# Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study

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## Summary

**Background** **The aim of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was to assess the safety and efficacy of intravenous alteplase as thrombolytic therapy within the first 3 h of onset of acute ischaemic stroke. Under European Union regulations, SITS-MOST was required to assess the safety profile of alteplase in clinical practice by comparison with results in randomised controlled trials.**

**Methods** **6483 patients were recruited from 285 centres (50% with little previous experience in stroke thrombolysis) in 14 countries between 2002 and 2006 for this prospective, open, monitored, observational study. Primary outcomes were symptomatic (a deterioration in National Institutes of Health stroke scale score of ≥4) intracerebral haemorrhage type 2 within 24 h and mortality at 3 months. We compared mortality, the proportion of patients with symptomatic intracerebral haemorrhage as per the Cochrane definition, and functional outcome at 3 months with relevant pooled results from randomised controlled trials.**

**Findings** **Baseline characteristics of patients in SITS-MOST were much the same as those in the pooled randomised controlled trials. At 24 h, the proportion of patients with symptomatic intracerebral haemorrhage (per the SITS-MOST protocol) was 1·7% (107/6444; 95% CI 1·4–2·0); at 7 days, the proportion with the same condition as per the Cochrane definition was 7·3% (468/6438; 6·7–7·9) compared with 8·6% (40/465; 6·3–11·6) in the pooled randomised controlled trials. The mortality rate at 3 months in SITS-MOST was 11·3% (701/6218; 10·5–12·1) compared with 17·3% (83/479; 14·1–21·1) in the pooled randomised controlled trials.**

**Interpretation** **These data confirm that intravenous alteplase is safe and effective in routine clinical use when used within 3 h of stroke onset, even by centres with little previous experience of thrombolytic therapy for acute stroke. The findings should encourage wider use of thrombolytic therapy for suitable patients treated in stroke centres.**

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## Introduction

Stroke is one of the leading causes of death and disability in developed countries.[1] Although considerable progress has been made in developing effective prevention and treatment, substantial challenges remain to improve the quality of care. In particular, concern has focused on the speed of emergency response, since the time taken to initiate thrombolytic treatment after the onset of stroke symptoms affects the extent of tissue damage and the possibility of recovery without impairment.[2]

Alteplase (recombinant tissue plasminogen activator) is currently the only approved medical therapy for patients with acute ischaemic stroke and is recommended as first-line treatment by most national and international stroke associations.[3–5] Intravenous treatment of ischaemic stroke with alteplase within a 3-h window of stroke onset has been shown to be safe and effective in randomised controlled trials.[2,6–10] Studies have shown that patients treated with alteplase are at least 30% more likely to have little or no disability at 3 months than those who did not receive this treatment,[10] and the estimated number of patients needed-to-treat to identify clinical benefit is only three.[11] However, concerns have been voiced over the applicability of data from randomised controlled trials to individuals in daily clinical practice, especially considering the short time within which treatment must be given and the potential risks of intracerebral haemorrhages when thrombolytic therapy is applied.

Alteplase was licensed for the treatment of acute ischaemic stroke in the USA in 1996, and in Canada in 1999, for selected patients treated within 3 h of symptom onset.[10] In the European Union (EU), a licence was granted in 2002 on two conditions: the setting in place of an observational safety study, the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) to assess the safety profile of alteplase in routine clinical practice within 3 h of the onset of stroke symptoms, and the initiation of a new randomised trial, the European Cooperative Acute Stroke Study (ECASS) III, with a therapeutic window extended beyond 3 h. The results of both studies will serve as a basis for the reassessment of the benefit/risk profile of alteplase for the thrombolytic treatment of acute ischaemic stroke in the EU.

The main aim of SITS-MOST was to investigate whether treatment with intravenous alteplase within 3 h of ischaemic stroke symptoms is as safe as is reported in randomised controlled trials[12,13] when incorporated into

clinical practice across a wide range of centres. Here, we report the primary and secondary outcome variables of SITS-MOST.

## Methods

### Patients and procedures

SITS-MOST was a prospective, open, multicentre, multinational, observational monitoring study for clinical centres practising thrombolysis for acute stroke within the member states of the EU as of 2002, plus Norway and Iceland. The study was established as a cohort of the existing SITS-International Stroke Thrombolysis Register (SITS-ISTR), an internet-based academic interactive thrombolysis register.[14] SITS-ISTR allows the continuous monitoring of thrombolytic treatment in acute ischaemic stroke, and enables participating clinical centres to compare their treatment results with those of other centres and collaborating countries in the register. SITS-ISTR also includes reports from stroke sites in countries outside the EU, or from those within the EU where clinicians were unwilling or did not qualify to participate in SITS-MOST, and includes patients who did not meet the inclusion or exclusion criteria of SITS-MOST.

See Online for webtable

Participation in SITS-MOST was possible for any medical centre within a country affiliated to the European Evaluation of Medicines Agency (EMEA), with applications for participation through the existing SITS website.[14] Appointed national coordinators for all participating countries certified that centres that applied for participation in SITS-MOST fulfilled the eligibility criteria set by the SITS-MOST protocol.[15] These criteria included national recognition as a stroke unit or similar, routine monitoring of patients during and after thrombolysis procedures, a policy of early mobilisation and rehabilitation of stroke patients, and clinical responsibility for the management of the stroke patients held by a neurologist or stroke physician with considerable experience in stroke care. Additionally, centres had to accept the fundamental rules for participation in SITS-ISTR—ie, a commitment to register all patients treated with thrombolysis at the centre, to accept source data monitoring, and to collaborate in the elucidation of causes of any treatment complications.

SITS-MOST was approved by the ethics committee of the Karolinska Institute in Stockholm, Sweden, as well as by the Swedish Medical Products Agency. The need for ethical approval differed between participating countries. Approval from local ethics committee was obtained in countries where required. In many countries, ethical approval was not required for the audit of a treatment that had received approval by regulatory authorities. In these cases, confirmation was obtained from the appropriate bodies before study commencement. Provided local requirements for ethics committee were met and regulatory approval granted, centres were activated for recruitment of patients.

Recruitment of patients in SITS-MOST opened on December 25, 2002, and closed on April 30, 2006. Eligibility was restricted by the terms of the alteplase conditional licensing approval to those individuals who presented within 3 h of stroke onset and were between 18 years and 80 years of age. Patients on the study received treatment with intravenous alteplase at a dose of 0·9 mg/kg, in accordance with the existing European summary of product characteristics. Patients with contraindications for stroke thrombolysis according to the current summary of product characteristics—eg, patients with severe stroke as indicated on baseline CT imaging or by a baseline National Institutes of Health stroke scale (NIHSS) score of 25 or higher—were not eligible for the study. Other exclusion criteria included patients who had a stroke episode within the previous 3 months or had a previous stroke with residual functional deficit in combination with treated diabetes mellitus, and those on current intravenous high-dose or oral anticoagulants at stroke onset (webtable). These criteria were chosen to align exactly with the summary of product characteristics.

Previous experience of stroke thrombolysis before participation in SITS-MOST varied widely between centres. Centres were asked to declare relevant experience on registration, and were designated experienced if they had participated in one or both of the ECASS studies or had routinely done at least five thrombolytic procedures in stroke patients before entering SITS-MOST. Centres that lacked such experience were designated new.

The SITS-MOST cohort was embedded within the interactive internet-based SITS-ISTR. Registered centres could enter data online[14] via an electronic case record form through a secure internet connection. Patients treated up to March 31, 2004, were allocated to SITS-MOST or SITS-ISTR by investigators, but the procedure was later amended so that the allocation was done automatically by an algorithm within the electronic case record form, which verified that the eligibility criteria were fulfilled (webtable). Baseline and demographic characteristics, stroke severity, time intervals, risk factors, and medication history were gathered. Outcome measurements requested were: NIHSS score at 2 h, 24 h, and 7 days; 22–36 h CT imaging scans; medications and subgrouping of patients; and modified Rankin score at 3 months. Any adverse drug reactions were also reported. Serious adverse drug reactions for SITS-MOST patients were reported in the SITS register and via a report form to the sponsor of the study, who reported such reactions to regulatory authorities.

Incomplete data entries could be saved for later updating, but data were not deemed to be complete or included in report generation unless confirmed by the investigators by electronic signature. To be included in the SITS-MOST cohort, all baseline data entry had first to be confirmed by the investigator. SITS-MOST report generation was updated every 24 h via an automatic statistical package, which displayed main outcome details, demographic and baseline statistics, logistic information,

and a recruitment report with indication of complete and delayed data. Registered centres could review statistical details for their own centres, and compare with country statistics and with the total SITS-MOST dataset. Reports could be restricted to the SITS-MOST cohort or expanded to include all SITS-ISTR data. Procedures within SITS-MOST were guided by the study protocol.[15]

Sample source data verification was done by professional monitors working with national coordinators in collaboration with the study sponsor (Boehringer Ingelheim). A minimum of 10% of patients recruited in SITS-MOST was monitored. In the UK, source data verification was done by independent clinical staff under the direction of the UK national coordinators. This monitoring also checked for completeness of registrations at all sites.

The primary outcome measures for SITS-MOST were symptomatic intracerebral haemorrhage and death within 3 months. Symptomatic intracerebral haemorrhage, per the SITS-MOST protocol,[15] was defined as local or remote parenchymal haemorrhage type 2[16,17] on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death. For the death endpoint, survival was assessed up to 3 months from initiation of therapy by hospital follow-up records, supported either by consulting official population registers (if available) or through contact with the patient's general practitioner. Functional independence (ie, a modified Rankin score of 0–2 at 3 months) was a secondary outcome of SITS-MOST. Functional independence was assessed at 3 months after stroke onset by face-to-face or telephone interview with the patient or carer or by letter reply form. Additional outcome measures were the proportion of patients with symptomatic intracerebral haemorrhage according to NINDS[10] and Cochrane reviews[12,13] (defined as any haemorrhage plus any neurological deterioration [NIHSS score ≥1] or that leads to death within 7 days); the proportion of patients with symptomatic intracerebral haemorrhage according to ECASS[16] (defined as any haemorrhage plus a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value after baseline to 7 days or leading to death); and complete recovery (ie, a modified Rankin score of 0–1 at 3 months). Haemorrhage rates were calculated from CT or MRI imaging scans done between 22 h and 36 h after alteplase treatment, and also from any additional post-treatment scans. The proportion of patients with modified Rankin scores of 0–6 at 3 months was also calculated.

## Statistical analysis

The proportion and 95% CI of patients with symptomatic intracerebral haemorrhage, mortality, and independence were calculated and compared with the corresponding proportions in the alteplase arms of the appropriate randomised controlled trials (0–3 h cohorts). We used a score method with continuity correction to calculate the upper and lower limits of the CI.[18] For comparison, baseline data from NINDS,[10] ECASS I-II[8,9] and ATLANTIS[6,7] were extracted and pooled for both placebo and alteplase-treated patients within 3 h of symptoms. For mortality and independence summary, data from randomised controlled trials were extracted from a recent Cochrane review of thrombolysis for acute ischaemic stroke.[13] For symptomatic intracerebral haemorrhage per the NINDS/Cochrane definition, data were extracted by combining the number of patients with symptomatic intracerebral haemorrhage from the Cochrane[13] and NINDS[10] published papers. For symptomatic intracerebral haemorrhage per the ECASS definition, data were extracted from the published results of ECASS II.[16] Data from randomised controlled trials for modified Rankin scores at 3 months were calculated from a pooled analysis of recent alteplase randomised controlled trials[2] by combining the modified Rankin score results from patients treated within the first 90 min and between 91–180 min of stroke onset. All analyses were done with Statistica version 7.0.

## Role of the funding source

The study protocol was drafted by SITS and developed in close collaboration between SITS, Boehringer Ingelheim, and EMEA. All data collection and analysis were done independently by SITS. Reports to EMEA were written twice a year in parallel by SITS and Boehringer Ingelheim independently of one another. Source data verification was done by Boehringer Ingelheim in collaboration with SITS national coordinators. In the UK, source data verification was done by independent clinical staff under the direction of K R Lees and G A Ford. Boehringer Ingelheim was responsible for reporting of serious adverse drug reactions to regulatory authorities. As the corresponding author and chairman of the SITS-MOST scientific committee, N Wahlgren had full access to all data in this study, and had the final responsibility for the preparation of this manuscript and its submission for publication.

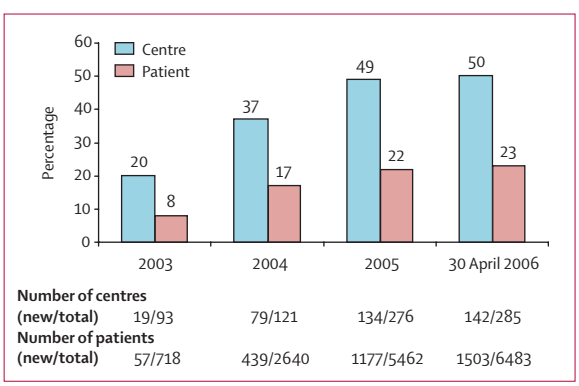


*Figure 1:* **Proportion of new centres with little or no experience in thrombolysis for stroke before joining SITS-MOST by year and proportion of patients treated in these centres**

## Results

6483 patients were included in SITS-MOST at 285 centres in 14 European countries between December, 2002, and April, 2006. The number of centres and patients recruited by country is shown in the webappendix.

See Online for webappendix

Acute follow-up data (up to 7 days) were obtained in 6476 (99·9%) patients. NIHSS data were complete at baseline in 6474 (99·9%), at 2 h in 6151 (94·9%), at 24 h in 6211 (95·8%), and at 7 days in 5423 (83·6%) patients. Follow-up data for modified Rankin score at 3 months were available for 6136 (94·6%) patients. For an additional 82 (1·3%) patients, modified Rankin score at 3 months was unknown, but the patients were confirmed as being alive by investigators. Baseline imaging studies were reported for 6450 (99·5%) patients, and follow up (22–36 h) imaging was available for 6283 (97·0%) patients.

Figure 1 shows how the recruitment of new centres in SITS-MOST progressed and gives the proportions of patients treated in these centres. The median number of patients treated per centre was 12 (IQR 5–31). One hospital treated more than 200 patients, seven centres treated at least 100 patients, and 67 centres treated fewer than five.

Table 1 shows baseline and demographic data including risk factors, presence of concomitant disease, and medical treatment at stroke onset for patients in SITS-MOST and those from the pooled randomised

| | SITS-MOST (n=6483) | Pooled randomised controlled trials,[2,7–10] 0–3 h | |
|---|---|---|---|
| | | Placebo (n=465) | Alteplase (n=464) |
| Age (years) | 68 (59–75) | 67·1 (59·5–74·2) | 69·6 (61·3–75·4) |
| Sex (female) | 2581 (39·8%) | 187 (40·2%) | 186 (40·1%) |
| Independence (modified Rankin score 0–1) before stroke | 5899/6337 (93·1%) | NA | NA |
| Hypertension | 3710/6318 (58·7%) | 282 (60·7%) | 277 (59·7%) |
| Diabetes mellitus | 1020/6374 (16·0%) | 88 (18·9%) | 98 (21·1%) |
| Hyperlipidaemia | 1967/5661 (34·8%) | NA | NA |
| Atrial fibrillation | 1507/6306 (23·9%) | 93 (20·0%) | 96 (20·7%) |
| Congestive heart failure | 467/6339 (7·5%) | 71 (15·3%) | 61 (13·2%) |
| Smoking (current=1474; previous=1169) | 2643/6114 (43·2%) | NA | NA |
| Aspirin at stroke onset | 1918/6441 (29·8%) | 134 (28·8%) | 169 (36·4%) |
| Anti-hypertensive | 2983/6429 (46·4%) | NA | NA |
| Blood glucose (mmol/L) | 6·4 (5·6–7·7) | 6·9 (5·9–8·4) | 6·6 (5·8–8·8) |
| Weight (kg) | 75 (68–85) | 79·4 (66–90·7) | 75 (65–84) |
| Systolic blood pressure (mm Hg) | 150 (137–166) | 152 (140–170) | 156 (140–170) |
| Diastolic blood pressure (mm Hg) | 81 (74–90) | 86 (77–95·5) | 84 (78–92) |
| Degree of neurological severity (NIHSS excluding distal motor function) | 12 (8–17) | 14 (9–19) | 13 (8–18) |
| Mild (NIHSS 1–7) | 1494 (23%) | .. | .. |
| Moderate (NIHSS 8–14) | 2409 (37%) | .. | .. |
| Severe (NIHSS ≥15) | 2571 (40%) | .. | .. |
| Previous stroke | 643/6395 (10·1%) | 59 (12·7%) | 64 (13·8%) |
| Previous stroke and reduced functional status (modified Rankin score >1) | 80/643 (12·4%) | .. | .. |
| Cause of stroke | | | |
| Large vessel disease with substantial carotid stenosis | 844 (13%) | .. | .. |
| Large vessel disease other than substantial carotid stenosis | 1435 (22·1%) | .. | .. |
| Cardiac origin | 2270 (35%) | .. | .. |
| Lacunar stroke | 535 (8·3%) | .. | .. |
| Other | 1171 (18·1%) | .. | .. |
| Unknown | 228 (3·5%) | .. | .. |
| Signs of current infarction on baseline imaging study | 1315/6450 (20·4%) | .. | .. |
| Stroke onset to treatment time (min) | 140 (115–165) | 138 (90–165) | 140 (90–168) |
| Mean delay between stroke onset and treatment (min) | 136 (33) | .. | .. |
| Treated within 90 min | 671 (10.6%) | .. | .. |
| Treated within 120–180 min | 4276 (66%) | .. | .. |
| Door-to-needle time (ie, from entering the facility to receiving treatment with alteplase) (min) | 68 (30) | .. | .. |

Data are median (IQR), mean (SD), or n (%).

*Table 1:* **Baseline characteristics of patients enrolled in SITS-MOST and pooled randomised controlled trials within 3 h of stroke onset to treatment**

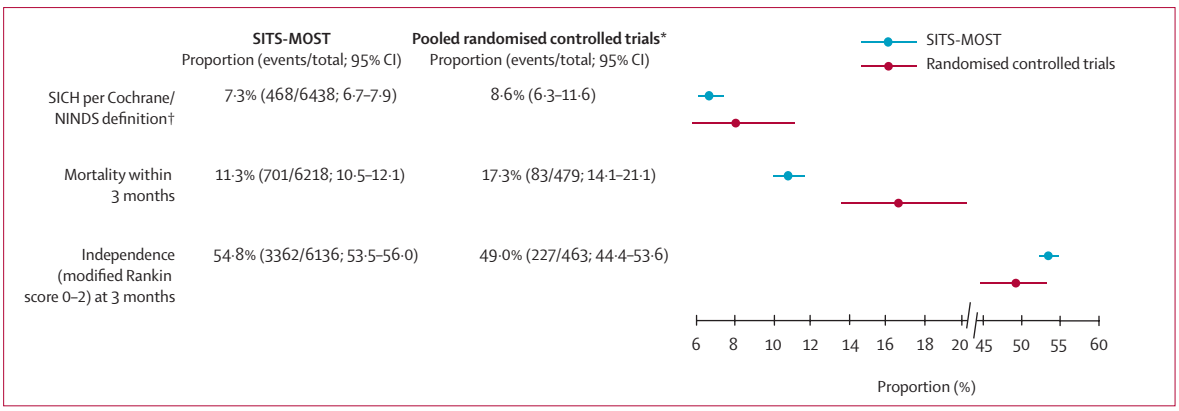


***Figure 2:*** **Proportions of patients with symptomatic intracerebral haemorrhage, including fatalities, and mortality and independence at 3 months in SITS-MOST and pooled randomised controlled trials[10,13]**

SICH=symptomatic intracerebral haemorrhage. *Active arms. †NIHSS≥1 and any haemorrhage.

controlled trials. Table 1 also shows the degree of neurological severity and cause of stroke for patients in SITS-MOST.

Treatment was withheld in six registered patients because the 3-h window for treatment was exceeded (n=2), there was rapid improvement of symptoms (2), or other reasons (2). A lower dose of alteplase was administered in 118 patients because of allergic reaction (5), clinical deterioration (26), and other reasons (87). The median dose of alteplase administered was 68 mg (IQR 60–77 mg).

Figure 2 shows a comparison between SITS-MOST and pooled randomised controlled trials for symptomatic intracerebral haemorrhage (as defined by the Cochrane definition), mortality, and independence for activities of daily living. The proportion of patients with symptomatic intracerebral haemorrhage according to the defined SITS-MOST criteria was 1·7% (107/6444; 95% CI 1·4–2·0). When haemorrhages on any post-treatment imaging studies within 7 days were included in the SITS-MOST definition of symptomatic intracerebral haemorrhage, the overall proportion was 2·2% (140/6445; 1·8–2·6). The proportion of patients with symptomatic intracerebral haemorrhage according to the ECASS definition was 4·6% (296/6442; 4·1–5·1), compared with 8·8% (36/407; 6·4–12·2) in the ECASS II study; pooled results from randomised controlled trials according to this definition are not available. The proportion of patients with fatal symptomatic intracerebral haemorrhage as per the SITS-MOST definition up to 24 h was 0·28% (18/6444; 0·17–0·45) and per the Cochrane or NINDS definitions up to 7 days was 2·2% (144/6438; 1·9–2·6). Table 2 shows the rates of local and remote haemorrhages recorded at follow-up imaging studies.

Of the 701 deaths that occurred within 3 months of treatment with alteplase, causes of death were available for 674 patients. In 96 (14% of deaths; 1·5% of treated patients) of these cases, death was considered by the investigators to be related to treatment. Causes of death were cerebral infarction (n=285), intracerebral haemorrhage (66), cerebral infarction or haemorrhage, unspecified (50), myocardial infarction (34), pulmonary embolism (22), pneumonia (92), other vascular deaths (37), and other causes (88).

We stratified baseline data (table 3) and main outcomes (figure 3) according to centres' previous experience with thrombolysis in acute stroke. The proportion of patients with symptomatic intracerebral haemorrhage according to ECASS definitions for experienced and new centres was 4·6% (227/4951; 95% CI 4·0–5·2) for experienced centres and 4·6% (69/6438; 3·7–5·8) for new centres. The rate of complete recovery (ie, a modified Rankin score of 0–1) at 3 months was 38·3% (1792/4675; 36·9–39·7) in experienced and 40·7% (594/1461; 38·2–43·2) in new centres. Any degree of local haemorrhage on any post-

| | Haemorrhages at 22–36 h imaging scans | Haemorrhages on any post-treatment imaging scans |
|---|---|---|
| **Local haemorrhages** | **n=6283** | **n=6352** |
| None | 5369 (85·5%) | 5267 (82·9%) |
| Haemorrhagic infarct type 1 | 338 (5·4%) | 402 (6·3%) |
| Haemorrhagic infarct type 2 | 250 (4·0%) | 297 (4·7%) |
| Primary intracerebral haemorrhage type 1 | 166 (2·6%) | 202 (3·2%) |
| Primary intracerebral haemorrhage type 2 | 160 (2·5%) | 184 (2·9%) |
| **Known remote haemorrhages** | **n=6282** | **n=6350** |
| No remote haemorrhage | 6111 (97·3%) | 6155 (96·9%) |
| Remote primary intracerebral haemorrhage type 1 | 105 (1·7%) | 113 (1·8%) |
| Remote primary intracerebral haemorrhage type 2 | 66 (1·1%) | 82 (1·3%) |

Data are n (%). Haemorrhagic infarct type 1=small petechiae along the margins of the infarct. Haemorrhagic infarct type 2=more confluent petechiae within the infarct area but without space-occupying effect. Primary intracerebral haemorrhage type 1=blood clot(s) not exceeding 30% of the infarct area with some mild space-occupying effect. Primary intracerebral haemorrhage type 2=blood clots exceeding 30% of the infarct area with substantial space occupying effect. Remote primary intracerebral haemorrhage type 1=small or medium sized blood clots located remote from the actual infarct; a mild space occupying effect could be present. Remote primary intracerebral haemorrhage type 2=large confluent dense blood clots in an area remote from the actual infarct; substantial space occupying effect might be present.

***Table 2:*** **Intracerebral haemorrhages detected by CT or MRI study at 22–36 h after treatment and any post-treatment imaging scans**

| | Experienced (n=4980) | New (n=1503) |
|---|---|---|
| Age (years) | 68·5 (59–75) | 68 (59–74) |
| Sex (female) | 1988 (39·9%) | 593 (39·5%) |
| Independence (modified Rankin score 0–1) before stroke | 4556/4861 (93·7%) | 1343/1476 (91·0%) |
| Hypertension | 2916/4856 (60·1%) | 794/1462 (54·3%) |
| Diabetes mellitus | 820/4892 (16·8%) | 200/1482 (13·5%) |
| Atrial fibrillation | 1161/4838 (24·0%) | 346/1468 (23·6%) |
| Congestive heart failure | 381/4861 (7·8%) | 95/1478 (6·4%) |
| Previous stroke | 507/4904 (10·3%) | 136/1491 (9·1%) |
| Aspirin at stroke onset | 1515/4904 (30·6%) | 403/1496 (26·9%) |
| Blood glucose (mmol/L) | 6·4 (5·6–7·8) | 6·4 (5·6–7·7) |
| NIHSS score excluding distal motor function | 12 (8–17) | 13 (8–18) |
| Systolic blood pressure (mm Hg) | 150 (138–166) | 150 (135–165) |
| Diastolic blood pressure (mm Hg) | 82 (75–90) | 80 (74–90) |
| Stroke onset to treatment time (min) | 140 (110–165) | 145 (120–165) |
| Alteplase dose (mg) | 68 (60–77) | 68 (60–76) |

Data are median (IQR) or n (%).

***Table 3:*** **Baseline characteristics of patients enrolled in SITS-MOST according to centres' previous experience with stroke thrombolysis before joining SITS-MOST**

treatment imaging study was reported in 17·5% (852/4875; 16·4–18·6) of patients in experienced centres and in 15·8% (233/1477; 14·0–17·8) for new centres; the figures for any remote haemorrhage were 3·1% (153/4875; 2·7–3·7) and 2·8% (42/1475; 2·1–3·9), respectively.

Median NIHSS score for SITS-MOST patients fell to 4·0 (IQR 1–11) at time of discharge or 7-day review. The median score had dropped to below 9·0 (IQR 4–15) within 2 h of starting therapy. The effect of treatment on median Rankin score at 3 months is compared with relevant pooled data from randomised controlled trials in figure 4. Complete recovery at 3 months was seen in 38·9% (2386/6136; 95% CI 37·7–40·1) of patients in SITS-MOST compared with 42·3% (196/463; 37·8–47·0) in randomised controlled trials.

## Discussion

The results from SITS-MOST confirm that alteplase, when used in routine clinical practice, has a safety profile at least as good as that seen in randomised controlled trials and is an effective treatment when used within 3 h of stroke onset, even in stroke centres with little previous experience

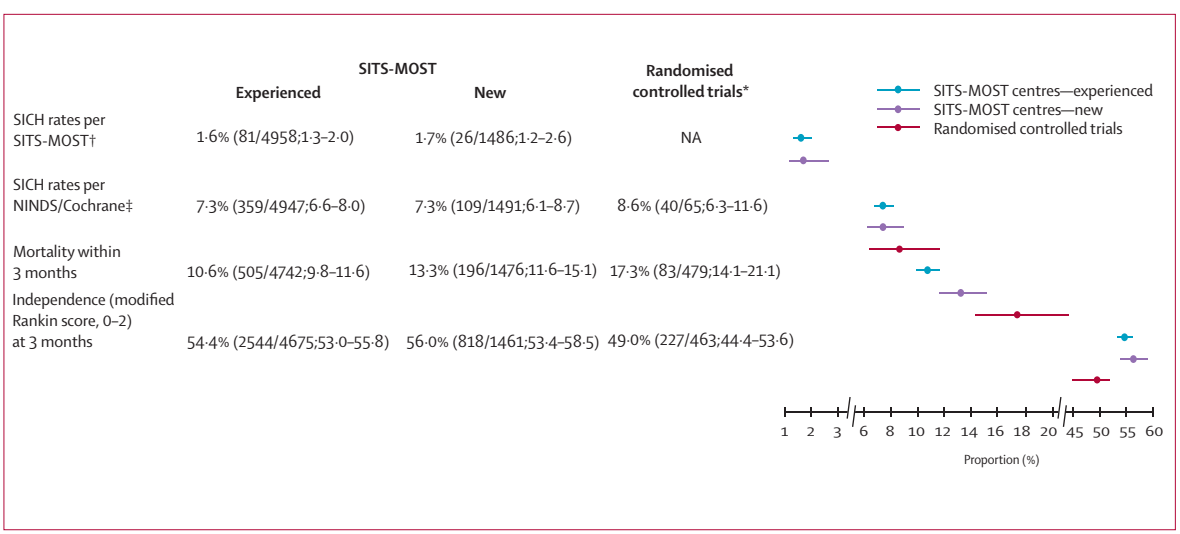


***Figure 3:*** **Proportions of patients with symptomatic intracerebral haemorrhage, including fatalities, and mortality and independence at 3 months in experienced and new SITS-MOST centres and pooled randomised controlled trials[10,13]**

Data are % (n/N; 95% CI). SICH=symptomatic intracerebral haemorrhage. *Active arms. †NIHSS≥4 and primary intracerebral haemorrhage/remote primary intracerebral haemorrhage type 2. ‡NIHSS≥1 and any haemorrhage.

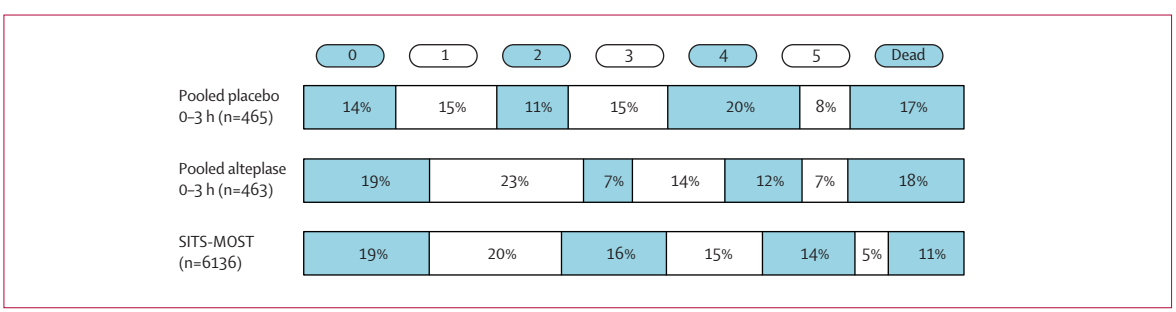


***Figure 4:*** **Proportion of patients with modified Rankin score of 0–6 at 3 months in SITS-MOST and in pooled randomised controlled trials for both placebo and alteplase patients[2]**

of thrombolytic therapy for acute stroke. Although mortality was higher in less experienced centres than in those with previous experience, it was lower than in randomised controlled trials, and the difference was not caused by haemorrhagic complications.

The number of patients recruited in SITS-MOST exceeded the projected minimum requirements of the regulatory authorities by more than six times. The use of an innovative internet-based data register ensured a high degree of compliance in data collection and completion. Data entries for the acute phase were completed in almost all cases, with follow-up data at 3 months available in about 95% of cases. One difficulty with a treatment registry study is to ascertain that all patients treated have been included in the dataset and that no biased reporting has occurred. Auditing of centre data in the SITS database did not reveal any indication of biased reporting during the course of SITS-MOST.

SITS-MOST was designed to measure the safety and effectiveness of thrombolytic therapy—intravenous alteplase—when used in a 3-h therapeutic window after the onset of stroke in a wide range of clinical settings. The aim was to establish whether the levels of safety seen in randomised controlled trial populations could be reproduced in routine clinical practice—especially with regard to intracerebral haemorrhage. Our results showed that the proportion of patients who developed symptomatic intracerebral haemorrhage in the SITS-MOST and alteplase randomised controlled trial populations was much the same when similar definitions for symptomatic intracerebral haemorrhage were applied. There was a trend towards a reduced incidence of intracerebral haemorrhage in SITS-MOST, although CI overlapped. There was, however, a noticeable reduction in mortality within the first 3 months of stroke onset in SITS-MOST compared with that seen within randomised controlled trials (11·3% *vs* 17·3%). Mortality in SITS-MOST was also much lower than that seen in the Canadian Alteplase for Stroke Effectiveness Study (CASES)—an observational cohort study of alteplase for stroke thrombolysis done between February, 1999, and June, 2001, where mortality was 22·3%.[19] One contributing factor for lower mortality in SITS-MOST could be that study recruitment was restricted to patients between 18 and 80 years, with an NIHSS score of 25 or lower, and with a maximum stroke onset-to-treatment time of 3 h. In CASES,[19] the median age was 73 years (*vs* 68 years in SITS-MOST), and the median NIHSS score was 14 (*vs* 12 here). Strokes were consequently less severe and the patient population younger in SITS-MOST than in the randomised controlled trials and CASES.[19] These limitations were part of a regulatory decision on the basis of the existing licence for alteplase in Europe. Another explanation could be improved stroke unit care, which has been shown to reduce mortality.[20] Other smaller observational multicentre studies, including a total of about 650 patients, have reported results in the same order[21,22] as SITS-MOST, although a high rate of symptomatic intracerebral haemorrhage was noted in one study.[23]

Randomised controlled trials have shown an improvement of about 10% in the number of patients who achieve functional independence in activities of daily living (defined as a modified Rankin score of 0–2) within 3 months of a stroke when treated with alteplase, compared with placebo.[2] A further slight increase in functional independence of around 5% occurred for patients treated in SITS-MOST within a routine clinical setting (figure 4). Complete recovery at 3 months was much the same in SITS-MOST and in the pooled randomised controlled trials (39% *vs* 42%); 32% of patients in CASES made a complete recovery.[19]

Monitoring of treatment safety by clinical centres without substantial previous experience of stroke thrombolysis before entering SITS-MOST was an important aspect of SITS-MOST. Lyden and colleagues[24] have previously commented on the uncertainty shown by less experienced practitioners of thrombolysis about incorporating the technique into their routine practice. In late 2002, when SITS-MOST was started, almost all participating centres were experienced at thrombolysis through trials or clinical routine. By the end of the study, recruitment of new centres had increased to about 50%, showing broad implementation, increased awareness, and growing practical ability to provide thrombolysis within the 3-h therapeutic window. Assessment of symptomatic intracerebral haemorrhage outcomes compared with those with experience showed that treatment safety could be maintained across all centres. Neither the proportion of patients with symptomatic intracerebral haemorrhage nor the degree of independence at 3 months differed between experienced and new centres. Although mortality was higher in new centres than in those that were experienced, the mortality in new centres remained lower than seen previously in randomised controlled trials, although the CI overlapped. Baseline stroke severity in new centres was higher (1 point higher median NIHSS score) than in experienced centres, which could explain the higher mortality levels. The extra deaths in new centres were not caused by haemorrhages, as shown by the similar rates of symptomatic and asymptomatic haemorrhages. A multivariate analysis is underway to examine further the trend of higher mortality in new centres compared with experienced centres.

Although there are still unanswered questions with regard to the role of stroke thrombolysis beyond the limitations of this study, our data suggest that thrombolysis should now be considered a part of routine care of suitable stroke patients.[25] We hope that these findings will encourage the uptake of routine thrombolytic therapy for suitable patients in stroke centres, whether experienced or new to stroke thrombolysis.

**Contributors**

N Wahlgren coordinated the study. N Wahlgren and N Ahmed wrote the initial draft of the manuscript. N Ahmed did the statistical analyses. Authors are members of the scientific committee of SITS-MOST, except for L Soinne and S Kuelkens who were leading recruiters of patients into the study. All authors have contributed to the overseeing of SITS-MOST and have read and commented on the first draft of this manuscript with regard to interpretation of the data and editing, and have seen and approved the final version and revisions. Analyses for reports to the EMEA were developed in close collaboration with Boehringer Ingelheim (Germany).

**Conflict of interest statement**

N Wahlgren, M Kaste, D Toni, A Davalos, V Larrue, K R Lees, G Vanhooren, M Grond, and G A Ford have received compensation from Boehringer Ingelheim, Germany, for serving on scientific advisory committees. N Ahmed is an employee of the SITS-International Co-ordination Office. N Wahlgren, W Hacke, A Davalos, and M Grond have undertaken speaking engagements for Boehringer Ingelheim. D Toni and R O Roine have undertaken speaking engagements for Boehringer Ingelheim, NovoNordisk, Pfizer and Sanofi-Aventis. G Vanhooren has acted as a consultant for AstraZeneca, Sanofi-Aventis, and AGFA, and has undertaken speaking engagements for Boehringer Ingelheim, AstraZeneca, Lundbeck, GSK, Sanofi-Aventis, and NovoNordisk. W Hacke and K R Lees have acted as consultants to PAION and Forest. L Soinne, M G Hennerici, and S Kuelkens have no conflicts of interest to declare. L Alder received funding from Boehringer Ingelheim for editorial assistance in the coordination of the submission.

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