

Thrombolysis for acute stroke in Australia: outcomes from the Safe Implementation of Thrombolysis in Stroke registry (2002–2008)

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Thrombolysis for acute stroke with recombinant tissue plasminogen activator (rt-PA) is increasingly being used in metropolitan and regional hospitals.^{1–3} In randomised controlled trials, rt-PA given within 3 hours of onset of stroke symptoms has been shown to improve outcome with reduced disability at 3 months, albeit with a small risk of serious harm, usually related to intracranial haemorrhage.^{4–6}

In response to concerns that rt-PA given in normal clinical practice might not have the same risk–benefit ratio as that given in trials, a consensus statement from the Karolinska Stroke Update meeting in 2000 recommended continuous audit of clinical rt-PA use.⁷ The result was Safe Implementation of Thrombolysis in Stroke (SITS), a collaborative of over 700 centres in 35 countries committed to the audit of thrombolysis for stroke with the aim of standardising services, maintaining safety and improving outcomes. The SITS International Stroke Thrombolysis Register (ISTR)^{8,9} has two main aims: to assess whether the favourable results from the original clinical trials are maintained in clinical practice; and to allow individual centres to monitor their own treatment time lines and outcomes, and compare these to national and international data.

For the first time, we report the Australian experience of thrombolysis for stroke from December 2002 to December 2008, as recorded in the SITS-ISTR, and compare these Australian data to worldwide data for the same period. We also used the Australian data to explore the demographic and clinical characteristics that may predict outcome after thrombolysis.

METHODS

In Australia, participation in the SITS-ISTR is not compulsory but is strongly encouraged for all centres administering rt-PA for stroke. Participating centres answer a series of questions on a password-protected, interactive website. Participants commit to registering all treated patients and consent to audit of the data. The inclusion criteria encompass all patients treated with rt-PA for

ABSTRACT

Objective: To report Australian outcomes from the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register (SITS-ISTR).

Design: Observational study using data collected prospectively from December 2002 to December 2008.

Setting: Centres administering thrombolysis for acute stroke in Australia and worldwide.

Patients: All patients treated with recombinant tissue plasminogen activator for acute stroke in participating centres, regardless of stroke severity, time of treatment and other clinical factors.

Intervention: Thrombolysis for acute stroke, administered according to local protocol.

Main outcome measures: Functional outcome as 3-month modified Rankin score (mRS), and frequency of symptomatic intracerebral haemorrhage (ICH).

Results: During the study period, a total of 32 countries participated, and confirmed baseline data were available for 581 Australian patients and 20953 patients in the rest of the world. Australian patients were older (median age, 73 v 69 years; $P < 0.001$), were less independent before stroke (premorbid mRS of 0–1, 87.5% v 91.2%; $P < 0.005$), and had more comorbidities and more severe strokes. Comparing the Australian cohort with the rest of the world, the odds ratio of 3-month mRS of 0–2 was 0.98 (95% CI, 0.88–1.08; $P = 0.63$), the odds ratio of symptomatic ICH was 0.98 (95% CI, 0.83–1.16; $P = 0.85$ [by the definition used by the National Institute of Neurological Disorders]) and the odds ratio of death was 1.04 (95% CI, 0.91–1.19; $P = 0.54$). Good outcome in the Australian cohort was predicted by younger age, presence of hyperlipidaemia, lower premorbid mRS, absence of infarct on early brain imaging, less severe stroke, and lower baseline blood glucose level.

Conclusion: Clinical outcomes after thrombolysis in Australia were similar to those worldwide.

MJA 2010; 193: 439–443

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ischaemic stroke, regardless of age, time of treatment or other clinical factors. De-identified data are collected on:

- patient demographics and medical history — age, sex, premorbid function as modified Rankin score (mRS) (Box 1), cardiovascular risk factors and premorbid drug therapy
- treating centre location and previous experience with rt-PA
- details of the acute stroke — time of stroke, arrival to hospital, brain imaging and treatment; classification of stroke according to the International Classification of Diseases (10th revision); and baseline National Institutes of Health Stroke Scale (NIHSS) score¹¹
- results of brain imaging — presence of infarct or haemorrhage on any scan, and findings from additional cerebrovascular imaging
- primary outcomes — presence of symptomatic intracerebral haemorrhage (ICH)

according to each of three recognised definitions (Box 2), mortality, and functional status at 3 months after stroke as mRS assessed by face-to-face or telephone interview (a “good functional outcome” was defined as an mRS of 0–2 at 3 months).

Details of any adverse events relating to thrombolysis are also provided. Centres receive a computer-generated report of their own data and those of the global dataset.

In addition, data on country of origin are entered into the SITS central database, which was searched for “Australia” or “other”. For this study, data for Australia were excluded from the worldwide dataset.

Statistical analysis

Statistical analyses were performed using Stata version 10.0 IC (StataCorp, College Station, Tex, USA). For comparison with

1 Modified Rankin score (mRS) — a scale for measuring global disability, widely used to assess outcome after stroke¹⁰

Score	Definition
0	No symptoms
1	No significant disability; despite symptoms, able to carry out all usual activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

worldwide data, only patients with confirmed baseline data were included; for the Australian-only analyses, patients were included if data were available for the relevant variable.

Unadjusted comparisons within the Australian dataset and between the Australian and worldwide datasets were performed using a *t* test or Mann–Whitney test for interval variables and χ^2 test or Fisher exact test for categorical variables, as appropriate. Adjusted analyses of primary outcomes were performed using logistic regression. Analysis of factors associated with good functional outcome within the Australian dataset was performed by a multilevel random effect logistic regression model, using treating hospital as a grouping variable. Due to negligible interhospital variability of the outcome, the clustering effect of hospitals was ignored and further analysis of factors predictive of good functional outcome within the Australian dataset was performed via backward stepwise logistic regression (significance level for removal from model, 0.2; significance level for addition to model, 0.1).

RESULTS

Between December 2002 and December 2008, 704 patients from 14 Australian centres were entered into the SITS-ISTR.

Confirmed baseline data were available for 581 patients; varying amounts of data were missing for the remainder — baseline clinical data were missing for six patients, brain imaging data were missing for 114, and outcome data were missing for 94. During the study period, 31 countries other than Australia participated and 20 953 patients with confirmed baseline data were entered into the SITS-ISTR. Demographic and baseline data for the two cohorts are summarised in Box 3. The Australian cohort was significantly older and less independent at baseline than the worldwide cohort.

Comorbidities and risk factors. Compared with the worldwide cohort, the Australian cohort included more patients with atrial fibrillation (35.7% v 21.9%, $P < 0.001$) and hyperlipidaemia (41.9% v 34.3%, $P < 0.001$), fewer current smokers (14.9% v 23.4%, $P < 0.001$), and more patients taking aspirin (35.8% v 30.9%, $P < 0.05$) and antihypertensives (53.2% v 45.9%, $P < 0.001$) before the stroke. There were no statistically significant differences in the prevalence of hypertension, diabetes, heart disease or previous stroke between cohorts.

Stroke severity and aetiology. The Australian patients had more severe strokes, with a median baseline NIHSS score of 13 (interquartile range [IQR], 8–19) compared with 12 (IQR, 8–17) for the worldwide cohort ($P < 0.001$) (Box 3). There was a higher proportion of patients who had cardioembolic strokes in the Australian cohort (50.5% v 34.5%, $P < 0.001$).

Speed of stroke treatment. There was no statistically significant difference in overall onset-to-treatment time between Australian and worldwide cohorts but, in Australia, the onset-to-door time was shorter ($P < 0.001$) and door-to-needle time was longer ($P < 0.001$) (Box 4).

Primary outcomes. After adjusting for clinical and demographic characteristics, there were no statistically significant differences in any primary outcomes (mortality, good functional outcome, or frequency of symptomatic ICH) between the Australian and worldwide cohorts. Adjustment was made for: age, sex, hypertension, diabetes, hyperlipidaemia, atrial fibrillation, cardiac failure, previous stroke, premorbid mRS, smoking, aspirin or other antiplatelet use at onset, signs of current stroke on baseline brain imaging, stroke onset-to-treatment time, systolic and diastolic blood pressure

2 Definitions of symptomatic intracerebral haemorrhage (ICH)

Study	Definition of symptomatic ICH
SITS-MOST	Local or remote parenchymal haemorrhage type 2 (defined as dense haematoma [$> 30\%$ of the infarcted area with substantial space-occupying effect] or as any haemorrhagic lesion outside the infarcted area) on the computed tomography scan performed 22–36 hours after treatment, combined with neurological deterioration of four or more NIHSS points from baseline or from the lowest NIHSS score between baseline and 24 hours, or neurological deterioration leading to death because of the ICH ¹²
ECASS	Any ICH combined with a neurological deterioration of more than four NIHSS points from baseline or from the lowest NIHSS score, or death due to ICH within 7 days ¹³
RCTs	Neurological deterioration of one or more NIHSS point within 7 days combined with any haemorrhage ⁶

SITS-MOST = Safe Implementation of Thrombolysis in Stroke Monitoring Study. NIHSS = National Institutes of Health Stroke Scale. ECASS = European Cooperative Acute Stroke Study. RCT = randomised controlled trial. ♦

and blood glucose level at presentation, baseline NIHSS score, weight and rt-PA dose. Odds ratios are shown in Box 5.

Mortality. In the Australian cohort, 118 of 634 patients (18.6%) for whom mortality data were available died; 10 of the 118 patients (8.5%) died between 0 and 24 hours, 55 (46.6%) died between 24 hours and 7 days, 49 (41.5%) died between 7 days and 3 months, and time of death data were missing for the remaining four patients. Causes of death were: the presenting ischaemic stroke (54/118, 45.8%); cerebral infarct with haemorrhagic transformation (14/118, 11.9%); ICH (14/118, 11.9%); pneumonia (10/118, 8.5%); myocardial infarction (5/118, 4.2%); pulmonary embolism (2/118, 1.7%); and other or unspecified causes. The fatal ICH rate among treated patients at 3 months was 2.2% (14/634).

Adverse events. Rates of symptomatic ICH among the Australian patients according to each of the three definitions were 1.3% (7 of 560 reported; Safe Implementation of

3 Demographic and baseline data in the SITS-ISTR

	Australia	Worldwide*	P
Median age (IQR), years	73 (63–80)	69 (60–76)	<0.001
Male	57.1%	58.5%	0.51
Median NIHSS score (IQR)	13 (8–19)	12 (8–17)	<0.001
Premorbid mRS of 0–1	87.5%	91.2%	<0.005
Median systolic blood pressure (IQR), mm Hg	148 (132–161)	151 (138–168)	<0.001

SITS-ISTR = Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register. IQR = interquartile range. NIHSS = National Institute of Health Stroke Scale. mRS = modified Rankin score. *Worldwide data represent 31 countries, excluding Australia. ◆

4 Speed of stroke treatment in the SITS-ISTR

	Australia	Worldwide*	P
Median onset-to-door time (IQR), min	60 (45–81)	65 (45–95)	<0.001
Median door-to-needle time (IQR), min	75 (57–98)	65 (46–90)	<0.001
Median onset-to-treatment time (IQR), min	145 (123–166)	145 (115–170)	0.93

SITS-ISTR = Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register. IQR = interquartile range. *Worldwide data represent 31 countries, excluding Australia. ◆

5 Adjusted primary outcomes in the SITS-ISTR

Australia v worldwide*	Odds ratio (95% CI)	P
Symptomatic ICH, per SITS-MOST definition	0.87 (0.59–1.27)	0.46
Symptomatic ICH, per RCT definition	0.98 (0.83–1.16)	0.85
Dead	1.04 (0.91–1.19)	0.54
3-month mRS of 0–2	0.98 (0.88–1.08)	0.63

SITS-ISTR = Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register. ICH = symptomatic intracerebral haemorrhage. SITS-MOST = Safe Implementation of Thrombolysis in Stroke Monitoring Study. RCT = randomised controlled trial. mRS = modified Rankin score. *Worldwide data represent 31 countries, excluding Australia. ◆

6 Odds ratios for predictors of good outcome according to SITS-ISTR data on Australian patients

Variable	Odds ratio (95% CI)	P
Age (per extra year of life)	0.97 (0.95–0.99)	<0.001
Hyperlipidaemia (present)	1.99 (1.21–3.29)	0.02
Premorbid mRS of 0–1	4.62 (1.96–10.85)	<0.001
Infarct on early computed tomography scan (present)	0.44 (0.26–0.75)	0.001
Baseline NIHSS score (per unit of increase)	0.85 (0.81–0.89)	<0.001
Baseline blood glucose level (per unit of increase)	0.99 (0.98–1.00)	0.004

SITS-ISTR = Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register. mRS = modified Rankin score. NIHSS = National Institute of Health Stroke Scale. ◆

Thrombolysis in Stroke Monitoring Study [SITS-MOST]), 6.6% (34 of 517 reported; European Cooperative Acute Stroke Study [ECASS]) and 8.3% (43 of 518 reported; randomised controlled trials [RCTs]). Three additional serious adverse events were reported in the Australian cohort: one

patient developed lingual angioedema requiring intubation and intensive care unit admission, one had a haemodynamically significant intraperitoneal haemorrhage, and one had episodes of asystole. There were 13 minor adverse events, including minor bleeding and allergy without angioedema.

Outcomes according to demographics.

Within the Australian cohort, there were no statistically significant differences in outcome according to sex in terms of mRS at 3 months or frequency of symptomatic ICH. Functional outcome at 3 months was significantly worse among patients aged ≥ 80 years than for patients aged < 80 years (proportion with 3-month mRS of 0–2, 30% v 55%; $P < 0.001$). The odds ratio for a good functional outcome for patients aged ≥ 80 years compared with patients aged < 80 years, adjusted for premorbid mRS, was 0.42 ($P < 0.001$). Analysis of the influence of age on outcome showed that for every year older the patient was, the odds of a good functional outcome decreased by 4%. However, there was no statistically significant difference in the frequency of symptomatic ICH, according to any of the three definitions used, between patients aged ≥ 80 years and those aged < 80 years.

Outcomes according to time of treatment.

Within the Australian cohort, 50 patients were treated more than 180 minutes after stroke onset (median time, 190 min [range, 181–311 min; IQR, 185–197 min]). Outcomes for these patients (mRS at 3 months and frequency of symptomatic ICH) did not differ from outcomes in patients treated earlier than 180 minutes.

Predictors of outcome in Australian cohort.

Multilevel logistic regression analysis showed that the observed interhospital variability was minimal (variance of random effect estimation, 0.001; intraclass correlation, < 0.001). Subsequent backward stepwise application of binary logistic regression revealed that the following factors were associated with good outcome: younger age; presence of hyperlipidaemia; premorbid mRS of 0–1; absence of infarct on early brain imaging; lower baseline NIHSS score; and lower baseline blood glucose level (Box 6).

DISCUSSION

Outcomes for Australian stroke patients treated with rt-PA in the SITS-ISTR were similar to those for the worldwide cohort. However, the Australian patients were older, less independent before the stroke, more likely to be taking aspirin and anti-hypertensives at the time of their stroke, and had a higher incidence of comorbidities, particularly atrial fibrillation. This was reflected by a more severe baseline stroke

severity and more common cardioembolic aetiology among Australian patients.

Despite the baseline differences, there was no statistically significant difference in the proportion of patients with post-treatment symptomatic ICH between the two cohorts. This finding is reassuring because symptomatic ICH is the most feared complication of rt-PA therapy. The original trials of rt-PA excluded patients aged ≥ 80 years, thus there is a paucity of data regarding the risks and benefits of treatment in this age group.⁶ In our study, older age was associated with a poorer outcome in terms of mRS, even after adjusting for premorbid mRS, which may be a reflection of older patients having more severe strokes and less functional capacity for recovery. Nevertheless, our data suggest that older patients are not at increased risk of harm after treatment with rt-PA, which may help to inform treatment decisions.

The reasons for the differences in patient populations treated with rt-PA may reflect local differences in treatment policy. The Australian National Stroke Foundation guidelines list age over 80 years as a relative contraindication to therapy,¹⁴ and the United Kingdom National Institute for Health and Clinical Excellence and European Stroke Organisation guidelines state that use of rt-PA in patients aged over 80 years is outside the marketing authorisation of the drug but may be used in selected patients.^{15,16} The American Stroke Association guidelines do not mention age.¹⁷ The differences in the proportion of patients with cardioembolic strokes may be associated with the older age of the patient population, or may reflect local differences in treatment rates for anticoagulation in atrial fibrillation.¹⁸

In both groups, the median door-to-needle time was longer than the target of 60 minutes suggested by the National Institute of Neurological Disorders and Stroke,¹⁹ and our data provide evidence of the need for further work to streamline the delivery of thrombolysis.

Recent RCT data on rt-PA suggest efficacy of thrombolysis beyond the 3-hour window and up to 4.5 hours after onset of stroke.^{5,20} Less than 10% of the Australian SITS-ISTR data that we analysed were from patients treated more than 3 hours after stroke onset, but the outcomes for these patients are comparable to results from studies that have specifically addressed thrombolysis in the 3–4.5-hour window.^{5,20}

The principal limitation of our study is the voluntary nature of the SITS-ISTR. It is not known precisely how many centres in Australia and worldwide are treating stroke patients with rt-PA outside the registry. Data reported to the Australian National Stroke Foundation by centres that treat with rt-PA suggest that at least 33 units were treating with rt-PA in Australia in September 2007,²¹ but only 14 were participating in SITS at that time. It is possible that standards of stroke care may differ between centres which report via the SITS-ISTR and those that do not participate.

Another limitation of our study is the quantity of missing data — largely brain imaging data — which may, in theory, have resulted in an underestimate of the proportion of symptomatic ICH. The SITS-ISTR does not receive specific funding for data entry, and there can be a lag between patients being treated and data being confirmed; some data were confirmed after the end of our study period. To improve the accuracy of SITS-ISTR as a reflection of clinical practice, we strongly recommend that all centres administering stroke thrombolysis participate in the SITS-ISTR and that all data entered are complete.

This study shows that outcomes and safety for stroke patients treated with rt-PA in Australia are similar to these measures worldwide, and supports the ongoing use of rt-PA for treatment of acute ischaemic stroke in Australian specialist stroke centres. We also encourage newer centres that are not yet treating with rt-PA to develop ways of doing so, to improve stroke treatment in accordance with current evidence.

ACKNOWLEDGEMENTS

Richard Lindley is supported by an infrastructure grant from NSW Health.

COMPETING INTERESTS

Helen Dewey is a member of the scientific advisory board for Boehringer Ingelheim (manufacturer of rt-PA) in Australia. Niaz Ahmed is an employee of SITS International, which received a grant from Boehringer Ingelheim for the SITS-MOST and SITS-ISTR studies on rt-PA. Romesh Markus has received honoraria from Boehringer Ingelheim for invited talks. Jon Sturm has received speaker fees to provide educational talks and travel support to attend national stroke meetings from Boehringer Ingelheim. David Blacker has received travel and accommodation support to attend meetings sponsored by Boehringer Ingelheim. Mark Parsons has received honoraria from Boehringer Ingelheim.

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(Received 29 Sep 2009, accepted 6 Jul 2010) □