and the median BI at day 4 was 0 (range, 0–2).

Treatment restrictions

In 36 of 49 incapacitated patients (74%), treatment restrictions had been installed at the time of study inclusion. The remaining 13 patients received full care. Table 10.1 shows the type of treatment restrictions installed. Reasons for the decision whether or not to install treatment restrictions are summarized in Table 10.2.

Table 10.1. Decisions on treatment restrictions in incapacitated patients

		Patients with discussions on treatment restrictions (n=41)	
	Patients without discussions on treatment restrictions (n=8)	Patients who previously expressed their wishes (written/ oral) (n=19)	Patients in whom was decided in their best interest (n=22)
Full supportive care	8	1	4
DNR	0	4	6
Withhold admission at ICU	0	6	9
No curative treatment of complications	0	1	0
Withhold artificial nutrition and hydration	0	7	3

DNR, Do not resuscitate; ICU, Intensive Care Unit.

Discussions on treatment restrictions

In 8 of 49 (16%) incapacitated patients, a discussion on treatment restrictions had not taken place, the treating physician had decided on full care in these cases. Reasons not to discuss treatment restrictions were a young age (88%) and the physician's expectation of a good functional recovery (88%) (Table 10.2).

Table 10.2. Physicians' reasons for restrictive or full care (more than one option possible)

		Incapacitated patients with full care (n=13)	
	Incapacitated patients with restrictive care (n=36)	Patients without discussions on treatment restrictions (n=8)	Patients with discussions on treatment restrictions (n=5)
Proxy and/or patient preferences n (%)	14 (39)	NA	3 (60)
Physicians' estimate of functional recovery n (%)	32 (89)	7 (88)	3 (60)
Age n (%)	24 (67)	7 (88)	1 (20)
Comorbidity n (%)	18 (50)	0 (0)	2 (40)
Discomfort n (%)	5 (14)	0 (0)	0 (0)
Religion n (%)	0 (0)	0 (0)	1 (20)

In the remaining 41 patients, treatment restrictions were discussed. Nineteen of them had previously expressed their wishes (one had a written advance directive and 18 had orally expressed their wishes (according to their proxies)) (Table 10.1).

Advanced directives and proxy opinions

In 41 of 49 incapacitated patients (82%), the decision on treatment restrictions was discussed with the patients' proxies. One patient had a written advance directive requesting restrictive care in case of dependency, a "do not resuscitate-order" was installed.

In the remaining 40 patients, treatment restrictions were based on proxy opinions. According to the proxies, their opinions were either based on previously expressed wishes of the patient (18 patients, resulting in restrictive care in 17 (94%) cases), or based on the perceived best interest of the patient in the absence of such previous expressions (22 patients, resulting in restrictive care in 18 patients (82%) and full care in four (18%)).

Follow up

At six months, 23 (47%) patients who were incapacitated at the time of the discussion on treatment restrictions had survived. Fifteen of them (65%) had a poor functional outcome.

Six of eight patients in whom no discussion on treatment restrictions had taken place had survived. All six patients had received full care after stroke. At six months, five of them retrospectively agreed with this decision.

The single patient with a written advance directive was one of the survivors at six months. This patient still agreed on the content of his advance directive (restrictive care in case of dependency).

Only three of 18 patients for whom treatment decisions were discussed with proxies and based on previously expressed wishes, survived up to six months. Remarkably, two of these survivors could not recall any of their alleged previously expressed wishes.

Of the 22 patients for whom proxies had decided in their best interest without known previously expressed wishes, 13 (59%) survived up to six months. Four of them could not complete the interview at six months, three because of aphasia and one patient was moribund at the time of follow-up. The remaining nine survivors retrospectively agreed with the decisions on treatment restrictions made in the early phase of their stroke.

DISCUSSION

This study shows that in incapacitated patients with a very recent stroke, discussions on treatment restrictions are complex. Advance directives are scarce. Patients' autonomy is mostly respected via proxies, who base their opinion on previously expressed wishes of the patient or decided in the best interest of the patient. This mostly resulted in restrictive care. It remained unclear whether proxies adequately reflected the patients' preferences. In a substantial part of incapacitated patients, no discussion on treatment restrictions between treating physicians and patients or their proxies had taken place.

In our study, an advance directive was available in only one out of 49 patients. This is most likely the consequence of the acute course of the disease, in combination with a low prevalence of advance directives in the general population.[8] The prevalence of advance directives in advanced stages of cancer has been estimated about 55%.[9,10] Most advance directives are written in the last days of life, which suggests that disease itself is an important reason to write an advance directive.[11] Population studies in The Netherlands show that only 7% of the general population has completed an advance directive.[12] The value of advance directives can be limited[5] as they often relate to very specific situations such as coma, and applying these wishes to a situation in which the patient has a focal deficit caused by stroke might not be appropriate.[13,14]

In case of incapacity of the patient to participate in decision-making process, the treating physician should discuss the condition of the patient with a legal representative, usually a family member. In many countries, legal representatives have a strong legal status.[15] In our study, two of the three patients in whom a proxy opinion was based on alleged previously expressed wishes, and who could be interviewed at six months, could not recall this expression. Although the number is very small, it raises questions about the accuracy of legal proxy opinions and is in line with the poor accuracy of surrogate decisions observed in hypothetical scenario studies.[16] The poor accuracy of legal representatives may be explained by stress and distraction, familial or social factors and recall bias.[5]

Two factors further complicate the use of advanced directives and proxy opinions in acute stroke patients. First, the 'disability paradox': the fact that patients often report greater happiness and quality of life than healthy people predict they would under the same circumstances.[17] Second, 'response shift': a considerable part of patients after severe stroke recaptures a good quality of life despite severe disability.[18] It is hard to identify patients in the acute stage after stroke who might adapt well to their new situation.[17,19,20]

As treatment restrictions are independently associated with mortality,[6] decisions on withholding or withdrawal of life-sustaining treatments should be taken with great caution. The treating physician carries the final responsibility for medical treatment decisions in incapacitated patients. It can be an enormous emotional burden for legal representatives to feel the sole responsibility for treatment restrictions and it is therefore essential to avoid giving families the impression they are being asked to make these major decisions on their own.[21-23]

To implement patient preferences in the decision-making process, we previously introduced a 5-step approach.[5] The first step is collection of evidence, in which the treating physician defines clinical problems and outweighs the risks and benefits of withdrawal or continuation of specific medical treatments. Second, the physician shares information with legal representatives, in which he/she explains the clinical problems and expected prognosis, and sketches scenarios in which specific medical treatment is withdrawn or given. A crucial part of this step is that legal representatives share patient preferences and values with the physician. Third, the physician critically appraises the collected information and addresses biases of both prognostication and patient preferences that could influence outcome. Fourth, the physician makes a recommendation and promotes shared-decision making. Finally, the physician provides adequate follow-up.

Limitations

This study has limitations. We included patients who were severely dependent but still alive at day four, because treatment restrictions are most often considered in these patients.[13] Therefore, our results cannot be extrapolated to situations at different points in time after stroke or in patients who are less severely disabled at day four, and we may have missed discussions and decisions on treatment restrictions at later stages.

Furthermore, information on the decision-making process was obtained from the treating physician and therefore reflects the physician's vision on patient preferences. However, this appears appropriate because it is the physician who finally makes the decision to withhold or continue specific treatments. At six-months follow-up, recall bias might have played a role, which may have led to more positive reflection on the process, and patients might have given desirable answers on questions about treatment limitations during home-visits. Finally, we did not contact proxies of deceased patients.

CONCLUSIONS

Our study shows that advance directives are scarce in patients with a major disabling stroke who cannot participate in the discussion whether treatment restriction should be installed. Proxy opinions are frequently used as a way to respect the patients' autonomy, but the treating physician should be cautious not to overestimate the capability of these proxies to reflect the opinion of the patient as based on previously expressed wishes.

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10

Chapter 11

General discussion

INTRODUCTION

This thesis describes the feasibility and safety of hypothermia as a new treatment strategy for acute ischaemic stroke. It also describes the challenges that accompany the end-of-life decision making process in patients with acute stroke.

PART I HYPOTHERMIA AS A NEW TREATMENT STRATEGY FOR ACUTE ISCHAEMIC STROKE

In **chapter 4** I describe the results of the COOLing for Ischaemic Stroke Trial (COOLIST), a phase II randomized clinical trial in which I assess the safety and feasibility of cooling to different target temperatures in awake patients with acute ischaemic stroke and a score on the NIHSS ≥6, initiated within 4.5 hours after symptom onset and maintained for 24 hours. I conclude that surface cooling is feasible to 35.0°C, but not to 34.5°C and 34.0°C. I also conclude that shivering and pneumonia are the most important side effects of treatment with hypothermia in awake patients with acute ischaemic stroke.

Since the start of COOLIST in October 2011, new insights regarding target temperature, timing and duration of hypothermia, and the role of intravenous thrombolysis and endovascular treatment after acute ischaemic stroke have been published.

Considering this, therapeutic hypothermia as a treatment for acute ischaemic stroke in awake patients needs further optimization before broader clinical implementation can be initiated. I here discuss strategies that might potentially overcome the most important side effects of therapeutic hypothermia and new insights that may further influence future perspectives of therapeutic hypothermia.

The side effects of therapeutic hypothermia

Shivering

Humans are homeotherms and need a relatively constant deep body temperature to survive.[1] In hot or cold circumstances, thermoregulation is evident in the form of sweating and shivering. These are effective ways to either loose or gain heat, and mechanisms necessary for survival. Any attempt to induce therapeutic hypothermia will lead to the activation of mechanisms to decrease heat loss: peripheral vasoconstriction and shivering. The shivering threshold is normally set around 35.5°C, which is about 1.0°C below the vasoconstriction threshold.[2] In therapeutic hypothermia, shivering is clearly counter-productive. It counteracts the treatment by rewarming the patient, and may also decrease the tolerability of cooling.

A solution to overcome shivering could be anesthesia. Several anesthetic drugs impair normal autonomic thermoregulatory control, and can markedly reduce cold-response thresholds.[3] Most

of these anesthetics however come with sedation. Patients with acute ischaemic stroke need frequent monitoring of the level of consciousness and focal deficits,[4] especially after treatment with alteplase or endovascular treatment. Sedation for several hours after ischaemic stroke is therefore in general not the preferred approach. Furthermore, deep sedation requires intensive monitoring and often mechanical ventilation on and intensive care unit, and the availability of intensive care beds is limited.

In COOLIST, we used a combination of low-dose buspirone and low-dose pethidine to prevent shivering. The combination has been shown to act synergistically to reduce the shivering threshols,[5] and has been used in patients treated with hypothermia for acute stroke before.[6-8]

Despite the anti-shivering regime, shivering occurred in all patients randomized to hypothermia in COOLIST. Shivering occurred more frequently between 2–8 hours after the initiation of cooling, when the inlet water temperature is lowest to reach the target body temperature, than during the maintenance phase when body temperature is kept on target.

A target temperature of 34.0°C or 34.5°C requires a longer course of active cooling than a target temperature of 35.0°C, which could explain the difficulty of reaching the target temperature. A more rapid administration of ice-cold saline to quickly reach target temperature might partially overcome this problem.

Other drugs that lower the shivering threshold, such as dexdemetomidine,[9] can also have an additive value in the prevention of shivering and come with only mild sedation. It is used previously in stroke patients.[10] Counter warming of the extremities could be an additional way to prevent shivering.[11] So far, this anti-shivering strategy has not been used in a protocolized way in phase II studies cooling awake patients with acute ischaemic stroke. Future studies on cooling awake patients could further optimize their anti-shivering regimes to reduce the amount of shivering.

Infections

Besides shivering, pneumonia was a common side effect in patients treated with hypothermia in COOLIST. Not only in patients treated with hypothermia for acute ischaemic stroke, but also in patients treated with hypothermia for other indications, pneumonia is a common side effect (**chapter 5**).

An increased risk of infection in patients treated with hypothermia might be expected because hypothermia decreases the secretion of proinflammatory cytokines and also inhibits leukocyte migration and phagocytosis. Suppression of neuroinflammation is one of the presumed neuroprotective mechanisms of therapeutic hypothermia, but this may come at the cost of an increased risk of infection.[12]

Awake stroke patients treated with hypothermia might be even more prone to pneumonia because the anti-shivering regime entails nausea and mild sedation, and in contrast to intubated patients, their airway is not protected, leading to an increased risk of (micro)aspiration.

As infections in stroke have been associated with a poor functional outcome,[13] therapeutic benefits of hypothermia might be partially decreased by the increased risk on pneumonia. Previous trials suggest that in stroke patients *not* treated with hypothermia prophylactic antibiotics do not decrease the risk of pneumonia if administered within 24[14] or 48 hours[15] after stroke onset and do not improve functional outcome after three months. However, in patients treated with hypothermia, preventive antibiotics might play a role in the prevention of pneumonia. This could be further assessed in future trials.

New insights of hypothermia for acute ischaemic stroke

Target temperature

In the past few years, it is suggested that the avoidance of hyperthermia, rather than therapeutic hypothermia, improves clinical outcome in patients with cerebral ischaemia.

Between 2002 and 2014, comatose patients after cardiac arrest were cooled to 32–34°C to improve neurological outcome.[16,17] In 2014 however, the results of a large randomized clinical trial were published, in which 950 unconscious adults after out-of-hospital cardiac arrest had been randomly allocated to targeted temperature management at either 33°C or 36°C. Hypothermia at a targeted temperature of 33°C did not confer a benefit (defined as mortality or poor neurological outcome) as compared with a targeted temperature of 36°C. The authors suggested that the prevention of hyperthermia, rather than hypothermia, would improve outcome after global cerebral ischaemia caused by cardiac arrest.[18]

Whether this also applies to ischaemic stroke is unclear. In observational studies, hyperthermia after acute ischaemic stroke has consistently been associated with a poor neurological outcome.[19-30] In a post-hoc subgroup analysis of the randomized Paracetamol (Acetaminophen) In Stroke (PAIS) trial, treatment with paracetamol for three days was associated with an improvement in functional outcome at three months in patients with a baseline body temperature of 37.0°C or above,[31] supporting a causal relationship between hyperthermia and functional outcome after acute ischaemic stroke.

Animal studies quite convincingly have shown that lower body temperatures are associated with a larger reduction in infarct volume,[32] suggesting that hypothermia is more effective than the prevention of hyperthermia alone. Whether this also applies in a clinical setting of acute ischaemic stroke should be assessed in phase III randomized clinical trials.

Timing and duration of cooling

In animal studies, the effect of hypothermia was most consistent when treatment was started before or at the onset of focal cerebral ischaemia, but the benefit remained substantial with treatment delays of up to 6 hours, without a clear time dependency.[32]

In animal models of focal cerebral ischaemia, the diverse pathophysiological processes which are invoked exert their deleterious effects over different time courses extending from the first hours to several days after vessel occlusion.[33] In the first days after stroke, temperature-dependent processes which lead to increased extracellular oedema, infarct swelling and restricted capillary flow in the ischaemic tissue, can increase ischaemic damage.[25]

In **chapter 2**, I show that higher body temperatures during the first days after ischaemic stroke, rather than on admission, are associated with larger infarct size and poor functional outcome. This suggests that prevention of high temperatures may improve outcome if continued for at least three days. The optimal duration of fever prevention should be assessed in future trials.

Intravenous thrombolysis and endovascular treatment

Intravenous thrombolysis with alteplase after acute ischaemic stroke significantly improves neurological outcome and is standard care in selected patients who can be treated within 4.5 hours after symptom onset. *In vitro* studies have shown that the fibrinolytic activity of alteplase is reduced at lower temperatures.[34] However, I found that in patients with acute ischaemic stroke and occlusion of an intracranial artery, body temperature on admission has no effect on arterial recanalization observed three days later, irrespective of treatment with intravenous alteplase (**chapter 3**). The difference between the in vitro studies and the in vivo findings can be explained by the *in vivo* setting of an acute thrombus. In vivo, there is a time-dependent pressure gradient from the cardiac pulse pressure. Such pressure gradients increase the penetration of thrombolytics into clots,[35] thus increasing the degree of clot lysis.

The management of acute ischaemic stroke has advanced greatly since endovascular treatment was proven effective in 2015.[36] Initiating hypothermia while the patient is undergoing endovascular treatment seems attractive. The feasibility and safety of this combination of neuroprotective strategies should be assessed in future trials.

Efficacy of therapeutic hypothermia for acute ischaemic stroke

COOLIST was a phase II study, not designed to assess the efficacy of therapeutic hypothermia for acute ischaemic stroke. Although therapeutic hypothermia is a promising new neuroprotective agent, its efficacy still needs to be proven in large phase III clinical trials.

Therapeutic hypothermia comes in a large tradition of many neuroprotective treatments that have been tested in animal studies and seemed promising. None has found its way to clinical practice.[37] Multiple reasons could explain the disappointing value of animal experiments for predicting the effectiveness of treatment strategies in clinical trials. Translational failure may be at least partially explained by methodological flaws in animal studies,[38] and publication bias leads to major overstatement of efficacy in up to one third of systematic reviews of animal stroke studies.[39] Hypothermia may be no exception. However, hypothermia still reduced the infarct size by

40% of studies with adequate methodological quality.[32] And even after adjustment for the effect of publication bias, the benefit of hypothermia remains substantial in a systematic meta-analysis of animal studies.[39] Hypothermia affects multiple steps in the cascade leading from ischaemia to cell death, in contrast to other neuroprotective agents that mostly affect one single step. These steps include energy depletion, disruption of the blood-brain barrier, free radical formation, excitotoxicity, and inflammation. Possibly mediated through these multiple and synergistic effects, the benefit of hypothermia in animal models is more consistent and robust than that of any other treatment strategy.[32]

Two phase III trials assessing the efficacy of therapeutic hypothermia after acute ischaemic stroke have been initiated. One phase III clinical trial has been stopped prematurely after endovascular treatment for ischaemic stroke had been proven effective. This ICTuS 2/3 trial was a prospective, randomized, blinded endpoint, multi-centre phase II/III study testing the combination of intravenous thrombolysis and endovascular cooling for 24 hours, versus intravenous thrombolysis alone for acute ischaemic stroke. Due to the publication of successful endovascular treatment trials, the enrolment was closed after including of 120 (of the planned 1600) patients at the end of 2014. No statistically significant differences in mortality or poor neurological outcome between the groups were noted, as expected, due to the small sample size.[40]

One phase III trial is still ongoing. The EuroHYP-1 trial is a European, open, randomised, phase III clinical trial which will assess the benefit of surface cooling for 12 hours in awake adult patients with acute ischaemic stroke. The trial aims to include 800 patients with acute ischaemic stroke.[41] The results of this trial have to be awaited before conclusions on the efficacy of hypothermia for acute ischaemic stroke can be drawn.

Feasibility of clinical trials

After inclusion of 22 of the planned 48 patients in COOLIST, the trial was stopped prematurely due to slow patient recruitment and lack of funding. The institutional review board of the initiating centre had significant concerns before approval, mostly regarding presumed risks of arrhythmia and respiratory insufficiency. Therefore, the approval of the trial was granted under specific conditions, including the continuous presence of a trial physician in the hospital during the 24 hours of cooling, and one-on-two nursing. These conditions could often not be met. This has largely contributed to the disappointing recruitment of patients in the trial.

Here, in my opinion, disproportionally strict regulations for clinical research did not protect research participants, but rather harmed the trial progress and thereby, possibly, also future patients with acute ischaemic stroke.

The conditions imposed by the institutional review board can be put in a broader perspective of continuously expanding regulations for the approval, conduct and monitoring of clinical

trials. In specific cases this can be disproportionate and bring a conceivable risk of the research. The increase in time and money that accompany these expanding regulations may discourage (mainly) investigator-initiated research, which threatens the development of new treatment options. I would like to advocate a joint responsibility for researchers, regulators and patients to keep clinical trials not only safe but also feasible in the future.

PART II CHALLENGES IN THE END-OF-LIFE DECISION MAKING PROCESS AFTER ACUTE STROKE

Despite the advances in acute stroke care in recent decades, the current lack of curative treatments for most patients means that the majority of patients with acute stroke have a poor outcome. While assessing a new treatment strategy for acute ischaemic stroke in part I of this thesis, I aimed to complement these findings with a further investigation of the end-of-life decision making process in patients with a poor outcome after stroke. Part II of this thesis presents the challenges that accompany the end-of-life decision making process in acute stroke patients.

Although treatment restrictions are installed in a majority of patients with severe acute stroke (**chapter 10**), it has received little attention in the literature. Part II of this thesis may serve as a starting point for further research on this topic. Although the evidence is still small, I here discuss future perspectives and cautiously suggest clinical implications which should ultimately lead to accurate prognostication after stroke, adequate identification of patients with a good or fair outcome after stroke, appropriate respecting of patients' autonomy in incapacitated patients and a proper timing of treatment restrictions after stroke.

Accurate prognostication after stroke

Accurate information about the expected outcome of the disease is required to guide physicians in making decisions related to withdrawal or withholding of life-sustaining treatments. In this thesis, I show that neither prognostic models in acute stroke (**chapter 6**) nor treating physicians' estimates (**chapter 8**) are sufficiently accurate to serve as the sole basis of decisions to limit treatment in the first few days after stroke. At the same time, the instalment of treatment restrictions is strongly associated with a treating physicians' estimation of an unfavorable outcome (**chapter 8**). This suggests that in clinical practice, physicians do use their informal prognostication to base end-of-life decisions on.

One explanation for a suboptimal accuracy of treating physicians' estimation on outcome may be a limited follow-up of stroke patients by their treating physicians. Probably, only few clinicians have followed up patients in whom they made intuitive predictions. I would therefore strongly encourage neurology residents to follow-up severe stroke patients over years after

discharge from the stroke unit. This will create an impression of the long-term course after stroke. It may help in not being overly pessimistic and being able to adequately inform patients and their relatives on their long-term perspectives.

Adequate identification of patients with a good outcome after stroke

The relation between a poor functional outcome and an unsatisfactory quality of life after severe stroke has been convincingly presented in previous work.[42,43] However, remarkable exceptions to this rule have also been published.[44] In a cohort of 47 patients with a locked-in-syndrome, the majority of patients reported a good quality of life.[45]

In **chapter 9**, I present the 3-year follow-up of patients with space-occupying hemispheric infarction enrolled in the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET).[46] In this cohort of patients with very severe stroke, I describe that despite a poor functional outcome in a majority of survivors (15 of 23 survivors had a modified Rankin Scale (mRS)[47] score >3), the majority had an acceptable quality of life (83% had a Visual Analogue Scale (VAS)[48] >60).

These findings are comparable to those in our cohort of 60 patients with severe ischaemic stroke or intracerebral haemorrhage. At six months, the majority of survivors had a poor outcome with respect to disability and were dependent on the help of others (19 of 30 survivors had a mRS >3), but 61% had an acceptable quality of life (VAS >60) (**chapter 10**).

Patients confronted with a life-threatening or chronic disease are faced with the necessity to accommodate to their illness. An important mediator of this adaptation process is 'response shift', which involves the change of internal standards, values and the conceptualization of quality of life.[49] Patients with a chronic disease will assimilate to their illness by redefining the factors that provide quality of life.

To clinicians, it may be hard to imagine their severely disabled patient to recapture a good quality of life on the long term. Here again, a long-term follow-up of severe stroke patients by neurologists or neurology residents will help creating an impression of the long-term course after stroke, including a potential recapturing of an acceptable quality of life.

Currently, it is unclear how to recognize patients who regain a good quality of life in the acute stage after stroke. Future research should focus on how to identify patients in the early stage of the disease who will adapt well to their new situation and recapture a good quality of life.

Incapacitated patients

The majority of patients with severe acute stroke is incapacitated to participate in end-of-life decisions in the early phase. This can be the result of aphasia, reduced consciousness or

cognitive impairment. In **chapter 10** I describe that in these cases, physicians mostly rely on proxies to respect patients' autonomy.

The principle of autonomy is considered one of the foundational principles of Western societies.[50] A direct translation of this principle in healthcare is the doctrine of informed consent. A capacitated patient can refuse any treatment for any reason. In The Netherlands, among other countries such as Belgium, Denmark and Canada, the requirement of informed consent is embedded by law.[51]

In incapacitated patients, treatment directives are accepted as a way to respect patients' autonomy, so that incapacitated patients can extend their right to informed consent. In The Netherlands, these treatment directives (that may be either a written advanced directive or a proxy directive) have a strong legal status. In principle, a directive has the same force as the current refusal of a capacitated patient.[51]

Based on the phenomena of response shift (patients with a chronic disease will assimilate to their illness by redefining the factors that provide quality of life[49]) and the disability paradox (patients often report greater happiness and quality of life than healthy people predict they would feel under the same circumstances[52,53]), one could argue the prospective character of treatment directives. If the incapacitated patient can be, or can become, so different from the person who once made the treatment directive, it is questionable whether it is acceptable to base end-of-life decisions in incapacitated patients on previously stated wishes and preferences.

In clinical practice, I suggest treatment directives to be a starting point of discussion in end-of-life decisions, rather than a rigid order that must be followed. In this scenario, physicians have an important role in explaining a potential recapturing of quality of life to patients' proxies. In **chapter 6**, I present a multiple-step approach for the decision making process in incapacitated patients. In this approach, the physician carries the responsibility to integrate disease characteristics and information on patients' personality, and ultimately advises whether treatment restrictions should be installed.

Timing of treatment restrictions after acute stroke

In **chapter 7** I show that treatment restrictions after the acute stage of severe stroke are associated with increased case fatality. Previous studies have shown similar findings, mainly in patients in the first day of hospitalization after intracerebral haemorrhage.[54-56]

Although treatment restrictions often mean that in case of prespecified conditions life-saving attempts will not be made (for example a DNR-orders order means that no attempt at resuscitation should be made in the event that a cardiopulmonary arrest occurs), a treatment restriction should not affect mortality if these conditions are not met. The most apparent explanation of the relation between treatment restriction and mortality seems that, in clinical practice, a treatment restriction is a proxy for overall lack of aggressiveness of care. This implies

that the overall aggressiveness of care at a hospital may be critically important in determining patients' outcome, irrespective of specific individual characteristics.

The relation between treatment restrictions and case fatality has important consequences for clinical practice. Physicians should realize that instalment of treatment restrictions may implicate an overall lack of aggressiveness of care, and by itself may increase the risk of death after stroke. US guidelines for patients with intracerebral haemorrhage recommend – if there is no advance directive – aggressive full care early after intracerebral haemorrhage and postponement of new 'do not resuscitate'-orders until at least the second full day of hospitalization.[57]

The relation between treatment restrictions and mortality in ischaemic stroke should be confirmed and further assessed in future studies, before these recommendations can be extended to ischaemic stroke patients. In the meantime, based on the combination of the association between treatment restrictions and mortality, the poor prognostic accuracy of physicians, and the inability to predict which patients will recapture a good quality of life despite severe disability, I would in general advocate to postpone end-of-life decisions in patients with acute stroke until after the acute stage of the disease. This will provide time for both physicians and family to assess the clinical situation, and will reduce the risk of prematurely forgoing treatments that could provide benefit. Exceptions on this rule can always be made on an individual basis.

For researchers it is important to be aware that treatment restrictions also affect mortality as an important outcome parameter, which may confound the results of clinical trials. An effective way to deal with this potential confounder could be to protocolize end-of-life decisions in clinical trials of acute ischaemic stroke.

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Chapter 12

Summary
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SUMMARY

Acute ischaemic stroke is a devastating condition, caused by an occlusion of a cerebral artery or arteriole. The clinical syndrome of brain tissue deprived of blood is characterised by the sudden onset of focal neurological deficits such as dysphasia, weakness or sensory loss.

Treatment of acute ischaemic stroke is challenging. Aspirin can be given to a broad range of patients, but benefit of aspirin is small: 79 patients have to be treated to prevent poor outcome in a single patient. Intravenous thrombolysis with alteplase and endovascular treatment is more effective, but can be given to a minority of patients. In case of a space-occupying ischaemic stroke, decompressive hemicraniectomy within 48 hours after stroke onset increases survival and improves functional outcome. Despite these treatment strategies, about half of patients have a poor functional outcome after acute ischaemic stroke.

New treatments strategies are clearly needed. Therapeutic hypothermia, the intentional reduction of body temperature, is a promising new treatment for acute ischaemic stroke. In part I of this thesis, I focus on the feasibility and safety of hypothermia as a new treatment strategy for acute ischaemic stroke.

The current lack of curative treatments means that many patients suffering from stroke have a poor outcome. Treatment restrictions are often discussed in patients with severe stroke. Most in-hospital deaths of patients with acute stroke follow a decision to withhold or withdraw life-sustaining treatments. The end-of-life decision-making process in stroke patients is fraught with difficulties.

While assessing a new treatment strategy for acute ischaemic stroke in part I of this thesis, I want to complement these findings with a further investigation of the end-of-life decision making process in patients with a poor outcome after stroke.

In part II of this thesis, I focus on the challenges that accompany the end-of-life decision making process in patients with acute stroke.

Part I Hypothermia as a new treatment strategy for acute ischaemic stroke

In **chapter 2** I assess the temporal profile of the relation between body temperature on the one hand and infarct size and functional outcome on the other, in 419 patients with acute ischaemic stroke.

I show that body temperature on admission was not associated with infarct size or poor outcome in adjusted analyses. By contrast, each additional 1.0°C in body temperature on day 1 was associated with 0.31 ml larger infarct size (95% confidence interval (CI) 0.04–0.59), on day 2 with 1.13 ml larger infarct size (95% CI, 0.83–1.43), and on day 3 with 0.80 ml

larger infarct size (95% CI, 0.48–1.12), in adjusted linear regression analyses. Higher peak body temperatures on days two and three were also associated with poor outcome (adjusted relative risks per additional 1.0°C in body temperature, 1.52 (95% CI, 1.17–1.99) and 1.47 (95% CI, 1.22–1.77), respectively). I conclude that higher peak body temperature during the first days after ischaemic stroke, rather than on admission, is associated with larger infarct size and poor functional outcome. This suggests that prevention of high body temperature may improve outcome if continued for at least three days.

Because recanalization of an occluded intracranial artery is influenced by temperature-dependent enzymes, including alteplase, I determine the relation between body temperature on admission and recanalization in **chapter 3**. For this, I included 278 patients with acute ischaemic stroke who had an intracranial arterial occlusion on admission CT angiography (CTA), within nine hours after symptom onset. Recanalization was measured with CTA at day three after stroke, and occurred in 80% of occluded arteries. There was no relation between body temperature and recanalization at three days, after adjustments for age, stroke severity on admission and treatment with alteplase (adjusted odds ratio per 0.1°Celsius, 0.99; 95% CI, 0.94–1.05; p=0.70). Results for patients treated or not treated with alteplase were essentially the same. I conclude that in patients with acute ischaemic stroke, there is no relation between body temperature on admission and recanalization of an occluded intracranial artery 3 days later, irrespective of treatment with alteplase.

Chapter 4 shows the results of the COOLing for Ischaemic Stroke Trial (COOLIST). Here I assess the feasibility and safety of surface cooling to different target temperatures in awake patients with acute ischaemic stroke. In this multi-centre, randomized, open, phase II clinical trial, I compare standard treatment with surface cooling to 34.0°C, 34.5°C or 35.0°C in awake patients with acute ischaemic stroke and a score on the NIHSS ≥6. Cooling was initiated within 4.5 hours after symptom onset and maintained for 24 hours. Primary outcome was feasibility, defined as the proportion of patients that had successfully completed the assigned treatment. Secondary outcome was safety.

Inclusion was terminated after 22 patients because of slow recruitment. Five patients were randomized to 34.0°C, six to 34.5°C, five to 35.0°C (cooling was initiated in four) and six to standard care. No (0%), one (17%) and three (75%) patients respectively, completed the assigned treatment (p=0.03). No (0%), two (33%) and four (100%) patients reached the target temperature (p=0.01). Pneumonia occurred in eight cooled patients and not in controls (absolute risk increase, 53%; 95% CI, 28–79%; p=0.002). I conclude that in the majority of awake patients with acute ischaemic stroke, surface cooling to 35.0°C, but not to 34.0°C and 34.5°C, appears feasible. Furthermore, I conclude that pneumonia is the most important adverse effect of treatment with hypothermia in awake patients with acute ischaemic stroke.

In **chapter 5**, I show the results of a systematic review and meta-analysis of randomized trials to examine the risk of infections in patients treated with hypothermia irrespective of the indication. I included 23 randomized controlled clinical trials of therapeutic hypothermia

induced in adults for any indication. A total of 2820 patients could be included, of whom 1398 (49.6%) were randomized to hypothermia. In patients treated with hypothermia, the incidence of all infections was not increased (Rate Ratio, 1.21; 95% CI, 0.95–1.54), but there was an increased risk of pneumonia and of sepsis (Risk Ratios, 1.44; 95% CI, 1.10–1.90 and 1.80; 95% CI, 1.04–3.10, respectively). This systematic review confirms that there is an association between therapeutic hypothermia and the risk of pneumonia, whereas no increase in the overall risk of infection was observed.

Part II Challenges in the end-of-life decision making process after acute stroke

In **chapter 6**, we provide a narrative review of the evidence to guide end-of-life decisions in patients with severe acute brain injury as a consequence of ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, trauma, or postanoxic encephalopathy after cardiac arrest. Based on this review, I conclude that decisions on treatment restrictions in patients with severe acute brain injury are often complex and are based only in part on evidence from published studies. Except for patients with postanoxic encephalopathy after cardiac arrest, no prognostic model has the accuracy to be the exclusive foundation of decisions to limit treatment. Furthermore, the availability and usefulness of advance directives are limited and surrogates too often do not accurately represent the patients' preferences. However, better alternatives to extend patients' autonomy are not available.

Treatment restrictions in the first two days after intracerebral haemorrhage have been independently associated with an increased risk of early death. In **chapter 7**, I assess whether treatment restrictions also affect mortality if they are installed several days after stroke onset. Sixty patients with severe functional dependence at day four after ischaemic stroke or intracerebral haemorrhage were included in this study, because these are the patients in whom treatment restrictions are most often considered. The presence of treatment restrictions was assessed at the day of inclusion. Information about mortality, functional outcome (modified Rankin scale (mRS) score), and quality of life (visual analogue scale (VAS)) was recorded six months after stroke onset. Poor outcome was defined as mRS >3. Satisfactory quality of life was defined as VAS ≥60. At six months, 30 patients had died, 19 survivors had a poor functional outcome and 9 survivors had a poor quality of life. Treatment restrictions were independently associated with mortality at six months, after adjustment for for age, sex, stroke severity, comorbidity and type of stroke (adjusted relative risk, 1.30; 95% CI, 1.06–1.59; p=0.01). I conclude that the instalment of treatment restrictions four days after stroke, by itself may increase the risk of death. In future stroke studies this potential confounder should be taken into account. Remarkably, quality of life was satisfactory in the majority of the survivors, despite considerable handicap.

In **chapter 8** I evaluate the predictive accuracy of physicians' estimates regarding mortality, functional outcome and quality of life in patients with severe stroke. Treating physicians predicted mortality, functional outcome (mRS), and quality of life (VAS) at six months in patients with severe ischaemic or haemorrhagic stroke. Patients were followed-up six months after stroke. I compared physicians' estimates and actual outcomes. Sixty patients were included, with a mean age of 72 years. Of 15 patients who were predicted to die, 1 actually survived at six months (positive predictive value (PPV), 0.93; 95% CI, 0.66–0.99). Of 30 patients who survived, 1 was predicted to die (false positive rate (FPR), 0.03; 95% CI 0.00–0.20). Results for unfavourable functional outcome were essentially the same (PPV, 0.93; 95% CI, 0.81–0.98; FPR, 0.30; 95% CI; 0.08–0.65). Prediction of non-satisfactory quality of life was less accurate (PPV, 0.63; 95% CI, 0.26–0.90). I conclude that in patients with severe stroke, treating physicians estimate the risk of death or unfavourable functional outcome at six months precisely, but the accuracy of their estimates is not sufficient to serve as the sole basis of decisions to withdraw or withhold life-sustaining treatments. Prediction of quality of life is less accurate.

In **chapter 9** I assess the long-term outcome of patients with surgical decompression for space-occupying hemispheric infarction. Patients with space-occupying hemispheric infarction enrolled in the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET), within four days after stroke onset, were followed-up at three years. Outcome measures included functional outcome (mRS), death, quality of life, and place of residence. Poor functional outcome was defined as mRS >3. Of 64 included patients, 32 were randomized to decompressive surgery and 32 to best medical treatment. Surgery had no effect on the risk of poor functional outcome at three years (absolute risk reduction (ARR), 1%; 95% CI, -21–22), but reduced case fatality (ARR, 37%; 95% CI, 14–60). Quality of life improved between one and three years in patients treated with surgery, and was satisfactory in the majority of patients.

Patients with severe stroke often do not have the capacity to participate in discussions on treatment restrictions because of a reduced level of consciousness, aphasia, or other cognitive disorders. In **chapter 10** I analyze the role of advance directives and proxy opinions in the decision-making process of incapacitated patients. Sixty patients with severe functional dependence (Barthel Index ≤6) at day four after ischaemic stroke or intracerebral haemorrhage were included in a prospective two-center cohort study. The decision-making process with respect to treatment restrictions was assessed by means of a semi-structured questionnaire administered to the treating physician at the day of inclusion. Forty-nine patients (82%) did not have the capacity to participate in the decision-making process. In eight patients, no discussion on treatment restrictions had taken place and full care was installed. One patient had a written advance directive. In the remaining 40 patients (82%), the decision whether to install treatment restrictions was discussed with a proxy. Proxies based their opinion on previously expressed wishes of the patient (18 patients) or decided in the best interest of the patient (22 patients). At six months, 23 of 49 patients had survived. In only three of them the decision to restrict treatment was based on previously expressed wishes. Remarkably, two of these survivors could

not recall any of their alleged previously expressed wishes. I conclude that in incapacitated patients after stroke, proxy opinions frequently serve as the best way to respect the patients' autonomy. Their accuracy remains unclear. Treatment restrictions were installed in the majority of incapacitated patients after stroke.

SAMENVATTING (SUMMARY IN DUTCH)

Een herseninfarct ontstaat door een plotselinge afsluiting van een bloedvat in de hersenen. Het deel van de hersenen dat door dit bloedvat wordt voorzien van bloed kan hierdoor niet meer functioneren, waardoor uitvalsverschijnselen ontstaan. Uitvalsverschijnselen zijn bijvoorbeeld een taalstoornis, krachtsvermindering of gevoelsstoornis. De afsluiting van het bloedvat ontstaat door een vastgelopen bloedstolsel. Het bloedstolsel is meestal het gevolg van aderverkalking in de halsslagader of is afkomstig uit het hart. Een herseninfarct dient te worden onderscheiden van een hersenbloeding. Bij een hersenbloeding gaat een bloedvat kapot, waardoor bloed de hersenen in stroomt. Een hersenbloeding komt veel minder vaak voor dan een herseninfarct. Ook bij een hersenbloeding ontstaan uitvalsverschijnselen.

Een herseninfarct is een ernstige aandoening, en moeilijk te behandelen. In de acute fase na een herseninfarct kan aspirine worden gegeven, maar het effect daarvan is klein: er moeten 79 patiënten worden behandeld om bij één patiënt een slechte functionele uitkomst te voorkomen. Intraveneuze trombolyse met alteplase, waarbij met medicatie via het infuus wordt geprobeerd het bloedstolsel op te lossen, en endovasculaire behandeling, waarbij het bloedvat van binnenuit wordt benaderd om het bloedstolsel te verwijderen of op te lossen, is veel effectiever, maar een minderheid van de patiënten komt hiervoor in aanmerking.

Bij een klein deel van de patiënten met een herseninfarct gaat het infarct zwellen, waardoor een verhoogde druk in de schedel ontstaat. In dat geval kan door middel van een chirurgische verwijdering van een deel van de schedel (decompressieve hemicraniëctomie) de kans op overleven en een goed functioneel herstel worden vergroot.

Ondanks deze behandelmogelijkheden heeft ongeveer de helft van de patiënten na een herseninfarct een slechte uitkomst.

Het is duidelijk dat nieuwe behandelingen nodig zijn. Therapeutische hypothermie, het intentioneel verlagen van de lichaamstemperatuur, is een veelbelovende nieuwe behandeling voor het herseninfarct. Dierstudies laten zien dat zelfs bij een lichte verlaging van de lichaamstemperatuur de grootte van het herseninfarct afneemt. Het effect van therapeutische hypothermie bij mensen met een herseninfarct is nog nauwelijks onderzocht.

In deel I van dit proefschrift beschrijf ik de haalbaarheid en veiligheid van therapeutische hypothermie als nieuwe behandeling voor het herseninfarct.

Vooralsnog hebben de meeste mensen met een herseninfarct of hersenbloeding een slechte uitkomst. Er worden dan ook vaak behandelbeperkingen afgesproken bij patiënten met een herseninfarct of hersenbloeding. De meeste overlijdensgevallen in het ziekenhuis na deze aandoeningen zijn voorafgegaan door een beslissing om levensverlengende behandeling te staken.

Ik heb daarom naast het onderzoeken van therapeutische hypothermie als nieuwe behandeling voor het herseninfarct in deel I van dit proefschrift, ook verder onderzoek gedaan naar beslissingen rondom het levenseinde bij patiënten met een slechte uitkomst na een herseninfarct of hersenbloeding.

In deel II van dit proefschrift beschrijf ik de moeilijkheden die beslissingen rondom het levenseinde bij mensen met een herseninfarct met zich meebrengen.

Deel I Therapeutische hypothermie als een nieuwe behandeling voor het herseninfarct

In **hoofdstuk 2** onderzoek ik wanneer een verhoogde lichaamstemperatuur na een herseninfarct het meest schadelijk is. Ik beschrijf het beloop in de tijd van de associatie tussen lichaamstemperatuur enerzijds, en infarctgrootte en functioneel herstel anderzijds. Ik heb hiervoor 419 patiënten met een herseninfarct onderzocht.

Ik laat zien dat een verhoogde lichaamstemperatuur bij opname in het ziekenhuis direct na het herseninfarct niet is geassocieerd met infarctgrootte en ook niet met een slecht functioneel herstel. Maar in de dagen na opname is dat anders: iedere 1,0°C toename in lichaamstemperatuur op dag 1 na het herseninfarct is geassocieerd met een toename van 0,31 ml in infarctgrootte (95% betrouwbaarheidsinterval (BI) 0,04–0,59), na correctie voor potentiële confounders. Op dag 2 is dit een toename van 1,13 ml in infarctgrootte voor iedere 1,0°C toename in lichaamstemperatuur (95% BI, 0,83–1,43), en op dag 3 0,80 ml toename in infarctgrootte voor iedere 1,0°C toename in lichaamstemperatuur (95% BI, 0,48–1,12). Een hogere lichaamstemperatuur op dag 2 en 3 na het herseninfarct is ook geassocieerd met een slechte functionele uitkomst (gecorrigeerd relatief risico per toegenomen 1,0°C in lichaamstemperatuur, 1,52 (95% BI, 1,17–1,99) en 1,47 (95% BI, 1,22–1,77), respectievelijk).

Ik concludeer hieruit dat een hogere lichaamstemperatuur tijdens de eerste dagen na het herseninfarct, maar niet bij opname, geassocieerd is met een groter infarctvolume en slechtere functionele uitkomst. Dit suggereert dat het voorkòmen van een verhoogde lichaamstemperatuur gedurende de eerste drie dagen na het herseninfarct de uitkomst na een herseninfarct kan verbeteren.

Omdat het oplossen van het bloedstolsel in een afgesloten bloedvat (rekanalisatie) in de hersenen beïnvloed wordt door temperatuurafhankelijke enzymen, waarbij lichaamstemperatuur het stolseloplossende medicijn alteplase zou kunnen beïnvloeden, onderzoek ik in **hoofdstuk 3** de relatie tussen lichaamstemperatuur bij opname en rekanalisatie. Ik heb 278 patiënten geïncludeerd met een herseninfarct, bij wie het afgesloten bloedvat in de hersenen te zien was op de eerste scan (CT angiografie) bij opname. Dit was maximaal binnen negen uur na het ontstaan van de klachten. Drie dagen na het herseninfarct werd opnieuw een scan gemaakt om rekanalisatie te onderzoeken. Het bloedvat bleek bij 80% van de patiënten weer gerekanaliseerd.

Ik vind geen relatie tussen lichaamstemperatuur bij opname in het ziekenhuis en rekanalisatie, nadat ik heb gecorrigeerd voor leeftijd, ernst van de uitval bij opname en behandeling met alteplase (gecorrigeerde *odds ratio* per 0,1°Celsius, 0,99; 95% BI, 0,94–1,05; p=0,70). De resultaten voor patiënten die wel behandeld waren met alteplase waren in essentie gelijk aan die voor patiënten die niet behandeld waren met alteplase. Ik concludeer daarom dat er bij patiënten met een herseninfarct geen relatie is tussen lichaamstemperatuur bij opname en rekanalisatie van het afgesloten bloedvat drie dagen later, onafhankelijk van behandeling met alteplase.

In **hoofdstuk 4** laat ik de resultaten zien van de COOLing for Ischaemic Stroke Trial (COOLIST). In deze studie onderzocht ik de haalbaarheid en veiligheid van behandeling met oppervlaktekoeling tot verschillende lichaamstemperaturen bij wakkere patiënten met een herseninfarct. In deze multicenter, gerandomiseerde, open fase II-studie, vergelijk ik standaardbehandeling met oppervlaktekoeling tot 34,0°C, 34,5°C en 35,0°C. De koeling werd gestart binnen 4,5 uur na het ontstaan van de klachten en gedurende 24 uur gehandhaafd. Ik onderzocht als primaire uitkomst de haalbaarheid, gedefinieerd als de proportie van patiënten die de toegewezen behandeling succesvol had afgerond. Als secundaire uitkomst onderzocht ik de veiligheid.

Na inclusie van 22 patiënten moest de studie worden gestaakt, omdat de studie te langzaam vorderde. Op dat moment waren vijf patiënten gerandomiseerd tot 34,0°C, zes tot 34,5°C, vijf tot 35,0°C (koeling werd gestart bij vier patiënten) en zes tot standaardbehandeling. Geen (0%), een (17%) en drie (75%) patiënten respectievelijk, hadden de toegewezen behandeling succesvol afgerond (p=0,03). Geen (0%), twee (33%) en vier (100%) patiënten bereikten de toegewezen lichaamstemperatuur (p=0,01). Acht gekoelde patiënten kregen een longontsteking (pneumonie), en geen van de patiënten die behandeld waren met standaardbehandeling kreeg een pneumonie (absolute risico toename, 53%; 95% BI, 28–79%; p=0,002).

Ik concludeer dat in de meerderheid van de wakkere patiënten met een herseninfarct, oppervlaktekoeling tot 35,0˚C, maar niet tot 34,0˚C of 34,5˚C, haalbaar lijkt. Verder leid ik uit de resultaten af dat het ontwikkelen van een pneumonie de belangrijkste complicatie is van behandeling met koeling.

In **hoofdstuk 5** laat ik de resultaten zien van een systematische review en meta-analyse naar het risico op infectie bij patiënten die behandeld worden met therapeutische hypothermie. In deze review combineer ik de resultaten van alle eerdere gerandomiseerde onderzoeken die het vóórkomen van infecties hebben gerapporteerd bij patiënten behandeld met hypothermie, onafhankelijk van de indicatie. Ik kon 23 gerandomiseerde klinische studies includeren, met in totaal 2820 patiënten van wie 1398 (49,6%) waren behandeld met hypothermie. Bij patiënten behandeld met hypothermie bleek de incidentie van infecties in het algemeen niet toegenomen (*Rate Ratio*, 1,21; 95% BI, 0,95–1,54), wel was er een toegenomen risico op pneumonie en op bloedvergiftiging (sepsis) (Risico Ratio's, 1,44; 95% BI, 1,10–1,90 en 1,80; 95% BI, 1,04–3,10, respectievelijk). Dit systematische review bevestigt dat er een associatie is tussen therapeutische hypothermie en het risico op pneumonie.

Deel II Beslissingen rondom het levenseinde bij mensen met een herseninfarct

In dit deel beschrijf ik moeilijkheden en uitdagingen bij het nemen van beslissingen rondom het levenseinde bij patiënten met een ernstig herseninfarct of ernstige hersenbloeding.

In **hoofdstuk 6** presenteer ik een overzicht van het wetenschappelijke bewijs dat beschikbaar is voor beslissingen rondom het levenseinde bij patiënten met acuut en ernstig hersenletsel. Gebaseerd op dit overzicht concludeer ik dat beslissingen rondom het levenseinde bij patiënten met acuut en ernstig hersenletsel vaak complex zijn en maar deels gebaseerd op bewijs uit wetenschappelijk onderzoek. Behoudens voor patiënten met een verlaagd bewustzijn na een hartstilstand, zijn er geen prognostische modellen beschikbaar die voldoende accuraat zijn om een behandelbeperking op te baseren. Bovendien is de beschikbaarheid en bruikbaarheid van een wilsverklaring in deze patiëntengroep beperkt en geven familieleden meestal de wens van de patiënt niet betrouwbaar weer. Echter, betere alternatieven om de autonomie van de patiënt te respecteren zijn er niet.

In **hoofdstuk 7** onderzoek ik of behandelbeperkingen ingesteld enkele dagen na een ernstig herseninfarct of ernstige hersenbloeding het risico op overlijden beïnvloeden. Zestig patiënten met een ernstige handicap op dag 4 na een herseninfarct of hersenbloeding werden onderzocht, omdat in deze groep behandelbeperkingen het meest worden overwogen.

Zes maanden na het herseninfarct of de hersenbloeding werd mortaliteit, functionele uitkomst (gemeten met de *modified Rankin Scale* (mRS) score, een score van 0 tot 6 waarbij 0 geen klachten en 6 overlijden is) en kwaliteit van leven (gemeten met de *Visual Analogue Scale* (VAS), een schaal van 0 tot 100 waarbij een hoger getal voor een betere kwaliteit van leven staat) bepaald. Slechte uitkomst was gedefinieerd als een mRS >3, een voldoende kwaliteit van leven als een VAS ≥60.

Zes maanden na het herseninfarct of de hersenbloeding waren 30 patiënten (50%) nog in leven. Negentien (63%) van de patiënten die nog in leven waren hadden een slechte functionele uitkomst. Negen (30%) van de patiënten die nog in leven waren hadden een onvoldoende kwaliteit van leven. Behandelbeperkingen waren onafhankelijk geassocieerd met mortaliteit na 6 maanden, na correctie voor leeftijd, geslacht, ernst van de uitvalsverschijnselen en co-morbiditeit (gecorrigeerd relatief risico, 1,30; 95% BI, 1,06–1,59; p=0,01).

Ik concludeer dat het instellen van een behandelbeperking na het acute stadium van een ernstig herseninfarct of ernstige hersenbloeding op zichzelf het risico op overlijden vergroot. Het was opvallend dat kwaliteit van leven voldoende was in de meerderheid van de patiënten, ondanks een ernstige handicap.

In **hoofdstuk 8** onderzoek ik hoe goed behandelend artsen mortaliteit, functionele uitkomst en kwaliteit van leven kunnen inschatten bij patiënten met een ernstig herseninfarct of ernstige hersenbloeding. Aan behandelend artsen werd gevraagd om in het acute stadium na het

herseninfarct of de hersenbloeding mortaliteit, functionele uitkomst (gemeten met de mRS) en kwaliteit van leven (gemeten met de VAS) na 6 maanden te voorspellen. Na 6 maanden werd de daadwerkelijke uitkomst onderzocht, en vergeleken met de voorspellingen.

Zestig patiënten werden geïncludeerd, met een mediane leeftijd van 72 jaar. Van de 15 patiënten van wie voorspeld was dat ze zouden overlijden, was er nog 1 in leven na 6 maanden (positief voorspellende waarde (PVW), 0,93; 95% BI, 0,66–0,99). Van de 30 patiënten die nog in leven waren na 6 maanden, was van 1 patiënt voorspeld dat deze zou overlijden (vals positieve ratio (VPR), 0,03; 95% BI, 0,00–0,20). De resultaten voor een slechte functionele uitkomst waren in essentie hetzelfde (PVW, 0,93; 95% BI, 0,81–0,98; VPR, 0,30; 95% BI, 0,08–0,65). Het voorspellen van een onvoldoende kwaliteit van leven was minder accuraat (PVW, 0,63; 95% BI, 0,26–0,90).

Ik concludeer dat bij patiënten met een ernstig herseninfarct of ernstige hersenbloeding, behandelend artsen het risico op overlijden en een slechte functionele uitkomst na 6 maanden redelijk goed kunnen voorspellen. Maar hun voorspellingen missen de accuraatheid om als enige basis te dienen voor een behandelbeperking.

In **hoofdstuk 9** heb ik de lange-termijnuitkomst van patiënten die een chirurgische decompressie van een ruimte-innemend herseninfarct ondergingen onderzocht. Patiënten die in verband met een zwelling van het herseninfarct in het kader van de *Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial* (HAMLET) een decompressieve hemicraniëctomie ondergingen, werden na 3 jaar thuis bezocht om functioneel herstel en kwaliteit van leven te onderzoeken. Slechte functionele uitkomst werd gedefinieerd als mRS >3.

Van de 64 onderzochte patiënten, ondergingen er 32 een chirurgische decompressie en 32 kregen de best beschikbare medicamenteuze behandeling. Decompressie had geen effect op het risico op een slechte functionele uitkomst na 3 jaar (absolute risico reductie (ARR), 1%; 95% BI, -21–22), maar reduceerde wel mortaliteit (ARR, 37%; 95% BI, 14–60). Kwaliteit van leven verbeterende sterk tussen een en drie jaar na het herseninfarct bij patiënten die een decompressie hadden ondergaan en was voldoende bij de meerderheid van de patiënten.

Patiënten met een ernstig herseninfarct of ernstige hersenbloeding kunnen door een verlaagd bewustzijn, een taalstoornis of ernstige cognitieve stoornissen vaak niet meer zelf meebeslissen over eventuele behandelbeperkingen. In **hoofdstuk 10** beschrijf ik de rol van wilsbeschikkingen en van familieleden in het proces van levenseindebeslissingen bij deze wilsonbekwame patiënten na een ernstig herseninfarct of ernstige hersenbloeding. Zestig patiënten met een ernstige handicap op dag 4 na het herseninfarct of de hersenbloeding werden geïncludeerd in deze studie, omdat dit een patiëntengroep is bij wie behandelbeperkingen het meest worden overwogen. Het proces rondom levenseindebeslissingen werd onderzocht door middel van een semigestructureerd interview met de behandelend arts.

Negenenveertig (82%) patiënten waren wilsonbekwaam om mee te beslissen over behandelbeperkingen. Bij acht van hen werd nooit gepraat over eventuele behandelbeperkingen, bij hen werd een volledig beleid gevoerd. Eén patiënt had een wilsbeschikking. De familie werd betrokken in de besluitvorming rondom behandelbeperkingen bij de resterende 40 patiënten (82%). Dit resulteerde in een beperkt beleid in de meerderheid van de gevallen. Familieleden baseerden hun mening op eerder geuite wensen van de patiënt (18 patiënten) of beslisten wat zij dachten dat goed was voor de patiënt (22 patiënten). Ik concludeer dat bij wilsonbekwame patiënten, na een ernstig herseninfarct of ernstige hersenbloeding, familieleden meestal worden ingezet om de autonomie van de patiënt te respecteren. Behandelbeperkingen worden in de meerderheid van deze patiënten afgesproken.

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CURRICULUM VITAE

Marjolein Geurts was born in 1986 in Tilburg, the Netherlands. In 2004 she finished secondary school at the Theresia Lyceum in Tilburg (Gymnasium, cum laude) and started medical school at Utrecht University, the Netherlands. She did her clinical rotations in ophthalmology in Pretoria, South Africa in 2008 and in social medicine in Bethlehem, Palestinian Territories in 2009. During her medical training, she was volunteering as the chair of the Dutch African Albino Foundation between 2010 and 2014.

During her clinical rotations she became intrigued by the complex and diverse world of neurology. Her scientific ambitions were triggered during various research internships under supervision of dr. H.B. van der Worp and prof. dr. G.J.E. Rinkel in the final year of medical school.

After obtaining her medical degree in 2010, she started her PhD research project on treatment and treatment restrictions in acute ischaemic stroke (supervision: dr. H.B. van der Worp and prof. dr. L.J. Kappelle), resulting in this thesis. She was the study-coordinator of the international, multi-center trial "COOLing for Ischaemic Stroke Trial" (COOLIST), and was a member of the Stroke Guideline committee of the Dutch Society of Neurology.

Since 2011, she is combining her PhD with her clinical training in Neurology at the University Medical Center in Utrecht. During her clinical work, she became fascinated by the field of neuro-oncology. To gain scientific experience in this field, she did a 3-month research fellowship on the role of microRNAs in glioblastoma in the James Comprehensive Cancer Center, the Ohio State University, Columbus, Ohio, USA (supervision: prof. dr. P.A.J. Robe and dr. A. Chakravarti), resulting in various co-authored publications. She will perform the specialization part of her neurology residency in the field of neuro-oncology in the Erasmus Medical Center (Rotterdam). She plans to complete her neurology residency in January 2019.

LIST OF PUBLICATIONS

This thesis

Geurts M, de Kort FAS, de Kort PLM, van Tuijl JH, van Thiel GJMW, Kappelle LJ, van der Worp HB. Advance directives, proxy opinions, and treatment restrictions in patients with severe stroke. Submitted.

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