Thrombolysis with alteplase 3–4·5 h after acute ischaemic stroke (SITS-ISTR): an observational study

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Summary

Background Intravenous alteplase is approved for use within 3 h of ischaemic stroke onset, although a meta-analysis of randomised controlled trials suggests treatment benefit up to 4·5 h. We compared outcome in patients treated between 3 h and 4·5 h versus those treated within 3 h, who were in the Safe Implementation of Treatments in Stroke (SITS), a prospective internet-based audit of the International Stroke Thrombolysis Registry (ISTR).

Methods We compared 664 patients presenting with ischaemic stroke and given intravenous alteplase (0·9 mg/kg total dose) between 3 h and 4·5 h with 11 865 patients treated within 3 h. All patients were otherwise compliant with European summary of product characteristics criteria and had been documented in the International Stroke Treatment Registry between Dec 25, 2002, and Nov 15, 2007. Outcome measures were symptomatic intracerebral haemorrhage within 24 h (haemorrhage type 2 associated with National Institutes of Health Stroke Scale [NIHSS] ≥4 points deterioration), and mortality and independence (modified Rankin scale of 0–2) at 3 months.

Findings In the 3–4·5-h cohort, treatment was started at a median of 55 min later after symptom onset (195 min [IQR 187–210] vs 140 min [115–165], p<0·0001), median age was 3 years younger (65 years [55–73] vs 68 years [58–74], p=0·0001), and stroke severity was lower (NIHSS score 11 [7–16] vs 12 [8–17], p=0·0001) than in the 3-h cohort. We recorded no significant differences between the 3–4·5-h cohort and the within 3-h cohort for any outcome measure—rate of symptomatic intracerebral haemorrhage: 2·2% (14 of 649) versus 1·6% (183 of 11 681) (odds ratio [OR] 1·18 [95% CI 0·89–1·55], p=0·24; adjusted OR 1·32 [1·00–1·75], p=0·052); mortality: 12·7% (70 of 551) versus 12·2% (1263 of 10 368) (OR 1·02 [0·90–1·17], p=0·72; adjusted OR 1·15 [1·00–1·33], p=0·053); and independence: 58·0% (314 of 541) versus 56·3% (5756 of 10 231) (OR 1·04 [0·95–1·13], p=0·42; adjusted OR 0·93 [0·84–1·03], p=0·18).

Interpretation Alteplase remains safe when given at 3–4·5 h after ischaemic stroke, offering an opportunity for patients who cannot be treated within the standard 3-h timeframe.

Funding Boehringer-Ingelheim, European Union Public Health Executive Authority.

Introduction Alteplase—a recombinant tissue plasminogen activator—was approved by the European Medicines Evaluation Agency (EMEA) in 2002 for the intravenous treatment of acute ischaemic stroke, with initiation within 3 h of stroke onset. The EMEA requested that treatment outcomes were monitored in the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). This study confirmed that the rates of symptomatic intracerebral haemorrhage, mortality, and independence in activities of daily living for patients treated in routine clinical practice were similar to the outcomes of randomised controlled trials. Minor differences were recorded in demographic factors and baseline variables between patients treated in randomised controlled trials versus those in the register, but outcomes were confirmed even after correction for these differences.

Hacke and colleagues analysed pooled data from six trials on intravenous alteplase in stroke and noted that the proportion of patients with full recovery decreased successively with increased time between stroke onset and treatment initiation; however, a significant benefit persisted for treatment initiation up to 4·5 h.

SITS (Safe Implementation of Treatments in Stroke) is a collaboration of more than 700 clinical centres in 35 countries for documentation of treatments for stroke in an interactive database over a secure internet portal. It is an international register of unselected patients who are given thrombolysis for acute stroke in accordance with broadly accepted guidelines, but includes a subgroup of patients from European centres who were treated according to the SITS-MOST criteria approved under the European marketing licence for alteplase. In addition to these criteria, centres might decide to treat patients with thrombolysis after individual assessment of neurological status and imaging studies. Centres participating in SITS commit themselves to register all treated patients in SITS-ISTR, irrespective of whether they fulfil the SITS-MOST criteria.

We hypothesised that outcomes for patients treated in routine clinical practice with intravenous alteplase between 3 h and 4·5 h after ischaemic stroke onset, who were documented in SITS-ISTR, would be similar to outcomes for patients treated within 0–3 h. We compared these two cohorts of patients in whom time to treatment
The main difference, to test for differences in the rates of symptomatic haemorrhage, death, and functional recovery due to treatment delay.

Methods

Study population and design

Details of the method, including data collection and management for SITS-ISTR and SITS-MOST, have been described previously. We included patients presenting with ischaemic stroke who were given intravenous alteplase (Boehringer-Ingelheim, Ingelheim, Germany) between 3 h and 4·5 h after symptom onset and registered in SITS-ISTR—a prospective, multinational, internet-based register for patients given this drug after acute stroke onset in SITS-ISTR—a prospective, multinational, internet-based register for patients given this drug after acute stroke onset and registered within 3 h and 4·5 h after symptom onset and registered in SITS-ISTR; this group included all participants of the previously published SITS-MOST register. A full dose of alteplase (0·9 mg/kg, with an upper limit of 90 mg) was given as a continuous infusion over 60 min, with 10% of the total dose administered as a bolus. All patients were fully compliant with other European summary of product characteristics criteria (webtable). Local investigators documented baseline and demographic characteristics, stroke severity measured by score on the National Institutes of Health stroke scale (NIHSS), onset to treatment time, risk factors, medication history, admission to hospital, and follow-up imaging scans data. Since SITS-ISTR is an indicator of real-life clinical practice, imaging scans were not read centrally. The NIHSS records the degree of neurological deficit on an ordinal scale that ranges from 0 to 42, with 0 representing normal.

The SITS International Coordination Office regularly monitored the SITS-ISTR data online and checked individual patient data every month to deal with errors or inconsistencies. For a sample of patients included in SITS-MOST (n=6483), source data were verified on-site by monitors under the supervision of their national coordinator.

The need for ethics approval or patient consent for participation in SITS-ISTR varied between participating countries, but approvals were obtained in countries in which it was a requirement; other countries approved the register for conduct as an anonymised audit. SITS-MOST was approved by the ethics committee of the Karolinska Institute in Stockholm, Sweden, and by the Swedish Medical Products Agency.

Outcome measurements

The SITS-MOST definition of symptomatic intracerebral haemorrhage requires a local or remote parenchymal haemorrhage type 2 on the imaging scan at 22–36 h after treatment, combined with a neurological deterioration of 4 or more points on the NIHSS from baseline, or from the lowest NIHSS score between baseline and 24 h, or leading to death. A grading of parenchymal haemorrhage type 2 for intracranial haemorrhage indicates a blood clot exceeding 30% of the infarct area, with substantial space occupation—ie, it is sufficient to exert some pressure on adjacent intact brain. In addition to this conservative definition, we used two more inclusive definitions to enable comparisons with earlier published data: first, a haemorrhage was regarded as symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of haemorrhage and any decline in neurological status (according to the definition from the National Institute of Neurological Disorders and Stroke [NINDS]); and second, any intracranial bleed and 4 or more points worsening on the NIHSS (ECASS [European-Australasian Acute Stroke Study] II definition). All assessments of imaging studies and neurological status were done according to clinical routine at the local centres.

Functional independence was defined as a score on the modified Rankin scale of 2 or less at 3 months. This scale is a measure of disability that ranges from 0 (recovery to an asymptomatic state), through 2 (symptoms causing loss of a previous activity without requiring substantial help for daily activities, and preserving mobility), and 5 (bedbound, with severe disability), to 6 (dead). For comparison with other published work, we
also report excellent recovery, defined as a score on the modified Rankin scale of 0 or 1 (no symptoms at all or no significant disability despite symptoms, able to carry out all usual duties and activities) at 3 months after treatment. We included all deaths within 3 months.

**Statistical analysis**

We examined descriptive statistics for baseline and demographic data. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases. For calculation of significant differences between proportions, we used the χ² method and for medians the Mann-Whitney U test. We calculated the upper and lower limits of the 95% CI for proportion of symptomatic intracerebral haemorrhages, mortality, and independence by a score method with continuity correction.16

SITS-ISTR is an ongoing audit, and we included all available evidence from the register at the cut-off date for the analysis; the present sample size allowed us to identify significant absolute changes between the cohorts treated at 3–4·5 h and within 3 h in the proportions of symptomatic intracerebral haemorrhage rate (SITS-MOST definition) (1%), mortality (3%), and independency at 3 months (5%). We considered the magnitude of these changes, which represent a two-fold extension of the 95% CI for the respective outcomes in the SITS-MOST study,1 as clinically significant. We also did a multivariable analysis to record any difference in outcome parameters between patients treated at 3–4·5 h versus those treated within 3 h, after adjustment for the following variables: age, sex, history of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, congestive heart failure, previous stroke, independence before present stroke (modified Rankin scale 0–1), smoking, aspirin treatment at stroke onset, baseline NIHSS, baseline blood glucose, baseline blood pressure, bodyweight, alteplase (mg/kg bodyweight), baseline antihypertensive therapy, and signs of present infarction in the baseline imaging study. Multiple analyses were done by logistic regression analysis within generalised linear or non-linear models. We did all analyses with Statistica software (version 8.0).

**Role of the funding source**

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in this study and had the final responsibility for the decision to submit for publication.

**Results**

We included data for 664 patients with alteplase treatment started between 3 h and 4·5 h after ischaemic stroke onset and for 11 865 patients treated within 3 h. Of 478 clinical centres in 31 countries that were actively documenting thrombolysis data, 203 centres from 25 countries registered treatments during 3–4·5 h.

Table 1 shows baseline and demographic characteristics of patients in both groups. In the 3–4·5-h cohort, treatment was started at a median of 55 min later after symptom onset, median age was 3 years younger, and stroke severity was 1 point lower (as measured by NIHSS score) than in the 3-h cohort (table 1). Patients treated between 3 h and 4·5 h less frequently had reported histories of hypertension or hyperlipidaemia, but imaging evidence of current infarction was more prevalent than in the 3-h cohort (table 1). 80% of the treatment decisions in the 3–4·5-h cohort were based on plain CT or MR rather than on multimodal imaging and 88% in the 3-h cohort. Patients in the 3–4·5-h cohort were treated less frequently in new centres than in experienced centres (table 1).

![Figure 1: Proportion of patients in the 3–4·5-h and within 3-h cohorts according to time from stroke onset to treatment](image-url)
The cohorts did not differ significantly in stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, apart from a lower frequency of large artery disease with significant carotid stenosis in the 3–4·5-h cohort than in the within 3-h cohort (10% [63 of 628] vs 13·2% [1487 of 11 244]; p=0·024). Figure 1 shows the variation in stroke onset to treatment time in both cohorts. About 60% of patients in the 3–4·5-h cohort were treated between 181 min and 200 min (figure 1).

Table 2 shows the rates of haemorrhage detected by follow-up imaging (CT or MR) after alteplase treatment for patients treated at 3–4·5 h compared with those treated within 3 h. We recorded no significant differences in the proportions of local or remote haemorrhage between the groups. Figure 2 shows the scores on the modified Rankin scale at 3 months. The proportions of patients within each score on the scale at 3 months were almost identical between patients treated within 3–4·5 h and those treated within 3 h.

The rate of symptomatic intracerebral haemorrhage did not differ significantly between the two cohorts (table 3); similarly, we recorded no significant differences when symptomatic intracerebral haemorrhage was assessed according to either of the alternative definitions (ECASS II and NINDS). At 3 months, we noted no significant difference between the cohorts in mortality, rates of functional independence (modified Rankin scale score 0–2), or rates of excellent recovery (table 3).

The two cohorts did not differ significantly in any primary cause of death. We recorded intracerebral haemorrhage as a primary cause of death for 1·2% (eight of 664) of patients treated between 3 h and 4·5 h and for 1·1% (131 of 11 865) of those treated within 3 h (p=0·92). Death from a cerebral infarct was the most common cause of death, occurring in 5·0% (33 of 664) of patients in the 3–4·5-h cohort versus 4·4% (519 of 11 865) of those in the within 3-h cohort (p=0·67).

In the multivariable analysis after adjustment for other prognostic factors, we recorded no significant difference in outcome between cohorts after stroke onset. Table 3 includes the adjusted odds ratio in the 3–4·5-h cohort compared with the within 3-h cohort for symptomatic intracerebral haemorrhage per SITS-MOST and per NINDS definition, mortality at 3 months, and functional independence at 3 months. The unadjusted absolute differences in symptomatic intracerebral haemorrhage (SITS-MOST definition) and mortality were small (0·6% and 0·5%, respectively).

**Discussion**

Our results show that the rates of symptomatic intracerebral haemorrhage, mortality, and independence at 3 months follow-up in routine clinical practice are similar between patients for whom treatment was started between 3 h and 4·5 h and for those treated within 3 h after ischaemic stroke onset. Our findings lend support to those of the meta-analysis suggesting a potentially longer timeframe for intravenous thrombolysis of 4·5 h. Although the meta-analysis findings need confirmation in a separate randomised controlled trial such as ECASS-III,9 the primary value of our analysis is to provide information about treatment safety within an extended timeframe in patients treated in a clinical routine setting.

Thrombolysis with alteplase for acute ischaemic stroke is a substantial advance in the treatment of a disabling and expensive disease. Its use has been restricted to the small proportion of patients who reach hospital within 3 h from stroke onset, and to hospitals with services that are able to deliver specialist care quickly. Concerns that safety and efficacy of treatment in routine use would be less favourable than that reported in the randomised...
controlled trials have been countered by the extensive experience reported from the SITS-MOST cohort. The time limit of 3 h for initiation of intravenous alteplase is now recommended as a standard in all international stroke treatment guidelines, on the basis of the finding of the NINDS study—one of the major studies contributing to randomised data for stroke thrombolysis—showing a significant benefit of thrombolytic treatment if given within 3 h of stroke onset; and on the basis of the insufficient efficacy recorded in other randomised trials in which treatment was started beyond or predominantly beyond the 3-h limit. Data from SITS centres show that only a small proportion (4%) of all treated patients receive thrombolysis—showing a significant benefit of thrombolytic treatment if given within 3 h of stroke onset; and on the basis of the insufficient efficacy recorded in other randomised trials in which treatment was started beyond or predominantly beyond the 3-h limit. The main difference between data from the SITS-MOST study and SITS-ISTR is the lower proportion of treated patients who received alteplase (11% versus 13% in SITS-MOST and 15% in SITS-ISTR, respectively). The rate of symptomatic intracerebral haemorrhage according to the NINDS definition was 8% in SITS-MOST and 7% in ATLANTIS, whereas 8% in SITS-ISTR and 7% in ATLANTIS had asymptomatic intracerebral haemorrhage according to the NINDS definition. The main difference between data from the SITS-MOST 3–4·5-h group and ATLANTIS B active group was the time difference (1·2 h 21 min difference between median onset to treatment time); however, the outcomes of both studies were remarkably similar.

One of the limitations of our cohort study and analysis for the outcome data in the 3–4·5-h cohort is the observational design. In large, multinational, multicentre registry studies aimed at collecting data indicative of routine clinical practice, perceptual and technical differences between centres are a possibility that could have affected the assessment of intracranial haemorrhages, which were self-reported by local investigators. Furthermore, the potential bias of patient selection for treatment beyond the 3-h timeframe is another consideration. A substantial proportion of patients were treated soon after 3 h, and although the outcomes were consistent between the early and late phase of the 3–4·5-h
interval, the interpretation should be made cautiously for the later part. Although we did a multivariable analysis to adjust for recorded baseline differences, this adjustment might not account for all imbalances. We noted no strong indication that patients treated between 3 h and 4·5 h were selected because of young age, sex, or stroke severity, although patients who were treated after 3 h were slightly younger and had slightly less severe neurological deficit at baseline (table 1). Moreover, they were less often hypertensive and less frequently had a history of hyperlipidaemia than patients treated within 3 h. However, in our experience, patients with severe stroke tend to arrive at stroke treatment centres earlier and therefore receive treatment earlier than do patients with milder stroke. Further, more patients with signs of fresh infarction (by CT scan) were treated during the extended timeframe, and these patients were more likely to be treated at centres with previous experience in stroke thrombolysis, suggesting that familiarity with thrombolytic therapy might affect the decision to start treatment later than 3 h.

This observational cohort study has investigated a large series of active alteplase treatments within 3.4–5.5 h, although other observational studies have included patients starting treatment beyond this established time.19,20 For a decision by regulatory authorities and clinical guideline groups on extension of the treatment timeframe for thrombolysis—a reasonable consideration in the planning of a future trial of ECASS III—for our safety data for routine clinical use of alteplase in a wide variety of clinical settings could be especially useful.

Our findings indicate that, in patients who otherwise fulfil European summary of product characteristics criteria for intravenous thrombolysis, alteplase remains safe when given with short treatment delays beyond 3 h. However, this finding should not slow efforts to facilitate rapid treatment, since the time-dependent benefit from thrombolysis seen in the analysis from pooled data from randomised controlled trials requires that systems be optimised for the earliest possible delivery of alteplase.

Contributors
NW coordinated the study. NW, NA, and KL wrote the initial draft of the report. NA did the statistical analysis. NW, AD, RR, DT, and KL were national coordinators of leading recruiting countries. MM and KM were two of the leading local recruiters of patients into the study. All authors have read and commented on the first draft with regard to interpretation of the data and editing of the report, and have seen and approved the final version. NW and NA have direct access to the original data and vouch for the accuracy and completeness of this report.

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Conflict of interest statement
NW has received fees from Boehringer Ingelheim for his role as member of the Steering Committee in relation to the ECASS III trial with alteplase and served as a consultant to Thrombogenics as chairman of the data safety and monitoring board. SITS International [chaired by NW] received a grant from Boehringer Ingelheim for the SITS-MOST/ SITS-ISTR study with alteplase. His institution has also received grant support towards administrative expenses for coordination of the ECASS III trial. NW has also received lecture fees from Boehringer Ingelheim and from Ferrer. NA is an employee of SITS International, which received a grant from Boehringer Ingelheim for the SITS-MOST/ SITS-ISTR study with alteplase. AD has received fees and expenses from Boehringer Ingelheim for his role as member of the Steering Committee of the ECASS III trial with alteplase and related lectures. He has also received fees and expenses from Paion, Forest, and Lundbeck for the DIAS trials with desmoteplase. WH has received fees and expenses from Boehringer Ingelheim for his role as chairman of the Steering Committee of the ECASS III trial with alteplase, and related lectures. He has also received fees and expenses from Paion, Forest, and Lundbeck for his role as chairman of the Steering Committee of the DIAS and DEDAS trials with desmoteplase. MM declares that he has no conflict of interest. KM has received fees for attending symposia sponsored by Boehringer Ingelheim. DT has served as a consultant for Boehringer Ingelheim and has been paid lecture fees during attending and speaking at workshops held by Boehringer Ingelheim, Sanofi-Aventis, and Novonordisk. KL has received fees and expenses from Boehringer Ingelheim for his role as chairman of the independent data safety monitoring board of the ECASS III trial with alteplase and related lectures. He has also received fees from Paion, Forest, and Lundbeck for the DIAS trials with desmoteplase. His institution has received grant assistance towards administrative expenses for coordination of SITS in UK.

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References


