INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE:
FROM RANDOMISED CLINICAL TRIALS TO DAILY PRACTICE

INTRAVENEUZE TROMBOLYSE VOOR HET ACUTE HERSENINFARCT:
VAN GERANDOMISEERDE KLINISCHE STUDIES NAAR DE DAGELIJKSE PRAKTIJK

maaike dirks

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Intraveneuze trombolyse voor het acute herseninfarct:
van gerandomiseerde klinische studies naar de dagelijkse praktijk

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"I know I'm paranoid and neurotic, I've made a career out of it."
Thom Yorke

CONTENTS

GENERAL INTRODUCTION

Chapter 1

In the Netherlands, as in most Western countries, stroke is a major contributor to the total burden of disease, with an estimated 39,600 hospital admissions, 9,000 deaths, and approximately 241,600 people living with the consequences of a stroke in 2009.[1] Fortunately, improvements are observed, stroke mortality is declining; due to a both declines in incidence of stroke as well as in case fatality.[2,3] New treatments like thrombolysis for acute ischaemic stroke are highly effective, but the main cause of increased survival rates after stroke is a better coordination of care, through widespread implementation of stroke units.[4,5] Thrombolysis refers to the breakdown of blood clots by stimulating fibrinolysis. In 1995 a large American study on the effectiveness of thrombolysis with intravenous alteplase (recombinant tissue plasminogen activator, rTPA) for patients with acute ischaemic stroke was published. Patients treated with intravenous alteplase had a better functional outcome at three months.[6] However two European trials (MAST I and MAST E) had unfavourable results and the ECASS I had inconclusive results.[7-9] The higher complication rate was attributed to a too high dose of thrombolytic and the lack of improvement was attributed to the extended time window of 6 hours. In 1998 the ECASS II trial was published, but it also showed inconclusive results.[10] A few years later in 2000 the Cochrane Review (including all the trials mentioned above) was published and showed that thrombolytic therapy appears to result in a significant net reduction in the proportion of dependency or death. The relative reduction in risk of poor outcome, defined as a modified Rankin Score >2, was 17.5% (95% CI: 7 to 26%).[11] The scepticism about treatment with rTPA gradually declined. Steadily but slowly, more and more hospitals started to treat acute ischaemic stroke patients with thrombolysis, but in daily practice, several circumstances and causes put a constraint on the number of patients who could be treated, the most important cause being the narrow time window for treatment. Taking that narrow time window into account, it was estimated that up to 24% of the stroke patients presenting at the emergency care might be eligible for thrombolysis.[12] In 2002-2003 however, the rate of thrombolysis in Dutch hospitals varied between 1% and 8%, with a few exceptions.[13] Clearly, improvements could be made. In addition, concern about bleeding complications remained an issue. A European license for alteplase was provided on the condition that safety and effectiveness would be monitored in a European registry. This resulted in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).[14]

Since the nineties we know that proof of the effectiveness of a new treatment alone is not sufficient to initiate an adequate use of the new treatment in daily practice. For instance in cardiology, the use of rTPA showed the same course, about a decade earlier; thrombolytic therapy was shown to reduce the mortality of acute myocardial infarction in several large trials published during 1986 -1988.[15-20] Analysis of the use of rTPA in daily practice in a representative English region in 1987-1992 showed that from a very low initial level, thrombolytic drug use rose slowly for several years after publication of the trial results and reached a plateau in 1991-1992: a lag of at least 3 years between the onset of a change in practice and attainment of a new steady state.[21] There was also a disparity between districts in the routine use of thrombolysis, this was strongly associated with participation in preceding multicentre trials.[21] Lastly, Ketley et al found an apparent under-use of thrombolysis represented by the steady state.[21]

For the delivery of thrombolysis for acute stroke Kwan et al described a list of observed treatment obstacles which we extended and classified into four categories: inter-organisational, intra-organisational, medical, and psychological, which served as pretexts for targeted intervention strategies.[22] Inter-organisational barriers relate to the proportion of patients arriving in time for treatment (pre-hospital delay). Intra-organisational barriers concern the availability of on-demand laboratory, CT scanning and skilled nursing facilities. Medical barriers are the appropriate application of contraindications for thrombolysis, which are important reasons for under-treatment.[12] Also, psychological factors including anticipation of regret and risk aversion may make neurologists conservative in treating patients with alteplase.[23,24]

Clearly, the full-scale implementation of thrombolysis has hampered in spite of the evidence on its safety and effectiveness. The question is a broader one and has to address how one can improve the provision of care effectively in general. Improvements of professional practice are more likely due to interventions tailored to prospectively identified barriers than no intervention or to dissemination of guidelines or educational materials.[25] For the purpose of betterment of implementation, quality improvement collaboratives are being used increasingly. This term is used for different multifaceted packages that focus on accelerating better outcomes. A well-known approach is the Breakthrough Series developed by the Institute of Healthcare Improvement.[26] It is a collaborative improvement model that seeks to use existing scientific knowledge. Some basic elements are: clear aims, repeated exchanges among teams, precise measurements systems, input from established experts, rapid tests of change, and an enabling social climate.[26] These elements are relevant for the improvement of the implementation of thrombolysis for acute stroke. The emphasis could be placed on clinicians and health care leaders, specifically because the infrastructure for thrombolysis for acute stroke (ambulance services, emergency departments) was readily available.

The primary aim of this thesis is to investigate whether the proportion of patients with acute ischaemic stroke treated with thrombolysis in hospitals can be increased in real-life settings through a multi-faceted implementation strategy aimed at resolving potential treatment barriers and whether this implementation strategy is cost-effective. Secondary aims are to assess the effectiveness of thrombolysis with intravenous alteplase for acute ischaemic stroke in a wider group of stroke patients i.e. in daily practice and in older patients. Additional aims were to describe the influence of organisational and structural characteristics on hospital thrombolysis rates for ischaemic stroke.

Contents of this thesis

Chapter 2 covers the rationale, background and design of the PRACTISE (PRomoting ACute Thrombolysis for Ischaemic StrokE) study; a cluster randomised controlled trial to assess the effect of implementation strategies on the rate and effects of thrombolysis for acute ischaemic stroke. Chapter 3 describes the results of an international Delphi study on the clinical contraindications for treatment with intravenous thrombolysis in acute ischaemic stroke based on the trial exclusion criteria. Chapter 4 reports the results of the PRACTISE study, a cluster-randomised controlled implementation trial promoting thrombolysis for acute ischaemic stroke. Chapter 5 focuses on the effectiveness of thrombolysis with intravenous alteplase for acute ischaemic stroke in daily practice (chapter 5.1) and in older patients (chapter 5.2). Chapter 6 describes the influence of organisational culture on hospital thrombolysis rates for ischaemic stroke (chapter 6.1), and whether centres with well-developed protocols, training and infrastructure are associated with higher rates of thrombolysis (chapter 6.2). Chapter 7 describes the real-life cost-effectiveness analysis of the multifaceted implementation program compared to a laissez-faire implementation of thrombolysis in acute ischaemic stroke. Chapter 8 and 9 provide a general discussion and summary of the results presented in this thesis.

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PROMOTING ACUTE THROMBOLYSIS FOR ISCHAEMIC STROKE

PROTOCOL FOR A CLUSTER RANDOMISED CONTROLLED TRIAL TO ASSESS THE EFFECT OF IMPLEMENTATION STRATEGIES ON THE RATE AND EFFECTS OF THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE

Chapter 2

Dirks M, Niessen LW, Huijsman R, van Wijngaarden J, Minkman MMN, Franke CL, van Oostenbrugge RJ, Koudstaal PJ, Dippel DWJ. *Promoting acute thrombolysis for ischaemic stroke. Protocol for a cluster randomised controlled trial to assess the effect of implementation strategies on the rate and effects of thrombolysis for acute ischaemic stroke.* International Journal of Stroke 2007;2;151–159.

Introduction

Thrombolysis with intravenous alteplase is an effective treatment for acute ischaemic stroke. The relative reduction in risk of poor outcome (dependency or death, modified Rankin score >2) with this treatment has been estimated at 17,5% (95% CI: 7 to 26%).[1] This implies an absolute risk reduction of 10% (95% CI: 4% to 17%). The number of treatable patients is limited because of the narrow time window, and because of contra-indications for treatment. There is worldwide consensus that treatment within 3 hours is effective and safe.[2,3] It is both surprising and disappointing that only a small proportion of the patients with acute ischaemic stroke is currently treated with thrombolysis. It has been estimated that less than 5% of all patients with acute stroke in the USA were treated with thrombolysis in 2001.[4] In the Netherlands, the situation does not seem to be better: in 2002, a thrombolysis service was available on a 24-hour basis in only half of all hospitals, and in one quarter it was not available at all.[5] The rate of thrombolysis in hospitals varies between 1% and 8%, with a few exceptions.[6]

Several circumstances and causes put a constraint on the number of patients who may be treated with thrombolysis, first and foremost the time-window of 3 hours. However, in a multi-centre survey in the Netherlands, 25% of the patients with acute stroke arrived at the emergency department within 2.5 hours, i.e. in time for treatment with thrombolysis.[7] In the Netherlands Stroke Survey, still more than 20% of the patients arrived in time for thrombolysis.[6] And in a recent survey in the southeast of the Netherlands, up to 24% of stroke patients were eligible for treatment with thrombolysis if delay could have been avoided.[8] This suggests that the rate of thrombolysis can be increased. Similar observations have been made in other countries.[9,10]

The narrow time window is probably not the only reason for the low proportion of treated patients. In a survey conducted in Cleveland, Ohio, only 20% of the patients arriving within 3 hours were treated. Most common reasons for not treating were 'mild neurological impairment' (77%) and 'rapidly improving symptoms' (44%).[10] Similarly, in the Netherlands Stroke Survey, only 7% of all acute stroke patients were treated with thrombolysis. The majority of eligible patients was not treated because of rapidly improving symptoms or because of mild neurological impairment.[11] Clearly, contra-indications for thrombolysis are important reasons for non-treatment. Most guidelines have used the exact phrasing of the exclusion criteria of the NINDS rTPA study to formulate contra-indications for treatment with thrombolysis. These exclusion criteria, however, have not been prospectively evaluated or fully operational and may be too strict.

Observational studies have focused on contra-indications for thrombolysis and may not have been able to uncover other factors. In a Delphi study of 30 international experts on thrombolysis we operated using these exclusion criteria from the NINDS rTPA trial into indications and contra-indications for thrombolysis. Consensus was reached for a definition of minimal neurological deficit sufficient to warrant treatment with thrombolysis as an NIHSS score of 2 to 3, and for several other parameters. This operationalisation may lead to a 2 to 3 times estimated increase in thrombolysis rate.

We adapted the categorisation of barriers to the delivery of thrombolysis from a recent review of observational studies of thrombolysis services.[12] They reported 7 barriers to the delivery of thrombolysis: (a) patient or family recognition, (b) the general practitioner was called first rather than the ambulance, (c) the paramedics and emergency department staff triaged stroke as non-urgent, (d) delays in neuroimaging, (e) inefficient process of in-hospital emergency stroke care, (f) difficulties in obtaining consent for thrombolysis, and (g) physicians' uncertainty about administering thrombolysis. The barriers mentioned above can be subdivided in 4 categories: inter-organisational (a & b), intra-organisational (c, d & e), medical (f & g) and psychological (g), to serve as pretexts for appropriate intervention strategies. The results of a short questionnaire survey among the vascular neurologists from 10 of the 12 participating centres confirmed that not only medical and inter-organisational factors are important, but also intra-organisational and psychological factors.

Inter-organisational barriers relate to the proportion of patients arriving in time for treatment. A large number of studies have looked into the time-delay between onset of symptoms and arrival at the emergency department.[7,13-17] The proportion of patients arriving within 2.5 hours ranged from 0 to 50%, which suggests that in a country with a high quality infrastructure, major improvements can be made.

Intra-organisational barriers relate to the extent to which all neurologists in a hospital are willing and able to attend to the patients with acute stroke in a manner that is required for safe and effective thrombolysis, but also to the availability of on-demand laboratory, CT and skilled nursing facilities, some of which are provided by other departments of the hospital. This may lead to financial constraints. Some hospitals in the Netherlands have an active policy to limit the use of expensive medication, which may include alteplase (€780 to €990 per treated patient).

At last, decision-making is influenced by psychological factors. Many neurologists have difficulties with clinical decision making in individual patients, even though the effectiveness of thrombolysis for acute ischaemic stroke within 3 hours from onset is now well established, through the publication of a Cochrane meta-analysis that indicated a favourable overall effect,[1] and the publication of the results of the reanalysis of the data by an independent committee, that took away all doubts about confounding effects caused by imbalances in baseline characteristics, such as stroke subtype.[18] However, the effect of thrombolysis in an individual patient is uncertain, and the risk of severe and often fatal complications, such as neurological deterioration from haemorrhage or reperfusion oedema is approximately 5% to 6%. Medical decision making under conditions of uncertainty, with a strict time constraint can be extremely demanding. Anticipation of regret[19] and (early) risk aversion, will most likely make neurologists conservative in their decision making process.[20]

We conclude that further implementation of thrombolysis for acute ischaemic stroke is necessary, considering the current low rate of treatment. An effective implementation

strategy should address medical, intra- and inter-organisational, as well as psychological constraints.

In a situation where the treatment is available, but there is a gap between daily practice and available knowledge from good practices or evidence-based guidelines, a Breakthrough approach could be helpful.[21,22] Basic elements of the Breakthrough model are clear aims, repeated exchanges among teams, precise measurement systems, input from established experts, rapid tests of change, and an enabling social climate to design widespread improvement efforts.[23] Improvement begins with setting aims because an organisation will not improve without a clear and firm intention to do so. Measures need to be identified to indicate whether a change that is made actually leads to an improvement. We modified the approach to fit the approach by emphasising the role of the neurologist as leader of the team, and change agent.[24,25]

Several questions have to be addressed. The primary question is whether it is possible to increase the rate of thrombolysis in general hospitals with a multifaceted implementation strategy based on the Breakthrough methodology. A simple before-after study, which compares rates of thrombolysis, may not be sufficient. It is in our view imperative that an implementation strategy is to be evaluated in a randomised design in order to adjust for autonomic developments towards increasing thrombolysis rates. For example, the Netherlands Heart Association launched an awareness campaign aimed at the general public. The resulting increase in thrombolysis rate could have wrongfully been attributed to the implementation-intervention itself, in a before-after design. The same could happen with less obvious trends.

Methods

Study design

Practise is a national cluster-randomised controlled trial for the evaluation of an intensive multi-dimensional implementation strategy for thrombolysis for acute ischaemic stroke. Randomisation has been done on hospital level, with stratification for prior thrombolysis rate. Randomisation by hospital is necessary because an intervention contrast cannot be made on patient level. Randomisation guarantees that no intentional imbalances will occur, but adjustments will be necessary because of the low number of centres involved. This protocol was set up according to CONSORT statement and revised CONSORT statement for cluster-randomised trials.[26,27]

Participating centres

Most of the twelve centres were recruited by setting out a call for participation in this project among 21 centres participating in a Breakthrough programme for improving organised stroke care in the Netherlands.[25]

Table 1 shows the participating centres with characteristics, complementary centre characteristics are assessed to determine a 'situation score', and the items are shown in table 2. Information is gathered by interviewing key providers of care in each centre, using a-priori-formulated questionnaires. We distinguished between structural characteristics, that are not expected to be changed within the given time frame of 2 years, and organisational characteristics, that can be changed within the time frame of the intervention study. Examples of structural characteristics outside the hospital are size of the geographical area that is related to the hospital, size and complexity of the care network in the region, and inside the hospital, the location of the CT scanning unit relative to emergency room (ER) and ward. Organisational characteristics that could be changed are level of education, protocols and procedures.

Collaboration and organisational fine-tuning is assessed intra- and extramurally on the level of: training and information, protocols and medical procedures, conditional services (infra-structure). The effect of implementation on the thrombolysis rate will be related to the changes in situation scores of the hospitals, in order to identify particularly successful implementation actions. The technique is based on the Assertive Community Treatment approach.[28]

Table 1 participating centres

hospital name	academic or non-academic	neurology training facility	n° of stroke admissions in 2003	n° of neuro-logists	n° of residents
Academisch Ziekenhuis Maastricht	academic	yes (full)	300	11	23
Spaarne ziekenhuis Hoofddorp	non-academic	no	250	4	2
Rijnstate ziekenhuis	non-academic	yes (partial)	345	7	4
Medisch Spectrum Twente	non-academic	yes (full)	400	9	9
Meander Medisch Centrum	non-academic	no	225	10	0
Atrium Medisch Centrum	non-academic	yes (full)	500	8	9
Catharina ziekenhuis	non-academic	no	330	7	2
Ziekenhuis Rivierenland	non-academic	no	100	3	2
Erasmus Medisch Centrum	academic	yes (full)	270	23	36
Amphia ziekenhuis	non-academic	no	500	11	5
Sint Franciscus ziekenhuis	non-academic	no	230	5	4
IJsselmeer ziekenhuizen	non-academic	no	125	4	0

Table 2 framework for the assessment of centre characteristics at baseline and follow-up

tools	**actors**	**indicators**
extramural		
agreements	general practitioners	coverage in percentage
¬ and protocols	triage nurses in GP-service	ibid
	ambulance personnel	ibid
	emergency incident room	ibid
training and	general public	coverage in percentage
¬ information supply	general practitioners	ibid
	ambulance personnel	ibid
infrastructure	hospitals	no of ambulance services
	ambulance service	¬ and no of hospitals in region
		average time to reach the
		¬ hospital by ambulance
intramural		
agreements and	staff emergency service	presence of treatment &
¬ protocols	staff priority ECG	¬ communication protocols
	staff priority CT	ibid
	staff priority lab-results	ibid
	allocated beds	ibid
	neurologists	ibid
training and	emergency nurses	general training or information
¬ information supply		¬ packages on stroke care
		'dummy-runs'
	nursing staff of general	training/information packages to
	¬ and neurology departments	¬ perform thrombolysis
		'dummy-runs'
	staff radiology department	information supply concerning
		¬ thrombolysis-related procedures
infrastructure	mededical staff for	n° of neurologists and assistants
	¬ thrombolysis treatment	hours a week that all resources are
		¬ available for thrombolysis

Patient population

All patients over 18 who are admitted with acute stroke (i.e. patients with an acute focal neurological deficit, which cannot be explained by a condition other than stroke) and are admitted within 24 hours from onset of symptoms are included in the trial. These patients will be registered, and a minimal set of baseline data will be registered. Data from patients with acute ischaemic stroke, who are admitted within 4 hours from onset of symptoms, will be assessed in more detail, and these patients will be followed up after 3 months.

Randomisation

The 12 hospitals that agreed to participate were assigned to the intensive multi-dimensional implementation strategy or the control group by random allocation after pair-wise matching. The pairing was based on the thrombolysis rate, the number of patients admitted with an ischaemic stroke in the year 2003 and hospital type (regional vs. urban and academic vs. non-academic) in reverse order (Table 1). Randomisation was performed with a table of random numbers, presented in pairs, by a statistician who was otherwise not involved in the study, and who was blind to the identity of the hospitals.

Treatment (Intervention and intervention contrast)

The intensive multi-dimensional implementation consists of the introduction of a set of implementation tools, aimed at the four levels where barriers are expected. Using the modified Breakthrough model, the local teams are asked to note specific barriers to further implementation in their centre, to set SMART (Specific, Measurable, Attainable, Realistic, Timely) goals, and to plan actions to reach these goals in a reasonable time-frame. An internet-based tool kit consisting of presentations, checklists, papers and revised protocols has been made available to the local team. The intervention comprises 2 years and includes 6 group training-sessions of 4-5 hours.

Blinding

Local and central investigators will not be blind to the treatment allocation. However, after discussing this with the data monitoring committee (DMC), it has been decided that the executive committee will refrain from interim analyses of the contrast in primary outcome, thrombolysis rate, in order to avoid specific data-driven implementation actions. Local neurologists will be unaware of the study, inasmuch that nurses and paramedical personnel will only be told that the hospital is participating in a project to register and enhance the rate of thrombolysis.
Members of the central trial office, who are unaware of the intervention assignment, will assess the three-month outcomes in patients admitted within 4 hours from onset.

Study outcomes

The primary outcome in all registered patients will be treatment with thrombolysis or not. Secondary outcomes will be admission within 4 hours after onset of symptoms, death or disability at 3 months (in the subgroup of patients with ischaemic stroke who

were admitted within 4 hours). Tertiary outcomes on the one hand, have been derived from detailed criteria for the organisational characteristics (e.g. protocols, trained personnel, availability of ER a CT services) and the process of stroke care (door to needle time, protocol violations) during the acute phase of stroke care. A cost-effectiveness analysis (CEA) will be carried out (computing QALYs/Euros2006) both performing an empirical costs analysis and a model-extrapolation on a lifetime basis. CEA input data will be supplemented and validated with data from the EDISSE evaluation of integrated stroke services,[29] and data from CEA based on major thrombolysis trials.[30-33] A limited amount of health- and medical costs data will therefore be collected, during the registration of other data. Measurement of healthcare costs will take place based on international national guidelines (WHO/CVZ). This approach measures the implementation costs as well as possible changes in patient-related costs. A new element will be the measurement of the costs related to the different organisational profiles to be defined in the first phase.

Study procedures and data quality
Data will be gathered by trained local personnel, who are not involved in the patient's treatment. Data are entered into web-based forms, linked to a central database, which is continuously updated. Data will be checked for consistency in a continuous process. Random checks of recorded data with source documents will be made in at least 10% of all patients.

Safety & Data Monitoring Body
During the period of recruitment, interim analyses of in-hospital mortality, intracranial and other serious haemorrhages, and of any other information that is available on major outcome events including serious adverse events believed to be due to treatment, will be supplied in strict confidence to the DMC, along with any other analyses that the committee may request. The DMC consists of three persons, two neurologists and one bio-statistician. They will meet four times, once before the start of the trial and each half-year during the trial. The DMC will advise the steering committee with regard to the appropriateness of continuing the study in the light of the available data on safety and outcome.

Sample size
The twelve participating hospitals will yield a two-armed trial of 2500 registered stroke patients per arm. We expect the thrombolysis rate in Dutch hospitals to increase with an autonomous trend of approximately 7.5%. The effect of the intensive multi-dimensional implementation was estimated as a relative increase of 50%, this would lead to a thrombolysis rate in the intervention hospitals of 11.25%. In order to obtain a power of 80% to detect such a difference in a trial with randomisation at patient level, approximately 1000 patients in each arm would suffice. However, adjustments for randomisation at centre level have to be made. We used the formula suggested by Kerry and Bland.[34-36]

$C=1 + (k-1)\ \sigma_B^2/(\sigma_P^2+\sigma_B^2)$
C is a correction factor to be applied to a standard patient-based sample size estimate, k is the number of patients per centre (415), σ_B the standard deviation of the treatment effect in a certain treatment group (σ_B =0.015), and σ_P is the standard deviation of success-rate in the patients in a centre (0.075 x 0.925)1/2= 0.26.
$\sigma_B^2/(\sigma_P^2+\sigma_B^2)$ is an estimate of the intra-cluster correlation. This would lead to C=2.34. The sample size should therefore be increased to 2340 patients in each arm. We allowed for inclusion of 2500 patients per arm, as we wanted to run the intervention for 2 years in all centres. This number of registered patients provides us with sufficient power to carry out subgroup analyses and to adjust for confounding factors on centre and patient level, using mixed (fixed and random effects) models.

Statistical analyses
The primary analysis of effectiveness will concern the comparison of the fraction of patients who were treated with thrombolysis in the intervention arm versus the control arm of the trial. The analysis will be carried out with a multilevel logistic regression model that incorporates the distribution of centre characteristics as a random factor, derived from the situation score, and fixed factors for patient characteristics.
The comparison of the secondary outcomes, i.e. patients treated with thrombolysis as a fraction of all patients admitted within 4 hours, patients admitted within 4 hours as a fraction of all admitted patients; and the tertiary outcomes, i.e. detailed criteria for the organisational characteristics, as well as the situation scores will be used to attribute the effects to the specific interventions.

Ethical considerations
Access to appropriate treatment and safety
All patients in the two arms of this trial will have access to the treatment that is indicated, including thrombolysis. The rate of thrombolysis in the intervention group may go up, leading to a higher than usual chance of being treated when indicated. Theoretically, a safety concern exists when patients who would not have been treated under normal contra-indications addressing safety issues, will undergo thrombolysis. However, we based the modified contra-indications on a Delphi analysis of the opinions of a representative group of international experts. Consensus was to be reached for crucial parameters in contra-indications that would not compromise effectiveness and safety of thrombolysis for ischaemic stroke, according to the panellists' opinion. A safety concern will not exist in case of treatment of patients with contra-indications addressing efficacy issues, such as "mild neurological deficit". The meta-analysis of all thrombolysis trials,[37] nor the pooled data from the rTPA trials suggest absence of effect, and observational studies suggest that the risks of thrombolysis in patients with minimal impairment is not high.[38]

Privacy
All registered stroke patients will be assigned a unique number. Name, address and date

of birth will be stored separately from the study data. Patients treated with thrombolysis will be asked for consent with treatment, after presenting them with standardised written or verbal information, according to local hospital policy. Informed consent will be asked to all patients who were admitted within four hours. The information describes the purpose of the study and the procedures for recording of clinical information and three month follow up (by telephone).

Consent with centre participation
The neurologists in each centre have agreed to participate in the study. The study protocol has been assessed by the Medical Ethics committee and Review Board of the Erasmus University Rotterdam. Further assessments of local feasibility have been carried out by the local medical ethics committees of each participating centre.

Discussion

The PRACTISE study addresses the barriers in the implementation of thrombolysis for acute ischaemic stroke. Using a cluster-randomised controlled trial it evaluates the effect of an intensive multi-dimensional implementation strategy compared to a laissez-faire implementation of thrombolysis to identify success factors and obstacles for implementation of thrombolysis. Data are obtained from each centre and from individual patients. Baseline measurements will be used to assess adequacy of the allocation process and provide information on the implementation process so far.[39] The primary endpoint will be the fraction of patients treated with thrombolysis analysed with a multilevel regression model. Baseline measurements will be used as a stratifying variable, to increase statistical power because relatively few hospitals are available for randomisation.[39] A controlled study is necessary to separate national trends (improvement of ambulance transport, effects of awareness campaigns), from the effect of the implementation programme. Not only will the trial results tell us whether this implementation approach works, but also, and perhaps more importantly, it should provide us a measure of the size of the effect and the costs of this kind of implementation.

This study design has several inherent limitations. A limitation of this study is above all the small number of hospitals, which makes the study very sensitive to drop-outs or non-co-operators, but also there is an increased likelihood of imbalance in performance between study and control groups. As mentioned before, baseline measurements could be incorporated in the analysis to increase statistical power. An important disadvantage of baseline measuring is the introduction of potential bias due to sensitisation of the study subject during the baseline measurements.[39] To minimise this bias we gathered information by interviewing key providers of care in and around each centre, who were blinded for the treatment allocation. As many fellow workers as possible were blinded for the treatment allocation to prevent the "Hawthorne effect". These are the non-specific effects of positive attention effecting from participants knowing that they are subject of a study and negative demotivation effecting from being allocated to a control rather than an intervention group.[39]

Cluster randomised trials cannot be blinded in the usual sense. Blinding in clinical trials ensures that the usual care is not influenced by knowledge of the "treatment"-assignment. This is not entirely possible in this study, but we have been able to leave the majority of the personnel of the control centres unaware of the intervention assignment. A second purpose of blinding is to keep the patient unaware of treatment assignment, in order not to let outcome reporting be influenced by knowledge of the nature of the intervention. This is not an issue, as patients do not need to be informed of the intervention-allocation and its exact purpose. Informed consent is only asked for 3-month follow-up from patients with ischaemic stroke, admitted within 4 hours from onset. The third purpose of blinding is to keep the assessors of outcome unaware of treatment assignment. The assessors of the primary outcome (thrombolysis) are not unaware of the intervention assignment, but the primary outcome leaves little room for subjective interpretation. Outcome-assessment at three months is blind, and will be used to check for biased reporting of adverse events, which is not blind.

The multifaceted aspect of the intervention will make it difficult to attribute a difference in the primary outcome to a specific aspect of the intervention. Careful monitoring of intermediate parameters (fraction of patients admitted within 4 hours, door-to-needle time, and fraction of patients with low NIHSS scores treated with thrombolysis) as well as monitoring of accomplished SMART tasks however may provide useful insight.

The primary outcome measure is relevant from the viewpoint of the purpose of the study, but perhaps not quite from the viewpoint of society or the patient. If we had used a more relevant measure such as handicap or functional health status as a primary outcome in this trial (instead of the thrombolysis rate) we should have to include approximately 10 times as many patients, to achieve the power we have now.
The results of this study may have important clinical consequences. When the intervention proves to be effective and cost-effective, the intervention used in this trial can be used to optimise the utilisation of thrombolysis in ischaemic stroke. If, on the other hand, this intervention does not prove to be effective, this trial could provide us with information about which factors are associated with the non-utilisation of thrombolysis and thereby which proper interventions might be implemented with more success.
It is not obvious that an effective treatment is implemented properly. Still the percentage of patients who are being treated with thrombolysis is alarmingly low, more than 10 years after publication of the first positive trial, and at least 5 years since most opinion leaders in stroke agreed that thrombolysis for acute ischaemic stroke is beneficial. This is not unique; the time lapse for implementation of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) was in the same order of magnitude. And even simpler treatments, like secondary prevention management, are not disseminating as fast as we would want them to.[6] Not only will this trial test the effectiveness of the chosen implementation tools (Breakthrough based approach & tool kit), it will also test its cost-effectiveness and provide information about the barriers to the delivery of thrombolysis. Clearly, this process has to be speeded up, and we need to

develop tools to help professionals change their practice more quickly when new evidence is available.

Is intensive multi-dimensional implementation safe? We cannot be sure; a focus on increasing thrombolysis rate may have the unwanted side effect of an increased rate of complications, because elderly patients or high risk patients or patients with minimal symptoms will be more likely to be treated. For this reason we considered it imperative to have an independent data-monitoring committee in the study organisation that reviews interim data on a regular basis.

Will the results of this study be adaptable to clinical centres in the western world? Twelve hospitals participated in this study; several important features differed like academic vs. non-academic, rural vs. urban, one building vs. several outbuildings, capacity of admission etc., which provides us information from these different settings. The implementation tools used have been well documented in each hospital; therefore information might become available on which implementation tools in a particular setting may be useful. The organisation of the healthcare system in a country is of course also quite relevant. In Europe there are many countries with general practitioners (GP) (UK, Belgium, Denmark, Sweden, Norway, Finland) and therefore some implementation tools aimed at GP's can be relevant in those countries as well. Different implementation tools have been used for different levels in the organisation of care of stroke patients and therefore one can extract the most relevant strategy for that particular country or organisation. Finally, though we made some changes due to the specific characteristics of the study, the time frame and the available budget, the Breakthrough based model used in the intervention group is a well-defined, established method for the implementation of an effective treatment.[22,23] Another interesting aspect of this trial is the information gathered to estimate the costs of the implementation strategy and the cost-effectiveness of the implementation of thrombolysis, using an existing stroke model.[40]

Study organisation and funding

PRACTISE is an independent academic trial. This study is run by an executive committee that consists of the members of the steering committee who are actually involved in carrying out the study on a daily basis. The central coordination is performed by the steering committee. They will meet at least once a year, and monitor the progress of the study. Decisions regarding continuation of the trial, amendments to the protocol, and publication of its results (taking into account the advice of the data monitoring committee) will be taken by this committee. The committee strives for consensus decisions. The study is funded by the Netherlands Organization for Health Research and Development (ZON-MW, grant number 945-14-217). ZON-MW is the national health council appointed by the Ministry of Health (VWS) and the Netherlands Organization for Scientific Research (NWO) to promote quality and innovation in the field of health research and care.

The PRACTISE study logo

practise

promoting
acute
thrombolysis for
ischaemic
stroke

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APPENDIX

Study personnel (alphabetical order)

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INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHAEMIC STROKE: FROM TRIAL EXCLUSION CRITERIA TO CLINICAL CONTRAINDICATIONS

AN INTERNATIONAL DELPHI STUDY

Chapter 3

Dirks M, Niessen LW, Koudstaal PJ, Franke CL, van Oostenbrugge RJ, Dippel DWJ.
Intravenous thrombolysis in acute ischaemic stroke: from trial exclusion criteria to clinical contraindications. An international Delphi study.
J. Neurol. Neurosurg. Psychiatry 2007;78;685-689.

Introduction

Thrombolysis with intravenous rTPA is an effective treatment for patients with acute ischaemic stroke.[1] Four large randomised placebo-controlled clinical trials of thrombolysis with intravenous rTPA have been carried out.[2-6] The National Institute of Neurological Disorders and Stroke (NINDS) rTPA Stroke Study reported a clinically and statistically significant benefit.[6] However, the proportion of patients who are treated with thrombolysis in survey studies ranges from only 3% to 7%.[7-10]

In most stroke guidelines, indications and contra-indications for intravenous thrombolysis are based on the inclusion and exclusion criteria of the NINDS Study.[11-14] Though reasonable, this approach may not be ideal. Criteria may be set to exclude patients who are expected not to benefit or are to suffer harm from the intervention. Such criteria clearly should also be used when the results are implemented in clinical practice. Other enrolment criteria for a study, however, are not designed to protect patients, but to exclude outliers and to ensure a homogenous patient population in statistical analysis. This applies for instance to the use of the exclusion criteria "mild neurological impairment", and "rapidly improving symptoms". In clinical practice it may be unnecessary to exclude patients based on these latter criteria, if they are not actually at increased risk from the treatment and if they may benefit. Secondly, not all exclusion criteria in the NINDS rTPA Stroke Study have been defined in terms that can be easily translated to clinical practice. This may have led physicians to withhold treatment in patients who could benefit from thrombolysis in a considerable number of cases. For example, in a survey conducted in Cleveland, Ohio, only 20% of the patients with acute stroke, admitted within three hours from onset of symptoms were actually treated with thrombolysis. The reasons for not treating, were 'mild neurological impairment' (77%) and 'rapidly improving symptoms' (44%).[15] These contra-indications were not further defined. Both criteria were not operationalised in the NINDS trial protocol. Other not operationalised exclusion criteria are "Patients who were taking anticoagulants or who had received heparin within the 48 hours preceding the onset of stroke and had an elevated partial-thromboplastin time" because no threshold INR (International Normalised Ratio) or partial-thromboplastin time are given. Overly conservative interpretation of these exclusion criteria of the NINDS rTPA Stroke Study undoubtedly reduces the number of treated patients. Lastly, analogous with treatment in acute myocardial infarction, clinicians may be withholding thrombolysis on account of perceived contraindications of increased haemorrhagic risk for which there is no evidence.[16]

Our study aim was to modulate clinical inclusion and exclusion criteria for thrombolysis in ischaemic stroke based on agreement among clinicians with scientific experience in treatment of acute stroke with thrombolysis.

Methods

We applied the Delphi technique on a group of international specialists in the field of thrombolysis in acute ischaemic stroke. Consensus methods to elicit expert opinion, in particular the Delphi technique, are recommended when information from clinical trials is limited.[17] A Delphi study uses expert judgements, and compares these judgements in several rounds with aggregate judgements of other experts, until consensus is reached for an item or group of items, according to pre-specified criteria. The method is robust and several Delphi studies already exist that provide useful and practical clinical recommendations in cerebrovascular disease.[18-22]

Proposed contraindications

Inclusion criteria for the NINDS rTPA Stroke Study were ischaemic stroke with clearly defined onset, with a measurable deficit on the NIH Stroke Scale, and a baseline CT scan of the brain without evidence of intracranial haemorrhage. We rephrased the NINDS inclusion and exclusion criteria into single propositions. We also determined clinically relevant ranges and units for each proposed contraindication in advance. A range started with the most conservative value as defined by the NINDS rTPA Stroke Study threshold value (Table 1). Three exclusion criteria were not included in the Delphi rounds: a history of intracranial haemorrhage, symptoms suggestive of subarachnoid haemorrhage and seizure at onset of the stroke. These criteria are beyond the scope of this study, not because they are not relevant or disputable, but because they are difficult to rephrase as propositions with other than a dichotomous calibration. The Appendix comprises all propositions as presented to the panellists.

Panellists

First or last authors of at least one publication on intravenous thrombolysis in acute ischaemic stroke in a peer-reviewed medical journal were eligible for membership of the Delphi panel. Panellists were required to have personal clinical experience with thrombolysis and fluency in the English language. For identification, we systematically searched the MEDLINE database from January 1966 to December 2004 (Figure 1). Panellists, or 'experts' in the Delphi methodology were invited by e-mail and asked if they met the above-mentioned criteria. They received information on the aim of the study and the Delphi procedure. Panel membership was not disclosed to other participants.

number	proposed contraindication	clinically relevant unit	range
1	maximum time between stroke onset and treatment	½ hour	3-6 hours
2	maximum patient's age	5 years	80-110 years
3	minimum time interval if previous stroke in history	1 month	3-0 months
4	minimum time interval if previous serious head trauma in history	1 month	3-0 months
5	minimum time interval if previous major surgery in history	1 day	14-0 days
6	minimum time interval if previous gastrointestinal haemorrhage in history	½ week	21-0 days
7	minimum time interval if previous urinary tract haemorrhage in history	½ week	21-0 days
8	minimum time interval if previous arterial puncture at a non-compressible site in history	1 day	7-0 days
9	minimum stroke severity, indicated by NIHSS score	1	5-0
10	maximum rate of improvement of symptoms	10 %	0-100% / hour
11	maximum systolic blood pressure	10 mmHg	180-250 mmHg
12	maximum diastolic blood pressure	5 mmHg	110-160 mmHg
13	maximum blood pressure reduction	10 mmHg	0-100 mmHg
14	minimum platelet count	10 x 10^{12}/ l	< 100-40 x 10^{12}/ l
15	maximum serum glucose level	2 mmol/ l	> 22.2-40 mmol/ l
16	minimum serum glucose level	1 mmol/ l	< 2.7-0 mmol/ l
17	maximum INR as a result of current anticoagulant treatment	0.2	1-2.2
18	maximum APTT as a result of treatment with heparin within the previous 48 hours	10 seconds	40-100 seconds

Table 1 eighteen exclusion criteria from the NINDS rTPA Stroke Study,[6] clinically relevant unit and range, the number correlates with the number of the listed propositions in the Appendix

Figure 1 MEDLINE search strategy

1. cerebrovascular accident [MeSH]
2. infarction, posterior cerebral artery [MeSH]
3. brainstem infarctions [MeSH]
4. infarction, middle cerebral artery [MeSH]
5. infarction, anterior cerebral artery [MeSH]
6. 1 OR 2 OR 3 OR 4 OR 5
7. thrombolytic therapy [MeSH]
8. 6 AND 7
9. 8 NOT myocardial infarction [MeSH]
10. 9 NOT infusions, intra-arterial [MeSH]
11. 10 NOT injections, intra-arterial [MeSH]
12. 11 NOT catheters, indwelling [MeSH]
13. 12 NOT nursing journals
14. 13 NOT letters
15. 14 not case reports [publication type]
16. 15 limits: english, human, adult

Delphi procedure

In the first Delphi round each panellist rated the propositions. They were asked for their opinion on contraindications of thrombolysis for acute ischaemic stroke with alteplase 0.9 mg/kg (with a maximum of 90 mg), administered intravenously. The instruction was: "Mark the most extreme value that in your opinion does not compromise the effectiveness and safety of thrombolysis for ischaemic stroke. Assume that all other symptoms and risk factors are well within a safe range." Each proposition had its appropriate scale and measurement unit within a clinically relevant range. The propositions were scored using a web-based form.

In the second and third Delphi round the panellists were informed of the group's median score, the inter-quartile range (the range between the seventy-fifth and twenty-fifth deciles) for each proposition, and their own rating in the previous round. They were asked to reconsider their answers in view of this information.

Analysis

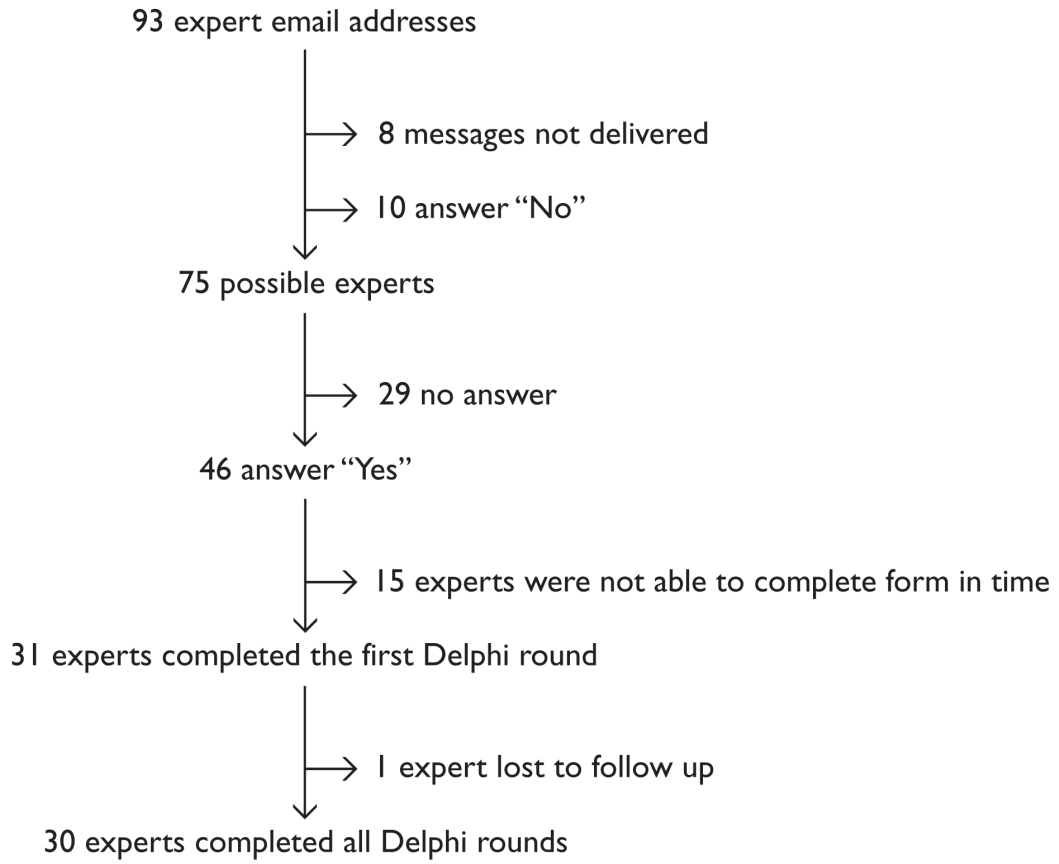
Consensus was considered to have been reached if the interdecile range (the difference between the ninth and first deciles) was within two clinically relevant units. As mentioned earlier these clinically relevant units were determined in advance. Crohnbach's alpha can be used as an index of reliability of a summation of entities.[23] In our analysis, we used it to quantify the reliability of the panellist's ratings. The acceptable level of Crohnbach's alpha, indicating good reliability, is 0.90.[23] To compute Crohnbach's alpha, all responses were standardised to a 0-1 range, with the 0 being the most conservative value.

Results

Panellists

On the basis of the MEDLINE search and review of the articles, we identified email addresses of 93 first and last authors. Of the 46 authors who agreed to participate, 31 completed the first form in time; a remaining 30 panellists completed all three Delphi rounds (Figure 2). The participating panellists were from ten countries (Argentina, Australia, Canada, Germany, India, Israel, Korea, Spain, the United Kingdom and the United States of America).

Figure 2 flow diagram of the formation of the Delphi panel



Analysis

The panellists reached consensus on twelve of the eighteen propositions (Table 2). In four of the twelve the median value was the same as the NINDS rTPA Stroke Study limits, i.e. for systolic and diastolic blood pressure, and maximum and minimum serum glucose levels. In three of the twelve the NINDS rTPA Stroke Study provided no limit, as in the case of minimum stroke severity, INR, and APTT. In the remaining five of the twelve the median value was different from the NINDS rTPA Stroke Study limit i.e. for previous stroke, previous head trauma, gastrointestinal haemorrhage, urinary tract haemorrhage, and platelet count.

No consensus was reached on six propositions. In three (minimum time interval if previous stroke, previous major surgery or previous arterial puncture at a non-compressible site in history) the NINDS rTPA Stroke Study limit was within the interdecile range of the last Delphi round. In two (maximum patient's age and maximum rate of improvement of symptoms) the NINDS rTPA Stroke Study had set no limit, and in the sixth (maximum blood pressure reduction) this limit was not within the interdecile range of the last Delphi round.
Crohnbach's alpha was 0.95 in the first round, 0.97 in the second, and 0.98 in the final round, indicating high reliability.

Table 2 all 18 propositions with the results in the three Delphi rounds (indicated with DI, DII and DIII) the results are presented in median score and interdecile range. The last column indicates whether consensus has been reached. The number correlates with the number of the listed propositions in the Appendix.

n°	keywords proposed contraindication	units	criterion	median DI	interdecile range DI	median DII	interdecile range DII	median DIII	interdecile range DIII	consensus
1	stroke onset to treatment time	hour	3	4.5	(3 - 6)	4.25	(3 - 5.9)	4	(3 - 4.5)	no
2	patient's age	years	—	92.5	(80.5 - 110)	90	(80 - 110)	90	(80 - 110)	no
3	previous stroke	month	3	1.5	(1 - 3)	1.5	(1 - 2.9)	**1.5**	(1 - 2)	yes
4	previous head trauma	month	3	2	(1 - 3)	2	(1.5 - 3)	**2**	(1.6 - 3)	yes
5	recent major surgery	day	14	14	(7 - 14)	14	(10 - 14)	14	(10 - 14)	no
6	recent gastro-intestinal haemorrhage	day	21	14	(9 - 28)	14	(14 - 21)	**14**	(14 - 21)	yes
7	recent urinary tract haemorrhage	day	21	14	(4 - 20.8)	14	(4.3 - 19.8)	**14**	(7 - 19.4)	yes
8	recent arterial puncture	day	7	6	(2 - 7)	6	(2.1 - 7)	5.5	(3 - 7)	no
9	stroke severity	NIHSS	—	3	(1 - 4.8)	3	(2 - 4)	**2.5**	(2 - 4)	yes
10	improvement rate	%	—	37.5	(20 - 80)	37.5	(20.5 - 79.5)	40	(30 - 74.5)	no
11	systolic blood pressure	mmHg	185	185	(180 - 208)	185	(180 - 200)	**185**	(180 - 199)	yes
12	diastolic blood pressure	mmHg	110	110	(106 - 120)	110	(110 - 119.5)	**110**	(110 - 110)	yes
13	blood pressure reduction	mmHg	0	30	(12 - 68)	30	(20 - 49)	30	(20 - 49)	no
14	platelet count	$x10^9/l$	100	90	(62 - 100)	90	(71 - 100)	**90**	(80 - 100)	yes
15	maximum serum glucose level	mmol/l	22.2	22	(22 - 28)	22	(22 - 25)	**22**	(22 - 25)	yes
16	minimum serum glucose level	mmol/l	2.7	2.7	(1.8 - 2.7)	2.6	(2.0 - 2.7)	**2.7**	(2.1 - 2.7)	yes
17	INR	—	—	1.5	(1.2 - 1.8)	1.5	(1.2 - 1.7)	**1.5**	(1.3 - 1.6)	yes
18	APTT	sec.	—	50	(40 - 60)	50	(40 - 50)	**50**	(40 - 50)	yes

Discussion

In this study, we used a Delphi approach to achieve consensus among an international group of specialists on indications and contra-indications for intravenous thrombolysis in acute ischaemic stroke. We obtained consensus in 12 of the 18 propositions, which may facilitate the difficult implementation of these treatment criteria.

Interestingly, our Delphi panellists did reach consensus on the INR value of 1.5, which is less than the 1.7 proposed in the guidelines of the American Heart Association.[14] They also agreed on a minimal NIHSS score of 2 to 3 to warrant treatment. This definition of stroke severity is clinically relevant as "minor symptoms" is a frequently mentioned contraindication in clinical practice although it was never defined and left to the clinicians' interpretation.[9] As the effect of treatment in these patients is consistent with the overall effect,[24] and 27% of the too-good-to-treat patients died or were not discharged home because of neurological worsening or persistent 'mild' neurological deficit we think the proposed limit of stroke severity is a useful definition which might result in higher treatment rates.[25]

Consensus was not reached in our study on some important contra-indications. The interdecile range for maximum stroke onset to treatment time was narrowed (from 3-6 to 3-4.5), but consensus was not reached. Results of on-going clinical trials like the IST-3 or ECASS-3 will be helpful since they are designed to study the time-effectiveness relation beyond the 3-hour window.[26] Neither was consensus reached concerning age. Age is a prognostic factor; risks of mortality and poor outcome steeply rise with advancing age.[27-29] Chen et al showed that patients over 80 years have similar rates of recanalisation, short-term improvement and symptomatic ICH as younger patients.[30] Whether there should be an upper age limit remains controversial, a meta-analysis across cohort studies could not answer this question.[31] Although cohort studies have demonstrated that age is an important outcome predictor, these studies were unable to evaluate the effectiveness of rTPA in patients with increasing age, because they could not compare 'standard treatment and rTPA' with 'standard treatment' alone.[32] Also, no consensus was reached concerning blood pressure management. In a large cohort study, elevated pre-treatment blood pressure was related to intracranial haemorrhage and poor outcome.[28] Larrue et al reported that for every mm Hg increase in baseline systolic blood pressure, the relative risk (odds ratio) of haemorrhagic transformation increased by 2%.[27] This information however, is not sufficient for justifying a treatment decision, as the modification of the treatment effect on overall outcome by blood pressure was not reported. In our opinion, the lack of consensus on the points mentioned above should not be surprising, given the availability of randomised evidence. It illustrates the differential nature and the quality of a Delphi method. More randomised evidence should be pursued in these areas. The lack of consensus on the proposition dealing with the improvement rate is probably due to difficult interpretation of this concept. We defined the improvement rate as the relative difference between the NIHSS score at 3 hours and the highest NIHSS score ever, but symptoms fluctuate over time. Because of the difficulty in interpreting the exclusion criterion "rapidly improving", we would propose to use only a threshold NIHSS score to treat, if it involves interpretation of symptoms.

Our study has some limitations. First, expert opinion can only be complementary to evidence from randomised clinical trials. However, whether thrombolysis is effective in subgroups of specific indications or contraindications remains unclear, because subgroup analyses from randomised trials of thrombolysis were not powered for this purpose.[1,33] The results of our Delphi study may also help to interpret existing guidelines for thrombolysis in ischaemic stroke in anticipation of the results of on-going clinical trials (IST-3, ECASS-3 and EPITHET).[20-22] In particular, IST-3 that seeks to recruit 6000 patients may provide information on the balance of risks and benefits in a much wider variety of patients than are defined by the NINDS trial criteria.[26] Second, of the 44 panellists who were invited to participate and to fill out the Delphi forms 29 (66%) responded. This can be explained by the short time allowed for reply in this methodology, and in our view does not suggest the introduction of bias. The relatively large number of participants contributes to the validity of this Delphi study. Moreover, 30 of the 31 panellists who began this consensus process by filling out the first questionnaire continued through each of the subsequent rounds and completed the study. Unavoidably, some panellists have also played a role in international guideline development; this may have influenced their opinion. The origin of the panellists was North America (13), Europe (11), Australia (2), Asia (3) and South America (1). We consider them a representative group of specialists.

The high reliability index (Crohnbach's alpha >0.95) suggests excellent reproducibility. Third, we selected the clinically relevant ranges and units for each proposed contraindication based on common clinical practice. One may challenge these initial choices on strict methodological grounds, but other selections would most likely lead to similar clinical judgements. And last, the extent of early ischaemic changes on pre-treatment CT was not included. We did not include this item because these changes do not seem to be independently associated with increased risk of adverse outcome, or lack of effect after rTPA treatment, and inter-observer reliability of these signs is limited.[34,35]

In conclusion, consensus was reached in one of the most frequently mentioned and clinically relevant criteria, namely the exclusion criterion of minor symptoms. Yet, no consensus was reached in the propositions concerning important issues like maximum stroke onset to treatment time, patient's age and treatment of elevated blood pressure. The Delphi panel results might be helpful to translate trial results on thrombolysis in acute ischaemic stroke in day-to-day clinical practice. The exact definition of "minor symptoms" may facilitate treatment decisions in many patients, using the demographic information from the cohort study of Katzan et al one could conclude that this may result in 2 to 3 times as many treated patients.[9]

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APPENDIX

A. — The members of the Delphi expert panel (alphabetical listing) and their current affiliation

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R.P. Atkinson, Sutter Institute for Medical Research | Sacramento, CA, USA
K. Butcher, Department of Neurology, Royal Melbourne Hospital | Parkville, Victoria, Australia
M. Castellanos, Department of Neurology, Hospital Universitari Doctor Josep Trueta | Girona, Spain
A. Davalos, Department of Neurosciences, Hospital Germans Tries i Pujol | Badalona, Spain
B.M. Demaerschalk, Mayo Clinic College of Medicine, Mayo Clinic Arizona | Scottsdale, AZ, USA
R.B. Foell, the Central East Ontario Stroke Program and the Huntsville District Memorial Hospital | Ontario, Canada
G.A. Ford, University of Newcastle upon Tyne | Newcastle upon Tyne, United Kingdom
S.E. Kasner, Comprehensive Stroke Center, University of Pennsylvania Medical Center | Philadelphia, PA, USA
I.L. Katzan, MetroHealth Medical Center and Cleveland Clinic Foundation | Cleveland, OH, USA
H.-C. Koennecke, Department of Neurology, Ev. Krankenhaus Königin Elisabeth Herzberge | Berlin, Germany
K.H. Lee, Department of Neurology, Samsung Medical Center | Seoul, Korea
E.C. Leira, Department of Neurology, University of Iowa College of Medicine | Iowa City, IA, USA
S.R. Levine, Stroke Center, Mount Sinai School of Medicine | New York, NY, USA
R.I. Lindley, Western Clinical School, University of Sydney | Westmead, New South Wales, Australia
J.E. Mendizabal, Corpus Christi Neurology | Corpus Christi, TX, USA
K. Nandigam, Department of Neurology, Jawaharlal Institute of Post Graduate Medical Education and Research | Pondicherry, India
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G. Saposnik, Department of Clinical Neurological Sciences, University of Western Ontario | London, Canada
P.D. Schellinger, Department of Neurology, University of Heidelberg | Heidelberg, Germany
P.A. Scott, Dept. of Emergency Medicine, University of Michigan | Ann Arbor, MI, USA
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R. Silbergleit, Department of Emergency Medicine, University of Michigan | Ann Arbor, MI, USA
J. Sobesky, Klinik und Poliklinik für Neurologie, der Universität zu Köln | Köln, Germany
D. Tanne, Dept. of Neurology, Sheba Medical Center | Tel Hashomer, Israel
D.C. Tong, CPMC Stroke Institute (CSI) | San Francisco, CA, USA
S. Wagner, Department of Neurology, University of Heidelberg | Heidelberg, Germany
C. Weimar, Neurologische Klinik und Poliklinik, Universität Duisburg-Essen | Essen, Germany
R.M. Zweifler, University of South Alabama Stroke Center | Mobile, AL, USA

B. — Propositions and instructions presented to the experts

Instructions:

Mark the most extreme value that does not compromise effectiveness and safety of thrombolysis for ischaemic stroke, according to your opinion. Assume that all other symptoms and risk factors are well within a safe range. For each item, we provide you the median score and interquartile range of the whole expert group together with your own previous answers (in the second and third round).
Treatment with thrombolysis implies intravenous administration of rTPA, 0.9 mg|kg, with a maximum of 90 mg. Treatment starts with a bolus of 10 % of the dosage rTPA, followed by the remaining 90 % as a continuous infusion in one hour.
Remember, we are interested in your personal opinion, not in what you think others may deem appropriate.

Propositions:

1. — Until what time after stroke onset could a patient with ischaemic stroke be treated with thrombolysis?
2. — What is the patient's maximum age for treatment of ischaemic stroke with thrombolysis?
3. — How much time should have elapsed after a previous stroke, before a patient with ischaemic stroke could be treated with thrombolysis?
4. — How much time should have elapsed after a serious head trauma, before a patient with ischaemic stroke could be treated with thrombolysis?
5. — How much time should have elapsed after major surgery, before a patient with ischaemic stroke could be treated with thrombolysis?
6. — How much time should have elapsed after a gastro-intestinal haemorrhage, before a patient with ischaemic stroke could be treated with thrombolysis?
7. — How much time should have elapsed after a urinary tract haemorrhage, before a patient with ischaemic stroke could be treated with thrombolysis?

8. — How much time should have elapsed after an arterial puncture at a non-compressible site before a patient with ischaemic stroke could be treated with thrombolysis?
9. — At what minimal NIHSS score would you consider thrombolysis for ischaemic stroke still indicated?
10. — At what improvement rate# would you consider thrombolysis for ischaemic stroke still indicated?
11. — What is the highest systolic blood pressure level at which you still consider treatment with thrombolysis for ischaemic stroke to be indicated?
12. — What is the highest diastolic blood pressure level at which you still consider treatment with thrombolysis for ischaemic stroke to be indicated?
13. — After what systolic blood pressure reduction (to your limit set at proposition 11) by medical treatment with for instance, labetalol or nitroprusside would you still consider thrombolysis for ischaemic stroke to be indicated?
NB: the value 0 indicates that you do not accept any blood pressure reduction by medical treatment.
14. — What is the lowest platelet count that leaves thrombolysis for ischaemic stroke still indicated?
15. — What is the highest serum glucose level that leaves thrombolysis for ischaemic stroke still indicated?
16. — What is the lowest serum glucose level that leaves thrombolysis for ischaemic stroke still indicated?
17. — What is the highest INR (as a result of current anticoagulant treatment) that leaves thrombolysis for ischaemic stroke still indicated?
18. — What is the highest APTT (as a result of current heparin treatment) that leaves thrombolysis for ischaemic stroke still indicated?

Improvement rate: expressed as the relative difference between the NIHSS score at 3 hours and the highest NIHSS score ever. A 50% improvement for example is reached by a patient with an initial NIHSS score of 16, who has a score of 8 at 3 hours from onset.

PROMOTING THROMBOLYSIS IN ACUTE ISCHAEMIC STROKE. PRACTISE, A CLUSTER-RANDOMISED CONTROLLED IMPLEMENTATION TRIAL

Chapter 4

Dirks M, Niessen LW, van Wijngaarden JD, Koudstaal PJ, Franke CL, van Oostenbrugge RJ, Huijsman R, Lingsma HF, Minkman MM, Dippel DWJ. *Promoting thrombolysis in acute ischaemic stroke.* Stroke. 2011 May;42:1325-1330.

Introduction

Thrombolysis with intravenous rTPA is widely accepted as an effective treatment for patients with acute ischaemic stroke, if treatment can be started within 4.5 hours after onset.[1,2] Although up to 25% of the patients might be eligible for thrombolysis,[3] in most western countries only a relatively small proportion of patients (3-7%) is actually treated. To tackle the problem of under-treatment we developed intervention strategies to remove barriers in the application of thrombolysis. We adapted a list of observed treatment obstacles by Kwan et al, and grouped them into four categories: inter-organisational, intra-organisational, medical, and psychological, which served as pretexts for targeted intervention strategies.[4] Inter-organisational barriers relate to the proportion of patients arriving in time for treatment. Intra-organisational barriers concern the availability of on-demand laboratory, CT scanning and skilled nursing facilities. Medical barriers contain appropriate application of contraindications for thrombolysis, which are important reasons for under-treatment.[3] Psychological factors include anticipation of regret and risk aversion, which may make neurologists conservative in giving thrombolysis.

In this study we investigated whether the proportion of patients treated with thrombolysis in hospitals can be increased in real-life settings through a multi-faceted implementation strategy aimed at resolving potential treatment barriers.

Methods

Practise (PRomoting ACute Thrombolysis in Ischaemic StrokE) is a national cluster-randomised controlled trial for the evaluation of a multi-faceted implementation strategy for thrombolysis. The Medical Ethics committees in each participating centre assessed the study protocol. The protocol has been set up according to the revised CONSORT statement for cluster-randomised trials,[5] and has been published earlier.[6] Twelve hospitals participated and were assigned to the intervention or control group by random allocation after pair-wise matching. Pairing was based on hospital type, previous thrombolysis rate, and size (number of stroke patients admitted per year).

Participating centres & Patient population

Stroke service characteristics of the 12 hospitals were assessed to determine a 'situation score' in line with the barriers mentioned before, and to identify potentially successful implementation actions. We collected these data through interviews with key providers of care in each centre, using pre-structured questionnaires. These included the presence and content of protocols, the level of formal education and the infrastructure around and within the hospital (for instance the number of ambulance services, specialists and residents). All single items received a rating between zero and one. The standardised sum-scores were calculated by adding all single items per category, divided by the maximum score and multiplied by ten so that all sum-scores had a standardised rating between zero and ten. All patients over 18 years with acute stroke who were admitted to hospital within 24 hours from onset of symptoms were included in the trial. Patients admitted within 4 hours were assessed in detail, and were followed up to 3 months after onset by telephone. The 4-hour time window was used because in the trial period the generally accepted time window for treatment with alteplase was 3 hours. The 4-hour time window was chosen in order not to miss patients who were for instance treated just outside the 3 hours' time window, and to have more information on the patients not arriving in time for treatment. Patients had to give consent for follow-up visits.

Intervention

The implementation strategy for thrombolysis consisted of intervention meetings based on the Breakthrough Series model.[7] We formed local teams that included a stroke neurologist and a stroke nurse. We asked the teams to note specific local barriers to further implementation in their hospital, to set goals, and to plan actions to reach these goals in a reasonable timeframe, and we monitored the results of their actions. Each team was asked to evaluate and update their acute stroke guideline. The intervention continued for two years and comprised five half-day intervention meetings and one closing session. The meetings started in May 2005, almost 6 months before the start of data collection.

Data collection, Blinding & Safety

Trained, local personnel not involved in the patient's treatment collected the data, which were entered into web-based forms. The central trial office provided the three-month follow up assessment and used simple questions to record the patient's dependency and health-related quality of life.[8] The two researchers who assessed outcome data were blinded to the intervention assignment. Local neurologists and paramedical personnel in intervention hospitals were aware that they participated in a program to enhance the rate of thrombolysis. Their colleagues in the control hospitals were only notified that they participated in a registration project. During the period of recruitment, interim analyses of in-hospital mortality, intracranial haemorrhages and other serious adverse events believed to be due to treatment, were confidentially reported to a data monitoring committee (DMC). The DMC met four times and advised the steering committee on continuation of the study.

Outcome measures

The primary outcome was treatment with rTPA in the total stroke population and in the subgroup of patients with an ischaemic stroke admitted within four hours. Secondary outcomes were admission within four hours after onset of symptoms, death or disability at three months measured with the modified Rankin Scale (mRS), and quality of life measured with the EuroQol (EQ5D).[9] The mRS and EQ5D were assessed only in the subgroup of patients with ischaemic stroke who were admitted within four hours. Tertiary outcomes were onset-to-door time and door-to-needle time, as process indicator of the timelines of acute stroke care.

Clinical definitions

Symptomatic intracranial bleeding was defined as a haemorrhage confirmed by CT-scan preceded by an increased deficit on the National Institutes of Health Stroke Scale (NIHSS).[10] Contraindications were identified by the treating physicians and checked retrospectively from source data by the investigators. Unambiguous contraindications refer to contraindications used in guidelines for thrombolysis on for instance blood pressure and laboratory findings.[11] The thrombolysis rate was calculated by dividing the total number of patients treated with rTPA by all stroke patients admitted within 24 hours of symptom onset (including ICH).

Sample size

With adjustments for randomisation at centre level, the expected size of our study (12 hospitals, 5,000 registered patients) was considered to be sufficient to detect a statistically significant (alpha=0.05) increase in thrombolysis rate in the intervention hospitals with a power of 80%. This calculation was based on the assumption of a relative increase of 50% in thrombolysis rate in the intervention hospitals superimposed on an secular, increasing trend, leading to an estimated thrombolysis rate of 7.5% in the control hospitals and 11.3% in intervention hospitals.[6]

Statistical analysis

Statistical analysis was carried out on an intention-to-treat basis. In the analysis of the primary and secondary outcome we used a multilevel logistic regression model, to adjust for potential clustering effects. In the analysis of the tertiary outcome, which are continuous outcome variables, we used a multilevel linear regression model. In addition, we adjusted for hospital size, type of hospital, and previous thrombolysis rates at hospital level. At individual patient level we adjusted for age and sex. In the group of patients admitted within four hours, we also adjusted for stroke severity and comorbidity. Intervention effects were reported as odds ratios with 95% confidence interval. We used STATA version 10 to analyse the data (STATA Corp, College Station, Texas USA).

Results

Patient registration ran from October 2005 until October 2007. The follow-up period was closed in January 2008. The overall participation in the intervention meetings was good. One hospital team dropped out of the intervention halfway during the trial, due to a change in medical staff. Members of the central trial office completed data collection in that hospital. Hospital size ranged from 100 to 500 stroke admissions a year (Table 1). Some of the larger hospitals were allocated to the intervention group and more patients were registered in that group. The extramural education score was better in the intervention hospitals, whereas the intramural protocol score was higher in the control group. At the end of the study, only the intramural protocol score had increased substantially in the intervention hospitals.

Table 1 baseline & end hospital characteristics

characteristic (mean [range])	**intervention [n=6]**		**control [n=6]**	
size [stroke admissions in 2003]	332 [125-500]		264 [100-400]	
academic | non-academic	1 | 5		1 | 5	
teaching hospital | no teaching hospital	3 | 3		2 | 4	
prior thrombolysis rate 2003	6 [3-10]		5 [0-10]	
organisational structure	baseline	end	baseline	end
extramural protocols [0-10]	2.3 [2.1-2.9]	2.4 [0.4-4.2]	2.3 [1.3-2.9]	2.4 [1.3-3.8]
extramural education [0-10]	4.8 [1.7-8.2]	4.3 [1.5-7.0]	3.6 [0.3-7.0]	3.6 [0.7-5.3]
extramural infrastructure [0-10]	4.1 [2.5-5.7]	4.1 [2.5-5.7]	4.3 [3.3-5.0]	4.3 [3.4-5.0]
intramural protocols [0-10]	1.9 [1.0-2.7]	3.2 [2.2-3.8]	2.8 [1.6-3.8]	3.2 [2.4-3.8]
intramural education [0-10]	2.6 [1.5-4.0]	2.5 [0-6.9]	2.9 [1.0-6.0]	2.1 [1.8-2.8]
intramural infrastructure [0-10]	4.5 [2.4-6.0]	4.5 [2.4-6.0]	4.3 [2.2-6.2]	4.3 [2.2-6.2]

Overall, 5,515 patients were registered, 2,990 in the intervention hospitals and 2,525 in the control hospitals (see Figure 1). There were no missing data in the minimal set of baseline data. Twenty-nine per cent (880) of the patients in the intervention hospitals and 31% (777) in the control hospitals were admitted within four hours. In total, 892 (16%) patients had an intracranial haemorrhage (Table 2). Follow-up assessment was complete in 1,589 of the 1,657 patients, 68 patients (4%) were lost to follow up or refused informed consent. The mean age in both arms was 72 years, sex was equally distributed, and the mean NIHSS score at admittance did not differ between intervention and controls. The intra-cluster correlation (ICC) from the actual analysis of the primary outcome was 0.0154.

Table 2 baseline patient characteristics

	intervention	control
all patients	**2990**	**2525**
mean age [range]	72 yrs. [19-105]	72 yrs. [25-100]
men	50% [1,489]	49% [1,248]
contraindication for thrombolysis:		
intracranial haemorrhage	17% [507]	15% [385]
onset-to-door time > 4 hours	54% [1,603]	54% [1,363]
patients with ischaemic stroke admitted within 4 hours	**880**	**777**
stroke severity [mean NIHSS score at admission]	8	8
previous cerebral ischemia	22% [195]	18% [136]
previous intracranial haemorrhage	1% [13]	1% [8]
previous myocardial infarction	12% [108]	15% [119]
peripheral artery disease	8% [68]	12% [90]
heart failure	9% [81]	7% [51]
hypertension	49% [435]	53% [411]
atrial fibrillation	15% [134]	21% [162]
diabetes mellitus	16% [145]	17% [129]
hypercholesterolaemia	32% [281]	46% [357]
current smoking	24% [213]	24% [185]

Figure 1 flow chart of the study

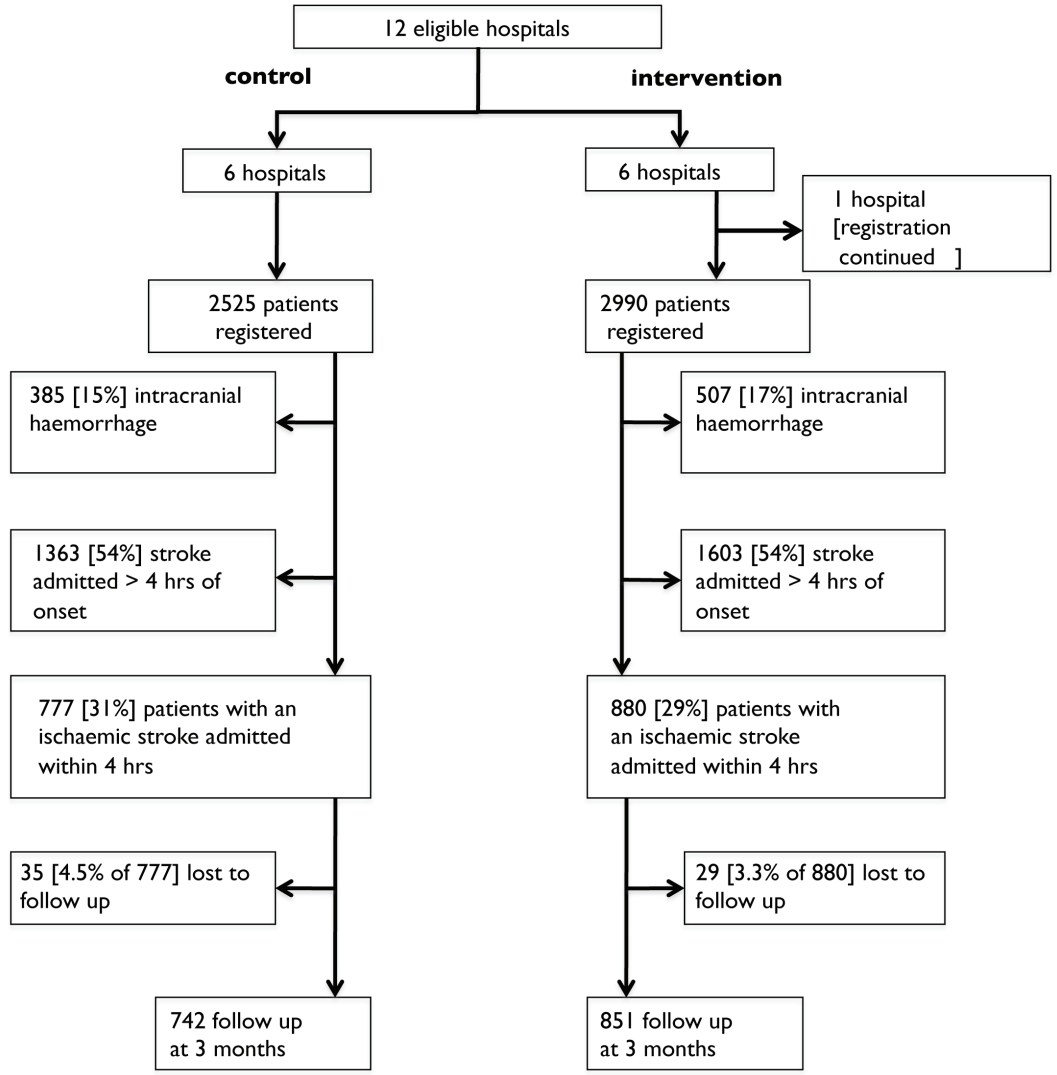


Table 3 patient outcomes and intervention effect

	intervention	control	effect (95% CI)	effect (95% CI)	effect (95% CI)
	n [%]	n [%]	cluster-adjusted for centre and patient characteristics	cluster-adjusted	unadjusted
all patients	2990	2525			
thrombolysis	393 [13%]	308 [12%]	1.25 [0.93-1.68]	1.28 [0.87-1.89]	1.08 [0.93-1.28]
onset-to-door time [minutes]	424	392	31 [−1-63]	30 [−2-61]	32 [−13-51]
patiens with ischaemic stroke and admitted within 4 hrs	880	777			
thrombolysis +	391 [44%]	305 [39%]	1.58 [1.11-2.27] ++	1.44 [0.93-2.22]	1.24 [1.02-1.51]
mRS <3 at 3 months +++	441 [52%]	429 [58%]	0.56 [0.42-0.74] ++	0.78 [0.63-0.98]	0.79 [0.65-0.96]
mortality at 3 months +++	141 [17%]	127 [17%]	1.05 [0.74-1.48] ++	0.96 [0.74-1.25]	0.96 [0.74-1.25]
EQ5D ++++	0.56	0.58	0.01 [−0.05-0.08] ++	−0.02 [−0.16-0.12]	−0.01 [−0.05-0.03]
onset-to-door time [minutes]	91	90	−1 [−7-5] ++	1 [−5-6]	1 [−4-6]
door-to-needle time [minutes]	70	73	−3 [−15-10] ++	−1 [−13-11]	−2 [−13-9]

Values are numbers and effects in Odds Ratios. In continuous variables values are means and effects are differences between mean values.

+ Five patients were treated with rTPA outside the 4 hours window.

++ Adjusted for hospital size, academic versus non-academic, and previous thrombolysis rate at hospital level. Adjusted for age, sex, stroke severity, history of ischaemic stroke, myocardial infarction, heart failure or peripheral artery disease, DM and atrial fibrillation at patient level.

+++ Data not available in 68 patients (4%).

++++ Data not available in 166 patients (10%).

Outcomes

Primary outcome & Safety

In the intervention hospitals 393 patients (13% of all acute stroke patients) were treated with thrombolysis, and 308 (12%) in the control hospitals (aOR: 1.25; 95% CI: 0.93 to 1.68) (Table 3). In the group of 1,657 patients with ischaemic stroke who were admitted within four hours from onset, 391 (44%) of 880 patients in the intervention centres were treated with rTPA and 305 (39%) of 777 patients in control centres (aOR 1.58; 95% CI: 1.11 to 2.27). Per hospital, the thrombolysis rate ranged between 9% and 22% in the intervention hospitals and between 7% and 16% in the control hospitals (Figure 2). Although the mean thrombolysis rates in the control centres rose steadily until the end of the study period, the intervention centres rose earlier and remained higher (Figure 2). The symptomatic intracranial bleeding complication rate of thrombolysis was 5.6% in the intervention hospitals and 4.6% in the control hospitals (relative risk: 1.23; 95% CI: 0.64 - 2.36). Other complications of thrombolysis were rare (Table 4).

Figure 2 thrombolysis rate in time: mean of thrombolysis percentages in the six hospitals of each arm, by half-year periods

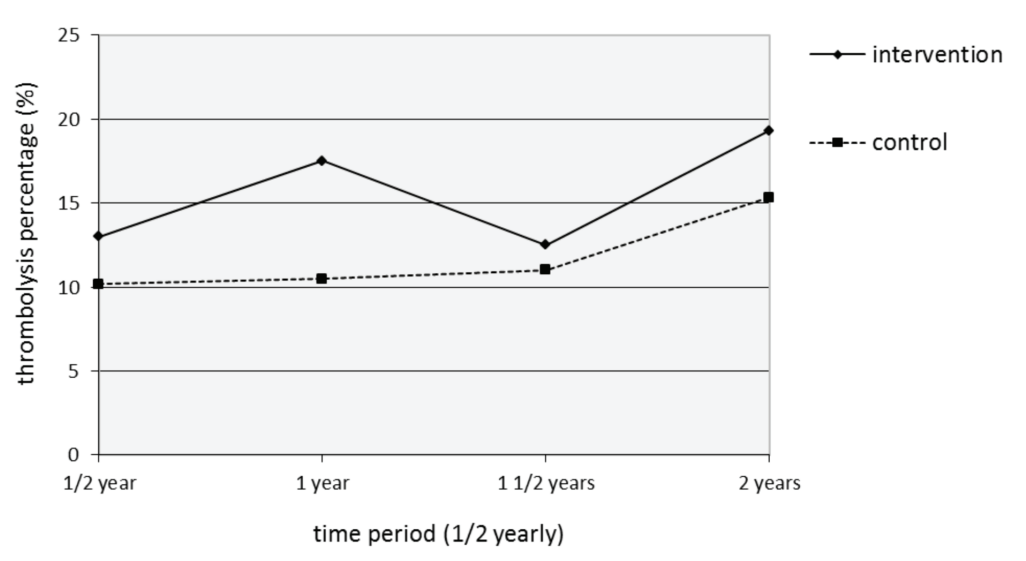


Table 4 adverse events in patients treated with thrombolysis

adverse event (n [%])	intervention (n=391)	control (n=305)
intracranial haemorrhage	22 [5.6%]	14 [4.6%]
hyper-perfusion syndrome	0	1 [0.3%]
anaphylactic reaction	4 [1.0%]	5 [1.7%]
other bleeding complications+	4 [1.0%]	3 [1.0%

+ epistaxis, haematuria and hematemesis

Secondary & tertiary outcomes

Good clinical outcome at three months (mRS<3) was observed in 441 (52%) patients treated in the intervention hospitals, slightly less than in the control hospitals (429, 58%) (aOR 0.56; 95% CI: 0.42 to 0.74). Of the patients treated with rTPA 51% had a good outcome in the intervention versus 49% in the control hospitals. The mortality rate was 17% in both groups, and the mean NIHSS-score at discharge was 4 in the patients treated in intervention hospitals and 5 in control hospitals, the mean EQ5D-derived utility weight was 0.56 versus 0.58 (adjusted difference 0.01; 95%CI:-0.05 to 0.08) (Table 3). The mean onset-to-door time in all registered stroke patients was 7 hours and 4 minutes in the intervention hospitals and 6 hours and 32 minutes in the control hospitals. The mean door-to-needle time was 70 minutes versus 73 minutes in the control hospitals, an adjusted difference of -3 minutes (95% CI: -15 to 10).

Contraindications

There was no clear difference in the proportion of patients with unambiguous contraindications, 21% in the intervention hospitals and 23% in the control hospitals (Table 5). However, 'mild or rapidly improving symptoms' as a contraindication was less frequent in the intervention hospitals 17% versus 26%. The median NIHSS-score in this group was 2 in both arms. Unconventional contraindications like haemorrhoids, menstruation or "bumped his head" were also less frequent in the intervention hospitals, 3.9% versus 5.4%. One patient in the control hospitals and 9 patients in the intervention hospitals who received alteplase had a contraindication for thrombolysis in retrospect. Of the patients with no unambiguous contraindications and an NIHSS score of 3 or more 69% (354/527) was treated with rTPA in the intervention hospitals, versus 60% (287/475) in the control hospitals (OR 1.48; 95% CI: 1.13 - 1.92).

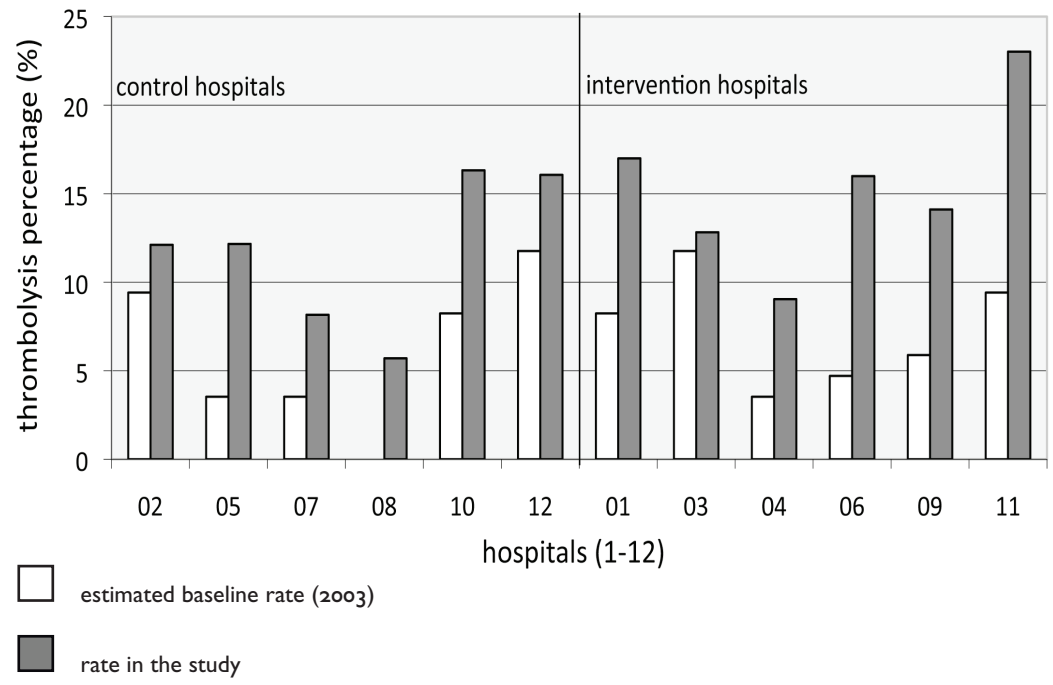
Table 5 reported contraindications for thrombolysis in patients with an ischaemic stroke admitted within 4 hours from onset of symptoms

contraindication (n [%])	intervention (n=880)	control (n=777)
unambiguous contraindication	195 [22%]	176 [23%]
minimal | rapidly improving symptoms +	152 [17%]	203 [26%]
unconventional contraindications ++	34 [4%]	42 [5%]
unknown contraindication	22 [3%]	10 [1%]
material | logistic problems	7 [1%]	4 [1%]
no contraindication	470 [53%]	342 [44%]

+ according to treating physician

++ according to investigators; un-conventional contraindications were: haemorrhoids, menstruation or "bumped his head"

Figure 3 thrombolysis percentages by hospital: thrombolysis percentage during the study period and estimated baseline thrombolysis percentage in 2003



Discussion

In this study, we found that the proportion of patients treated with rTPA increased through a multi-faceted implementation strategy in real-life settings. Among the patients admitted within four hours after onset, the likelihood of treatment with rTPA was higher in the intervention centres also after adjustment for pre-specified centre and patient-characteristics. The rate of symptomatic intracranial bleeding complications was non-significantly higher in the intervention group and an important increase in bleeding rate is not ruled out. However the complication rate was similar to the rate in clinical trials and registries, indicating that our implementation actions did not lead to increased adverse health effects.[1,12]

We observed a significant effect of the intervention on only one of the two both primary outcome measures. The first outcome measure treatment-with-rTPA-in-the-whole-registered-stroke-population was chosen mainly to be able to detect a shift in onset-to-door time and to compare it with previous numbers. The second primary outcome measure treatment-with-rTPA-in-patients-with-ischaemic-stroke-admitted-within-four-hours-of-symptom-onset was chosen because it is easier to interpret. The size and

direction of the effect was similar in both primary outcomes. The ICC we used in the sample sized estimation (0.0032) was smaller than the ICC from the actual analysis of the primary outcome (0.0153), which led to a larger design effect (i.e. 7.35 instead of the assumed 2.34). This means that the study will have had lower than expected power to identify the estimated 50% relative effect. The intervention did not have an effect on the timelines of admission and therefore there was no significant effect on thrombolysis rate in all patients registered. Our study lacked sufficient power to detect changes in clinical outcomes; such an outcome study would need to be much larger. The proportion of patients with dependency according to the mRS was higher in the intervention group. The mortality rate, mean NIHSS score at discharge, and the mean quality of life measured on the EQ5D at three months were similar in both groups. The statistically non-significant difference in complication rates between the intervention and control hospitals could not explain the higher mRS scores in the intervention hospitals. Within the patient-group treated with rTPA good clinical outcome was similar in both study arms. The effect on mRS was not consistent with the effect of intervention on other clinical outcomes, and may be due to chance, or to unregistered co-morbidity other than cardiovascular co-morbidity or cardiovascular risk factors.

Strength of the study is the extent of blinding and lack of contamination risk: the neurologists (except for the principal investigator) and paramedical personnel in the control group were not made aware of the treatment allocation. Patients with a stroke were transported to the nearest hospital and were unaware of the study. All acute stroke patients were registered and most outcome measures were routine data collected by local personnel not involved in the patient's treatment. In the intervention hospitals more health care professionals (stroke nurses, all neurologists) were aware of the study because the intervention is a deliberate implementation that needed cooperation of these professionals. A more conservative design would be unrealistic and the intervention effect would then be artificial. Additional outcome measures were assessed blinded for treatment allocation. The participating hospitals are representative of a large spectrum of hospital types: from small urban and regional hospitals to the larger academic hospitals. Intervention adherence varied from very active to doing as little as possible, probably a good reflection of daily practice. The number of centres involved is a limitation of the study; only 12 hospitals of the approximately 110 hospitals in The Netherlands (11%) participated. This makes the study more sensitive to non-compliance on centre level. The hospital that dropped out of the intervention did not participate in the intervention meetings and did not perform any implementation assignments. However, members of the central trial office completed data collection in that hospital and the statistical analysis was carried out on an intention-to-treat basis. Despite of this dilution of possible effect we observed an overall significant effect in thrombolysis rate in patients with an ischaemic stroke admitted within 4 hours of symptom onset. In the hospital that stopped participating in the intervention strategy we observed an initial increase in thrombolysis rate during active participation in the study, and a decrease in thrombolysis rate after the hospital dropped out. This suggests that implementation needs to be a continuous process of measuring, adaptation and feedback. In addition, the time period between the Breakthrough sessions may have been too long, which may have led to lower compliance and loss of motivation.

Dissemination of simple thrombolysis referral guidelines to primary care and local emergency departments increases the proportion of intravenous thrombolysis.[13] In the Get With The Guidelines (GWTG) stroke project, participation was associated with increased adherence to several stroke care performance measures,[14] and the use of rTPA increased dramatically over time. However, the GWTG stroke project is an uncontrolled study, which could not distinguish between an autonomous time trend and an intervention effect. To our knowledge, there are no published randomised trials evaluating active implementation strategies in acute stroke care. In the treatment of acute myocardial infarction, a randomised controlled trial evaluated guideline implementation through clinician education by local opinion leaders and performance feedback in 37 community hospitals in Minnesota. It showed that guided quality improvement interventions could accelerate adoption of effective treatments in community practice in the treatment of acute myocardial infarction.[15]
The evaluation of a complex multi-faceted intervention is difficult. Further research is needed to examine whether this benefit can be maintained and increased, by implementing a structured and on-going audit of thrombolysis practice. We found no single component or combination of components in the structure of the stroke service that could explain the intervention effect. However, we did observe that in the intervention hospitals more patients were treated with alteplase with a lower NIHSS score and there were less ambiguous contra-indications. These two particular items were emphasised during the intervention meetings when the neurologists were instructed to update their treatment protocol that resulted in an increase in intramural protocol score. The mean onset-to-door time was even longer in the intervention hospitals reflecting that there was no improvement in the extramural organisation of stroke care. This finding can probably be attributed to the generally short distances between homes and hospitals in the Netherlands. The patient composition within the subgroup of patients with an ischaemic stroke admitted within 4 hours of symptom onset might be influenced by the intervention itself. If the intervention had affected the onset to door time, the analysis of those admitted within 4 hours would not have been easily interpretable. Also the intervention effect of our study was small in comparison with the autonomous time trend. This emphasises the need for better implementation methods.

Summary

This study shows that a multi-faceted implementation strategy can increase the proportion of patients treated with rTPA. A major component of the intervention effect we found was more appropriate application of contraindications of thrombolysis. Critical assessment of justified contraindications in our study reveals that if all patients who were

eligible for treatment with rTPA in this study were actually treated, an overall thrombolysis rate of 18% of all stroke patients could have been achieved. Naturally, the ultimate goal of an improved implementation of thrombolysis would be an increase in patients with a good outcome.

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THE EFFECTIVENESS OF THROMBOLYSIS WITH INTRAVENOUS ALTEPLASE FOR ACUTE ISCHAEMIC STROKE IN DAILY PRACTICE

Chapter 5.1

Dirks M, Niessen LW, van Wijngaarden JD, Koudstaal PJ, Franke CL, van Oostenbrugge RJ, Dippel DWJ. *The effectiveness of thrombolysis with intravenous alteplase for acute ischaemic stroke in daily practice*. Int Journal of Stroke 2011; (in press).

Introduction

Thrombolysis with intravenous alteplase is widely accepted as an effective treatment for patients with acute ischaemic stroke, if treatment can be started within 4.5 hours after stroke onset.[1-3]

However, effects observed in randomised clinical trials may be larger than in daily practice. Patients in real life may be older and have more co-morbidity.[4,5] Moreover, doctors may be somewhat less experienced and may not adhere as strictly to guidelines and instructions as in a trial environment. This may also affect the incidence of complications. Several studies and registries have shown similar outcomes and risks of complications in patients treated with alteplase in daily practice.[6-8] However, outcome in patients treated with alteplase compared with those not treated with alteplase has not been studied outside randomised clinical trials. The aim of this study was to assess the effectiveness and safety of thrombolysis in an unselected observational cohort of stroke patients in daily practice.

Methods

This study was a sub-study of the PRACTISE study, a cluster-randomised trial in which we evaluated an intensive multifaceted implementation strategy aiming to increase the proportion of patients treated with intravenous alteplase.[9]

Patient population

During a two-year period, all patients over 18 years with acute ischaemic stroke who were admitted within 4 hours from symptom onset were registered in 12 hospitals in the Netherlands. Patient data included demographics, baseline characteristics like the patients' medical history, cardiovascular risk factors, and stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS). All patients were admitted to a Stroke Unit and treatment with alteplase was registered. All hospitals used their own treatment guidelines based on national guidelines and on evidence from clinical trials. All patients were followed up after 3 months by telephone, for which they had given consent. The central trial office provided the three-month follow up assessment and used simple questions to record the patient's dependency and health-related quality of life. The two researchers who analysed outcome data were blinded to the treatment received.

Outcome measures

The primary outcome was death or disability at 3 months measured with the mRS and good outcome was defined as a score on the mRS of 2 or less.[9] We performed additional analyses in which we defined good outcome as a score on the mRS of 0 or 1. The safety endpoints were mortality and symptomatic intracranial bleeding complication (sICH) of thrombolysis, defined as a haemorrhage confirmed by CT scan and leading to an increased deficit on the NIHSS. Most hospitals adapted the SITS most sICH criteria, a deterioration in National Institutes of Health stroke scale score of 4 or more. During the PRACTISE trial data collection, data were being checked for consistency in a continuous process. When the NIHSS score at admission was lower than the NIHSS score at discharge an explanation was asked from the principal investigator.

Statistical methods

In order to adjust for differences in prognostic factors between treated and untreated patients, we used a multivariable logistic regression model with adjustment for age, sex, systolic blood pressure, NIHSS score at admission, diabetes mellitus, atrial fibrillation, history of previous stroke, and heart failure. We also performed a multi-level analysis to adjust for differences in patient population between hospitals. Treatment effects are reported as odds ratios with 95% confidence intervals. We used STATA version 11 to analyse the data (STATA Corp, College Station, Texas USA, 2009).

Results

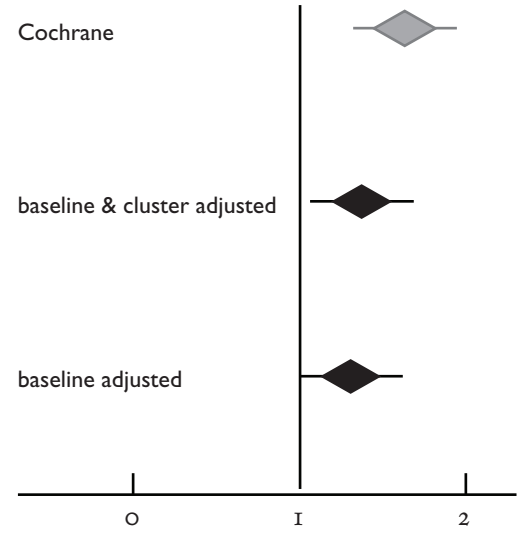
In total, 5,515 patients were registered in the PRACTISE trial. The present analysis concerns the 1,657 patients with acute ischaemic stroke, who were admitted within 4 hours from onset of symptoms, 696 (42%) of whom were treated with alteplase (Table 1). The overall thrombolysis rate was 12.6% of all 5,515 patients, including the patients with an intracerebral haemorrhage. Follow-up assessment was complete in 1,589 (96%) patients and 68 (4%) were lost to follow up after discharge from the hospital, or refused consent. Patients treated with alteplase were on average 2 years younger and less often aged over 80, but they had on average, a 4-point higher score on the NIHSS (Table 1). The vast majority (91%) of the patients receiving thrombolysis were treated within 3 hours from onset of symptoms. The median onset to treatment time was 135 minutes (interquartile range: 110-165). Ten patients were treated with alteplase despite contra-indications identified in retrospect. Patients were not treated with alteplase for the following reasons: 363 (38%) had unambiguous contra-indications like blood pressure over 180/110 mmHg or increased INR; 353 (27%) had minor or rapidly improving symptoms; in 11 (1%) patients there were material or logistic problems; 76 (8%) had unconventional contraindications like haemorrhoids or menstruation; 127 (13%) had no contra-indications and in 31 (3%) patients the contra-indication was unknown.

Table 1 baseline patient characteristics according to treatment group

characteristic	alteplase (n=696)		no alteplase (n=961)	
age (yr)	69 ± 14		71 ± 13	
age 80 and over	163/696	(23%)	283/961	(29%)
female sex	314/696	(45%)	441/961	(46%)
history of stroke	109/691	(16%)	222/960	(23%)
history of myocardial infarction	88/695	(13%)	139/960	(14%)
history of heart-failure	53/696	(8%)	79/959	(8%)
history of peripheral artery disease	54/695	(8%)	104/958	(11%)
diabetes	91/696	(13%)	183/961	(19%)
current smoker	173/696	(25%)	225/959	(24%)
atrial fibrillation	101/694	(15%)	195/961	(20%)
hypertension	337/696	(48%)	509/960	(53%)
hypercholesterolaemia	247/696	(35%)	391/961	(41%)
blood pressure (mmHg)	(n=693)		(n=964)	
— mean systole (plus-minus standard deviation)	159 ± 27		164 ± 31	
— mean diastole (plus-minus standard deviation	84 ± 16		85 ± 15	
NIHSS score	(n=696)		(n=961)	
— mean (plus-minus standard deviation)	10 ± 6		6 ± 6	
— median (interquartile range)	9	(5 - 15)	4	(2 - 8)

Good functional outcome at three months (mRS<3) was observed in 333 (50%) of patients treated with alteplase, which was less often than in patients not treated with alteplase (537, 58%). However, after adjustment for stroke severity and other baseline prognostic variables, treatment with alteplase was significantly associated with favourable outcome (adjusted Odds Ratio [aOR] 1.3; 95% confidence interval [CI] 1.0 to 1.7). After further adjustment with multi-level logistic regression analysis, the aOR for good outcome was 1.4 (95% CI 1.0 to 1.8) (Figure 1). With a good outcome defined as a score on the mRS of 0 or 1, the aOR for good outcome was 1.2 (95% CI 0.9 to 1.6). Mortality at 3 months was 130 (19%) in the alteplase-treated group and 138 (14%) in the group not treated with alteplase. Mortality was not significantly different between the two treatment groups after adjustment for stroke severity, other baseline prognostic variables, and potential clustering effect (aOR 0.9 95% CI 0.7 to 1.3).

Figure 1
- analysis adjusted for age, sex, NIHSS score at admission, diabetes mellitus, atrial fibrillation, history of previous stroke, and heart failure.
- analysis adjusted for potential clustering effect and confounding baseline variables (see a).
- Cochrane systematic review 2009, alteplase within 3 hours, good outcome defined as mRS <3.[3]



Symptomatic intracranial bleeding complications (sICH) occurred in 36 (5%) of the 696 patients treated with alteplase, 22 (3%) of those intracranial bleeding complications were fatal. The proportion of good outcomes varied per hospital between 41% and 62%, and the proportion of sICH between 0% and 9% (Table 2).

Table 2 population, treatment and outcome variation between the 12 hospitals*

hospital	total †	age (y)	NIHSS	thrombolysis	sICH	good outcome
1	117	63 ± 15	8 ± 6	59 (50%)	3 (5.1%)	62 (56%)
2	130	73 ± 13	10 ± 8	50 (38%)	2 (4.0%)	77 (62%)
3	310	71 ± 13	7 ± 6	109 (35%)	10 (9.2%)	163 (54%)
4i	184	70 ± 13	7 ± 7	75 (41%)	6 (8.0%)	97 (55%)
5i	191	69 ± 13	7 ± 6	60 (31%)	1 (1.7%)	113 (61%)
6	156	71 ± 14	8 ± 8	85 (54%)	3 (3.5%)	72 (47%)
7i	126	71 ± 14	7 ± 6	37 (29%)	3 (8.1%)	72 (61%)
8ii	28	69 ± 12	9 ± 7	11 (39%)	1 (9.1%)	17 (61%)
9	71	71 ± 14	9 ± 7	34 (48%)	0	30 (43%)
10	169	72 ± 13	8 ± 7	78 (46%)	3 (3.9%)	90 (56%)
11	42	74 ± 10	9 ± 5	29 (69%)	0	17 (41%)
12	133	71 ± 13	10 ± 7	69 (52%)	4 (5.8%)	60 (48%)

* plus-minus values are means ± standard deviation.
† total of registered patients over 18 years with acute ischaemic stroke, and admitted within 4 hours from onset of symptoms during a two-year period.
"i" indicates hospitals with limited experience in thrombolysis for acute ischemic stroke.

This judgement was based on the proportion of treated patients in 2002 & 2003. "ii" started alteplase treatment during the study.

Discussion

This study confirms that thrombolysis improves the likelihood of good outcome also in an unselected observational cohort of patients with acute ischaemic stroke. To the best of our knowledge, outcome in patients treated with alteplase compared with those not treated with alteplase has not been studied outside randomised clinical trials. The hospitals that participated are representative of the whole spectrum of hospital types: from small urban and regional hospitals to the larger academic centres. The mean age, the proportion of elderly patients, and the distribution of stroke severity suggest that our study population is a representative patient group for daily practice.[3,6-8] Our study population is similar to that of the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST).[8] In that large survey the mean age was 68 years and in our study it was 69 years, and the median NIHSS score was 12, which is marginally higher than the median of 9 in our study. In SITS-MOST, 55% of the patients treated with alteplase had a good outcome, defined as an mRS score of 2 or less, and in our study 50%. The OR for good outcome in the Cochrane analysis for alteplase treatment within 3 hours is 1.6 (95% CI 1.2 to 2.0) which is marginally higher than the 1.4 found in our study.[3] Mortality in patients treated with alteplase was 19% in our study compared to 11% in the SITS-MOST registry and 13% in the Cochrane analysis.[3,8] Difference in good outcome and mortality might be explained by the exclusion of patients with a severe stroke (NIHSS more than 25) in the SITS-MOST study, and the exclusion of patients over 80 years of age in the SITS-MOST study and most randomised trials.[1,8,10,11] In contrast, 23% of the patients treated with alteplase in our study were 80 years or older.

We based our definition of sICH on the one used in the NINDS rTPA study and Cochrane analysis: haemorrhage accompanied by neurological deterioration or leading to death within 7 days. Symptomatic intracranial bleeding complications occurred in 5% in our study compared with 6% in the NINDS rTPA study, 7% in the SITS-MOST registry and 8% in the Cochrane analysis.[2,3,8] In our study all patients underwent neurological examination including NIHSS assessment after treatment, but in most hospitals post-treatment imaging was performed on indication only. Therefore, some mild sICH could have been missed.

Since alteplase treatment was not randomly allocated in our study, adjustments for prognostic variables are necessary. Despite these adjustments there may still be unknown factors that cannot be fully adjusted for, therefore some reservation is needed. By definition the assessment of the effectiveness of alteplase in daily practice cannot be determined in a randomised trial. Consequently, the patients who were not treated with alteplase constitute a very heterogeneous group, including those with one or more contra-indications, or with completely resolved neurological deficit. However, most contra-indications for thrombolysis are not important prognostic factors and therefore do not influence patient outcome in untreated patients. Our results therefore support the notion that thrombolysis for acute ischaemic stroke is also effective and safe in daily practice.

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THE EFFECTIVENESS OF THROMBOLYSIS WITH INTRAVENOUS ALTEPLASE FOR ACUTE ISCHAEMIC STROKE IN OLDER PATIENTS

chapter 5.2

Dirks M, Niessen LW, van Wijngaarden JD, Koudstaal PJ, Franke CL,
van Oostenbrugge RJ, Dippel DWJ; on behalf of the PRACTISE investigators.
The effectiveness of thrombolysis with intravenous alteplase for acute ischemic stroke in older patients. The Journal of the American Geriatrics Society. 2011;Nov;59:2169-71.

Introduction

Thrombolysis with intravenous alteplase is widely accepted as an effective treatment for patients with acute ischaemic stroke, if treatment can be started within 4.5 hours after stroke onset.[1-3] Only few patients aged 80 or over have been included in the thrombolysis trials, even in the absence of a formal age limit, as in the NINDS trial.[1,2,4,5] Older patients are often excluded from treatment with alteplase because of their age,[6,7] despite some evidence of a benefit from thrombolysis also in the older age group.[8-10] In the European Community, alteplase is not labelled for use in stroke patients aged over 80. The risk-benefit ratio of thrombolysis might become less favourable with increasing age because of a higher risk of adverse events.[11,12] Several studies have shown similar risks of complications in older versus younger patients treated with thrombolysis.[8-10,13] Also outcome in older patients treated with alteplase has been analysed, mostly compared with younger patients.[8-10,12,14] However, in order to make a firm conclusion concerning the appropriateness of treating older patients with thrombolysis, one should also contrast treatment with no treatment. Studies comparing older patients with younger patients are difficult to interpret, because patients with stroke of 80 and over have a higher risk-adjusted case-fatality, longer hospitalisation, and are less likely to be discharged to their original place of residence than younger patients.[15] Multiple underlying conditions may affect outcome like the increasing prevalence of arterial hypertension, atrial fibrillation, dyslipidaemia, comorbid conditions, but also altered metabolism, lower medication compliance, and more frequent drug interactions due to polypharmacy.

The results of a recent collaborative project suggest that patients over 80 derive similar benefit from treatment with intravenous alteplase as younger patients.[16] This study however used patient data from different sources, the data concerning patients treated with alteplase were obtained from the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) and the control data were taken from patients in the VISTA neuroprotection trials who did not undergo thrombolysis. SITS is a voluntary thrombolysis register, and VISTA is a trial registry, and it has been argued that selection bias may have affected the comparison between alteplase treatment and control.[17]

The aim of the present study was to assess the effectiveness of thrombolysis in relation to age in an unselected prospective observational cohort of patients, where all patients with an ischaemic stroke admitted within 4 hours of symptom onset were registered.

Methods

This study was a sub-study of the PRACTISE study, a cluster-randomised trial in which we evaluated an intensive multifaceted implementation strategy aiming to increase the proportion of patients treated with intravenous alteplase.[18] Our Medical Ethics Committee and Research Board approved the trial.

Patient population

During a two-year period from 2005 to 2007, all patients over 18 years with acute ischaemic stroke admitted within 4 hours from symptom onset were registered in 12 hospitals in the Netherlands. Patient data included demographics, baseline characteristics like the patients' medical history, cardiovascular risk factors, and stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS). All patients were admitted to a Stroke Unit and treatment with alteplase was registered. All patients were followed up at 3 months after hospitalisation by telephone, for which they had given consent. The central trial office provided the 3-month follow up assessment and used simple questions to record the patient's dependency and health-related quality of life. The two researchers who analysed outcome data were blinded to the treatment received. All hospitals used their own treatment guidelines based on the existing evidence and national guidelines before the start of our study, none of the hospitals employed an upper age limit for treatment with alteplase.

Outcome measures

The primary outcome was good functional outcome, defined as a score on the mRS of 2 or less.[18] The safety endpoints were mortality and symptomatic intracranial bleeding (sICH) complication of thrombolysis, defined as a haemorrhage confirmed by CT scan and leading to an increased deficit on the NIHSS.

Statistical analysis

To assess whether the benefit of alteplase changes within the age groups we analysed the data with a multivariable logistic regression model to estimate the odds ratio for good outcome in the two age categories (<80 and >=80). We adjusted for age, sex, systolic blood pressure, NIHSS score at admission, diabetes mellitus, atrial fibrillation, history of previous stroke, and heart failure. The systolic blood pressure was divided in three categories: lower than 140 mmHg, between 140 and 180 mmHg, and above 180 mmHg.[19] Treatment effects were reported as odds ratios with 95% confidence intervals. Next, we computed the Mantel-Haenszel odds ratio for good outcome by treatment, stratified for age categories and controlled for the NIHSS score at admission to test for heterogeneity of treatment effects. We used STATA version 11 to analyse the data (STATA Corp, College Station, Texas USA, 2009).

Results

Overall, 1657 patients were registered, of whom 446 were aged 80 or older and 1211 were less than 80 years of age (Table 1). Thirty-seven per cent (163) of the patients 80 or older were treated with alteplase against 44% (533) of the patients less than 80. The mean onset to treatment time was similar on both age groups. In the older age category the mean age was 85 years in both treatment groups. The mean age in the younger age category was 66 years in patients not treated with alteplase and 64 years in the patients who received alteplase. Heart failure and atrial fibrillation were more frequent in the older age category. In the younger patients, hypercholesterolemia was more frequent.

The NIHSS score was higher in the patients treated with alteplase (mean NIHSS scores of 10 and 11) than in patients who were not treated (mean NIHSS scores of 5 and 8) in both age categories (Figure 1). Diabetes mellitus on the other hand, was more frequent in patients who were not treated with alteplase. Overall, 68 (4.1%) patients were lost or withdrew consent for follow up, 14 (3.1%) of the older patients and 54 (4.5%) of the patients in the younger age category.

Figure 1 baseline imbalance in distribution of NIHSS at admission between patients aged 80 and over, who were treated and not treated with alteplase.

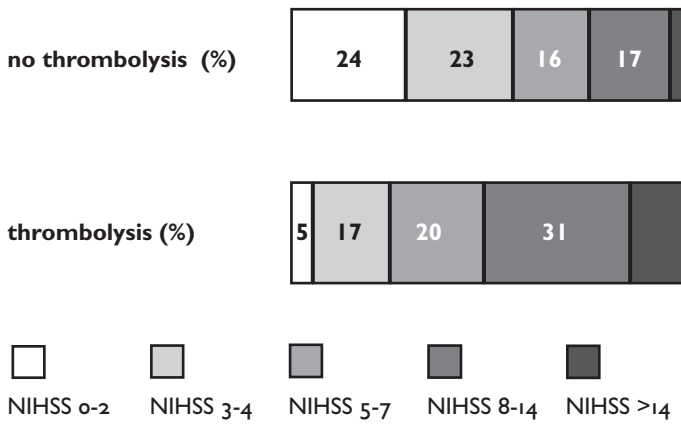

Table 1 baseline patient characteristics by treatment & age category; 100% is the total patients registered within one age category per treatment arm

age category	**80 years and over**				**Less than 80**			
thrombolysis	no		yes		no		yes	
total registered	285		163		678		533	
age, mean in years [sd]*	85	[4]	85	[4]	66	[11]	64	[12]
male sex	120	[42%]	70	[43%]	400	[59%]	312	[59%]
onset to needle time, mean in minutes [sd]*			141	[34]			137	[41]
NIHSS score, mean [sd]*	8	[8]	11	[7]	5	[6]	10	[6]
prior stroke or TIA	64	[23%]	31	[19%]	158	[23%]	78	[15%]
myocardial infarction	45	[16%]	22	[14%]	94	[14%]	66	[13%]
peripheral artery disease	39	[14%]	14	[9%]	65	[10%]	40	[8%]
heart failure	35	[12%]	22	[14%]	44	[7%]	31	[6%]
hypertension	153	[54%]	80	[49%]	356	[53%]	257	[48%]
atrial fibrillation	96	[34%]	44	[27%]	99	[15%]	57	[11%]
diabetes Mellitus	52	[18%]	23	[14%]	131	[19%]	68	[13%]
hypercholesterolaemia	86	[31%]	31	[19%]	305	[45%]	216	[41%]
systolic blood pressure, mean in mmHg [sd]*	168	[30]	162	[29]	162	[32]	158	[26]
diastolic blood pressure, mean in mmHg [sd]*	82	[19]	81	[17]	86	[17]	84	[15]

*sd is standard deviation

Outcomes

Overall, good outcome at 3 months was observed in 96 (35.3%) patients of 80 and older who were not treated and in 46 (28.8%) patients who were treated with alteplase (Table 2). Patients who were treated with alteplase had a worse outcome, the unadjusted odds ratio (OR) for good outcome was: 0.74 (95% CI 0.49-1.13). After adjustment for stroke severity (NIHSS score), a strong predictor of outcome, the OR for good outcome was 1.27 (95% CI 0.76-2.12) and after further adjustment with other prognostic factors it became 1.19 (95% CI 0.71-1.98).

In patients younger than 80 good outcome was observed in 441 patients (67.6%) not treated with alteplase, and in 287 (56.8%) patients treated with alteplase (Table 2). The unadjusted odds ratio for good outcome was 0.63 (95% CI 0.50-0.80). After adjustment for stroke severity the odds ratio was 1.65 (95% CI 1.21-2.25), after further adjustment it became 1.48 (95% CI 1.08-2.04).

Table 2 patient's outcome comparing patients treated with or without thrombolytics, by age.

	alteplase	good outcome	no alteplase	good outcome	crude OR (95% CI)	OR adjusted for stroke severity*	OR fully adjusted†
all	665	333 [50.8%]	924	537 [58.1%]	0.72 [0.59-0.88]	1.54 [1.18-2.01]	1.42 [1.09-1.86]
>=80	160	46 [28.8%]	272	96 [35.3%]	0.74 [0.49-1.13]	1.27 [0.76-2.12]	1.19 [0.71-1.98]
<80	505	287 [56.8%]	652	441 [67.6%]	0.63 [0.50-0.80]	1.65 [1.21-2.25]	1.48 [1.08-2.04]

* Mantel Haenszel adjusted OR
† multiple logistic regression models, including age, gender, atrial fibrillation, diabetes mellitus, previous stroke, blood pressure at admission.

We tested for heterogeneity between age strata by computing Mantel-Haenszel odds ratios by treatment, stratified for age categories, and adjusted for NIHSS score at admission. The overall OR for good outcome was 1.54 (95% CI 1.18-2.01). In the older age category, the OR for good outcome was 1.27 (95% CI 0.76-2.12) and in the younger age category it was 1.65 (95% CI 1.21-2.25). There was no evidence for heterogeneity of odds ratios between the age categories (test of homogeneity of OR's p=0.39).

The risks associated with treatment were not increased in patients of 80 years and older, 76 patients (27.4%) who were not treated with alteplase had died at three months, and 60 (37.3%) patients who were treated had died. In the younger age group 62 (9.4%) patients who were not treated with alteplase had died, against 70 (13.7%) patients who were treated with alteplase. There was no significant difference in mortality between the age-categories comparing patients not treated with alteplase with patients treated with alteplase (test of homogeneity of OR's p=0.93). When compared to younger patients, those age 80 and older with stroke had a higher case fatality and a higher rate of sICH when treated with thombolysis (7.4% vs. 4.5%; Relative Risk: 1.51 (95%CI: 0.77-2.97)).

Discussion

This survey of unselected patients suggests that thrombolysis for acute ischaemic stroke leads to improved outcome also in patients aged 80 or more. The stratified analysis shows a significant overall effect of thrombolysis with no evidence for heterogeneity within the different age strata.
The hospitals that participated in the PRACTISE trial are representative of a large spectrum of hospital types, from small urban and regional hospitals to the larger academic hospitals located in different parts of the Netherlands. Distribution of age, sex and stroke severity in our study suggest that our patients are representative of patients with acute ischaemic stroke in general. A quarter of the acute ischaemic stroke patients was 80 years or older, the stroke severity observed in our study population is similar to the mean NIHSS scores found by Zeevi et al in a cohort of the Stroke Center at Hartford Hospital (USA).[20] Other baseline characteristics including diabetes, hypertension, prior stroke, atrial fibrillation and heart failure have a similar frequency as in other cohorts.[8-10,12,13,21] Regarding patient outcomes, the mortality rate of the older patients treated with alteplase is similar to the rates found in Europe, USA and Canada.[10,13,20] The 7.4% sICH rate observed in our study falls within the range observed in other studies, ranging from 2.2 to 13%.[8-10,13,20]

The SITS-ISTR is the largest prospective observational study of outcomes from thrombolysis in patients over 80 with in total 21,242 patients of whom 1,831 were aged over 80. The main finding of the SITS investigators is that the overall rate of symptomatic and asymptomatic intracerebral haemorrhage was not increased in the over 80-year-old group and that the observed early improvement in neurological impairment suggests that it is likely that patients over 80 years have a similar extent of successful reperfusion as younger patients. Therefore they concluded that thrombolysis is an appropriate treatment for carefully selected patients over 80 years.[10] Also the Canadian Alteplase for Stroke Effectiveness Study (CASES) collected data prospectively of patients treated with alteplase, 1,135 patients were registered of whom 270 were aged 80 or over. They compared the baseline characteristics, complications, in-hospital mortality and outcome at 90 days between patients aged less than 80 to those aged 80 years or over. This study showed that the risk of ICH after thrombolysis was the same in both patient groups. Besides, age of 80 years or over was not an independent predictor of symptomatic haemorrhage.[13] The principal comparison in these large studies was between older and younger patients. This provides some indirect information, but the touchstone should be the comparison of patients treated with thrombolysis with those not treated with thrombolysis, similar as has been done in younger patients, and preferably in a randomised controlled trial (RCT). Mishra et al. found that increasing age is associated with poorer outcome but the association between thrombolysis treatment and improved outcome is maintained in very elderly people. They concluded that age alone should not be a barrier to treatment.[16] A limitation of this study is the composed patient data from different sources, and the SITS-ISTR being a voluntary registry, it is impossible to guarantee completeness of inclusions and to exclude selection bias.[22] However the Odds Ratio for good outcome in the older age category reported by Mishra et al. (1.4 (1.3-1.6)) is similar with the Odds Ratio found in our study.[16]

Our study concerns an unselected observational cohort of patients, representative in the way patients are treated in daily practice. Each participating hospital allowed thrombolysis in the patients aged 80 or older, although there were reasonable differences

between the treating physicians. Since alteplase treatment was not randomly allocated in our study, adjustments for prognostic variables are essential. However, there may still be unknown factors that cannot be fully adjusted for, therefore some reservation is needed. Stronger evidence will be provided by the Third International Stroke trial; this randomised controlled trial seeks to determine whether a wider range of patients may benefit from alteplase, including patients aged over 80.[23]

We present additional evidence for a beneficial effect of intravenous alteplase for treatment of ischaemic stroke in patients aged 80 or over. In our opinion, we should not withhold this treatment from elderly patients, but rather treat them directly, or –when there is substantial doubt about the effect of treatment–ask these patients to participate in randomised clinical trials.

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HOSPITAL RATES OF THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE: THE INFLUENCE OF ORGANISATIONAL CULTURE

Chapter 6.1

van Wijngaarden JD, Dirks M, Huijsman R, Niessen LW, Fabbricotti IN, Dippel DWJ.
Hospital rates of thrombolysis for acute ischaemic stroke: the influence of organisational culture.
Stroke 2009;40;3390-3392.

Introduction

In most hospitals only 2% to 10% of all admitted stroke patients are treated with thrombolysis, although 25% might be eligible for treatment.[1] Research on improving delivery of thrombolysis has been focused primarily on characteristics of stroke patients. Some attention has been paid to structural characteristics of the organisation, such as the availability of protocols and training,[2] but none at all to the influence of organisational culture. In this study we assessed the association between thrombolysis rates in hospitals and organisational cultural characteristics.

Methods

This study was designed as a cohort study in 12 centres, covering 11% of all hospitals in the Netherlands. At the start of the study the participating hospitals had a mean thrombolysis rate of 5% (range: 0% to 10%, similar to the mean thrombolysis rate in the Netherlands at that time.

We used a mixed methods approach with both quantitative and qualitative research methods based on a Delphi approach.[3] During the study-period of two years all patients over 18 with acute stroke were included and clinical characteristics that might be related to the delivery of thrombolysis were recorded. The primary outcome in all registered patients was treatment with thrombolysis or not. On hospital level, we calculated a thrombolysis rate by dividing the number of stroke patients treated with thrombolysis, by the total number of stroke patients admitted during the inclusion period.

We identified eight cultural characteristics from a qualitative case study on improving door-to-balloon times for patients with acute myocardial infarction.[4] We added two additional cultural characteristics that might be related to (lack of) resistance to change: unanimous partnership and cooperative partnership (Appendix A).[5,6]

During the study period a vascular neurologist in each centre kept a diary of their activities to improve the rate of thrombolysis and onset-to-needle time. These diaries were used as input for 'face to face' interviews with neurologists and telephone interviews with a stroke nurse in each centre, conducted by a neurologist and an organisational scientist (Appendix B).

The data were used to attribute a score between zero and ten for each hospital on each of the ten characteristics. A sum score was made for each centre by adding up all scores for each characteristic and dividing by ten.

The full transcripts of both interviews were made anonymous and were analysed independently by two scorers (R.H. and I.F.) with a modified Delphi approach. If after three rounds no consensus could be reached a third scorer (J.W.) was involved to tip the balance.

For the analysis of the association between treatment with thrombolysis and several cultural characteristics we used a multilevel logistic regression model, to be able to adjust for the potential clustering effect. If the analysis showed a relevant association, we subsequently adjusted for hospital size and teaching facilities.

Results

Of the 5,515 registered stroke patients, 701 (12.7%) were treated with intravenous rTPA. Thrombolysis rates varied from 5.7% to 21% (Table 1). There were no significant associations between patient characteristics and cultural characteristics.

Table 1 baseline characteristics of twelve hospitals admitting 5,515 patients in the Netherlands over a two year period.

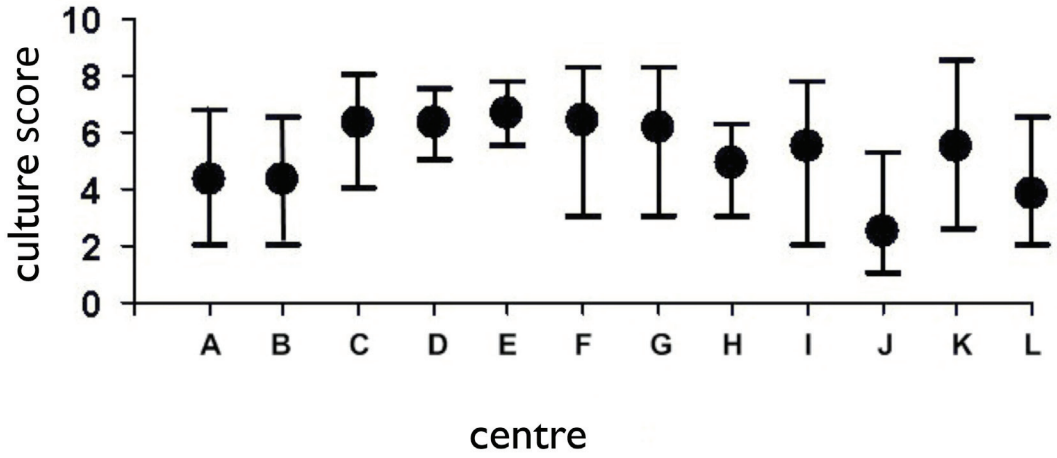
	low		medium		high	
hospitals categorised by tertiles of the sum score ¬ of cultural characteristics						
characteristics of the hospitals in each tertile						
mean sum score of cultural characteristics per tertile	3.7		5.5		6.4	
number of hospitals	4		4		4	
teaching hospital	1		1		3	
university hospital	1		1		0	
characteristics of patients admitted over a 2 year period						
A. — Stroke, admitted within 24 hours						
number of patients	1655		1525		2335	
mean age (SD)	72	(12)	71	(14)	72	(13)
male sex (n,%)	806	(49%)	779	(51%)	1152	(49%)
B. — Ischaemic stroke, admitted within 4 hours						
number of patients (n,%)	428	(26%)	440	(29%)	791	(34%)
median NIHSS (IQR)	6	(3-12)	5	(3-11)	5	(3-11)
history of stroke (n within 4 hours, %)	96	(22%)	95	(22%)	141	(18%)
history of MI	60	(14%)	69	(16%)	98	(12%)
history of heart failure	28	(7%)	21	(5%)	84	(11%)
diabetes mellitus	75	(18%)	64	(15%)	135	(17%)
atrial fibrillation	60	(15%)	82	(19%)	155	(20%)

One centre acted as an outlier and was omitted from the further analyses. The unadjusted multilevel logistic analysis showed a significant association between thrombolysis rate and several cultural characteristics. A statistically significant association between "informal and formal feedback", "learning culture" "uncompromising, individual clinical leadership" and "explicit goals" and the likelihood of receiving thrombolysis was observed (Table 2). Also, the overall sum score of cultural characteristics was associated with thrombolysis. Adjustments for hospital size and teaching versus non-teaching hospital did not change the size and direction of these associations. When these characteristics (minus the sum score) were combined into one multivariable multilevel logistic regression model only "feedback" showed a significant association with thrombolysis rate (OR 1.19; 95% CI 1.04 – 1.36). Increases in thrombolysis rate were not associated with an increase in non-adherence to protocols or occurrence of adverse events.

Table 2 association of cultural characteristics with the likelihood of being treated with intravenous thrombolysis in eleven centres (without outlier centre L) in the Netherlands (the odds ratio represents the relative increase in likelihood of being treated per point item score)

	mean	range (0 – 10)	OR	95% CI
sumscore of cultural characteristics	5.3	(2.5 – 6.7)	**1.12**	**1.02 – 1.23**
1. — explicit goals	5.1	(1 – 7.8)	**1.08**	**1.01 – 1.17**
2. — senior management support	3.5	(1 – 6.5)	1.05	0.94 – 1.16
3. — innovative protocols	4.5	(2 – 6.3)	1.09	0.97 – 1.22
4. — flexible protocols	5.6	(3 – 8)	1.07	0.97 – 1.18
5. — clinical leadership	5.6	(2 – 7.8)	**1.12**	**1.03 – 1.23**
6. — interdisciplinary team	3.6	(1 – 7)	1.08	0.97 – 1.20
7. — feedback	5.2	(2.8 – 7)	**1.18**	**1.09 – 1.28**
8. — learning culture	5.7	(2 – 8)	**1.12**	**1.02 – 1.23**
9. — unanimous partnership	6.7	(5 – 8.3)	1.05	0.90 – 1.24
10. — cooperative partnership	6.6	(4.5 – 8.5)	1.03	0.90 – 1.18

Figure 1 distribution of cultural scores per centre: minimum, mean and maximum.



Discussion

This study shows that the availability of certain cultural characteristics increases the likelihood of receiving thrombolysis for patients. Based on our calculations a reasonable improvement in cultural sum score of halve a standard deviation might lead to an absolute increase of 1% in thrombolysis rate. This makes organisational culture an interesting target for interventions aimed at improving thrombolysis rates.

Our results suggest that centres need to have explicit, shared goals concerning door-to-needle time and thrombolysis rate. These should be monitored continuously and feedback should be regularly provided. Clinical leaders need to be identified, appointed and or trained who are respected by their peers, who both inspire and push 'individuals and the organisation to achieve a high standard of care'.[7]

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APPENDIX

A. — Description of cultural characteristics

Explicit goal: a shared and explicit goal focused on improving door-to-balloon time, for which all involved held each other to account.
Senior management support: management shows their support by 'providing resources, increasing the visibility of performance data and addressing individuals' resistance to recommended changes'.
Innovative protocols: protocols and innovations are developed by analysing processes 'using quality improvement techniques such as root-causes analysis, flowcharting, and brainstorming'.
Flexible protocols: protocols are continuously refined. Often new procedures are tried out by hospital staff, to see if it improves door-to-needle time.
Clinical leadership: there is a clinical leader, respected by his/her peers, who calls his colleagues and other health professionals to account based on results and keeps on pushing for improvement.
Interdisciplinary team: a team with different professionals from each department, including key physicians, works together to improve door-to-balloon time.
Feedback: both informal and formal feedback is 'commonplace among team members and across departments and disciplines'.
Learning culture: an organisational culture which supports improvements and learning through a 'non-blaming approach and a shared vision of improving the patients' health'.
Unanimous partnership:* agreement among the partnership of neurologists on the effectiveness, treatment and division of roles concerning thrombolysis for ischaemic stroke. This also involves discussions of variations in practice.
Cooperative partnership:* the neurologists operate as a team. This involves an open friendly and improvising style of communication and a democratic decision making structure.

* these were added by the research team

B. — Questionnaire for face to face interviews with neurologists

This study is aimed at the organization of care for acute stroke patients and how that influences the thrombolysis rate.
1 — How long have you been working in this hospital?
2 — When did thrombolytic treatment start in this hospital?
3 — Were you involved in the introduction and what was your role?
4 — Are there any targets set concerning thrombolysis? If so:
5 — What are those targets?
6 — Have these targets been modified? Why and when?
7 — Who sets these targets?
8 — Are all involved professionals aware of these targets: General Practitioners, ambulance personnel, personnel working at the emergency department, and the departments of radiology and neurology, as well as the central laboratory?
9 — How have these persons been made aware of the targets?
10 — In your experience, are all involved professionals actively trying to reach these targets (or actively trying to reduce door-to-needle time and | or thrombolysis rate)? How can you tell?
11 — Are you holding each other accountable? How is this done?
12 — Do you measure door to needle time (DTNT) and onset to needle time (OTNT) and | or thrombolysis rate? How? How often? Who is informed about the results?
13 — Is there someone who actively stimulates others (including the neurologists) to reduce OTNT and DTNT and to increase the thrombolysis rate? How does (s)he do this? How do other professionals respond (neurologists)?
14 — Are managers (head of the department etc.) holding professionals accountable based on DTNT and OTNT or thrombolysis rates? How? How often? Are there any consequences involved?
15 — Are thrombolysis rates and | or DTNT|OTNT discussed by upper management with you?
16 — Could you tell me how the pathway from unset to needle is organised; who are involved, did you develop clinical pathways and protocols, what agreements have been made and which facilities are available? Let us start with the general public; how they are informed, and then work our way through to the actual thrombolytic treatment.
17 — How do you determine which facilities and agreements would be necessary to organise an effective and efficient clinical pathway?
18 — Did you involve professionals from outside the hospital? How?
19 — Do you keep in contact with these professionals? How? How often? Are they made aware of the results? Is there any form of feedback?
20 — Are these professionals willing to participate in improvements? Are they open about problems and mistakes: can you give examples?
21 — How are professionals from hospital departments involved in improving the pathway from unset-to-needle?
22 — Do you keep in contact with these professionals? How? How often? Are they made aware of the results? Is there any form of feedback?
23 — Are these professionals willing to participate in improvements? Are they open about problems and mistakes: can you give examples?
24 — How did you develop the protocols you use? Who were involved?
If copied from other hospitals: Did you need to adapt these; how was that done?
25 — Do you have any procedures on how and when protocols are adjusted? How is this done? How often has this been done? Who takes the initiative?
26 — Are there any differences of opinion between neurologists in this hospital about the effectiveness of thrombolysis? If so; what are the consequences?
27 — Are there any differences of opinion concerning the treatment between these neurologists? Do you know if there are differences in actual treatment?

28 — What part did the partnership of neurologists play in the introduction of thrombolytic treatment? What part did the partnership of neurologists play in the improvement of the pathway?
29 — Is thrombolysis a topic of discussion in the meetings of the neurologists? What is discussed? How? How often?
30 — Did you experience any problems concerning thrombolysis or the pathway? Which problems and when?
31 — How were these problems dealt with?
32 — Were these problems discussed with other neurologists? When? How?
33 — Do you discuss specific cases (concerning thrombolysis) in the meetings of the neurologists? How? How often has this happened?
34 — Do neurologists consult each other concerning thrombolysis? When? How often? Can you give examples?
35 — When one if the neurologists doesn't uphold the agreements; what happens? Has this happened?
36 — Is there a division of labour within the partnership of neurologists?
37 — I want you to characterise the partnership of neurologists in this hospital on a scale from one to ten: One being a divided collection of individuals, ten being a cohesive team. Could you clarify?
38 — How would you characterise the communication and cooperation in their meetings on a scale from one to ten? Could you clarify?
¬ One: focused on doing announcements; ten: focused on discussion
¬ One: compliant; ten: incompliant
¬ One: open; ten: closed
¬ One: friendly; ten: aggressive
¬ One: Improvising; ten: rigid
39 — How would characterise the decision making process within the partnership on a scale from one to ten (one: democratic; ten: hierarchical)? Could you clarify this?
40 — What are in your experience the most important success factors to increase the thrombolysis rate?
41 — What are in your experience the most important obstacles to increase the thrombolysis rate?
42 — Is it in your opinion possible to further increase the thrombolysis rate in this hospital?
43 — How can this be achieved?
44 — Are there any relevant issues we didn't discuss concerning your views and experiences with improving thrombolysis rates?

Thank you very much for your cooperation.

DO CENTRES WITH WELL-DEVELOPED PROTOCOLS, TRAINING AND INFRASTRUCTURE HAVE HIGHER RATES OF THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE?

Chapter 6.2

van Wijngaarden JDH, Dirks M, Niessen LW, Huijsman R, Dippel DWJ. *Do centres with well-developed protocols, training and infrastructure have higher rates of thrombolysis for acute ischaemic stroke?* QJM. 2011;Sep;104:785-91.

Introduction

Treatment of acute stroke patients with recombinant tissue Plasminogen Activator (rTPA), within 3h after onset of the symptoms, may save 1 in 10 patients from death or dependency.[1] Even in the 3 to 4.5 hour window a considerable effect has been demonstrated.[2] Still, only a limited proportion of stroke patients receive thrombolytic treatment in most hospitals.[3,4] Research suggests that both inside and outside the hospital, there are barriers to quick referral and management of these patients.[5,6]

Considering the available scientific evidence, the European Stroke Initiative (EUSI) Executive Committee has suggested different measures to lift these barriers. The EUSI emphasises that 'teaching the public about symptoms and signs of stroke is one of the highest priorities of public medical education'.[7] Health professionals need to learn that they are 'important and competent partners in the team providing acute stroke care'.[7] Second, they point out that 'written protocols are a prerequisite for standardised patient care'.[7] Furthermore, surveys suggest that infrastructure and availability of resources may also be of influence.[6]

Although the recommendations of the EUSI have a high face value, a beneficial effect has not always been firmly established.[5] Research did show however that the introduction of training programs and protocols as part of a larger focused quality improvement effort can improve thrombolysis rates.[8] The purpose of this study is to identify which (combination of) structural characteristics influence the thrombolysis rate, in a cohort study of twelve hospitals in the Netherlands. We particularly addressed differences in training; in the availability of protocols and infrastructure.

Methods

Study design and sample

This study was designed as a cohort study in 12 centres covering 11% of all hospitals in the Netherlands; it ran from October 2005 to October 2007. Centres were recruited by setting out a call among 21 centres participating in a program for improving organised stroke care. At the start of the study the participating hospitals had a mean thrombolysis rate of 5% (range: 0-10%), similar to the mean rate in the Netherlands at that time.

Because structural characteristics are often multidimensional and involve complex social interactions, we used a mixed methods approach[9] with both qualitative and quantitative methods based on a Delphi approach.[10]

Patient population

During a period of two years all patients over 18 were included who were admitted with acute stroke, i.e. patients with an acute focal neurological deficit. Onset of symptoms was not more than 24 hours before admission. For all patients age, sex, time since onset of symptoms and treatment with thrombolysis were registered. For patients with an ischaemic stroke admitted within 4 hours from onset, more detailed clinical data was gathered; stroke severity (NIH stroke scale), contra-indications for thrombolysis, and cardiovascular risk factors. For patients who were treated with thrombolysis door-to-needle time was also registered.

Outcomes

The primary outcome in all registered patients was treatment with thrombolysis or not. On hospital level, we calculated a thrombolysis rate by dividing the number of stroke patients treated with thrombolysis, by the total number of stroke patients admitted within 24 hours from symptom onset during the inclusion period.

Structural characteristics

Structural characteristics that are expected to influence thrombolysis rates were identified by international publications[5,7] and the results of a survey we did among 15 Dutch hospitals.[6] We distinguished between factors focused on lifting barriers outside the hospital (extramural) and inside the hospital (intramural). We focused on training given in the preceding two year period, because from previous research it is known that it is important to use periodic reinforcement messages in public campaigns[11] and changes in personnel should be taken into account. Furthermore, the Netherlands is densely populated and there is always a hospital with thrombolysis facilities in reach within 15 minutes driving. In urban areas there are often more hospitals, not all of which perform thrombolysis treatment or have beds available at a certain moment. The number of hospitals in a region is therefore a relevant infrastructural characteristic. For these and each other factor an indicator was developed (Table 1).

Table 1 structural characteristics in the continuum of care for thrombolysis in stroke

tools	**actors**	**indicators**
extramural		
agreements and protocols	general practitioners	protocol present (0,1)
	triage nurses in GP-service	ibid
	ambulance personnel	ibid
	emergency incident room	ibid
training	general public	coverage in percentage (0-1)
	general practitioners	ibid
	ambulance personnel	ibid
infrastructure	hospitals	no of hospitals in region (1/n)
intramural		
agreements and protocols	staff emergency service	protocol present (0,1)
	staff priority ECG	ibid
	staff priority CT	ibid
	who interprets CT: (resident-)	ibid
	¬ radiologist/neurologist)	ibid
	staff priority lab-results	ibid
	allocated beds	ibid
	stroke nurses	completeness of protocols (0-1)
	eeurologists	completeness of protocols (0-1)
training	emergency nurses	coverage of general training/information
		¬ packages on stroke care (0-1)
	nursing staff of general and	'dummy runs' (0,1)
	¬ neurology departments	coverage training/information packages to
		¬ perform thrombolysis (0-1)
		'dummy runs' (0,1)
	staff radiology department	coverage of information supply concerning
		¬ thrombolysis-related procedures (0-1)
		no of neurologists and assistants
infrastructure	medical staff for thrombolysis	hours a week that all resources are available for
	¬ treatment	thrombolysis (n/168)

Acquisition of centre related data

Data on structural characteristics were gathered during the two-year inclusion period. The leading neurologists in all twelve centres were asked to keep a diary of their activities to improve the thrombolysis rate and onset-to-needle time. These diaries were used as input for face-to-face interviews with them. Also, representatives of each unit involved in the care-process (from onset of stroke, to admission on the stroke unit) of all participating hospitals were interviewed by telephone. These units were general practitioners in the region, ambulance services, casualty, laboratory, department of radiology and neurology. An open-ended questionnaire was developed for each unit, based on the indicators (Table 1). All interviews were audio taped and transcribed by an independent transcriptionist.

Scoring procedure

The data from the interviews and the protocols were used to attribute scores to each of the structural characteristics (Table 1). Each indicator was scored 0, 0.5 or 1, depending on presence. Protocols for both neurologists and nurses on thrombolysis were also judged on completeness based on a scoring list developed by two neurologists (Table 2). Finally, sum scores were made for all structural characteristics. The sum score for (intramural) protocols is a combination of the presence and completeness scores. The full transcripts of the interviews were made anonymous and were analysed independently by two scorers (M.D. and D.D) in a modified Delphi approach. If after three rounds no consensus could be reached a third scorer (L.N.) was involved to tip the balance.

Table 2 checklist for completeness of protocols for stroke nurses and neurologists

		score for availability of information in protocol
	date, author, subject	Yes (1), Partly (.5), No (0)
patient level	indications	Yes (1), Partly (.5), No (0)
	contra-indications	Yes (1), Partly (.5), No (0)
	patient information	Yes (1), Partly (.5), No (0)
implementation	preparation of infusion	Yes (1), Partly (.5), No (0)
	administration route	Yes (1), Partly (.5), No (0)
	how to administer	Yes (1), Partly (.5), No (0)
	frequency vital signs monitoring	Yes (1), Partly (.5), No (0)
	limits for checks	Yes (1), Partly (.5), No (0)
complications	what to do in case of complications	Yes (1), Partly (.5), No (0)
	whom to call in case of complications	Yes (1), Partly (.5), No (0)
total score		**total score/11**

Statistical analysis

For the analysis of the association between treatment with thrombolysis and structural characteristics we used a multilevel logistic regression model, in order to adjust for the potential clustering effect.[12] Statistical significance was set at 5%. We performed both an unadjusted analysis and an analysis with adjustments for hospital size and teaching facilities. We considered confounding by differences in distribution of patient characteristics between the centres. This was explored by correlating patient characteristics to quantiles of the sum score of both training and protocols. Data were analysed using STATA version 10 (Stata Corp, College Station, Texas USA).

Results

Overall 5515 stroke patients were registered, 701 (12.7%) were treated with intravenous rTPA. Thrombolysis rates varied between 5.7% and 21.7% for the twelve centres, for a mean of 12.7%, standard deviation 3.9%. Increases in thrombolysis rate were not associated with an increase in non-adherence to protocols or occurrence of adverse events. The proportion of patients who were not treated, but had no contra-indication was higher in the group of patients from hospitals with low structural scores (18% vs. 10%; p=0.001). Also, the proportion of patients who were treated but actually had a contra-indication was higher in the group of patients from hospitals with low structural scores (3% vs. 1%; p=0.003). We did not have to adjust for patient characteristics, because no relevant statistical
associations were found with quantiles of the sum score of structural characteristics. Also, no statistical associations were found between door-to-needle time and quantiles of the sum score of structural characteristics (Table 3).

Table 3 baseline characteristics of the twelve hospitals and the admitted stroke patients in the Netherlands over a two-year period by quantiles of the sum score of structural characteristics

	low sumscore	high sumscore
hospital characteristics*		
sumscore of structural characteristics (median, range)	16 (12.6-18.7)	21 (20.5-27.4)
number of hospitals	6	6
teaching hospital	1	4
university hospital	1	1
mean thrombolysis rate	12.1%	14.4%
patient characteristics		
A. — stroke, admitted within 24 hours		
number of patients	2630	2885
mean age (SD)	71 (13)	70 (14)
male sex (n,%)	1303 (50%)	1434 (50%)
B. — ischaemic stroke, admitted within 4 hours		
number of patients (n,%)	714 (27%)	943 (33%)
mean age (SD)	71 (13)	70 (14)
male sex (n, %)	390 (54%)	512 (54%)
median NIHSS (IQR)	6 (3-12)	5 (3-10)
onset to door time (median, IQR)	75 (50-120)	80 (53-123)
door to needle time (median, IQR)	60 (46-80)	64 (45-85)
absence of contraindications in rTPA-treated patients	70 (18%)	57 (10%)†
absence of contraindications in not-rTPA-treated patients	308 (97%)	377 (99%)‡
history of stroke (n, %)	137 (24%)	124 (21%)
history of myocardial infarction (n, %)	90 (15%)	76 (14%)
history of heart failure (n, %)	33 (6%)	69 (12%)
diabetes mellitus (n, %)	91 (16%)	100 (17%)
atrial fibrillation (n, %)	84 (14%)	103 (18%)

*data are averages over centres as units of observation
†P=0.001 X^2
‡P=0.03 X^2

Association between structural characteristics and thrombolysis rates

The unadjusted multilevel logistic regression shows a significant association between thrombolysis rates and intramural protocols. A higher score on intramural protocols (sum score; presence of all intramural protocols and completeness of protocols for neurologists and nurses) increases the likelihood for patients of being treated with thrombolysis (OR 1.46; 95% CI 1.12 - 1.91). After adjusting for hospital size and teaching versus non-teaching hospital the strength of the association increased (aOR 1.77; 95% CI 1.30 - 2.39). The analysis also shows a significant association between extramural training and thrombolysis rate after adjustment (aOR 1.14; 95% CI 1.01 - 1.30). An analysis of all the individual factors (Table 1) that make up the sum scores of extramural training and intramural protocols, showed no significant association with thrombolysis rate. When extramural training and intramural protocols are combined in one multilevel logistic regression model, only intramural protocols showed a significant association with thrombolysis rate (OR 1.68; 95% CI 1.15 - 2.46) (Table 4).

Table 4 association of structural characteristics with the likelihood of being treated with intravenous thrombolysis in twelve centres in the Netherlands. The odds ratio represents the relative increase in likelihood of being treated per point item score.

score	mean	range	OR (unadjusted)	95% CI (unadjusted)
structural characteristics	19.5	(12.6 – 27.4)	1.03	0.98 – 1.08
training	6.7	(1.5 – 12.5)	1.04	0.98 – 1.10
protocols	5.8	(2.6 – 7.8)	1.02	0.87 – 1.19
infrastructure	7	(4.7 – 10.5)	1.03	0.91 – 1.16
extramural training	4.3	(0.7 – 7)	1.11	0.99 – 1.25
extramural protocols	2.6	(0.42 – 4.2)	0.92	0.77 – 1.11
extramural infrastructure	4.2	(2.5 – 5.7)	2.41	0.19 – 30.48
intramural training	2.4	(0 – 6.9)	1.03	0.93 – 1.14
intramural protocols	3.2	(2.2 – 3.8)	1.46	**1.12 – 1.91**

Discussion

This study shows that differences in thrombolysis rates between centres can partly be explained by differences in extramural training and intramural protocols. For extramural training we looked at the availability of education and training in the last two years, for the general public in the region, general practitioners, and ambulance personnel. Separately these items have no significant association with thrombolysis rates, but combined and after adjustment for hospital size and teaching versus non-teaching hospital, a higher score increased the likelihood of receiving thrombolysis per patient. Intramural protocols have the strongest association with thrombolysis rates. This characteristic is a sum score made up of the evaluation of thrombolysis protocols for different departments. For the neurologists and stroke nurses we also scored, using a checklist, how complete their protocols are. Again, the individual item-scores (of protocols for different departments and completeness of protocols for neurologists and nurses) have no significant association with thrombolysis rates, but combined they have a strong association. The data suggests that protocol adherence is better in centres with well-developed protocols, as treatment or non-treatment is stronger related to the presence of contra-indicators in these centres. When extramural training and intramural protocols are evaluated together in one multilevel regression model, only intramural protocols show a significant association with thrombolysis rates. It seems that centres with well-developed protocols are also often active in extramural training.

Our findings confirm the EUSI recommendations for public education, professional training and written standards for in-hospital delays.[7] Based on our calculations a reasonable improvement in intramural protocol score of halve a standard deviation (0.3 points) might lead to increases of 20% (1% absolute) in thrombolysis rates.

As a single item public education showed no significant association with thrombolysis rates, probably because the differences between centres were small. Moreover, all centres may have benefitted from a national campaign in 2006, informing the Dutch public about stroke. Intramural training and extramural protocols also showed no significant association with thrombolysis rates. Intramural training was defined as; at least one formal training or presentation given in the last two years. In most hospitals formal trainings were given more than two years ago. This may still be sufficient if knowledge is passed on to new employees during day-to-day practice. Although there were differences in extramural protocols for GP's, triage nurses and incident emergency rooms, all ambulance services used the same standardised protocols. Extramural training may also be more effective then extramural protocols. Furthermore, infrastructure both extramural and intramural showed no significant association with thrombolysis rates. The Netherlands is very densely populated and for most inhabitants a hospital is in reach by ambulance within 15 minutes. Also if ambulance services have good protocols, it does not matter if there are more hospitals in the region. This also applies for the number of neurologists that are involved. Finally, although there is a large

difference in how many hours a week a neurologist is actually present who can decide to perform thrombolysis (58 hours versus 168 hours), there is no significant association with thrombolysis rate. Possibly because in all centres a neurologist can be present within half an hour and there is always personnel that can start the routing for thrombolysis (EKG, CT, Laboratory).

A limitation of this study is the number of centres involved; only twelve hospitals participated of the approximately 100 hospitals in the Netherlands (11%). However, these hospitals cover the whole spectrum of hospital types: from small rural hospitals to the larger academic hospitals and the very large community hospitals. The limited number of hospitals also made it possible to collect not only patient-related numerical data, but also rich contextual information from the different centres. Moreover, we were able to interview a substantial number of health professionals (in total approximately 100). We have tried to compensate for subjective bias by using data from different sources; interviews, protocols and diaries to confirm our findings (triangulation).

Although it has been estimated that 25% of patients with acute stroke could be treated with intravenous rTPA,[3,13,14] only 2% to 10% receive this treatment in most hospitals.[3,4] This study shows that to improve the thrombolysis rate, extramural training and the introduction of complete intramural protocols involving all relevant professionals are important factors to address.

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REAL-LIFE COST-EFFECTIVENESS ANALYSIS OF CLUSTER-RANDOMISED IMPLEMENTATION PROGRAM TO INCREASE THROMBOLYSIS IN ACUTE ISCHAEMIC STROKE

THE PRACTISE TRIAL

Chapter 7

Dirks M, Baeten SA, Dippel DWJ, van Exel NA, van Wijngaarden JDH, Huijsman R, Koudstaal PJ, Niessen LW, for the PRACTISE investigators. *Real-life cost-effectiveness analysis of cluster-randomised implementation program to increase thrombolysis in acute ischaemic stroke;* accepted Neurology.

Introduction

Stroke care costs are high, mostly due to rehabilitation and nursing home care after initial hospitalisation.[1,2] Treatment of acute ischaemic stroke with intravenous rTPA (alteplase) has been found cost-effective in many studies as it decreases rehabilitation needs.[3,4] Yet, so far, only a relatively small proportion (3-7%) of patients with acute ischaemic stroke is treated with thrombolysis, while 24% of them may be eligible for treatment.[5] Numerous, often costly, implementation strategies have been designed to improve practice and narrow the gap between efficacy trials and real-life settings. The relative effectiveness and cost-effectiveness of such strategies in real-life settings is unclear.[6] Despite the potential effectiveness of implementation strategies to change daily practice,[7] the lack of evidence on the cost-effectiveness of common methodologies hampers decision making to promote large-scale change.[8] Reviews of improvement strategies show that only 29% include economic information and well-designed cost-effectiveness evaluations are rare.[6,8]

The PRACTISE study incorporates a Breakthrough Series implementation program to increase the proportion of patients treated with thrombolysis in real-life settings.[9] This implementation program increased the likelihood of receiving thrombolysis in individual patients by 1.58 (OR; 95%CI: 1.11 to 2.27).[10] This increase may seem uncertain and modest while intensive implementation interventions in stroke are time-consuming for staff and costly.[11] The present study reports the cost-effectiveness analysis of the intensive implementation program as compared to a laissez-faire implementation of thrombolysis.

Methods

Full details of the study design and study conduct have been reported previously.[10] To summarise,[12] hospitals were randomised to a Breakthrough Series implementation program to increase thrombolysis or a very limited implementation. The implementation program included five intervention meetings based on the Breakthrough Series model;[12] the program consisted of assignments, recommendations on logistics, and discussions aimed at improving medical decision making. The control hospitals organised implementation actions among themselves. Stroke teams in both trial arms registered the human resources and time spent in all these actions in a log-book.

Subjects & Hospitals

Twelve hospitals and 5,515 patients were included in the PRACTISE study; 308 patients (12.2%) in the control centres and 393 patients (13.1%) in the intervention centres were treated with thrombolysis. In this cost-effectiveness study we included only the 1,657 patients with ischaemic stroke admitted within 4 hours from onset (880 in the intervention centres and 777 in the control centres). Table 1 shows the characteristics. The mean age was 70 years in the intervention and 71 years in the control group. The mean National Institutes of Health Stroke Scale (NIHSS) score was 8 in both groups and gender was equally distributed. Two academic hospitals, eight large regional hospitals, and two small urban hospitals participated and were randomised. Their stroke admissions ranged from 100 to 500 a year.

Table 1 summary of input baseline patient characteristics and hospital characteristics

	intervention	control
patient data		
registered patients	880	777
age in years [sd]*	70 [14]	71 [13]
men	485 [55%]	417 [54%]
NIHSS score [sd]	8 [6]	8 [7]
number of hospitals	6	6
stroke admissions in 2003 [range]	332 [125-500]	264 [100-400]
hospital type		
— academic	1	1
— regional	4	4
— rural	1	1
teaching hospital	3	2

* standard deviation

Study Question & perspective

The study evaluated the cost-effectiveness of a Breakthrough Series implementation program compared to laissez-faire implementation of thrombolysis by comparing costs, thrombolysis rate, and quality-adjusted life years (QALYs) from a health care perspective in individual patients with acute ischaemic stroke. Patient-related costs of hospitalisation, rehabilitation, and long-term care were all included, as well as the extra costs related to implementation efforts.

Form of Evaluation

We used individual patient data from the two trial arms to calculate both short and long-term outcomes, in particular outcomes at the end of the follow-up in the PRACTISE trial (three months) and lifetime outcomes using an individual-based disability-stratified stroke life table (see below). Results were expressed differences in outcome with a 95% CI, adjusted for intra-cluster correlation.

Measure of Benefit

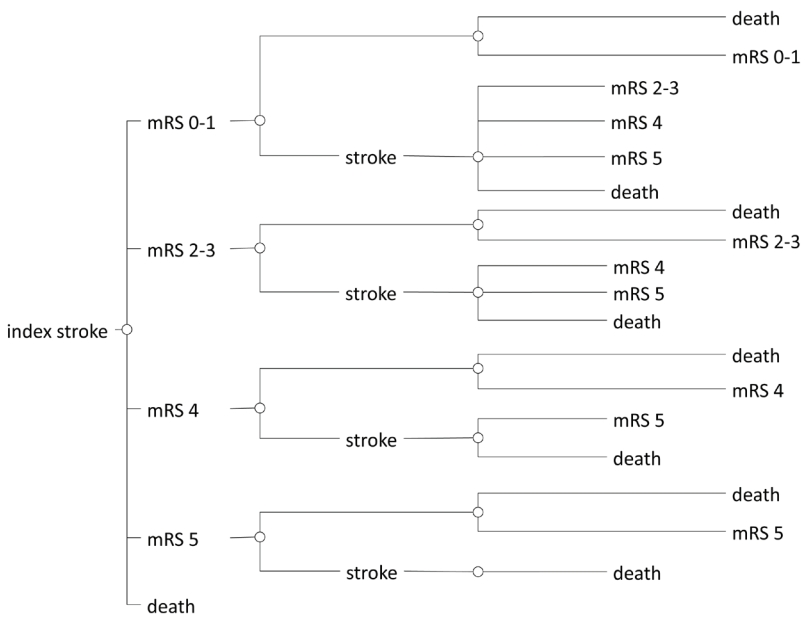
The primary outcome of the PRACTISE trial was treatment with alteplase; therefore we defined treatment with alteplase as the measure of benefit.[13] We included QALYs as a secondary outcome. The EuroQol five-dimensional questionnaire (EQ-5D) was used at three months,[14] applying measured disability-specific utility weights by modified Rankin

Scale (mRS) to estimate the number of expected lifetime QALYs per individual patient.[15] The PRACTISE trial data included the EQ-5D scores for each individual patient, by age, gender, neurological deficit during admission and at discharge, by cardiovascular risk factors, medical history, and thrombolysis treatment. This eliminates the random base-line difference in clinical status and allows for a baseline-corrected health effect from thrombolysis empirically measured during the PRACTISE trial.

Probabilistic life-table

We used validated, probabilistic, disability-stratified stroke life tables to extrapolate our trial findings.[16,17] These tables allow for occurrence of discrete events in six months' time steps – recurrent strokes, stroke deaths, deaths from ischaemic heart disease, and deaths from other causes – in a cohort of stroke patients (Figure 1). The stroke states include four disability mRS categories and death.[17] We entered the individual patient-level three months trial data on stroke severity, health care costs, and health-related quality of life into the life tables in a probabilistic bootstrap way, allowing for multiple draws per patient (Microsoft Excel add-in: Palisade's @Risk 4.5). In each iteration we drew one patient randomly from the intervention group simultaneously with a randomly selected patient from the control group, matched by age, gender, and initial stroke severity.

Figure 1 stroke patient transitions by disability state in the probabilistic multidimensional life-table. Patients from both trial arms enter the model at hospital admission. They may suffer a recurrent stroke and are readmitted, may become more disabled or die. All run through the model in half year time steps until death. Discharge is to a rehabilitation centre, a nursing home, or home, given disability status and age.



Measure of costs

Costs included implementation costs, cost of thrombolysis, short-term healthcare costs (hospital admission costs), and long-term health care costs (Table 2a). We did not include other societal, indirect costs, in particular loss of work-related earnings, as this was not considered relevant given the age-distribution of the patient-group. The implementation costs included the costs of the implementation i.e. the staff time spent, as recorded in the time logbook in the two treatment arms, as well as the overall cost of the Breakthrough Series implementation program in the intervention group (PRACTISE data). The treatment cost of alteplase accounted for the dosage of alteplase, the cost of additional nursing time (1 hour) and physician time (15 minutes) to prepare and administer the drug, and the time for the consultant neurologist for treatment assessment outside office hours (15 minutes). Hospital admission cost accounted for the days at the stroke unit, the additional costs for academic hospitals, and the Computer Tomography scans (PRACTISE data)(Table 2b). Follow-up costs were estimated using the EDISSE data and were determined by patients' disability scores. Patients in the mRS 0-1 category were discharged home with no extra costs. Patients in the mRS 2-3 category were discharged home with additional home care and remedial therapy costs (based on EDISSE data).[18] Patients in the mRS 4 category were discharged (depending on age) to a rehabilitation centre (if younger than 65 years) or a nursing home (if aged 65 years or older). Patients in the mRS 5 category were discharged to a nursing home. The cost index year is 2010.

Table 2a Summary of unit costs ($) and source of information (year of reference 2010)

cost component	unit cost ($)	unit	data source
implementation costs			
implementation program (intervention)	75,779	total	CBO*
costs of thrombolysis			
alteplase	268.18	20 ml	CVZ[22]*
	671.00	50 ml	
personnel for administration of rTPA:			
¬ nurse	33.87	hour	CVZ
¬ physician	22.51	15 minutes	
additional cost for consultant	22.51	15 minutes	CVZ
early healthcare costs (hospital admission costs)			
CT scan	177.42		CVZ
stroke unit care:			
¬ general hospital	496.97	day	EDISSE[18]
¬ academic hospital	681.01		
long term health care costs			
rehabilitation care:			
¬ rehabilitation centre	444.86	day	
¬ nursing home	272.74	day	CVZ
¬ remedial therapy	91.36	week	
		[3 sessions]	
home care	60.96	day	CVZ | EDISSE
		[1½ hrs | day]	

*CBO – Dutch Institute for Healthcare Improvement
*CVZ – the Health Care Insurance Board

Table 2b Resource use in mean values per patient

	intervention	**control**
implementation costs		
total implementation costs [US$]	144	70
costs of thrombolysis		
total costs treatment with alteplase [US$]	478	427
early healthcare costs (hospital admission costs)		
number of CT scans	1.4	1.6
cost CT scan [US$]	252	280
duration hospital admission [days]	9.7	9.9
cost hospital admission [US$]	4,555	4,759
long term health care costs		
discharged home	32%	32%
discharged home with remedial therapy & home care	51%	52%
discharged to a nursing home	2%	3%
died at 3 months	15%	14%
costs follow up residence [US$]	3,763	4,112

Cost-effectiveness analysis

We performed multiple simulation rounds of 10,000 iterations to ascertain the robustness of the average individual outcome estimates on lifetime health (QALYs) and lifetime costs (2010 US$) in both arms. Incremental costs and health effects were plotted in a cost-effectiveness plane, including confidence ranges (5%, 50%, and 90%) around a central point-estimate.

Adjustment for timing of costs and benefits

We used a 3% annual discount rate for future costs and health effects.[19]

Results

Cost effectiveness at 3 months

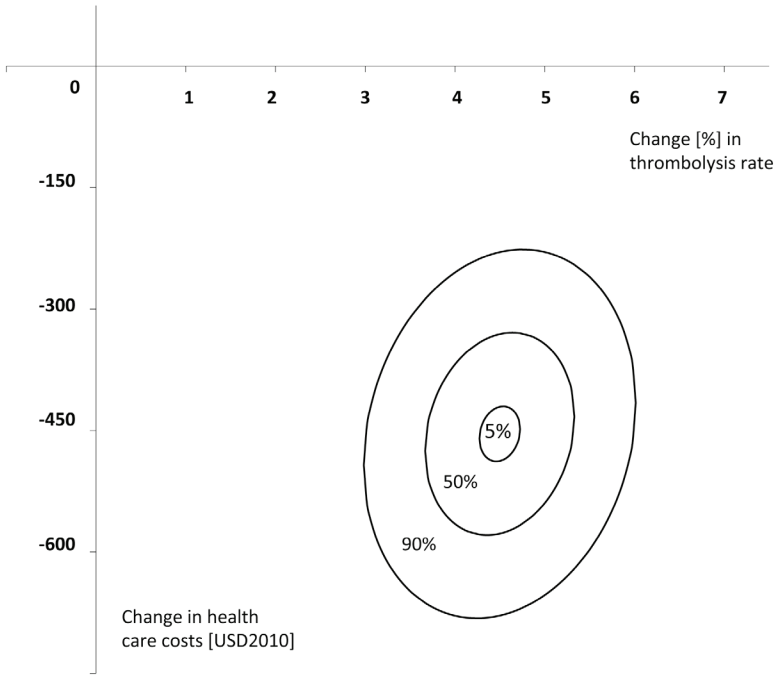
At the end of the implementation effort the overall thrombolysis rate in the intervention group was 44.3% and in the control group 39.8%, mean difference of 4.5% (95%CI: 3.1% to 5.9%), confirming our earlier findings. The mean costs at three months in the intervention group was $9,192 and $9,647 in the control group (difference: -$455; 95%CI: -$679 to -$232) (Table 3). Incremental cost effectiveness ratios were not calculated as the Breakthrough Series implementation program showed to be the dominant option, with a significant increase in thrombolysis rate at lower costs. When we remove the patients dying at 3 months, the mean costs - as expected - increase, yet the costs remain less in the intervention group ($9,656 in the control group versus $10,146 in the intervention group, (difference: -$489; 95%CI: -$739 to -$255)). Hence, the cost savings are not due to increase in death rate. The incremental costs and effects were plotted in

a cost-effectiveness plane with ellipse-shape confidence ranges of 5%, 50%, and 90% around the central point estimate (Figure 2). The 90% uncertainty ellipse falls in the southeast quadrant, indicating a high likelihood that a Breakthrough Series implementation program leads to a significant increase in thrombolysis rate at lower costs.

Table 3 Health effects and costs per patient at 3 months and lifetime

	intervention	**control**	**difference**	**95% CI**	**95% CI**
at 3 months:			(intervention - control)		**cluster adjusted**
¬ thrombolysis rate	44.3%	39.8%	4.5%	3.1%-5.9%	3.1%-5.9%
¬ costs [US$]	9,192	9,647	-455	-675 to -235	-679 to -232
lifetime:					
¬ QALY	3.89	3.84	0.05	-0.03 to 0.14	-0.04 to 0.14
¬ costs [US$]	22,994	24,315	-1,321	-1,715 to -928	-1,722 to -921

Figure 2 cost-effectiveness plane of a Breakthrough Series implementation program versus conventional approach with 90%, 50%, and 5% confidence interval ellipses; expressed in changes in thrombolysis frequency and health care cost at three months (multiple 10,000 patient iterations).



Lifetime cost-utility
Average discounted lifetime measured in QALYs for patients in the intervention group was 3.89 and for those in the control group was 3.84 (difference: 0.05; 95%CI: -0.04 to 0.14). The average discounted lifetime costs in the intervention group were $22,994 against $24,315 in the control group (difference: -$1,321; 95%CI: -$1,722 to -$921).

Discussion

Our study shows that a Breakthrough Series-based implementation program is effective to increase thrombolysis rates in ischaemic stroke, and leads to health care cost savings on the short- and long-term. Earlier cost-utility studies in acute ischaemic stroke included thrombolysis versus placebo controls, yet did not evaluate an implementation program in an empirical, naturalistic, trial setting in hospital care.

The PRACTISE implementation efforts showed a significant effect on thrombolysis rate, within the group of patients admitted within 4 hours the rate of thrombolysis increased by 4.5%. Costs related to implementation efforts were about twice as high in the intervention group as in the control group, while also the total costs of thrombolysis were higher. Hospital admission costs decreased in the intervention group due to lower use of CT scans and shorter hospital stays. The additional, one-time costs of implementation for the hospitals were compensated by lower hospital admission costs, most likely as the structured implementation approach increased efficiency in stroke care. The PRACTISE design as an implementation trial did not aim to detect statistically significant improvement in clinical outcomes (the study sample would need to be about ten times larger). Therefore, long-term health benefits could not be demonstrated. On a population level our results can nevertheless be substantial: an increase of 1% in the proportion of acute stroke patients treated with thrombolysis in the Netherlands with 16 million inhabitants and an estimated 37,000 admissions for acute strokes per year would lead to an increase of 370 patients treated with thrombolysis per year. Average rehabilitation costs were lower as fewer patients were discharged to nursing homes and fewer received remedial therapy and home care. The random 1% difference in deaths in the intervention group as compared with the control group did not contributed significantly to cost savings, as tested by eliminating deaths in the analyses. Furthermore, the empirical study does not show an increased death rate in the intervention group. The small imbalance in death rate occurs after patients enter the model in which patients were matched conforming their age, sex, and neurological symptoms.

No other studies have evaluated the cost effectiveness of an implementation program to increase thrombolysis in acute stroke care. One can compare components of our analysis to outcomes of other economic evaluations of thrombolysis in acute stroke in various national settings. Most of these evaluation studies were based on a hypothetical population, a cohort with a mean age between 67 and 69 years.[3,4,20,21] Long term health outcomes were estimated by means of probabilistic modelling and were fairly similar in

outcomes: a survival of about 3 QALYs over a lifetime, with the exception of the study of Sinclair et al (13 lifetime QALYs), that did not include long-term recurrent stroke and other vascular events.[4] The comparison between these studies and ours is hampered by differences in health care structure and patient-population mixes as our study was a pragmatic study in real-life, day-to-day care settings. As program and intervention costs estimates are usually context specific, it is difficult to extrapolate our findings to different settings. However, comparing the in-hospital cost components related to stroke care across studies we expect some similar changes. Most of the in-hospital costs are a composite of costs of hospital stay and extra costs related to alteplase treatment (medication costs, administration costs, and costs of treatment assessment). The cost data in the studies mentioned above are estimates for hypothetical populations. The PRACTISE study collected actual data of these single components used in each patient, and these costs therefore better represent real-life changes. Only Ehlers et al included implementation costs of thrombolytic treatment, estimated as $33.66 per patient, similar to the $70 per patient implementation costs in the control group in our study. Furthermore, one can expect large cross-national differences in the lifetime costs of stroke especially due to differences in residence costs. The mean costs of one day of hospitalisation is $1,000 in the United States versus $365 in the UK and $500 in the Netherlands.[3,21,22]

The strength of the present study is the cluster-randomised trial setting and the fact that all patients in the participating hospitals in both arms were registered and actual data on resource use (number of CT scans, rTPA dose, and length of hospital stay) were collected for each individual patient and used in the economic analysis. Our cost-effectiveness study made maximum use of real and detailed patient data. In addition, in each hospital, the vascular neurologists registered the time spent on implementation in an activities diary. They also registered the time and type of the extra staff involved in the implementation effort. Therefore our study makes also a realistic estimate of the extra implementation costs. Lastly, most former studies assessed the effectiveness of thrombolysis in acute stroke in clinical trials by including a selected population.[3,4,20] The present analysis is based on an unselected population-based cohort of patients admitted to the participating general and academic hospitals and therefore reflects the effectiveness of implementation effects and thrombolysis in daily practice. As the thrombolysis rates are relatively high in our study we would expect larger effects and cost reductions in regions with rates that are still low.

Conclusions

Treatment of acute ischaemic stroke with intravenous alteplase has been found effective and cost-effective in many studies. This study on promoting appropriate care shows that an implementation program to increase thrombolysis is certainly cost-saving both in the short- and long-term; it leads to an increase in thrombolysis rate with lower costs at three months due to reduction of inpatient stroke care costs and of residential costs, increasing the efficiency in stroke care.

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GENERAL DISCUSSION

Chapter 8

Stroke continues to be a major contributor to the total burden of disease in most Western countries, in spite of huge mortality declines over the past century, likely due to improved treatment of risk-factors in the general population, and improvement of acute care and prevention of complications.[1] One of the relatively new treatments for acute ischaemic stroke, thrombolysis with intravenous alteplase has been found effective,[2] yet its implementation has been lingering and needed improvements. This has been the topic of this thesis.

The primary aim of this thesis was to investigate whether the proportion of patients with acute ischaemic stroke treated with thrombolysis in hospitals could be increased in real-life settings through a multi-faceted implementation strategy aimed at resolving potential treatment barriers and whether this implementation strategy is cost-effective. The PRACTISE study was a cluster randomised trial in which twelve hospitals in the Netherlands participated; six hospitals were randomised to a Breakthrough Series implementation program to increase thrombolysis, and the other six hospitals received no further help with the implementation of thrombolysis. The implementation program consisted of assignments, recommendations on logistics, and discussions aimed at improving medical decision making.

Assignments were: execute a 'dummy run' with a real patient to test in-hospital logistics, teach ambulance personnel and emergency department personnel about thrombolysis, and inform general practitioners. Recommendations on logistics were: start treatment with alteplase immediately after the CT scan before transporting the patient, perform a finger-prick glucose test, and parallelise processes. Discussion on medical decision making resulted in the advice not to wait for laboratory results if patients do not take anticoagulants. Important here was the discussion about appropriate application of contra-indications, this is an important medical barrier and an important reason for under-treatment.[3] Indications and contra-indications for intravenous thrombolysis are based on the inclusion and exclusion criteria of the NINDS Study in most stroke guidelines.[4-7] Though reasonable, this approach may not be ideal. Criteria may be set to exclude patients who are expected not to benefit or are to suffer harm from the intervention. Such criteria clearly should be used when the results are implemented in clinical practice. Other enrolment criteria for a study, however, are not designed to protect patients, but to exclude outliers and to ensure a 'homogenous' patient population in statistical analysis and to exclude remote risks, which might well be taken in clinical decision regarding individual patients. We applied a Delphi technique on a group of international specialists in the field of thrombolysis in acute ischaemic stroke, and discussed these results in the intervention meetings.

In the 12 participating hospitals all patients over 18 years with acute stroke who were admitted within 24 hours from onset of symptoms were registered. Stroke service characteristics of the 12 hospitals were assessed by interviewing key providers of care in each centre, using pre-structured questionnaires at the beginning and at the end of the study. Stroke teams in both trial arms registered the human resources and time used in all implementation actions in a log-book. This allowed us to evaluate whether the multi-faceted implementation program is cost effective compared to a laissez-faire implementation of thrombolysis. Numerous implementation strategies have been designed to improve practice and narrow the gap between efficacy trials and real-life settings. The effectiveness and cost-effectiveness of such strategies in real-life settings is unclear.[8] Despite the importance of implementation strategies to change daily practice,[9] the lack of evidence on the cost-effectiveness of common methodologies hampers decision making to promote this change.[10] Implementation interventions in stroke can however be time-consuming for staff and costly.[11]

Secondary aims of this thesis were to assess the effectiveness of thrombolysis with intravenous alteplase for acute ischaemic stroke in daily practice in general, and particularly in older patients. We considered it important to estimate the effect of treatment in an unselected series of patients because reluctance to treat with rTPA in specific individual cases is related to the uncertainty about the effect and risks of the treatment. In randomised clinical trials thrombolysis with intravenous alteplase is an effective treatment for patients with acute ischaemic stroke, if treatment can be started within 4.5 hours after stroke onset.[2,12,13] But, effects observed in these trials may be larger than in daily practice. Patients in real life may be older and have more co-morbidity.[14,15] Moreover, doctors may be somewhat less experienced and may not adhere as strictly to guidelines and instructions as in a trial environment. This may affect the incidence of complications. Several studies and registries have shown similar outcomes and risks of complications in patients treated with alteplase in daily practice.[16-18] Yet, describing outcome only in patients treated with alteplase does not provide sufficient information about the effectiveness of thrombolysis in these subgroups of patients. To answer this question comparison of patients treated with rTPA with those not treated with rTPA is crucial. This has not been done outside randomised clinical trials. Likewise, older patients are often excluded from treatment with alteplase because of their age,[3,19] despite some evidence of benefit from thrombolysis in the older age group.[20-22] Only few patients aged 80 or over have been included in the thrombolysis trials, even in the absence of a formal age limit, as in the NINDS trial.[12,13,23,24] In the European Community, alteplase is not labelled for use in stroke patients aged over 80. The risk-benefit ratio of thrombolysis might become less favourable with increasing age because of a higher risk of adverse events.[25,26] Several studies have shown similar risks of complications in older versus younger patients treated with thrombolysis.[20-22,27] The PRACTISE study offers a very good basis for answering this question because patients were consecutively admitted and included, without age restrictions. The oldest patient included in the study was 105 years old, and the oldest patient treated with thrombolysis was 96 years old.

Additional aims were to describe the influence of organisational culture on hospital thrombolysis rates for ischaemic stroke and whether centres with well-developed protocols, training and infrastructure are associated with higher rates of thrombolysis. To increase the number of patients treated with thrombolysis one should perceive the delivery of patients to and within the hospitals. Research on improving the delivery of thrombolysis has been focused primarily on characteristics of stroke patients, but none at all to the influence of organisational culture. Structural barriers to quick referral and management of acute stroke patients, both inside and outside the hospital have been described earlier.[28,29] Considering the available scientific evidence, the European Stroke Initiative (EUSI) Executive Committee has suggested different measures to lift these barriers. The EUSI emphasised that 'teaching the public about symptoms and signs of stroke is one of the highest priorities of public medical education'.[30] Health professionals needed to learn that they are 'important and competent partners in the team providing acute stroke care'.[30] Second, they pointed out that 'written protocols are a prerequisite for standardised patient care'.[30] Although these recommendations of the EUSI may have a high face validity, the evidence on beneficial effects and cost-effectiveness has not been completely documented.[31] Research did show however that the introduction of training programs and protocols as part of a larger focused quality improvement effort can improve thrombolysis rates.[32]

Main Findings

In an attempt to facilitate the appropriate application of contra-indications, we applied a Delphi technique on a group of international specialists in the field of thrombolysis in acute ischaemic stroke, a consensus method to elicit expert opinion. We rephrased the NINDS inclusion and exclusion criteria into single propositions. Study enrolment criteria designed to exclude outliers and to ensure a homogenous patient population in statistical analysis, and criteria that have not been defined in terms that can be easily translated to clinical practice were modulated into easier applicable indications or contra-indications. We obtained consensus on 12 of the 18 propositions, consensus was reached in one of the most frequently mentioned and clinically relevant criteria, namely the exclusion criterion of minor symptoms. Yet, no consensus was reached in the propositions concerning important issues like maximum stroke onset to treatment time, patient's age and treatment of elevated blood pressure. The Delphi panel results might be helpful to translate trial results on thrombolysis in acute ischaemic stroke in day-to-day clinical practice and may facilitate the difficult implementation of these treatment criteria. We used the results of the Delphi panel to discuss the application of contra-indications of thrombolysis in the intervention meetings of the PRACTISE trial.

The results of the PRACTISE trial showed that the proportion of patients treated with rTPA could be increased through a multi-faceted implementation strategy in real-life settings. Among the patients admitted within four hours after onset of symptoms, the likelihood of treatment with rTPA was higher in the intervention centres also after adjustment for pre-specified centre and patient-characteristics. The rate of symptomatic intracranial bleeding complications was non-significantly higher in the intervention group and an important increase in bleeding rate is not ruled out. However, the complication rate was similar to the rate in clinical trials and registries, suggesting that our implementation actions did not lead to increased adverse health effects.[2,18] A large part of the intervention effect could be explained by more appropriate application of contraindications for thrombolysis. Critical assessment of justified contraindications in our study reveals that if all patients who were eligible for treatment with rTPA in this study were
actually treated, an overall thrombolysis rate of 18% of all stroke patients could have been achieved, instead of the 13% we observed in our study. Important to mention here is that these percentages include intracranial haemorrhages in the denominator, if we exclude these ICH's the percentages would respectively be approximately 21% and 15%. Data from the PRACTISE study showed that thrombolysis improves the likelihood of good outcome in an unselected observational cohort of patients with acute ischaemic stroke in day to day practice. The mean age, the proportion of elderly patients, and the distribution of stroke severity suggest that our study population is a representative patient group for daily practice.[2,16-18] In patients aged 80 or more thrombolysis for acute ischaemic stroke reliably leads to improved outcome. The stratified analysis of the data from the PRACTISE study showed a significant overall effect of thrombolysis with no evidence for heterogeneity within the different age strata.

Next, we assessed the association between thrombolysis rates in hospitals and organisational cultural characteristics and showed that the presence of certain cultural characteristics increases the likelihood of receiving thrombolysis for patients. Our results suggested that centres need to have explicit, shared goals concerning door-to-needle time and thrombolysis rate. These should be monitored continuously and feed-back should be regularly provided. Clinical leaders need to be identified, appointed, and trained who are respected by their peers, who both inspire and push 'individuals and the organisation to achieve a high standard of care'.[33] Besides, we tried to identify which (combination of) structural characteristics influence the thrombolysis rate and found that extramural training and the introduction of complete intramural protocols involving all relevant professionals are important factors to address.

Lastly, we performed an economic evaluation of the multifaceted implementation program of the PRACTISE study compared to a laissez-faire implementation of thrombolysis. This evaluation showed that an implementation program to increase thrombolysis saves costs at the short- and at the long-term. It leads to an increase in thrombolysis rate with associated measured cost savings in the short- at three months due to reduction of inpatient stroke care and residential costs, increasing efficiency in stroke care.

Methodological Considerations

This section discusses some general cross-cutting topics and study limitations across the thesis chapters in the study design of the PRACTISE trial in relation to sample size, selection of centres, the study population, and the identification of intervention effects.

Sample size and cluster effects

For the sample size calculation we expected the thrombolysis rate in the intervention hospitals to increase relatively with 50% superimposed on an autonomous trend. This would lead to a thrombolysis rate in the intervention hospitals of 7.5 x 150% = 11.25. This 50% relative anticipated effect might intuitively appear as unrealistically high. In absolute terms however, an increase in thrombolysis rate from 7.5% to 11.25% means that a smaller hospital of 100 stroke admissions a year would treat only four patients more. The implementation requires a lot of effort and therefore this 50% increase was chosen as clinically relevant. Furthermore, important here is that the estimated effect resulting in a thrombolysis rate of 11.25% is well within the course of the estimated overall maximum of 21-24%.[3] In order to calculate the sample size in a trial with randomisation at centre level a correction factor has to be applied to a standard patient-based sample size estimate. This correction factor is also called the design effect and is calculated using the intra-cluster coefficient (ICC). In our sample size estimation the ICC was: 0.0032, leading to a design effect of 2.34. The ICC from the actual analysis of the primary outcome however, was larger (0.0153), which led to a larger design effect in the actual analysis (i.e. 7.35 instead of the assumed 2.34). This retrospective finding implies that the study would have had a lower power to identify the expected 50% relative effect than anticipated.

Selection of study centres

A considerable limitation of the study involves the selection and the number of centres that participated. Most of the 12 centres were recruited by setting out a call for participation in a project among 21 centres participating in an existing Breakthrough programme for improving organised stroke care in the Netherlands.[34] These centres were highly motivated to improve stroke care and this could have introduced selection bias. However, only half of these centres had an rTPA treatment percentage above the national average before the start of the study. The number of centres that participated is limited; only 12 hospitals of the approximately 110 hospitals in the Netherlands (11%). A higher number of intervention clusters is recommended.[35] More centres would decrease the design effect and therefore increased the power of the study. This would have made the study less sensitive to non-compliance (or drop out) on centre level and it would increase the generalisability of the study within the Netherlands and elsewhere. A smaller number of centres however, would be easier to manage logistically, and would enable a more tailored implementation approach with more attention paid to each centre.

Study population

The study population consisted of a cohort of all stroke patients admitted within 24 hours of symptom onset and a sub-cohort of acute ischaemic stroke patients admitted within 4 hours of symptom onset. The purpose of the total cohort was to be able to analyse the onset-to-door time of patients in the intervention hospitals compared to the control hospitals. The sub-cohort of patients with ischaemic stroke admitted within 4 hours of symptom onset was the target population. In reality, the patients treated with rTPA are to be in this group. Both patients groups are relevant for the analysis of the primary outcome (treatment with rTPA). The disadvantage of considering the total cohort of all stroke patients is dilution of effect, because the target population is only a small part of the total cohort. However, focussing on the target population doesn't provide the overall picture; the purpose of the multifaceted implementation programme is to increase the odds on thrombolysis in both patients groups, not just in the target population. This approach provided a basis for additional analyses to identify a more general and larger implementation effect.

Identification of intervention effect

Local and central investigators were not blind to the intervention. Not all clinicians in the control hospitals were aware of the purpose of the trial. This is in contrast with those in the intervention hospitals, where all were involved. In the intervention meetings we emphasised that all the personnel involved with thrombolysis should be made aware of the study as part of the intervention package. It is important to realise that therefore the observed effect of the intervention was made up of two components: the effect of the multi-faceted implementation strategy and the effect due to clinicians knowing that their thrombolysis practice was being monitored ('Hawthorn' effect). This is almost unavoidable in implementation research. A design where all participating clinicians were informed of the purpose of the study would certainly lead to pollution and to a decrease of the intervention contrast and would be less close to the real life setting and therefore not reflect the intervention contrast we wanted to test.

The intervention was a multi-faceted implementation strategy and the final challenge in the analysis of the intervention effect is to examine what specific element of the intervention is effective and whether this element can be broadly used and thereby makes the intervention generalisable. This is a rather black-box approach, typical for complex interventions. From previous research we know that dissemination of simple thrombolysis referral guidelines to primary care and local emergency departments increases the proportion of intravenous thrombolysis.[36] In the Get With The Guidelines (GWTG) stroke project, participation was associated with increased adherence to several stroke care performance measures,[32] and the use of rTPA increased dramatically over time. However, the GWTG stroke project is an uncontrolled study, which could not distinguish between an autonomous time trend and an intervention effect. In the treatment of acute myocardial infarction, a randomised controlled trial evaluated guideline

implementation through clinician education by local opinion leaders and performance feedback in 37 community hospitals in Minnesota. It showed that guided quality improvement interventions could accelerate adoption of effective treatments in community practice in the treatment of acute myocardial infarction.[37] In both studies mentioned here good quality, simple guidelines appeared to be an important factor in the implementation process. We observed that in the intervention hospitals more patients were treated with alteplase with a lower NIHSS score and there were less ambiguous contra-indications. These two particular items were emphasised during the intervention meetings as the neurologists were instructed to update their treatment guideline. Thus, in our study the treatment guidelines played an important role too. However, we already know that interventions tailored to prospectively identified barriers are more likely to improve professional practice than to dissemination of guidelines or educational materials alone.[38] We found no single component or combination of components in the structure of the stroke service that could explain the intervention effect. Possibly the intervention effect consisted of a combination of structural effects (training of extra-mural care,[39] clear treatment guidelines with unambiguous indications and contra-indications),[39,40] cultural aspects (explicit shared goals and opinion leaders),[41] and perhaps other factors we did not monitor in the PRACTISE trial.

Economic evaluation

The results of the economic evaluation show that an implementation program to increase thrombolysis is cost-saving both in the short- and long-term. It is unclear whether the cost savings are due to less disability, or to improved and more structured care, or due to both. As the study is not sampled to show health effects this cannot be disentangled. Yet is important to know if the implementation efforts led to 'just' better organised care or to specific effects of thrombolysis. The decrease in residential cost might indicate better health conditions.

Clinical Relevance

Numerous implementation strategies have been designed to improve practice and narrow the gap between efficacy trials and real-life settings. The PRACTISE study applied a multi-faceted implementation program to increase the proportion of patients treated with thrombolysis and this implementation intervention increased the likelihood of receiving thrombolysis for individual patients by 1.58 (OR; 95%CI: 1.11 to 2.27) in the patient group with ischaemic stroke admitted within 4 hours of symptom onset.[40] A 1% increase in the proportion of acute stroke patients treated with thrombolysis in a country such as the Netherlands with 16 million inhabitants and with an estimated 39,600 admissions for acute strokes per year[42] will lead to an extra 396 patients treated every year. If all hospitals could raise the proportion treated patients to 15%, as in our study, 5,940 patients would be treated with thrombolysis and 10% more patients would achieve independence.

New treatments for acute stroke are evolving; one of them is intra-arterial treatment: arterial catheterisation with a micro-catheter to the level of occlusion and delivery of a thrombolytic agent or fragmentation, aspiration, or retraction of the occluding embolus with a mechanical device.[43-45] It is a multi-disciplinary treatment with the involvement of a neurologist, (neuro)radiologist and the interventionist. For this new treatment a good organisation and coordination is vital, the implementation of intra-arterial thrombolysis is challenging. Result from the PRACTISE trial could provide some elements in the implementation strategy to strengthen the implementation. Important elements that need to be considered are: training of extra-mural personnel,[39] clear treatment guidelines with unambiguous indications and contra-indications,[39,40] explicit, shared goals and opinion leaders.[41]

Future implementation research

Meta-analysis of the effectiveness of quality improvement collaboratives has shown that although these collaboratives play an important part in current strategies focussed on accelerating improvement, they may have only modest effects on outcomes at best.[8] The term 'Quality Improvement Collaboratives' is used for different multifaceted packages that focus on accelerating better outcomes. Better insight in the variability within collaboratives and the analysis of the barriers enables refining the tailoring process. The understanding of the success factors is crucial for the improvement of implementation tools, in other words make them more effective.[8] More specifically for the implementation of thrombolysis in acute stroke more insight is needed in the effect of national campaigns on the swift referral of stroke patients to hospitals. In the PRACTISE study the emphasis of the multi-faceted implementation strategy was placed on the organisation within the hospitals. An increase in patients treated with rTPA in the intervention hospitals compared with the control hospitals was observed without an increase in patients admitted within 4 hours of symptom onset. This observation suggests that the multi-faceted implementation strategy used in the PRACTISE study was able to improve clinical practice within the hospital, but was insufficient to reach the public or extramural domain. A recent Australian study reported that the public awareness of stroke is limited.[46] Another study showed a limited increase in ambulance dispatches after National Stroke Foundation campaigns.[47] In the Netherlands, door to needle time is quality indicator, and made public for each hospital. Since its introduction, door to needle times have improved considerably. One wonders what could have been the effect if the proportion of patients treated with intravenous rTPA would be introduced as general quality indicator of stroke care. Furthermore, what implementation strategies are more effective to reach the extramural domain and to obtain a fairly constant effect? Is it more effective to emphasise campaigns on a target population within the public, for instance people with cardiovascular risk factors? These are still unanswered questions. Lastly, further research is needed to examine whether the benefit of the implementation can be maintained and increased, for example by implementing an on-going audit and monitoring systems.

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SUMMARY | SAMENVATTING

Chapter 9

Summary

In the Netherlands stroke is a major contributor to the total burden of disease, fortunately improvements are observed and stroke mortality is declining; due to a both reductions in incidence of stroke as well as in case fatality. New treatments like thrombolysis for acute ischaemic stroke are highly effective; patients treated with intravenous alteplase have a better functional outcome at three months. In time more and more hospitals started to treat acute ischaemic stroke patients with thrombolysis, but in daily practice, several circumstances and causes put a constraint on the number of patients who could be treated, the most important cause being the narrow time window for treatment. In this thesis, I describe our research that investigated whether the proportion of patients with acute ischaemic stroke treated with thrombolysis in hospitals can be increased in real-life settings through a multi-faceted implementation strategy aimed at resolving potential treatment barriers. Chapter 2 covers the rationale, background and design of the PRACTISE study; a cluster randomised controlled trial to assess the effect of implementation strategies on the rate of thrombolysis for acute ischaemic stroke.

One of the barriers for the implementation of thrombolysis for ischaemic stroke is the difficulty of appropriate application of contra-indications. Chapter 3 describes a Delphi approach we used to achieve consensus among an international group of specialists on indications and contra-indications for intravenous thrombolysis in acute ischaemic stroke. We obtained consensus in 12 of the 18 propositions, which may facilitate the difficult implementation of these treatment criteria. Consensus was reached in one of the most frequently mentioned and clinically relevant criteria, namely the exclusion criterion of minor symptoms. Yet, no consensus was reached in the propositions concerning important issues like maximum stroke onset to treatment time, patient's age and treatment of elevated blood pressure.

Chapter 4 reports the results of the PRACTISE study, a cluster-randomised controlled implementation trial promoting thrombolysis for acute ischaemic stroke. In this study, we found that the proportion of patients treated with rTPA increased through an intensive implementation strategy in real-life settings. Among the patients admitted within four hours after onset, the likelihood of treatment with rTPA was higher in the intervention centres also after adjustment for pre-specified centre and patient-characteristics (adjusted Odds Ratio (aOR) 1.58; 95% confidence interval (CI): 1.11 to 2.27). A major component of the intervention effect we found was more appropriate application of contraindications of thrombolysis.

Chapter 5 focuses on the effectiveness of thrombolysis with intravenous alteplase for acute ischaemic stroke in daily practice (chapter 5.1) and in older patients (chapter 5.2). Effects observed in randomised clinical trials may be larger than in daily practice. Patients in real life may be older and have more co-morbidity. Moreover, doctors may be somewhat less experienced and may not adhere as strictly to guidelines and instructions as in a trial environment, this may also affect the incidence of complications. The risk-benefit ratio of thrombolysis might become less favourable. Our study confirms that thrombolysis improves the likelihood of good outcome also in an unselected observational cohort of patients with acute ischaemic stroke (aOR 1.3; 95% CI 1.0 to 1.7). Since alteplase treatment was not randomly allocated in our study, adjustments for prognostic variables are necessary. By definition the assessment of the effectiveness of alteplase in daily practice cannot be determined in a randomised trial. Consequently, the patients who were not treated with alteplase constitute a very heterogeneous group, including those with one or more contra-indications, or with completely resolved neurological deficit. However, most contra-indications for thrombolysis are not important prognostic factors and therefore do not influence patient outcome in untreated patients. Our results therefore support the notion that thrombolysis for acute ischaemic stroke is also effective and safe in daily practice. In patients aged 80 or more thrombolysis for acute ischaemic stroke leads to improved outcome; the stratified analysis shows a significant overall effect of thrombolysis with no evidence for heterogeneity within the different age strata (overall aOR for good outcome was 1.54 (95% CI 1.18-2.01), test of homogeneity of OR's p=0.39).

Chapter 6.1 describes the influence of organisational culture on hospital thrombolysis rates for ischaemic stroke. The study shows that the availability of certain cultural characteristics increases the likelihood of receiving thrombolysis for patients; centres need to have explicit, shared goals concerning door-to-needle time and thrombolysis rate. These should be monitored continuously and feedback should be regularly provided. Centres with clinical leaders, who are respected by their peers have higher thrombolysis rates; reasonably because they can push "individuals and the organisation to achieve a high standard of care." Chapter 6.2 describes whether centres with well-developed protocols, training and infrastructure are associated with higher rates of thrombolysis. Extramural training (aOR 1.14; 95% CI 1.01 - 1.30) and intramural protocols (aOR 1.77; 95% CI 1.30 - 2.39) are important tools to increase thrombolysis rates for acute ischaemic stroke in hospitals and should be aimed at all relevant professionals.

Stroke care costs are high, mostly due to rehabilitation and nursing home care after initial hospitalisation. Numerous, often costly, implementation strategies have been designed to improve practice and narrow the gap between efficacy trials and real-life settings. Despite the potential effectiveness of implementation strategies to change daily practice, the lack of evidence on the cost-effectiveness of common methodologies hampers decision making to promote large-scale change. Chapter 7 reports the cost-effectiveness analysis of the intensive implementation program as compared to a laissez-faire implementation of thrombolysis. This study shows that an implementation program to increase thrombolysis is cost-effective; it leads to an increase in thrombolysis rate (mean difference of 4.5% (95%CI: 3.1% to 5.9%) with likely cost savings in the long run (average discounted lifetime costs in the intervention group were $22,994 against

$24,315 in the control group with a difference of: -$1,321; 95%CI: -$1,722 to -$921) and certainly lower costs at three months (mean costs in the intervention group was $9,192 and $9,647 in the control group with a difference of: -$455; 95%CI: -$679 to -$232) due to reduction of inpatient stroke care costs and increased efficiency in stroke care.

In Chapter 8 our findings are discussed and reviewed in a broader context. Furthermore, this chapter contains methodological considerations and describes suggestions for further implementation research.

Samenvatting

Beroerte is een veel voorkomende aandoening en is verantwoordelijke voor een groot deel van de totale ziektelast in Nederland. Gelukkig zijn er verbeteringen in de zorg en behandeling van beroerte en neemt de mortaliteit door beroerte af, door zowel een afname in de incidentie van beroerte (primaire preventie) als door een afname in case fatality (secundaire preventie). Nieuwe behandelingen zoals trombolyse voor het acute herseninfarct zijn hoogst effectief; patiënten behandeld met intraveneuze trombolyse hebben een betere functionele uitkomst op 3 maanden. In de loop van de tijd startten meer en meer ziekenhuizen met de behandeling van patiënten met een acuut hersen-infarct met trombolyse, maar in de dagelijkse praktijk zijn er meerdere factoren die het totaal aantal patiënten die met rTPA behandeld kan worden beperken. De belangrijkste factor is het krappe tijdsinterval waarbinnen de behandeling gegeven kan worden. In dit proefschrift beschrijf ik onze studie die onderzocht of het percentage patiënten met een herseninfarct dat behandeld wordt met trombolyse verhoogd kan worden in een dagelijkse setting door een multilaterale implementatiestrategie, die gericht is op het oplossen van barrières voor de behandeling. Hoofdstuk 2 beschrijft de ratio, achtergrond en het ontwerp van de PRACTISE studie; een cluster gerandomiseerde, gecontroleerde trial naar het effect van implementatiestrategieën op het percentage van trombolyse voor het acute herseninfarct.

Een van de barrières voor de implementatie van trombolyse voor het herseninfarct is de moeilijkheid in het toepassen van de indicaties en contra-indicaties van de behande-ling. Hoofdstuk 3 beschrijft een Delphi benadering die we gebruikte om consensus te bereiken binnen een groep internationale specialisten over het “vertalen” van in- en exclusiecriteria van onderzoek naar indicaties en contra-indicaties voor intraveneuze trombolyse voor het acute herseninfarct. We bereikten consensus in 12 van de 18 proposities, waardoor de moeilijke implementatie van deze behandelcriteria vergemakkelijkt zou kunnen worden. Consensus werd bereikt bij een van de meest genoemde en klinisch meest relevante criteria, namelijk het exclusie criterium ‘beperkte neurologische uitval’. Er werd echter geen consensus bereikt in de proposities die gingen over het maximale tijdsinterval tussen ontstaan van de beroerte en start van de behandeling, maximale leeftijd van de patiënt en de eventuele behandeling van een te hoge bloeddruk.

Hoofdstuk 4 rapporteert de resultaten van de PRACTISE studie, een clustergerandomiseerde, gecontroleerde implementatie studie die trombolyse voor het acute herseninfarct bevordert. In deze studie, vonden we dat het percentage patiënten dat behandeld werd met rTPA steeg door een intensieve implementatie strategie in een dagelijkse setting. Onder de patiënten die binnen de 4 uur na het ontstaan van het herseninfarct waren opgenomen, was de kans om behandeld te worden met rTPA hoger in de interventie ziekenhuizen; ook na het justeren voor van te voren gespecificeerde ziekenhuis en patiënt kenmerken (gejusteerde Odds Ratio (OR) 1,58

met een 95% betrouwbaarheidsinterval (BI) van 1,11 tot 2,27). Een belangrijke component van dit interventie-effect dat we gevonden hebben is een betere toepassing van de contra-indicaties van trombolyse.

Hoofdstuk 5 richt zich op de effectiviteit van trombolyse met intraveneuze alteplase voor het acute herseninfarct in de dagelijkse praktijk (hoofdstuk 5.1) en bij ouderen (hoofdstuk 5.2). Resultaten van wetenschappelijk onderzoek leiden soms tot een rooskleurige inschatting van het effect van een behandeling, omdat patiënten die deelnemen aan een onderzoek gemiddeld een wat betere prognose hebben en de behandeling onder meer gecontroleerde omstandigheden wordt uitgevoerd dan in de dagelijkse praktijk. Toch bevestigt onze studie dat trombolyse de kans op een goede functionele uitkomst vergroot, ook in deze niet-geselecteerde patiënt populatie met een acuut herseninfarct (gejusteerde OR 1,3 met een 95% BI van 1,0 tot 1,7). Omdat de behandeling met alteplase niet willekeurig was toegewezen in de studie, is er een correctie voor prognostische variabelen noodzakelijk. Per definitie kan de effectiviteit van alteplase in de dagelijkse praktijk niet bepaald worden in een gerandomiseerde studie. Als gevolg hiervan bestaat de patiëntengroep die niet behandeld is met alteplase uit een zeer heterogene groep, variërend van patiënten met één of meerdere contra-indicaties tot patiënten die geen neurologische uitval meer hebben. Belangrijk te vermelden is dat de meeste contra-indicaties voor trombolyse geen belangrijke prognostische factoren zijn en daardoor de functionele uitkomst niet beïnvloeden bij de niet behandelde patiënten. Onze resultaten ondersteunen het idee dat trombolyse ook in de dagelijkse praktijk effectief is. Bij patiënten van 80 jaar en ouder leidt trombolyse voor het acute herseninfarct ook tot een betere functionele uitkomst; de gestratificeerde analyse toonde een significant totaal effect van trombolyse zonder aanwijzingen voor heterogeniteit tussen de verschillende leeftijdsstrata (gejusteerde OR over het totaal voor een goede functionele uitkomst: 1,54 (met een 95% BI van 1,18 tot 2,01) test van homogeniteit van de OR's p=0,39).

Hoofdstuk 6.1 beschrijft de invloed van de organisatie cultuur op het percentage met trombolyse behandelde patiënten met een herseninfarct in een ziekenhuis. De studie toont dat de aanwezigheid van bepaalde culturele karakteristieken de kans op trombolyse voor patiënten vergroot; ziekenhuizen moeten expliciete, gezamenlijke doelen hebben omtrent de 'door-to-needle' tijd en trombolyse percentage. Deze doelen zouden continu gecontroleerd moeten worden en van feedback moeten worden voorzien. Ziekenhuizen met klinische leiders, die gerespecteerd worden door hun collegae, hebben hogere percentages met trombolyse behandelde patiënten, waarschijnlijk omdat zij "zowel individuen als de organisatie kunnen inspireren om een hoge standaard van zorg te leveren". Hoofdstuk 6.2 beschrijft of ziekenhuizen met goed ontwikkelde protocollen, goede scholing en infrastructuur ook hogere trombolyse percentages hebben. Een hoog trombolyse percentage was geassocieerd met goede scholing buiten het ziekenhuis (gejusteerde OR 1,14; 95% BI van 1,01 tot 1,30) en goede protocollen binnen het ziekenhuis (gejusteerde OR 1,77; 95% BI van 1,30 tot 2,39), hierdoor zijn zij belangrijke instrumenten om het trombolyse percentage te verhogen. Het is belangrijk dat dit onderwijs en deze protocollen gericht zijn op alle relevante professionals buiten en binnen het ziekenhuis.

De kosten voor beroerte zijn hoog, voornamelijk door de revalidatiekosten en kosten van verpleeghuizen na de ziekenhuisopname. Verschillende, vaak dure, implementatie-strategieën zijn ontworpen om de praktijk te verbeteren en het gat te dichten tussen het aantal patiënten wat behandeld zou moeten worden (op basis van het geleverde bewijs in de effectiviteittrials) en het aantal patiënten wat in de dagelijkse praktijk behandeld wordt. Ondanks de potentiële effectiviteit van deze implementatiestrategieën, zorgt het gebrek aan bewijs over de kosteneffectiviteit hiervan voor stagnatie van een bredere grootschalige bevordering. Hoofdstuk 7 geeft de kosteneffectiviteitsanalyse weer van het intensieve implementatieprogramma zoals uitgevoerd in de interventieziekenhuizen in de PRACTISE studie, tegenover een 'laissez-faire' implementatie van trombolyse. Deze studie toonde dat dit intensieve implementatieprogramma effectief in het verhogen van het trombolyse percentage ook kosteneffectief is; het leidt tot een verhoging van het trombolyse percentage (gemiddeld verschil van 4.5% (95% BI van 3,1% tot 5,9%) met waarschijnlijk kostenbesparing over de lange termijn (gemiddelde verdisconteerde levenslange kosten in de interventie groep waren $22.994 tegenover $24.315 in de controle groep met een verschil van -$1.321; 95% BI van -$1.722 tot -$921), maar zeker tot kostenbesparing op de korte termijn (binnen 3 maanden, gemiddelde kosten in de interventie groep waren $9.192 en $9.647 in de controle groep met een verschil van -$455; 95% BI van -$679 tot -$232) door vermindering van ziekenhuiskosten waarschijnlijk door een toegenomen efficiëntie in de zorg voor beroerte.

In Hoofdstuk 8 worden onze bevindingen bediscussieerd en besproken in een bredere context. Daarnaast bevat dit hoofdstuk methodologische overwegingen en beschrijft het suggesties voor verder implementatieonderzoek.

EPILOGUE

Chapter 10

Dankwoord (Acknowledgment)

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About the author

The author was born on May 26th 1976 in Beverwijk. She graduated from the Berlingh College (grammar school) in 1994 and started medical school at the University of Amsterdam. In 2001 she graduated from medical school and started working as a resident in neurology at the Slotervaart ziekenhuis in Amsterdam, followed by a residency at the Academic Medical Centre in Amsterdam. In 2003 she moved to Rotterdam and started working as a resident in neurology at the Erasmus Medical Centre, from 2006 she is trained as a neurologist under prof. dr. P.A.E. Sillevis Smitt. From 2004 to 2007 she set up and coordinated the PRACTISE trial under the supervision of prof. dr. D.W.J. Dippel and prof. dr. L.W. Niessen, the research underlying this thesis. As additional tasks she is a member of the junior neurologist board of the Dutch Neurology Society from 2007; she participates in the Visitation Committee, the Plenary Consultation Neurology of the Dutch Neurology Society with membership of the working party e-portfolio, and Disputes Committee of The Royal Dutch Medical Association (KNMG).

Over de auteur

De schrijfster van dit proefschrift werd op 26 mei 1976 geboren in Beverwijk. Na de middelbare schoolopleiding (VWO) op het Berlingh College ging zij in 1994 geneeskunde studeren aan de Universiteit van Amsterdam. In 1999 haalde zij haar doctoraal examen Geneeskunde gevolgd door het artsexamen in 2001. Aansluitend begon zij haar carrière als AGNIO neurologie in het Slotervaart ziekenhuis te Amsterdam en daarna in het Academisch Medisch Centrum te Amsterdam. In 2003 verhuisde zij naar Rotterdam en begon ook daar als AGNIO neurologie in het ErasmusMC, vanaf 2006 startte zij haar opleiding tot neuroloog (opleider: prof. dr. P.A.E. Sillevis Smitt).
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Vanaf 2007 is zij lid van de aios vereniging neurologie in het ErasmusMC en is zij de vertegenwoordiger vanuit het ErasmusMC in het bestuur van de Vereniging Arts-Assistenten in opleiding tot Neuroloog (VAAN) waarvoor zij in verschillende commissies zit: de Visitatie Commissie, het Plenair Consilium Neurologie met daaruit voortkomend de werkgroep e-portfolio en de Commissie voor Geschillen van het KNMG.

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PhD portfolio
Research School: coeur

1 — PhD training

year	Workload (ECTS)	General courses
2005	3	*Biomedical English Writing and Communication (nihes)*
2005	6	*Classical Methods for Data-analysis (nihes)*
2006	1.5	*Medical Demography Fundamentals and Applications (nihes)*
2007	15	*Research Fellow at the Institute for Management & Technology*
		¬ Assessment of the Erasmus University Rotterdam
2007	1.5	*Health* Eco*nomics (nihes)*
2007	2	*Regression Analysis (nihes)*
2007	1.5	*Advanced Modelling Methods for Health Economic Evaluation,*
		¬ Glasgow [Collaboration between the University of York & the
		¬ University of Glasgow]
2005	1.5	*Cardiovascular Medicine (coeur)*
2006	1.5	*Clinical Cardiovascular Epidemiology (coeur)*
2007	2	*Summer School Barcelona, European Stroke Initiative (eusi)*
2007	1.5	*Cardiovascular Pharmacology (coeur)*
		Specific courses
2005-'07	2.5	*5x Workshop intervention PRACTISE trial*
2007	0.5	*Multidisciplinary symposium vascular medicine*
2008	2	*Concluding symposium of the PRACTISE trial*
		Seminars and workshops
2006	1.5	*COEUR Research seminar "from trial exclusion criteria to (contra)*
		¬ indications for thrombolysis in acute ischemic stroke, a Delphi approach"
		Presentations
2008	1.5	*COEUR Research seminar "a cluster randomised trial evaluating an*
		¬ intensive multi-dimensional implementation strategy for thrombolysis
		¬ with iv rtPA in acute ischaemic stroke"
		International conferences
2005	1	*European Stroke Conference, Bologna (poster presentation ongoing trial)*
2006	1	*European Stroke Conference, Brussels (poster presentation ongoing trial)*
2007	1	*European Stroke Conference, Glasgow (poster presentation ongoing trial)*
2008	1	*European Stroke Conference, Nice (poster presentation): PRACTISE:*
		¬ Promoting Acute Thrombolysis for Ischaemic Stroke. A cluster-
		¬ randomised trial of high intensity versus regular intensity
		¬ implementation of thrombolysis

year	Workload (ECTS)	International conferences
2008	1	*European Stroke Conference, Nice (oral presentation): Relationship*
		¬ between stroke service characteristics and onset-to-CT time in patients
		¬ with acute ischaemic stroke
2008	1	*European Stroke Conference, Nice (oral presentation): Effect of*
		¬ intravenous thrombolysis in acute ischaemic stroke on outcome in daily
		¬ practice; data from the PRACTISE study.
2008	1	*World Stroke Conference, Vienna (oral presentation): promoting*
		¬ thrombolysis for acute ischaemic stroke [PRACTISE]: results of a
		¬ cluster-randomised trial to resolve barriers to the delivery of
		¬ intravenous thrombolysis
2009	1	*European Stroke Conference, Stockholm (oral presentation): The effect of*
		¬ thrombolysis with intravenous rtPA in patients with minimal symp-
		toms. Data from the PRACTISE trial.
2009	1	*European Stroke Conference, Stockholm (oral presentation): The effect*
		¬ of thrombolysis with intravenous rtPA in the very elderly. Data from
		¬ the PRACTISE trial.
2011	1	*European Stroke Conference, Hamburg (oral presentation; 2nd author):*
		¬ Women with acute ischemic stroke are treated less often with
		¬ intravenous alteplase than men.

2 — Teaching

		lecturing
2005	0.5	*nurses of neurology department*
2006	0.5	*physisians and nurses of casualty*
2007	0.5	*radiology laboratory assistants*
2010	0.5	*ambulance nurses*

57 total Workload (ECTS)