EARLY OUTCOMES OF THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE IN A SOUTH AFRICAN TERTIARY CARE CENTRE

By:

Dr Sean Wasserman

Student Number: WSSSEA001

Supervisor:

Prof Alan Bryer

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Faculty of Health Sciences

University of Cape Town

DECLARATION

I, **Sean Wasserman**, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I was solely responsible for analysing the data, researching and writing the literature review and writing the original manuscript. Professor Bryer supervised this project and edited the final version of the dissertation, including the published article.

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DEDICATION

To the remarkable women in my life: Jade, Mom, Jess, and Zia.

I have deep admiration and love for each of you.

Thank you for your support and kindness.

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ABSTRACT

Background

Stroke is an important cause of death and disability in sub-Saharan Africa. Recombinant tissue plasminogen activator (tPA) thrombolysis is effective in treating acute ischaemic stroke, but may not be a viable option in developing countries.

Methods

This prospective observational study was designed to assess the short-term outcomes and safety of tPA for the treatment of stroke at Groote Schuur Hospital. Data was collected from January 2000 to February 2012, and included patients with a clinical diagnosis of acute stroke with onset of stroke symptoms within 4.5 hours of receiving thrombolysis. Exclusion criteria were based on the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial protocol (upper age limit was 75 years). Primary outcomes were the proportion of patients achieving significant early neurological recovery defined as an improvement of 4 or more points on the National Institutes of Health stroke scale (NIHSS) score and functional independence defined as a modified Rankin score of 2 or less at discharge. The primary safety measures were the rates of symptomatic intracranial haemorrhage (SICH) and death.

Results

From January 2000 to February 2011 42 patients were thrombolysed, with a mean time to tPA infusion of 160 minutes (standard deviation (SD) 50; range 60 - 270). By discharge the median NIHSS score fell from 14 (interquartile range (IQR) 10.5 - 17) to 7.5 (IQR 1 - 15); 28 (66.7%) achieved significant neurological improvement, and 17 (40.5%) were functionally independent. Two patients (4.8%) suffered SICH and there were 3 (7.1%) deaths.

Conclusion

Thrombolysis in routine clinical practice in a South African setting has similar safety and early efficacy outcomes to controlled trials and open-label studies in developing and developed countries.

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1. STROKE AS A CAUSE OF DISABILITY AND DEATH IN THE DEVELOPING WORLD

1.1 Global burden

1.1.1 According to data from the Global Burden of Disease study, of the 5.4 million individuals who died of stroke in 2001, fewer than 1.0 million lived in high-income countries. Cerebrovascular disease was the second leading cause of death in low-and-middle-income countries, accounting for 9.5% of the total, similar to high-income countries where it caused 9.9% of all deaths [Lopez, 2006].

1.2 Prevalence

1.2.1 Although mortality in sub-Saharan Africa is dominated by infectious and perinatal diseases, it is estimated that 355 000 stroke deaths (3% of all deaths) occurred in this region in 2001 [Connor, 2007]. That year the prevalence of stroke ranged from 0.07 to 0.3% in a systematic review of published articles from sub-Saharan Africa [Dalal, 2011]. This data is supported by Southern African Stroke Prevention Initiative (SASPI) study of a rural South African community in Agincourt, Limpopo, where stroke prevalence in 2001 was calculated at 290 per 100000 (95% CI 238 to 343) for those over the age of 15 years, with a steep age gradient. The age-specific prevalence of 598 per 100 000 was similar to that recorded in New Zealand (615 per 100000) [Connor, 2004].

1.2.2 The Agincourt study site was established in 1992 in order to examine the burden of disease amongst rural black South Africans. Investigators performed an annual census of the community as well as verbal autopsies to determine contributors to mortality. Over the period 1992 to 1995, the proportionate mortality rate from stroke was 5.5% of all deaths. Stroke was the commonest cause of death in the age 55 to 74 years group (11%), and the second most common cause of death in the age 35 to 54 years group (10%) and over age 75 years group (6%). Stroke was responsible for 22% of deaths due to non-communicable disease [Kahn, 1999]. When extended to 2005 the age-standardised deaths due to all non-communicable diseases increased (1.15 [0.99 – 1.33]; p = 0.066) along with the massive 6-fold rise in deaths due to infectious causes. In this cohort deaths due to stroke, ischaemic heart disease, and hypertension increased by 65% (1.65 [0.99 – 2.76]; p = 0.056) in adults aged over 65 [Tollman, 2008]. Thus, despite

the rise in mortality due to HIV and TB, non-communicable disease remains a growing and important cause of disease burden.

1.3 Morbidity

1.3.1 Morbidity and mortality of stroke in sub-Saharan Africa is high. Sixty-six percent of stroke survivors from the Agincourt district site required assistance with at least one activity of daily living, equating to a prevalence of 200/100000 [Connor, 2004]. This is much higher compared to stroke survivors from a New Zealand community, only 22% of whom required help with self-care activities [Bonita, 1997]. In three Tanzanian sites the 15 to 64 years age-adjusted stroke mortality rates were statistically higher than in England and Wales [Walker, 2000].

1.3.2 An observational study performed at a rural site in Kwazulu-Natal showed an overall mortality of 30% at 3 months after stroke, much higher than the all stroke fatality of 20% in high-income countries. Most of the strokes resulted in severe disability, placing a burden on family carers in a poor socio-economic environment [Wasserman, 2009].

1.4 Emerging epidemic

1.4.1 Although the overall prevalence of stroke is lower than in high-income regions, disabling stroke prevalence may be at least as high in sub-Saharan Africa [Connor, 2007]. This is consistent with a so-called bipolar health transition where infectious and non-communicable diseases co-exist and both contribute significantly to chronic illness [Frenk, 1989]. There is evidence that hypertension and obesity are highly prevalent in rural and urban areas in South Africa [Rayner, 2010]. This, together with increasing rates of communicable disease, represents the early phase of a health transition in the region. A clinical survey using blood pressure, body mass index and ankle brachial index measurements demonstrated a high prevalence of sub-clinical atheroma and other vascular risk factors in adults from the rural Agincourt district [Thorogood, 2007], an indication of progression to later phases of the transition characterised by complications of atherosclerotic disease. South Africa may thus be facing an emerging epidemic of vascular disease that may potentially place a significant economic burden on the country.

2. MODELS OF CARE

2.1.1 A number of studies have been conducted in South Africa with the aim of identifying factors to be included in a model of stroke care for both rural and urban communities. Prevention strategies are paramount and need to be developed in order to deal with the risk factors that form the basis of the emerging epidemic of non-communicable diseases. But there is currently a lack of public health education in rural areas with a high prevalence of hypertension and poor blood pressure control in stroke survivors, as well as limited use of anti-hypertensives and medication for secondary prevention [Wasserman, 2009]. Contributing factors include limited access to health care facilities because of transport costs and poor infrastructure, and lack of basic equipment [Thorogood, 2004]. Hypertension is also poorly detected and managed in South African urban areas [Rayner, 2010].

2.1.2 There is robust evidence that the management of patients in a dedicated stroke unit reduces mortality and disability after acute stroke. Stroke units are dedicated and geographically defined areas in a hospital that provide care for the acute and post-acute phase of stroke. They comprise specialist medical and nursing staff that follows established protocols for management of acute stroke and its complications and work within the framework of a multidisciplinary team including dieticians, occupational and physiotherapists and social workers [Bryer, 2010].

2.1.3 The latest Cochrane review of stroke unit trials published in 2007 showed a 14% reduction in death (OR 0.86; 95% CI 0.76 to 0.98; p = 0.02) at a median time of one year after acute stroke. This analysis also demonstrated that patients treated in stroke units are more likely to be alive and independent (OR 0.82; 95% CI 0.73 to 0.92; p = 0.001) and to return home (OR 0.82; 95% CI 0.73 to 0.92; p = 0.0006) compared with controls from 31 trials involving almost 7000 patients. Length of stay was not significantly increased [Stroke Unit Trialists' Collaboration, 2007].

2.1.4 These results were replicated in a systematic review of observational studies of stroke unit implementation in routine clinical practice, which showed a comparable reduction in death (OR 0.79, 95% CI 0.73 to 0.86; p = 0.00001) and in institutionalisation

or dependency (OR 0.87, 95% CI 0.80 to 0.95; p = 0.002) at one year [Seenan, 2007]. A general review of effectiveness of acute stroke interventions published in 1999 strongly supported the implementation of stroke units because of its suitability as a model to manage all patients with stroke. In this analysis, organised care in a stroke unit was estimated to reduce death and dependency at one year after stroke from 62.0% to 56.4% (a relative risk reduction of 9% and an absolute risk reduction of 5.6%); translating into a NNT of 18. The impact of stroke units on a population depends on their accessibility, and this varies between countries. By treating 80% of stroke patients from a population of 1 million people in stroke units, approximately 107 fewer deaths or dependent survivors would result each year. Furthermore, assuming no impact on length of stay, the cost of treating patients in stroke units may be similar to routine care [Hankey, 1999].

2.1.5 There are few dedicated stroke units in the South African public health sector, with only two in the Western Cape. A study from one of these sites at a secondary-level hospital demonstrated improved outcomes in patients with acute stroke who were managed by a multidisciplinary team. Despite an increased length of stay by 2 days (6.8 versus 5.1 days before the establishment of the stroke unit), the authors demonstrated improved stroke care without the requirement of additional funding and staff [de Villiers, 2009]. The South African Stroke Society recommends that all acute stroke patients should be managed in a stroke unit and that they should be incorporated into existing models of stroke care [Bryer, 2010].

3. THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE

3.1 Early trials

3.1.1 Optimal acute stroke management requires rapid pre- and in-hospital assessment and medical treatment with a focus on maintenance of normal homeostasis [Leys, 2007; Bryer, 2010]. However, this approach is purely supportive, and a specific intervention for acute stroke has been sought for decades. It was hypothesised that early recanalisation of an occluded artery may assist recovery of reversibly ischaemic tissue. Thrombolytic agents were identified as candidates for this on the basis of their potential to dissolve microthrombi and to prevent thrombus extension with resultant infarct enlargement if

administered early [Fletcher, 1976]. The first trials testing this were conducted with streptokinase. Although there was angiographic evidence of increased lysis, the results were disappointing because of unacceptably high rates of intracranial bleeding and worse outcomes than in the control group [Meyer, 1965]. An alternate fibrinolytic agent, urokinase, was subsequently tested in patients with acute stroke in 1976. In this small trial of 31 patients the investigators demonstrated a substantial increase in plasma thrombolytic activity with production of relatively minor blood coagulation defects. However, there were significant bleeding complications with no evidence of early clinical improvement [Fletcher, 1976]. It should be noted that these patients were given urokinase up to 36 hours after the onset of symptoms, and that haemorrhagic strokes were not reliably excluded with brain imaging prior to the intervention.

3.1.2 Despite these early setbacks, interest in thrombolytic therapy for acute stroke re-emerged towards the end of the 1980s. A number of open label [Brott, 1992; Haley, 1992] and subsequently randomised placebo-controlled pilot studies [Haley, 1993; Yamaguchi, 1993] were performed which demonstrated potential efficacy as well as safety of a new generation thrombolytic agent, recombinant tissue plasminogen activator (tPA). This compound, called alteplase, is marketed by Genentech under the trade name Activase. It is a recombinant form of an endogenous human serine protease that acts by converting plasminogen to plasmin. Unlike streptokinase and urokinase, tPA is fibrin-selective and preferentially activates fibrin-bound plasminogen [Wechsler, 2011].

3.1.3 In the first large open-label safety trial of tPA, 74 patients with acute ischaemic stroke were recruited from three centres in the United States (US) from 1987 to 1989. A dose-escalation design was used with dosing tiers allocated on the basis of complication rates. Exclusion criteria were ages over 80 or below 18 years, any clinical or radiological suggestion of intracranial or subarachnoid haemorrhage, prothrombin time (PT) > 15 seconds, a platelet count of <100,000/mm3 or known bleeding diathesis (patients receiving heparin were eligible if the partial thromboplastin time [PTT] immediately before treatment was normal), a history of trauma or significant surgery within the previous 14 days, a history of gastrointestinal or urinary tract haemorrhage within 21

days, lumbar puncture or arterial puncture of a noncompressible site within the previous 7 days, a pre-treatment blood pressure >200 mm Hg systolic or >120 mm Hg diastolic, previous cerebral haemorrhage or ischemic infarction within 3 months, other serious medical illness that might interfere with the study, and inability to obtain informed consent. Additional exclusion criteria were added following the occurrence of major bleeding complications in two patients: mean arterial blood pressure >133 mm Hg, recent transmural myocardial infarction and pericarditis. In this study patients were eligible only if they demonstrated a measurable severe neurological deficit, and were able to receive the intervention within 90 minutes of onset. Serial clinical evaluations were performed during the admission, and at 3 months using the National Institutes of Health Stroke Scale (NIHSS), a validated [Brott, 1989] standardised neurological examination tool. Clinical improvement was defined as an improvement of ≥4 points on the NIHS scale at 24 hours after thrombolysis. Uncontrasted CT scans were performed routinely on presentation, at 18 to 30 hours, 7-10 days, and 3 months post-tPA.

Symptomatic intracranial haemorrhage (SICH) occurred in 4% of patients, and was significantly related to higher doses of tPA. None of the 58 patients treated with ≤ 0.85 mg/kg developed intracranial haematoma. Major neurological improvement occurred in 34 patients (46%) at 24 hours from the initiation of tPA, and was not related to tPA dose or stroke sub-type [Brott, 1992].

3.1.4 A second, smaller open label dose-escalation study of 20 patients was conducted in three US hospitals between 1988 and 1989. The time window for administration of tPA was extended to include those with symptoms of 91 to 180 minutes' duration. This study again demonstrated an increased risk of intracerebral haemorrhage (ICH) with doses ≥0.85 mg/kg, with the 2 fatal ICHs occurring in this high range. Asymptomatic haemorrhagic conversion of the infarction was observed on the follow-up head CT scans in four of the patients and was not dose related. SICH in this series was 10% overall and 17% at the two higher dose tiers. Major clinical improvement was observed at 24 hours in only 15%, significantly lower than in the ≤ 90-minute cohort. This could possibly be attributed to worse baseline NIHSS scores. The authors concluded that further randomised, placebo-controlled trials be conducted to more rigorously evaluate the

efficacy and safety of both the higher dose range and extended time window [Haley, 1992].

3.2 Definitive trials

3.2.1 In response to these recommendations and in preparation for a larger more definitive trial, a bridging study was conducted over 1 year from 1990 to 1991 across 13 American hospitals. Patients with acute stroke were randomised to receive either alteplase 0.85mg/kg or placebo within 3 hours of onset of symptoms. The primary endpoint tested efficacy of the intervention, and was defined as an improvement in the NIHSS of ≥4 points at 24 hours determined by a separate blinded evaluator. Of the 20 patients randomised within 90 minutes, significantly more (6 out of 10 patients) improved in the tPA group compared to those who received placebo (1 out of 10) [Haley, 1993]. This clear demonstration of benefit paved the way for the pivotal National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study [NINDS, 1995], which in turn led to FDA approval for the use of intravenous tPA for acute stroke in 1996.

3.2.2 Part 1 of the NINDS rt-PA trial was designed to measure the activity of tPA by testing whether a greater proportion of patients receiving the intervention had neurological improvement at 24 hours compared with those given placebo. The primary outcome was defined as an improvement by 4 or more points in the NIHSS score or a complete resolution of the neurological deficit.

Part 2 assessed whether tPA provided sustained clinical benefit at 3 months; the primary hypothesis was that a greater proportion of patients treated with tPA compared with placebo would recover with minimal or no deficit 3 months after treatment. Four outcome measures were used: the Barthel Index which measures ability to perform activities of daily living; the modified Rankin score (mRS) as a global assessment of disability; the Glasgow Outcome Scale as a measure of overall function; and the NIHSS to measure neurological deficit. Favourable outcomes were defined as scores of ≤1 on the NIHSS and mRS, 1 on the Glasgow Outcome Scale, and 95 or 100 on the Barthel index.

Patients from both parts of the trial were further divided into three strata of time to treatment after stroke onset: 0 to 90, 91 to 180, and 0 to 180.

Eligibility criteria for inclusion were similar to those used in the open label safety study of 1992. The investigators considered patients for randomisation who had suffered an ischaemic stroke with a clearly defined time of onset, had a measurable deficit on the NIHSS, and had no evidence of intracranial haemorrhage on baseline CT scanning. In this study patients were excluded if they had a systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg or if aggressive treatment was required to reduce their blood pressure to these limits. Other exclusion criteria were rapidly improving or minor symptoms or a seizure at the onset of stroke, and glucose concentrations below 2.7 mmol/l or above 22.2 mmol/l.

Safety monitoring was performed with CT scanning at 24 hours, 7 to 10 days, and when haemorrhage was clinically suspected. Symptomatic intracranial haemorrhages were defined as any new haemorrhage detected on CT scanning accompanied by a decline in neurological status or preceded by a clinical suspicion of haemorrhage.

A total of 624 patients underwent randomisation to receive either placebo or alteplase at a dose of 0.9mg/kg. Treatment groups were well matched in terms of demographic characteristics and baseline neurological deficit, except for age and prior aspirin use, which were slightly higher in the tPA group. There were minimal protocol deviations. In part 1 of the trial no significant difference was seen in the primary outcome between patients receiving tPA and those receiving placebo for any time stratum (47% and 39%, respectively; relative risk with tPA, 1.3; 95% CI 0.9 to 1.6; p = 0.21 for treatment between 0 to 180 minutes). However, for the additional 333 patients randomised to part 2, the rate of a favourable outcome was significantly greater with intravenous (IV) tPA than with placebo with each of the 4 outcome measures and across all time strata at 3 months (odds ratio, 1.7; 95% CI 1.2 to 2.6; p = 0.008). This translated into a 12% absolute increase in the number of patients with minimal or no disability on the Barthel index, an 11% absolute increase in the number of patients with NIHSS scores of 0 or 1, and a 13% absolute increase in the number of patients achieving score of ≤1 on the mRS for the

group receiving tPA. Similar benefit with tPA was seen for both secondary outcomes of part 1 and in the combined analysis. Importantly this greater benefit after tPA therapy as compared with placebo treatment was not accompanied by an increase in severe disability or mortality.

Early SICH occurred more frequently in the tPA group (6.4% versus 0.6%; $p < 0.001$ for the combined analysis). Patients with severe deficits and cerebral oedema at baseline had higher rates of symptomatic intracranial bleeding, but post-hoc analysis demonstrated that these subgroups nevertheless derived overall benefit from tPA [NINDS t-PA Stroke Study Group, 1997]. The rate of asymptomatic intracerebral haemorrhage was similar in the two groups. The improved clinical outcome and reduced incidence of intracranial bleeding compared with other randomised trials of thrombolysis for acute ischaemic stroke was attributed to the early use and lower dose of tPA in this study.

3.2.3 Another large randomised placebo-controlled trial of tPA for acute hemispheric stroke was undertaken in 75 European centres from 1992 to 1994 [Hacke, 1995]. Eligible patients were between the ages of 18 to 80 with moderate to severe stroke who presented within 6 hours of symptom onset. Patients with mild strokes defined by a Scandinavian Stroke Scale (SSS) > 50 were excluded. The primary endpoint was a difference in ADLs defined as an increase of 15 or more points on the Barthel Index, and the secondary endpoint measured global disability and death using the mRS, both at 3 months.

A total of 620 patients were included in the intention to treat (ITT) analysis, and 511 were randomised to receive either tPA at 1.1mg/kg or placebo. There were no significant demographic differences between the two groups, as well as in stroke type and severity. Significant improvement in Rankin scores at 90 days for patients who received tPA was seen in both the ITT and target population (TP) analyses. The OR for being asymptomatic or independent after treatment with tPA was 1.29 (95% CI 1.09 to 1.54) and NIHSS scores were significantly better at both 24 hours and 3 months. Mean duration of hospital stay was shorter in those treated with tPA. Although the ITT analysis

revealed more deaths at 90 days in the treatment group, most of these were in patients with major protocol violations including major early infarct signs and concomitant heparin use. In the TP analysis no significant difference in the incidence of haemorrhage-related death was found (4.2% in the tPA group and 2.7% in the placebo group, p = 0.37), however, parenchymal haematoma was significantly more frequent in the tPA group, occurring in 19.8%. The incidence of haemorrhagic transformation of the infarct was not statistically different in treated (42.8%) and placebo (36.8%) patients.

The authors concluded that thrombolysis was effective in improving functional outcomes, but that this benefit did not outweigh the increased mortality rate at 3 months. They emphasised the need for careful patient selection, specifically to exclude those with extended infarct signs on CT scanning in order to avoid high complication rates. This trial can be criticised for three reasons. Firstly, the investigators elected to use a higher dose of tPA even after the publication of dose-escalation studies in the USA (described above) which showed increased rates of significant bleeding in the patients randomised to >0.85mg/kg tPA. Secondly, they used a time window of up to 6 hours after symptom onset, again after other studies demonstrated worse outcomes beyond 90 minutes. Finally, a significant minority (17%) of patients included in the analysis had protocol violations, mostly including extensive ischaemic changes on baseline CT.

3.2.4 As a result of these findings a second large multi-centre European-Australasian trial, designated ECASS II [Hacke, 1998], was designed to assess the safety and efficacy of thrombolysis with alteplase at the same dose used in the NINDS study within 6 hours of acute stroke. Eligibility criteria were the same as for ECASS I, except that patients with brain swelling exceeding 33% of MCA territory were excluded. The primary endpoint was the proportion of patients with a favourable outcome as defined by a mRS of 0 to 1 at 3 months. SICH was defined as bleeding at any site in the brain accompanied by any clinical deterioration or an increase in the NIHSS score by 4 or more points.

A total of 800 patients were randomised between October 1996 and January 1998. There was no significant difference in baseline variables between the alteplase and control groups. All patients were included in the ITT analysis. The primary endpoint was

achieved in 40.3% (95% CI 35.6 to 45.4) of patients in the alteplase group and 36.6% (95% CI 31.8 to 41.6) in the placebo group, giving a non-significant absolute difference of 3.7% in favour of alteplase (p = 0.277). A post-hoc analysis showed that significantly more patients in the alteplase group were independent (mRS 0 to 2) compared with the placebo group (54.3% [49.5 – 59.1] versus 46.0% [41.1 - 50.9]; p = 0.024) at day 90. There was no difference in overall mortality at both 7 days and 3 months (10.3% in the alteplase group). Intracranial haemorrhage occurred in 48.4% and 40.2% of patients in the alteplase and placebo groups respectively. There was a 2.5 fold excess in symptomatic intracranial bleeds with alteplase, but this did not impact on overall morbidity or mortality.

3.2.5 Lower baseline median NIHSS scores of 11, and improved early stroke care are possible explanations for better placebo response and lower mortality in ECASS II compared with ECASS I and the NINDS study. ECASS II was underpowered to define the optimal time interval for administration of thrombolysis and failed to show efficacy of thrombolytic treatment given in the 6 hour time window. However the safety data was consistent with those of the NINDS trial, thus supporting the use of alteplase for routine management of acute ischaemic stroke within 3 hours of symptom onset, and possibly beyond.

3.3 Consolidating the evidence

3.3.1 Subsequent large observational trials and meta-analyses have provided good evidence for the efficacy and safety of alteplase for treatment of acute ischaemic stroke. The latest Cochrane review included 26 placebo-controlled trials with a variety of thrombolytic agents and ranges of times from stroke onset to treatment involving 7152 patients [Wardlaw, 2009]. Over half of the data was from trials testing tPA. They found that treatment within three hours of stroke significantly reduced the proportion of patients who were dead or dependent (mRS ≥ 3) at 3 to 6 months after stroke (OR 0.71, 95% CI 0.52 to 0.96), with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86 to 1.48). This overall benefit was demonstrated despite an increased risk of SICH which occurred in 7.7% of patients receiving thrombolysis versus 2.1% of those allocated to control (OR 3.49, 95% CI 2.81 to 4.33).

3.3.2 Intra-arterial fibrinolysis has a theoretical advantage over IV tPA because of greater ability to recanalise large arterial occlusions and is an emerging form of treatment in specialised units. A recent meta-analysis of 5 randomised controlled trials including 395 patients with proximal vessel occlusions showed that IA thrombolysis within 6 hours of stroke symptom onset was associated with increased good and excellent outcomes at 90 days according to mRS criteria (numbers needed to treat = 6.8 and 7.7, respectively). Similarly to IV tPA there were increased rates of symptomatic bleeding, but this did not result in higher mortality compared to placebo (20.5% vs 24.0%; OR 0.82; 95% CI 0.48 to 1.39) [Lee, 2010]. IA thrombolysis with or without mechanical clot disruption or extraction may be an option for patients with major ischaemic stroke due to occlusion of middle cerebral or basilar arteries who are otherwise not candidates for IV tPA presenting within 6 hours of stroke onset [Bryer, 2010].

3.3.3 Bridging therapy with IV tPA followed by IA tPA has shown promise in an open label study with high recanalisation rates and similar clinical outcomes to the NINDS rt-PA trial [IMS Study Investigators, 2004], but no clinical trials have been performed to adequately assess this treatment modality.

3.4 Use in routine practice

3.4.1 There were concerns that similar results might not be achieved with tPA outside of clinical trial settings, and this has been investigated in a number of open label studies. A meta-analysis of 15 open-label studies including 2639 patients treated with alteplase in routine clinical practice was published in 2003 [Graham, 2003]. It found slightly lower rates of SICH 5.2% (95% CI 4.3 to 6.0) and overall ICH rates (11.5%) compared with the NINDS-tPA trial, with a similar number of patients (37%) achieving modified Rankin scores of ≤1.

3.4.2 In Canada tPA therapy for acute stroke was granted a conditional licence in 1999 pending the results of a prospective observational cohort study designed to assess the safety and efficacy of thrombolysis in routine clinical practice. The CASES study included all patients given alteplase over the period February 1999 to June 2001. The primary endpoint was excellent functional outcome (mRS 0 to 1) compared to disability or death,

and secondary endpoints included independence (mRS 0 to 2) and complete neurological recovery (NIHSS score 0 to 1). SICH was defined as any decline in clinical neurological status associated with a new bleed detected on CT scan.

Data on 1135 patients from 60 Canadian centres were collected. The cohort consisted of 54.9% males and had a median age of 73 (IQR 63 - 80). Stroke severity was high with a median NIHSS score of 14 (IQR 9 - 19). The median time from stroke onset to treatment was 155 minutes (IQR 130 - 175). The rate of excellent outcome according to adjusted mRS was 36.8%, not significantly different to that reported in other series. SICH occurred in 4.6% (95% CI 3.4 to 6.0) and 28.9% of patients had some degree of intracranial bleeding. The overall 90-day mortality was 22.3% (95% CI 20.0 to 25.0). No differences in the rates of excellent outcome or SICH were observed in patients treated in the high-volume and low-volume centres or between the tertiary care hospitals and the community hospitals. Based on the findings that tPA has similar safety and efficacy profiles in routine practice to clinical trials, the authors recommended widespread development of infrastructure to enable delivery of thrombolysis to people suffering acute ischaemic stroke [Hill, 2005].

3.4.3 The European Medicines Evaluation Agency allowed registration of tPA for acute stroke in 2002 on condition of the implementation of an observational safety study (SITS-MOST) and of a prospective, randomised, placebo-controlled trial of tPA administered between 3 and 4.5 hours after stroke onset (ECASS III).

The SITS-MOST study was also designed to address concerns about the applicability of data from randomised controlled trials to individuals in daily clinical practice. Patients were recruited into this prospective open multicentre observational study from centres across Europe with varying degrees of experience in stroke thrombolysis. Inclusion and exclusion criteria were similar to those used in the NINDS trial: any patient between the ages of 18 and 80 with acute ischaemic stroke treated with alteplase within 3 hours of symptom onset with no contraindications to thrombolysis. Primary outcome measures were SICH (defined in the SITS-MOST protocol as local or remote parenchymal bleeds combined with deterioration in neurological function of 4 or more points in the NIHSS)

or death at 3 months. A secondary outcome measure was functional independence defined by mRS of 0 to 2. The proportion of patients with mortality, SICH (using the NINDS/Cochrane definition of any bleed plus any neurological deterioration or death within 7 days) and independence were compared with pooled results from randomised trials.

6483 patients from 285 centres were included between the years 2002 and 2006. Baseline and demographic data, as well as stroke severity were similar for the SITS-MOST cohort and patients from the other trials. The median age was 68 years and the median NIHSS score was 12.

The proportion of patients with SICH according to NINDS criteria was 7.3% (95% CI 6.7 to 7.9) compared with 8.6% (95% CI 6.3 to 11.6) in the pooled data. The number of SICH as defined by the stricter SITS-MOST protocol was 1.7% (107/6444; 95% CI 1.4 to 2.0), and rose to 4.6% (296/6442; 95% CI 4.1 to 5.1) when using the ECASS criteria (described in section 3.2.4). The number of patients with any intracerebral haemorrhage was approximately 17.3%. Mortality at 3 months was 11.3% (95% CI 10.5 to 12.1), and 54.8% (95% CI 53.5 to 56.0) of patients were independent (mRS 0 – 2), both better outcomes than in controlled trials. Complete recovery at 3 months was seen in 38.9% (95% CI 37.7 to 40.1) of patients in SITS-MOST compared with 42.3% (95% CI 37.8 to 47.0) in randomised controlled trials. At the time of discharge the median NIHSS score had fallen to 4 (IQR 1 - 11). There were no significant differences in the rates of complete recovery or SICH between experienced and new centres. The results of this study confirmed that alteplase is an effective treatment if administered within 3 hours of stroke onset and has a similar safety profile to that in randomised controlled trials when used in routine clinical practice [Wahlgren, 2007].

3.5 Optimal time window

3.5.1 The efficacy of thrombolytic therapy has a clear inverse association with the interval between onset of stroke symptoms and administration of treatment. An analysis of the

NINDS study data showed a significant improvement of outcomes at both 24 hours and at 3 months in the group given alteplase between 0 and 90 minutes of stroke onset-to-treatment (OTT) compared with those thrombolysed at 91 to 180 minutes. The adjusted odds ratio for a favourable outcome at 3 months was 2.11 (1.33 - 3.35) in the 0 to 90 minute stratum and 1.69 (1.09 - 2.62) in the 91 to 180 minute stratum, a significant OTT-treatment interaction. For improvement at 24 hours, the odds ratios were 1.71 (95% CI 1.09 to 2.70) and 1.12 (95% CI 0.71 to 1.76, p 5 0.62) for the earlier and later OTT groups respectively. There was no effect of OTT on the occurrence of ICH [Marler, 2000].

3.5.2 Similar findings were demonstrated in a pooled analysis of 2775 patients from 6 randomised trials of tPA given over a range of OTTs from 3 to 6 hours. The median age was 68 years (IQR 60 - 74) with median baseline NIHSS scores of 11. Compared with controls, the hazard ratios for death at 3 months in those treated with tPA were not significant over OTT periods up until 270 minutes, but exceeded 1 (1.45 [1.02–2.07]) in patients treated later. Although substantial intracerebral haemorrhages were seen more frequently in the tPA group (5.9% versus 1.1% $p < 0.0001$) and in older patients (median age 72, IQR 65 - 76), they were not associated with OTT ($p = 0.71$). In terms of outcomes, the benefit from treatment increased as OTT decreased: the odds ratio of a favourable outcome for patients treated with tPA compared with controls was 2.81 (1.75 – 4.50) for those treated within 90 min and 1.55 (1.12 – 2.15) for those treated within 91–180 min. This benefit was shown to extend beyond 3 hours with demonstration of an odds ratio of 1.40 (95% CI 1.05 to 1.85) for favourable outcome for those treated within 181 – 270 minutes [Hacke, 2004].

3.5.3 This evidence, together with a request by the European Medicines Agency, led to ECASS III, a randomised placebo-controlled trial designed to test the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of acute ischaemic stroke.

In this study 821 patients from 130 European sites were randomised between July 2003 and November 2007 to receive either alteplase 0.9mg/kg or placebo between 3 and 4.5 hours after stroke onset. Both groups were well matched for baseline and clinical

characteristics except for initial stroke severity (worse in the placebo group, median NIHSS scores 9 versus 10 in the treatment group) and history of prior stroke. The primary efficacy endpoint was disability at 3 months, assessed as favourable with mRS 0 to 1 and as unfavourable with scores from 2 to 6. A secondary endpoint included mRS scores dichotomised as 0 to 2 and 3 to 6. Safety endpoints included overall mortality at 90 days, any intracranial haemorrhage and SICH defined as bleeds identified as the predominant cause of neurological deterioration leading to an increase in 4 or more points on the NIHSS scale or death.

Compared with placebo, significantly more patients in the tPA group achieved a favourable outcome (52.4% versus 45.2%; OR 1.34 (1.02 - 1.76), p = 0.04). This represented an absolute improvement of 7.2%, and translates into 1 patient having a favourable outcome for every 14 patients treated in the extended time window. The benefit was maintained after adjustment for confounding baseline variables (odds ratio, 1.42; 95% CI 1.02 to 1.98; p = 0.04). Despite the significantly higher rates of total (27.0% vs. 17.6%; OR 1.73 (1.24 - 2.42) p = 0.001) and symptomatic intracranial bleeding (2.4% vs. 0.2%; OR 9.85 (1.26 - 77.32) p = 0.008) in the patients who received thrombolysis, there was no difference in 3 month mortality between the two groups: 7.7% versus 8.4% for placebo; OR 0.90 (0.54- 1.49), p = 0.68.

The authors noted that although alteplase was associated with significant improvement in clinical outcome when administered between 3 and 4.5 hours after the onset of stroke symptoms, this benefit can be maximised by receiving treatment as early as possible as demonstrated by the results of the pooled analysis [Hacke, 2008].

3.5.4 An updated pooled analysis incorporating data from 8 trials (including ECASS III) with 3670 patients was published in 2010 and confirmed that benefit is seen with tPA up to 4.5 hours after onset of stroke symptoms. The confidence intervals for favourable outcomes, defined both by mRS less than 1 and a composite endpoint of global function test scores, crossed the no-effect line at 270 minutes from OTT. There was no interaction of large intracranial bleeds with OTT, although predictably more, 4.2% (OR 5.37, 95% CI 3.22 to 8.95, p<0.0001), haemorrhages occurred in the alteplase group.

Despite this, the analysis found a significant increase in mortality with alteplase (OR 1.49 (1.00 to 2.21), p = 0.0501) only after a delay of approximately 4.5 hours. In their discussion the authors noted that "the effectiveness of thrombolysis is beyond dispute" but that there is evidence of significant harm with treatment beyond 270 minutes, reinforcing the message that alteplase is more effective when given sooner [Lees, 2010].

3.5.5 In summary, there is good evidence from both randomised, placebo-controlled trials and real-world observational open-label studies that tPA is an effective treatment for acute ischaemic stroke. When given alteplase at 0.9mg/kg within 3 hours of stroke symptom onset, patients are more than 30% more likely to have minimal or no disability at 3 months, resulting in a 12% absolute increase in the number of patients with mRS below 1. The benefit to the community would be an additional 120 independent survivors per 1000 patients treated. This benefit is maintained when used in routine clinical practice, even at inexperienced centres. Alteplase is efficacious up to 4.5 hours after symptom onset with an odds ratio of 1.34 for near complete recovery. Early is treatment is essential, however; the number needed to treat (NNT) increases as the gap between symptom onset and thrombolysis widens. At a time window of 0 to 90 minutes, the NNT is approximately 5, but at 181 to 270 minutes 15 patients need to be thrombolysed to achieve 1 additional excellent outcome attributable to treatment. The increased risk of symptomatic intracranial haemorrhage is substantial, but is not affected by later treatment and does not come at a cost of increased mortality or disability: "tissue plasminogen activator has no net risk for acute stroke therapy" [Bambauer, 2006]. As a result of the above evidence, the South African Stroke Society endorsed thrombolysis with tPA within 4.5 hours of symptom onset as standard of care for acute ischaemic stroke in facilities able to provide this type of treatment according to the stipulated recommendations [Bryer, 2010].

3.6 Thrombolysis delivery

3.6.1 Tissue plasminogen activator represents a significant therapeutic breakthrough in the treatment of stroke. However, its impact on the general population has been limited. This is mainly due to the narrow time window allowed for administration but also as a result of the various other restrictions to ensure safety. The CASES study

estimated that only 1.4% of 90200 patients with ischemic stroke received thrombolysis over the 2.5-year study period [Hill, 2005]. It has been calculated that between 1.8 to 3.0% of all ischaemic stroke patients are treated with tPA in the United States [Qureshi, 2005; Kleindorfer, 2008]. In an analysis of 495186 ischemic stroke admissions in the USA between the years 2005 and 2007, only 2.4% received tPA. There was a wide range (0% to 23%) of individual hospital-reported treatment rates: 64.2% reported no treatments with tPA for ischemic stroke, 18.8% reported tPA rates between 0 and 2.4%, 16.0% reported tPA rates between 2.4 and 10%, and only 0.9% reported 10% treatment rates. The most important factor for an association with treatment rates was bed numbers, with smaller hospitals providing less thrombolysis, but rural designation and population density were also significant. An estimated 40% of the US population was served by hospitals thrombolysing less than 2.4% of their patients [Kleindorfer, 2009].

3.6.2 A retrospective population-based study of 1.3 million people in the greater Cincinnati area was conducted between 1993 and 1994 to identify factors affecting the eligibility of stroke patients for tPA. Of the 2308 patients with ischaemic infarcts, only 39% had documentation of exact stroke times. Less than a quarter (22%) of all patients presented to an emergency department within 3 hours of stroke onset; 19% presented in less than 2 hours. Half of the patients arriving before 3 hours were ineligible for tPA on the basis of mild stroke severity, medical and surgical history, or blood tests. On the basis of this data, the authors estimated that only approximately 8% of ischaemic stroke patients presenting to an ED were eligible for tPA [Kleindorfer, 2004].

3.6.3 Over the years 1996 to 1999, 2165 patients presenting to a Canadian teaching hospital with acute stroke were prospectively studied to identify barriers to receiving tPA. Almost three quarters (73.1%) of those diagnosed with ischaemic strokes were excluded because of delay in presentation to the emergency department beyond 3 hours. Reasons for delay included uncertain time of onset (24.2%), patients waiting to see if symptoms would improve (29%), transfer from an outlying hospital (8.9%), and inaccessibility of treating hospital (5.7%). Of those patients arriving within 3 hours of symptom onset, only 26.7% received thrombolysis. The most common reason for exclusion in this group was either mild or resolving symptoms, although 32% of these

patients remained dependent at hospital discharge or died during hospital admission. It was estimated that only 4.7% of ischaemic stroke patients admitted in the region over the study period received tPA [Barber, 2001].

3.6.4 A systematic review analysed 54 studies over the years 1990 to 2001 that assessed barriers to delivery of thrombolysis for acute stroke [Kwan, 2004]. In European hospitals the proportion of patients arriving within 3 hours of stroke onset ranged from 25 to 61%, in the USA/Canada 30 to 56%, and in Asia 24 to 50%. Delay to treatment over 3 hours or unknown onset time was the commonest reason (up to 94%) for tPA ineligibility. The most consistent pre-hospital barrier was the patient's or family's poor knowledge of stroke symptoms. Lack of knowledge of the risks and benefits of thrombolysis may have led to a refusal to consent in up to 10%. Another barrier identified was initial presentation to a GP rather than the emergency department. Other US reviews also identified lack of public knowledge of stroke symptoms and tendency not to seek immediate care as major factors in treatment delay [Bambauer, 2006].

3.6.5 A prospective study of all patients diagnosed with acute ischaemic stroke across 11 hospitals in California showed that the overall rate of thrombolytic treatment would have increased from 4.3 to 28.6% if patients had called emergency services immediately after symptom onset. The authors estimated that 57% could have been treated if all patients with known time of symptom onset had presented within 1 hour and had received optimal care [CASPR Investigators, 2005].

3.6.6 Centres that have implemented acute stroke response systems have demonstrated improved rates of thrombolysis delivery. A Canadian study showed that a pre-hospital triage initiative resulted in a doubling of the number of stroke patients arriving within 2.5 hours at a regional hospital with thrombolysis capabilities. Their protocol included identification of acute stroke by paramedics allowing for direct routing to a thrombolysis centre and pre-hospital notification of an on-call stroke team. Compared with a four-month period before the implementation of the protocol, the tPA treatment rate increased from 9.5 to 23.4% [Gladstone, 2009].

3.6.7 These findings have been supported by a recent publication from a stroke centre in Paris [Dalloz, 2012]. After the implementation of a pre-notification system, 59.6% of 213 confirmed hyperacute ischaemic strokes received thrombolysis. A systematic review performed by the same authors showed that door-to-needle time was shorter and rates of thrombolysis were significantly higher (mean 54.7% among 609 patients) in hospitals that used a pre-notification stroke code compared with those that did not (mean 18.2% among 297 patients). An integrated acute stroke referral network has also been successfully piloted in a developing country as described below in section 4.1.10 [Muengtaweepongsa, 2010].

3.6.8 Fear of emergency physicians about the increased risk of intracerebral bleeds and perceived lack of efficacy with tPA is another obstacle limiting its use. A survey found that 40% of emergency department physicians would not use alteplase for acute stroke, with 65% citing risk of intracerebral haemorrhage as the reason for not using tPA, and 23% of physicians citing perceived lack of benefit [Brown, 2005]. This view has also been expressed in South Africa [Lahri, 2011].

3.7 Cost

3.7.1 Some authors in the US feel that inadequate funding may be the greatest obstacle to the use of tPA in acute stroke management. Physician reimbursement rates have not been in line with the substantially increased expense of administering tPA in hospital. In a comparison of hospital expenses for over 110000 stroke in-patients in California between 1998 and 2000, the average cost for those treated with tPA was almost $18000 greater than for those who were not. This may reflect the higher baseline stroke severity amongst patients who are thrombolysed, as well as the more intensive care and investigations they receive [Bambauer, 2006].

3.7.2 Despite the increased early expense, tPA has been shown to be both a cost-effective and even a cost-saving treatment. In the NINDS trial, the average length of stay was significantly shorter in tPA-treated patients than in placebo-treated patients (10.9 versus 12.4 days; $p = 0.02$) and more tPA patients were discharged to home than to inpatient rehabilitation or a nursing home (48% versus 36%; $p = 0.002$). It was estimated that for

every 1000 patients treated with tPA, there would be an additional 55 intracranial haemorrhages but 116 more patients would be discharged home compared with placebo. A cost analysis predicted a 1 year cost savings of about $600000 per patient receiving tPA. This is due to reduction in nursing home and rehabilitation requirements [Fagan, 1998]. An economic analysis for the National Health Service in the United Kingdom suggested cost-effectiveness or cost savings with tPA use in ischaemic stroke, particularly for longer term health outcomes. This study estimated a 78% probability of a gain in quality-adjusted survival during the first year, even including data of patients treated up to 6 hours after stroke [Sandercock, 2004].

4. THROMBOLYSIS IN DEVELOPING COUNTRIES

4.1 Delivery

4.1.1 There are few reports on the use of tPA for ischaemic stroke in developing countries. A search of Medline does not reveal any publications on thrombolysis for stroke in Africa. This treatment option is only available in a minority of developing countries including Brazil, Argentina, Senegal, Iran, Pakistan, China, Thailand, and India; and even in the places where it is offered, the number of patients receiving alteplase for stroke is very low [Durai Pandian, 2007].

4.1.2 The Argentinean National Stroke Registry (ReNACer) collected data from 1991 patients with acute ischaemic stroke from 74 medical facilities offering various levels of care. Only 5.7% of all patients were admitted to stroke units, and a total of 21 (1.05%) patients received thrombolysis over a 2-year period from 2004 [Sposato, 2008].

4.1.3 Over the years 2001 to 2004, only 2.1% of 1624 acute stroke patients presenting to an urban referral hospital in Bangkok received thrombolysis [Suwanwela, 2006].

4.1.4 In an Indian cohort, 54 out of 1096 patients (≈5%) with acute stroke were thrombolysed over four years at a tertiary hospital in Delhi. The most common reason for ineligibility was arrival at hospital outside of the treatment window (38%). Over a quarter of otherwise eligible patients did not receive tPA because of inability to afford the drug [Padma, 2007].

4.1.5 The first report of thrombolysis outcomes in Pakistan demonstrated even lower rates of tPA utilisation. From 2005 to 2007 only 18 out of 1185 (1.5%) stroke patients at Aga Khan Hospital were thrombolysed, while at Liaquat National Hospital the rate was 3 out of 575 (0.52%) stroke patients over 1 year in 2007. The authors identified factors contributing to the low rates of thrombolysis in Pakistan. These included limited centres with CT scanners, an unreliable supply of on-site tPA, poor public awareness of stroke symptoms, and financial constraints in a fee-for-service health care system where the cost of tPA is higher than the per capita annual income [Wasay, 2010].

4.1.6 Another study from India reported that of 64 rural patients screened for thrombolytic therapy, 31% reached hospital within 3 hours and 16% were eligible to receive tPA, but none received the intervention. The main reasons for this included the high cost of alteplase and inability of poor patients to afford it, the lack of 24 hour emergency CT scanning, dependence on the public transport system to get to hospital, and a low level of awareness of the importance of time in acute stroke management [Nandigam, 2003].

4.1.7 A hospital in the low income and densely populated Indian region of Uttar Pradesh was able to thrombolyse 32 of 584 patients (≈5%) with acute stroke over a 3-year period from September 2004. The most common reason for disqualification from tPA therapy was arrival outside of the 3 hour window period, occurring in 48%. Of those who would have otherwise been eligible, 40% could not afford tPA [Sharma, 2008].

4.1.8 At a single centre in Ho Chi Min City, Vietnam, only 121 out of 6171 patients (2.1%) with acute ischaemic stroke were thrombolysed over a 3-year period from 2006. The majority were ineligible because of late presentation to hospital: only 8.7% arrived within 3 hours of symptom onset [Nguyen, 2010].

4.1.9 At a referral hospital in Punjab, India, 72 out of 489 (14.7%) stroke patients presented within 3 hours after symptom onset. Of the 22 tPA-eligible patients only 5

actually received the drug, the remainder being unable to afford the high cost of alteplase [Pandian, 2005].

4.1.10 In the face of these challenges shared by most developing countries, a community-based Thai hospital demonstrated improved rates of thrombolysis after the implementation of an integrated acute stroke referral network. The network covered 25 rural (10- to 60-bed) hospitals, 2 regional (120-bed) hospitals, and 2 provincial (500-bed) hospitals, all located within 80 km of the referral centre. After arrival at their local hospital, usually by private transport, patients were immediately screened by trained clerks and nurses using a modified Cincinnati prehospital stroke tool. If acute stroke with onset less than 3 hours was suspected, the stroke fast track was activated whereby patients were immediately sent to the emergency department for baseline investigations, insertion of IV lines and urgent transfer arranged to the referral centre for CT scanning and assessment for thrombolysis. Over a 16-month period from October 2007, 458 patients were admitted with acute ischaemic stroke. A high proportion (21%) received IV tPA, and of these 100 patients, 59 had been transferred from a hospital in the acute stroke referral network. A total of 41% of the referred patients were thrombolysed, and the mean OTT was 160 minutes (range 60 to 270 minutes). These data indicate that integration of an acute stroke referral network into a protocol of IV thrombolysis for acute stroke is feasible in a developing country, and helps to increase the rate of tPA use [Muengtaweepongsa, 2010].

4.2 Efficacy and safety

4.2.1 A number of observational studies have shown comparable efficacy and safety of thrombolysis when used in developing countries. The patients from the Uttar Pradesh study, described in section 4.1.7, had a mean age of 66 years with a mean baseline NIHSS score of 14 (range 8 to 22). The mean door to needle time was around 30 minutes, well within the recommended period of less than an hour. At 48 hours 65.6% had improved their NIHSS score by 4 or more points. There was only 1 SICH and 1 death unrelated to treatment. At one-month follow-up a favourable Barthel index score of 75 was documented in over three quarters of the patients [Sharma, 2008].

4.2.2 The larger study from New Delhi of 54 patients with comparable baseline characteristics showed similar positive results. None of these patients suffered SICH and there were no mortalities at discharge; 65% had significantly improved NIHSS scores by 48 hours. Of note, the mean door to injection time was only 26.8 minutes (range 25 to 67) [Padma, 2007].

4.2.3 The safety outcomes of 21 patients thrombolysed at two tertiary hospitals in Karachi were less reassuring. In this group the mean age was 62 (range 27 to 77) years, the mean time delay from stroke onset to tPA infusion was 169 minutes (range 95 to 200), but stroke severity was not reported. A total of 4 patients (19%) died, 3 of a fatal intracranial haemorrhage. There were protocol violations for all patients who had complications [Wasay, 2010]. The small numbers and retrospective design were major limitations, and the findings of this study should be interpreted in this context.

4.2.4 The largest published cohort of stroke patients receiving tPA in Asia is from three referral hospitals in Ho Chi Min City, Vietnam. Prospective data was collected on 121 patients over the period 2006 to 2009. Just over 40% of the patients could not afford a second ampoule of alteplase and were treated with a lower dose (mean 0.62mg/kg). The mean age and NIHSS scores were 57 years and 12, respectively. In the lower dose group 56.3% had achieved functional independence (mRS 0 to 1) by 3 months, the proportion in the standard dose group was 34.2%. The rate of SICH was higher in the standard dose group at 5.5% versus 2.1% in those receiving lower dose tPA. There were a total of 10 deaths in the cohort (8.3%), only 2 (1.7%) resulting from bleeding complications [Nguyen, 2010].

4.2.5 The results of two prospective studies of tPA in Thailand showed comparable results to published trials from developed countries. The first reported 34 cases of severe stroke (median NIHSS score 20) thrombolysed over the period 2001 to 2004. Significant neurological improvement was achieved by 70.6%, with only 2 cases (5.9%) having symptomatic intracranial bleeds resulting in 1 death [Suwanwela, 2006]. The other Thai study described above showed equally promising results. At 3 months 42% of patients

had achieved excellent recovery (mRS 0-1) with a mortality rate of 14%. Only 2% of patients suffered SICH [Muengtaweepongsa, 2010].

4.2.6 In summary, thrombolysis for acute ischaemic stroke is offered in very few developing countries. In the places where it is available, the rates of delivery are low, ranging from 1 to 5%. The two main reasons for this appear to be difficulty in arriving at hospital within the treatment window period and the high cost of alteplase. A study did show, however, that integration of an acute stroke referral network in developing countries might help to increase the number of patients receiving thrombolysis. Despite concerns about efficacy and safety of tPA for routine use in developing countries, results from a number of observational studies of a variety of patient populations showed comparable favourable outcomes and complication rates to landmark trials performed in Western environments.

5. Rationale for the study

5.1.1 As sub-Saharan Africa progresses through a health transition the incidence of cerebrovascular disease is expected to rise. Currently there is evidence of similar prevalence rates to high-income countries, although the burden of mortality and disability from stroke is much higher in poorer regions. This emerging epidemic of non-communicable disease places increasing demands on an already strained economy and health service. The establishment of organised stroke units has been shown to improve outcomes in acute stroke care for all categories of patients, and is a promising intervention for low-and-middle-income countries.

Thrombolysis with tissue plasminogen activator is the only specific therapy for acute ischaemic stroke. The efficacy and safety of this intervention has been demonstrated in over 4000 patients in controlled trials, and continues to show reproducible benefit in large open-label studies on different continents. The proportion of patients receiving thrombolysis who achieve significant neurological improvement at discharge and excellent functional outcomes at 3 months is greater than those treated with placebo. Although this comes at a cost of increased rates of intracranial haemorrhage, there is no impact on overall mortality.

There are a number of barriers to the implementation of this effective intervention, limiting its use in most clinical settings to around 2% of patients with acute stroke. In order to maximise benefit and reduce complications, tPA needs to be administered within 4.5 hours from onset of stroke symptoms. This narrow window of opportunity represents the largest obstacle to more widespread use because of inefficient public transport systems and low levels of awareness about stroke. Another important barrier is the high cost of the drug and inability of patients in poorer countries to afford it.

Despite early concern that thrombolysis may not be a viable option for treating stroke in developing countries, there is growing evidence of its comparable efficacy and safety when used in these settings. The introduction of an acute stroke support network in Thailand demonstrated that increased rates of tPA use is feasible and efficacious in a poorly resourced region. There are no published data on thrombolysis for acute ischaemic stroke in Africa. We therefore set out to investigate whether tPA can be safely used in routine practice at a tertiary stroke referral centre in South Africa, and if this results in the early neurological improvement seen with its use in other settings.

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PART B: JOURNAL-READY MANUSCRIPT

Copy of published article in appendix 1: S Afr Med J 2012; 102(6): 541-544

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CONTENTS

1. INTRODUCTION

Stroke is an important cause of death and disability in sub-Saharan Africa, where it was estimated that 355 000 stroke deaths occurred in 2001,[1] with a similar age-specific prevalence to developed countries,[2] but resulting in much higher levels of disability.[3] Cerebrovascular disease is a growing problem in South Africa,[4] and places a heavy burden on family carers in poor socioeconomic environments.[5]

Thrombolysis with recombinant tissue plasminogen activator (tPA, alteplase) is the only effective specific treatment for acute ischaemic stroke. The landmark National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial[6] in the USA in 1995 demonstrated that patients receiving this intervention were 30% more likely to survive with minimal disability resulting in a 12% absolute increase in the proportion having excellent functional outcomes at 3 months. The benefits of thrombolysis have been consistently reproduced when used in routine clinical practice across different patient populations.[7-9] Although its use increases rates of intracranial haemorrhage, thrombolysis has no impact on overall mortality.[10]

Net benefit can be achieved if tPA is administered within 4.5 hours of onset of stroke symptoms.[11] This narrow window of opportunity represents the largest obstacle to more widespread use because of inefficient public transport systems and low levels of awareness about stroke.[12] This and other issues, such as cost and the availability of resources required to administer this treatment, have caused concerns that thrombolysis may not be a viable option for treating stroke in developing countries. However, there is growing evidence of of its comparable efficacy and safety when used in these settings.[13-17]

The new South African national stroke guidelines recommend tPA as treatment for acute ischaemic stroke within 4.5 hours of symptom onset.[18] However, there are no published data on the use of thrombolysis in Africa. We aimed to evaluate the early outcomes and safety of this intervention in a South African setting.

2. METHODS

This was a prospective, open, observational study of all patients receiving tPA for acute ischaemic stroke at Groote Schuur Hospital (GSH) from January 2000 to February 2011. The hospital has a comprehensive stroke unit as defined by the national stroke guidelines.

Patient eligibility was defined by the Stroke Unit protocol and included patients with a clinical diagnosis of acute stroke in whom it was ascertained that the time of onset of stroke symptoms was within 3 hours of receiving thrombolysis. After publication of the ECASS III trial[19] in 2008 this time window was extended to 4.5 hours. Exclusion criteria were based on the NINDS rt-PA trial6 protocol (in our study the upper age limit was 75 years), which broadly restricts eligibility to those without evidence of intracranial blood on baseline computed tomography (CT) scanning, low risk of bleeding, and those without rapidly resolving symptoms or severe neurological deficit (National Institutes of Health stroke scale (NIHSS) >25).

Baseline and demographic characteristics, stroke type and severity, time intervals, risk factors, and medication history were recorded. Neurological impairment and functional disability were assessed on arrival and at discharge using the NIHSS score and the modified Rankin scale (mRS), respectively. CT scans were performed at baseline and within 36 hours of thrombolysis, or on evidence of clinical deterioration.

The primary outcome measure was the proportion of patients achieving significant early neurological recovery defined as an improvement of 4 or more points on the NIHSS score at discharge. The safety endpoint was the rate of symptomatic intracranial haemorrhage (SICH) and death. SICH was defined according to the NINDS rt-PA/Cochrane criteria[6,20] as any new evidence of intracranial blood on CT or magnetic resonance imaging (MRI) accompanied by a neurological deterioration of 4 or more points on the NIHSS score from baseline. Functional independence (i.e. an mRS score of 0 - 2) or an improvement of two or more points on the mRS achieved at discharge were secondary outcomes.

The proportion of patients with SICH, mortality, independence, and neurological improvement were calculated and compared with the corresponding proportions in the alteplase arm of the NINDS rt-PA and ECASS III trials, and with observational studies in developed and other developing countries.

Demographic profiles were compared with a cohort of unmatched patients who suffered ischaemic strokes but who were managed conservatively in our stroke unit. The latter patients were ineligible for thrombolysis, and their data were recorded in the same register as those who received tPA from January 2000 to April 2006.

Written informed consent was obtained either from the patients or from a close family member. Alteplase was administered in consultation with the attending neurologist or stroke physician. An intravenous (IV) dose of alteplase (0.9 mg/kg, with 10% given as a bolus followed by an infusion over 1 hour) was administered in the emergency department after the baseline CT scan was reviewed. Selected patients received intra-arterial (IA) alteplase.

This study was approved by the UCT-GSH Human Research Ethics Committee (Ref: 386/2011).

3. RESULTS

Forty-two patients were thrombolysed at GSH from January 2000 to February 2011. Their mean age was 60 (SD 12.26, range 24 - 79) and the median baseline NIHSS score was 14 (interquartile range (IQR) 10.5 - 17). Approximately 60% were clinically assessed to have large-vessel atheroembolic aetiologies. Thirty-six (85.7%) received IV tPA, 4 (9.5%) received IA tPA and 2 (4.8%) received bridging treatment with IV tPA followed by an endovascular procedure including IA tPA. Three (7.1%) patients were over the age of 75 years.

Table 1 shows clinical data, including stroke type and severity. NIHSS data were complete at discharge in 39 (93%) patients and the mRS was recorded for all

patients. The mean time to tPA infusion was 160 minutes (SD 50, range 60 - 270). Most patients (29, 72.5%) were thrombolysed within 180 minutes. Median duration of hospital stay was 12 days (IQR 8 - 15.8). Table 2 compares demographic data of the patients receiving tPA, and unmatched patients with acute ischaemic stroke managed conservatively in the same unit. Of the patients who received thrombolysis, 25/42 (59.5%) arrived at hospital using their own transport; the next most common referral source was from private hospitals (5/42, 11.9%) (Fig.1).

Fig. 2 illustrates early neurological outcomes grouped by severity. The median NIHSS score fell to 7.5 (IQR 1 - 15) by the time of discharge. Forty-eight per cent of patients scored in the mild range (0 - 7), compared with only 5% on arrival. At discharge 18 (42.9%) patients had improved their mRS by 2 or more points and 17 (40.5%) were functionally independent. Over half (53.8%) of our patients were discharged home. Fig. 3 compares the proportion of patients who achieved significant neurological improvement in this study with that of other studies.

Fig. 4 compares our patients and results from other studies for SICH (using the NINDS rt-PA/Cochrane definition) and mortality. Only 2 (4.8%) of our patients suffered SICH. Adverse effects were not significantly related to time of tPA infusion, age or stroke severity. All three patients aged >75 years experienced bleeding complications with one, aged 76, suffering a symptomatic intracranial haemorrhage (NIHSS 8). Another, aged 79, had an asymptomatic intracranial haemorrhage (NIHSS 28), and the third patient, aged 78, developed a femoral haematoma (NIHSS 19).

At the time of discharge a total of 3 (7.1%) patients had died, all of whom had admission Rankin scores of 5. Besides the single patient with fatal intracranial haemorrhage the deaths were unrelated to treatment; one patient died of an acute myocardial infarction, and the other from an additional cerebral infarct and nosocomial pneumonia.

4. DISCUSSION

Two-thirds of our patients achieved significant neurological improvement after receiving tPA, which compares favourably with the NINDS rt-PA trial.[6] Smaller studies from other developing countries reported similar results.[13-17] The European Medicines Evaluation Agency allowed registration of tPA for acute stroke in 2002, on condition that an observational safety study be performed to address concerns about the applicability of data from randomised controlled trials to individuals in daily clinical practice. At 3-month follow-up, 54.8% of patients in this SITS-MOST cohort were functionally independent,[7] compared with 40.5% at the time of discharge in our study. Although other studies demonstrated sustained clinical benefit of thrombolysis,[20] this could not be assessed with our study design which was limited by a short follow-up period. However, the functional outcomes of our patients may be comparable with those of the SITS-MOST study as improvement after tPA typically occurs early because of vessel recanalisation, and further recovery would be anticipated in our surviving patients with rehabilitation in the 90 days post discharge.

Our patients had a lower rate of SICH compared with the NINDS rt-PA trial (4.8% v. 6.4%)[6] and the large open-label SITS-ISTR study (8.0% for patients treated between 3 and 4.5 hours and 7.3% for patients treated within 3 hours).[9] Pooled data from five observational studies from developing countries show a lower proportion of patients suffering SICH, 9/293 (3.1%), but the rates ranged from 0 to 5.9% between the different centres.[13-17] Although the number is small and does not represent a significant association, all three of our patients over the age of 75 had bleeding complications. Studies in the developed world support the safety of tPA in patients over 80 years.[21] However, more caution may be needed in our setting when thrombolysing elderly patients.

Our in-patient mortality was similar to that of the NINDS rt-PA trial (7.4%), but could not be compared with large observational studies such as SITS-MOST and CASES as these only reported 3-month mortality rates. The 7-day mortality of 11 621 patients treated within 3 hours in routine practice across Europe was similar to ours at 6.5%;

the rate for those treated between 3 and 4.5 hours in the same registry was 7.5%.[9] In 3 studies from developing countries the mortality at discharge ranged from 0 to 5.9%.[13,14,16]

It is estimated that <2% of patients with ischaemic stroke in our hospital drainage area received thrombolysis, which seems comparable with data from other developing countries.[15,16] However, our reported thrombolysis rate is an overestimation for the general population, as most patients with acute stroke are managed conservatively at lower level facilities where thrombolysis is not available.

This study was not designed to identify barriers to accessing thrombolysis, but inferences may be drawn from our findings in this regard. Most patients who qualified for tPA used their own transport to hospital, suggesting that delays in the emergency medical services transport system may be a cause for arrival outside of the 4.5 hour window period. A greater proportion of patients who received thrombolysis were employed, and lived in brick houses compared with conservatively managed patients, suggesting that those with higher incomes are more likely to arrive at hospital within the narrow time window required for this intervention. As in other studies,[10,12] low levels of public awareness of stroke may be another barrier to thrombolysis in our setting as reflected by the difference in education levels between the patient groups. Certain quarters in South Africa's emergency medicine community[22] and elsewhere are reluctant to use tPA for stroke,[23] and this may also have contributed to the small numbers of patients referred from secondary level hospitals.

A study limitation is the relatively small number of patients with ischaemic stroke in the GSH cohort that received tPA. Nevertheless, the data indicate that the use of thrombolysis in routine clinical practice in a South African setting has similar safety and early efficacy outcomes to developed and other developing countries. Thrombolysis is specialised and is not available to most South Africans. However, its benefits for reducing disability for stroke victims should be promoted in the lay and medical community. Implementing an acute stroke response network in the

emergency services must be considered to facilitate early arrival and assessment at a designated stroke centre where thrombolysis is available.

5. FIGURES AND TABLES

Table 1: Baseline clinical characteristics of patients receiving tPA (n = 42)

Variable	
Age	62 (52 - 67.5)
Male sex	54.8%
Married	24 (57.1%)
Systolic blood pressure (mmHg)	149 (134 - 170)
Diastolic blood pressure (mmHg)	84 (76 - 90)
Degree of neurological severity (NIHSS)	14 (10.5 - 17)
- Mild 0 - 7	2 (4.8%)
- Moderate (8 - 14)	19 (45.2%)
- Severe (≥ 15)	18 (42.9%)
Cause of stroke	
- Large vessel atheroembolic	25 (59.5%)
- Lacunar	3 (7.1%)
- Cardioembolic	9 (21.4%)
- Other	3 (7.1%)
- Unknown	2 (4.8%)
Stroke onset to treatment time (min)	160 (±50)

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

Table 2: Demographic characteristics of patients receiving tPA (n = 42) compared with unmatched patients with acute ischaemic stroke managed conservatively (n = 882)

	tPA	non-tPA
Education		
- School (years)	10 (8.5 - 12)	8 (6 - 10)
- Tertiary	6 (14.3%)	57 (6.5%)
Income		
- Employed	17 (40.5%)	228 (25.9%)
- Grant	20 (47.6%)	432 (49%)
Housing		
- House	41 (97.6%)	736 (83.4%)
- Shack	1 (2.4%)	96 (10.8%)

Data are median (IQR) or n (%)

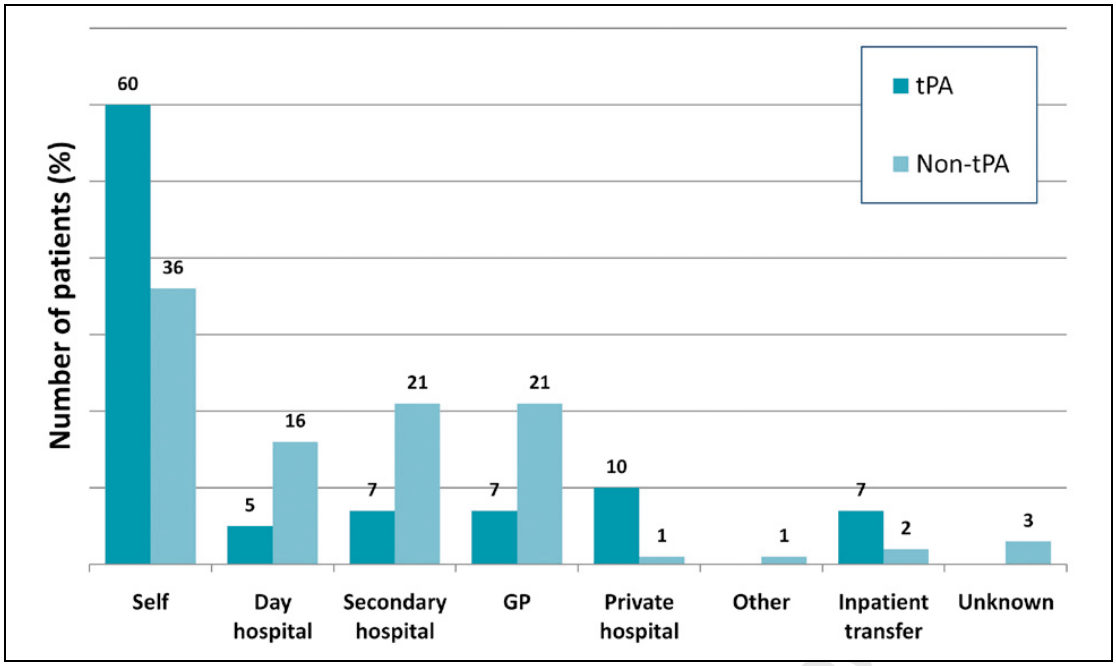

Figure 1: Referral sources of patients recieving tPA and those who were managed conservatively

Data are %. tPA = tissue plasminogen activator

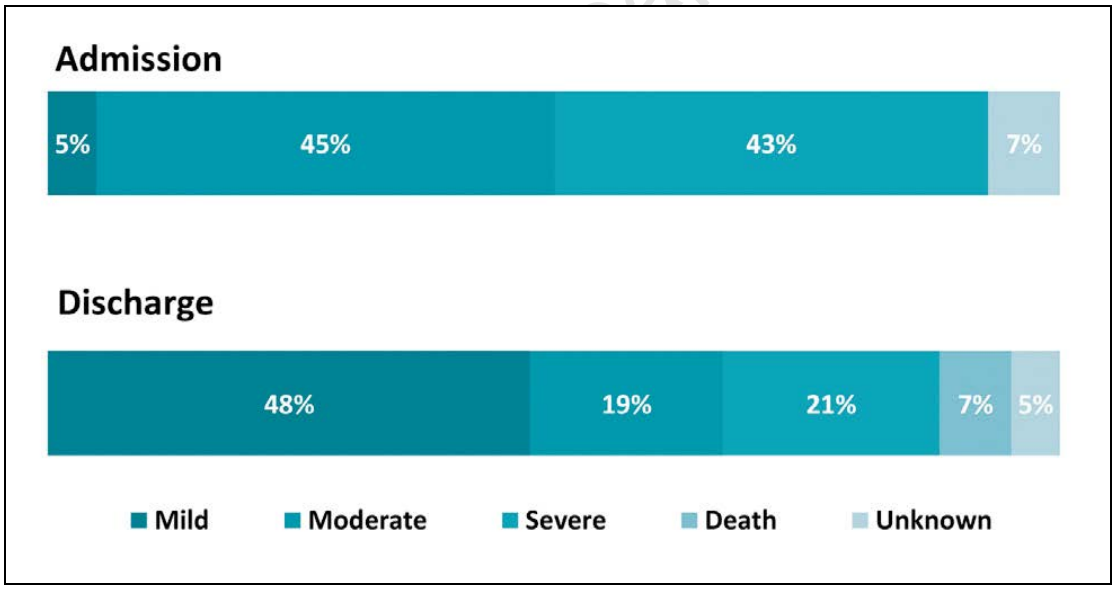

Figure 2: Early neurological outcomes grouped by severity

Mild = NIHSS 0 to 7; moderate = NIHSS 8 to 14; severe = NIHSS ≥ 15

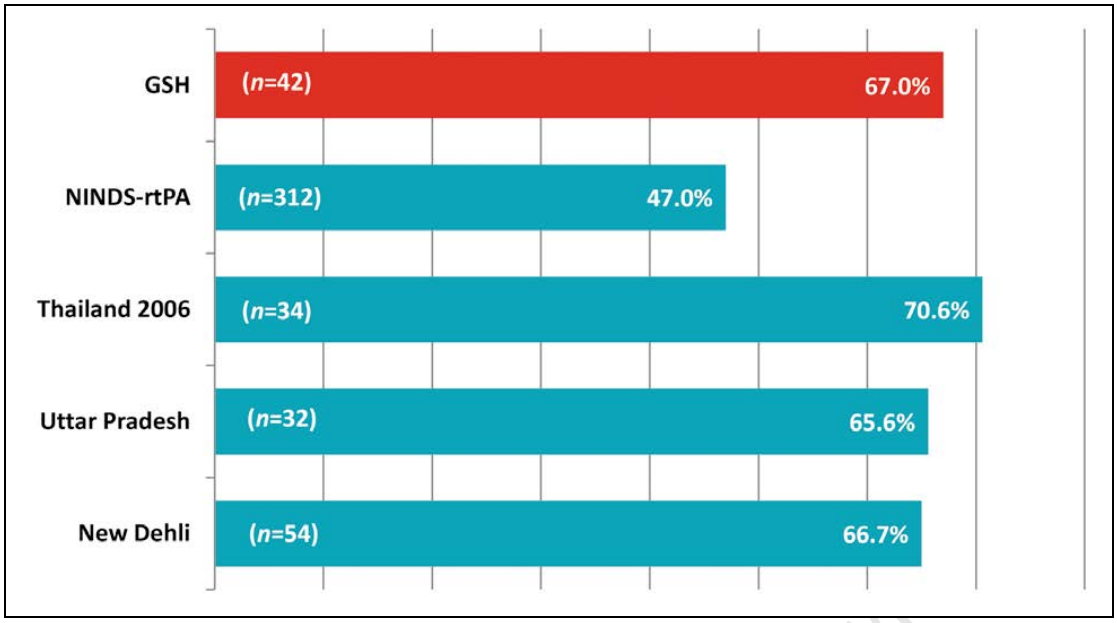

Figure 3: Proportion of patients achieving early neurological improvement (NIHSS ≥ 4 points) compared to other studies[6, 13, 14, 16]

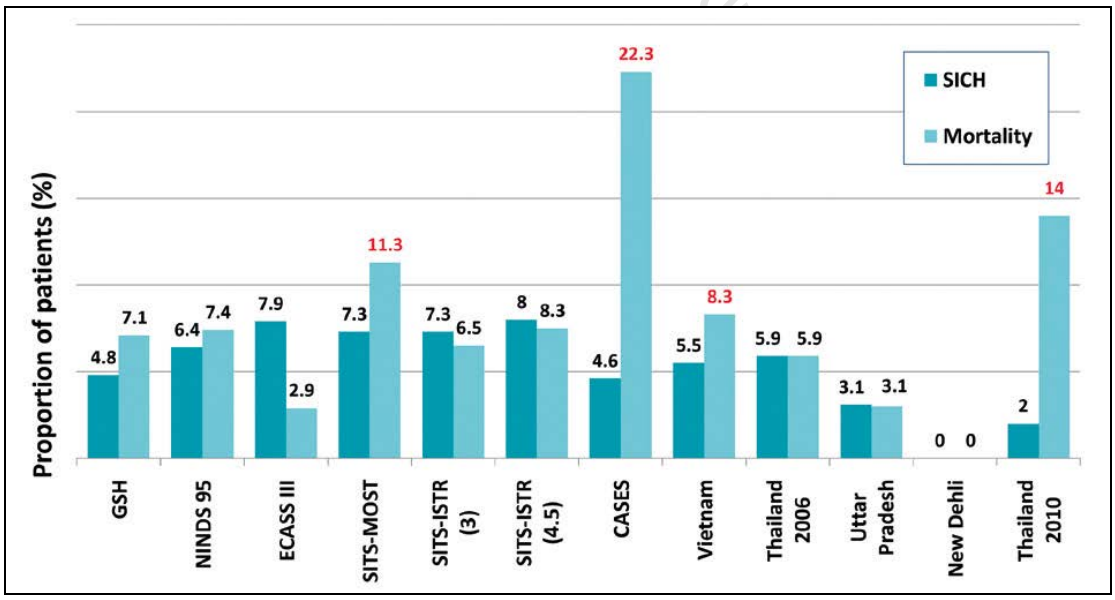

Figure 4: Proportion of patients with symptomatic intracranial haemorrhage and mortality in the GSH cohort and other trials,[6, 19] as well as observational studies.[7, 8, 9, 15, 16, 13, 14, 17]

Data are %. SICH = symptomatic intracranial haemorrhage. Percentages in red = 3 month data, in black = data at discharge

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PART C: APPENDICES

CONTENTS

Early outcomes of thrombolysis for acute ischaemic stroke in a South African tertiary care centre

Sean Wasserman, Alan Bryer

Background. Stroke is an important cause of death and disability in sub-Saharan Africa. Recombinant tissue plasminogen activator (tPA) thrombolysis is effective in treating acute ischaemic stroke, but may not be a viable option in developing countries.

Methods. We assessed the short-term outcomes and safety of tPA for the treatment of stroke at Groote Schuur Hospital from the year 2000. Patients with a clinical diagnosis of acute stroke with onset of stroke symptoms within 4.5 hours of receiving thrombolysis were included. Exclusion criteria were based on the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial protocol (upper age limit was 75 years). Primary outcomes were the proportion of patients achieving significant early neurological recovery defined as an improvement of 4 or more points on the National Institutes of Health stroke scale (NIHSS) score and functional independence defined as a modified Rankin score of 2 or less at discharge. The primary safety measures were the rates of symptomatic intracranial haemorrhage (SICH) and death.

Results. From January 2000 to February 2011 42 patients were thrombolysed, with a mean time to tPA infusion of 160 minutes (standard deviation (SD) 50; range 60 - 270). By discharge the median NIHSS score fell from 14 (interquartile range (IQR) 10.5 - 17) to 7.5 (IQR 1 - 15); 28 (66.7%) achieved significant neurological improvement, and 17 (40.5%) were functionally independent. Two patients (4.8%) suffered SICH and there were 3 (7.1%) deaths.

Conclusion. Thrombolysis in routine clinical practice in a South African setting has similar safety and early efficacy outcomes to controlled trials and open-label studies in developing and developed countries.

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Stroke is an important cause of death and disability in sub-Saharan Africa, where it was estimated that 355 000 stroke deaths occurred in 2001,[1] with a similar age-specific prevalence to developed countries,[2] but resulting in much higher levels of disability.[3] Cerebrovascular disease is a growing problem in South Africa,[4] and places a heavy burden on family carers in poor socioeconomic environments.[5]

Thrombolysis with recombinant tissue plasminogen activator (tPA, alteplase) is the only effective specific treatment for acute ischaemic stroke. The landmark National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial[6] in the USA in 1995 demonstrated that patients receiving this intervention were 30% more likely to survive with minimal disability resulting in a 12% absolute increase in the proportion having excellent functional outcomes at 3 months. The benefits of thrombolysis have been consistently reproduced when used in routine clinical practice across different patient populations.[7-9] Although its use increases rates of intracranial haemorrhage, thrombolysis has no impact on overall mortality.[10]

Net benefit can be achieved if tPA is administered within 4.5 hours of onset of stroke symptoms.[11] This narrow window of opportunity represents the largest obstacle to more widespread use because of inefficient public transport systems and low levels of awareness about stroke.[12] This and other issues, such as cost and the availability of resources required to administer this treatment, have caused concerns that thrombolysis may not be a viable option for treating stroke in developing countries. However, there is growing evidence of of its comparable efficacy and safety when used in these settings.[13-17]

The new South African national stroke guidelines recommend tPA as treatment for acute ischaemic stroke within 4.5 hours of symptom onset.[18] However, there are no published data on the use of thrombolysis in Africa. We aimed to evaluate the early outcomes and safety of this intervention in a South African setting.

Methods

This was a prospective, open, observational study of all patients receiving tPA for acute ischaemic stroke at Groote Schuur Hospital (GSH) from the year 2000. The hospital has a comprehensive stroke unit as defined by the national stroke guidelines.

Patient eligibility was defined by the Stroke Unit protocol and included patients with a clinical diagnosis of acute stroke in whom it was ascertained that the time of onset of stroke symptoms was within 3 hours of receiving thrombolysis. After publication of the ECASS III trial[19] in 2008 this time window was extended to 4.5 hours. Exclusion criteria were based on the NINDS rt-PA trial[6] protocol (in our study the upper age limit was 75 years), which broadly restricts eligibility to those without evidence of intracranial blood on baseline computed tomography (CT) scanning, low risk of bleeding, and those without rapidly resolving symptoms or severe neurological deficit (National Institutes of Health stroke scale (NIHSS) >25).

Baseline and demographic characteristics, stroke type and severity, time intervals, risk factors, and medication history were recorded. Neurological impairment and functional disability were assessed on arrival and at discharge using the NIHSS score and the modified Rankin scale (mRS), respectively. CT scans were performed at baseline and within 36 hours of thrombolysis, or on evidence of clinical deterioration.

The primary outcome measure was the proportion of patients achieving significant early neurological recovery defined as an improvement of 4 or more points on the NIHSS score at discharge. The safety endpoint was the rate of symptomatic intracranial haemorrhage (SICH) and death. SICH was defined according to the NINDS rt-PA/Cochrane criteria[6,20] as any new evidence of

Department of Medicine, Groote Schuur Hospital and University of Cape Town
Sean Wasserman, MB ChB

Stroke Unit, Division of Neurology, Department of Medicine, Groote Schuur Hospital and University of Cape Town
Alan Bryer, PhD

Corresponding author: *S Wasserman (sean.wasserman@uct.ac.za)*

intracranial blood on CT or magnetic resonance imaging (MRI) accompanied by a neurological deterioration of 4 or more points on the NIHSS score from baseline. Functional independence (i.e. an mRS score of 0 - 2) or an improvement of two or more points on the mRS achieved at discharge were secondary outcomes.

The proportion of patients with SICH, mortality, independence, and neurological improvement were calculated and compared with the corresponding proportions in the alteplase arm of the NINDS rt-PA and ECASS III trials, and with observational studies in developed and other developing countries.

Demographic profiles were compared with a cohort of unmatched patients who suffered ischaemic strokes but who were managed conservatively in our stroke unit. The latter patients were ineligible for thrombolysis, and their data were recorded in the same register as those who received tPA from January 2000 to April 2006.

Written informed consent was obtained either from the patients or from a close family member. Alteplase was administered in consultation with the attending neurologist or stroke physician. An intravenous (IV) dose of alteplase (0.9 mg/kg, with 10% given as a bolus followed by an infusion over 1 hour) was administered in the emergency department after the baseline CT scan was reviewed. Selected patients received intra-arterial (IA) alteplase.

This study was approved by the UCT-GSH Human Research Ethics Committee (Ref: 386/2011).

Results

Forty-two patients were thrombolysed at GSH from January 2000 to February 2011. Their mean age was 60 (SD 12.26, range 24 - 79) and the median baseline NIHSS score was 14 (interquartile range (IQR) 10.5 - 17). Approximately 60% were clinically assessed to have large-vessel atheroembolic aetiologies. Thirty-six (85.7%) received IV tPA, 4 (9.5%) received IA tPA and 2 (4.8%) received bridging treatment with IV tPA followed by an endovascular procedure including IA tPA. Three (7.1%) patients were over the age of 75 years.

Table 1. Baseline clinical characteristics of patients receiving tPA (*N*=42)

Variable	
Age (years), median (IQR)	62 (52 - 67.5)
Male sex, %	54.8
Married, *n* (%)	24 (57.1)
Systolic blood pressure (mmHg), median (IQR)	149 (134 - 170)
Diastolic blood pressure (mmHg), median (IQR)	84 (76 - 90)
Degree of neurological severity (NIHSS)	14 (10.5 - 17)
Mild (0 - 7), *n* (%)	2 (4.8)
Moderate (8 - 14), *n* (%)	19 (45.2)
Severe (≥15), *n* (%)	18 (42.9)
Cause of stroke	
Large-vessel atheroembolic, *n* (%)	25 (59.5)
Lacunar, *n* (%)	3 (7.1)
Cardioembolic, *n* (%)	9 (21.4)
Other, *n* (%)	3 (7.1)
Unknown, *n* (%)	2 (4.8)
Stroke onset to treatment time (min), mean (SD)	160 (±50)

Table 2. Demographic characteristics of patients receiving tPA compared with unmatched patients with acute ischaemic stroke managed conservatively

	tPA (*N*=42)	Non-tPA (*N*=882)
Education		
School (years), median (IQR)	10 (8.5 - 12)	8 (6 - 10)
Tertiary, *n* (%)	6 (14.3)	57 (6.5)
Income		
Employed, *n* (%)	17 (40.5)	228 (25.9)
Grant, *n* (%)	20 (47.6)	432 (49)
Housing		
House, *n* (%)	41 (97.6)	736 (83.4)
Shack, *n* (%)	1 (2.4)	96 (10.8)

Table 1 shows clinical data, including stroke type and severity. NIHSS data were complete at discharge in 39 (93%) patients and the mRS was recorded for all patients. The mean time to tPA infusion was 160 minutes (SD 50, range 60 - 270). Most patients (29, 72.5%) were thrombolysed within 180 minutes. Median duration of hospital stay was 12 days (IQR 8 - 15.8). Table 2 compares demographic data of the patients receiving tPA, and unmatched patients with acute ischaemic stroke managed conservatively in the same unit. Of the patients who received thrombolysis, 25/42 (59.5%) arrived at hospital using their own transport; the next most common referral source was from private hospitals (5/42, 11.9%) (Fig.1).

Fig. 2 illustrates early neurological outcomes grouped by severity.

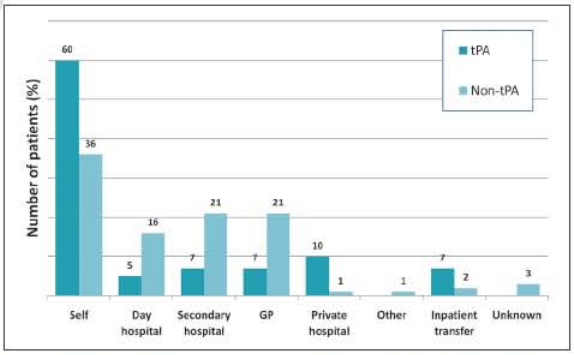

Fig. 1. Referral sources of patients receiving tissue plasminogen activator (tPA) and those managed conservatively.

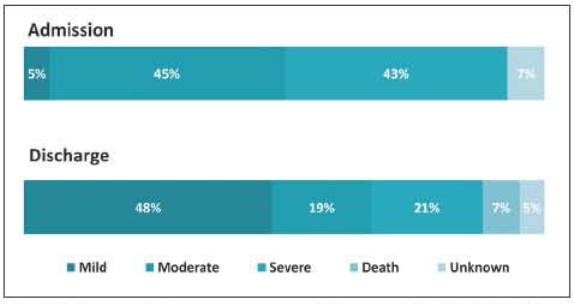

Fig. 2. Early neurological outcomes grouped by severity (mild = NIHSS 0 - 7; moderate = NIHSS 8 - 14; severe = NIHSS ≥15).

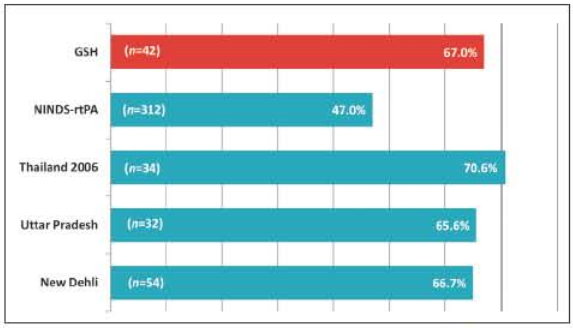

Fig. 3. Proportion of patients achieving early neurological improvement (NIHSS ≥4 points) compared with other studies.[6,13,14,16]

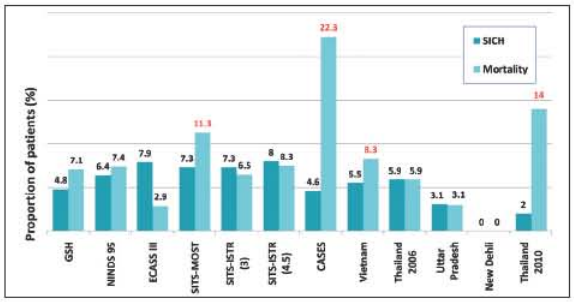

Fig. 4. Proportion of patients with symptomatic intracranial haemorrhage and mortality in the GSH cohort and other trials,[6,19] *as well as observational studies.*[7-9,13-17] *SICH = symptomatic intracranial haemorrhage. Percentages in red = 3-month data, in black = data at discharge.*

The median NIHSS score fell to 7.5 (IQR 1 - 15) by the time of discharge. Forty-eight per cent of patients scored in the mild range (0 - 7), compared with only 5% on arrival. At discharge 18 (42.9%) patients had improved their mRS by 2 or more points and 17 (40.5%) were functionally independent. Over half (53.8%) of our patients were discharged home. Fig. 3 compares the proportion of patients who achieved significant neurological improvement in this study with that of other studies.

Fig. 4 compares our patients and results from other studies for SICH (using the NINDS rt-PA/Cochrane definition) and mortality. Only 2 (4.8%) of our patients suffered SICH. Adverse effects were not significantly related to time of tPA infusion, age or stroke severity. All three patients aged >75 years experienced bleeding complications with one, aged 76, suffering a symptomatic intracranial haemorrhage (NIHSS 8). Another, aged 79, had an asymptomatic intracranial haemorrhage (NIHSS 28), and the third patient, aged 78, developed a femoral haematoma (NIHSS 19).

At the time of discharge a total of 3 (7.1%) patients had died, all of whom had admission Rankin scores of 5. Besides the single patient with fatal intracranial haemorrhage the deaths were unrelated to treatment; one patient died of an acute myocardial infarction, and the other from an additional cerebral infarct and nosocomial pneumonia.

Discussion

Two-thirds of our patients achieved significant neurological improvement after receiving tPA, which compares favourably with the NINDS rt-PA trial.[6] Smaller studies from other developing countries reported similar results.[13-17] The European Medicines Evaluation Agency allowed registration of tPA for acute stroke in 2002, on condition that an observational safety study be performed to address concerns about the applicability of data from randomised controlled trials to individuals in daily clinical practice. At 3-month follow-up, 54.8% of patients in this SITS-MOST cohort were functionally independent,[7] compared with 40.5% at the time of discharge in our study. Although other studies demonstrated sustained clinical benefit of thrombolysis,[20] this could not be assessed with our study design which was limited by a short follow-up period. However, the functional outcomes of our patients may be comparable with those of the SITS-MOST study as improvement after tPA typically occurs early because of vessel recanalisation, and further recovery would be anticipated in our surviving patients with rehabilitation in the 90 days post discharge.

Our patients had a lower rate of SICH compared with the NINDS rt-PA trial (4.8% v. 6.4%)[6] and the large open-label SITS-ISTR study (8.0% for patients treated between 3 and 4.5 hours and 7.3% for patients treated within 3 hours).[9] Pooled data from five observational studies from developing countries show a lower proportion of patients suffering SICH, 9/293 (3.1%), but the rates ranged from 0 to 5.9% between the different centres.[13-17] Although the number is small and does not represent a significant association, all three of our patients over the age of 75 had bleeding complications. Studies in the developed world support the safety of tPA in patients over 80 years.[21] However, more caution may be needed in our setting when thrombolysing elderly patients.

Our in-patient mortality was similar to that of the NINDS rt-PA trial (7.4%), but could not be compared with large observational studies such as SITS-MOST and CASES as these only reported 3-month mortality rates. The 7-day mortality of 11 621 patients treated within 3 hours in routine practice across Europe was similar to ours at 6.5%; the rate for those treated between 3 and 4.5 hours in the same registry was 7.5%.[9] In 3 studies from developing countries the mortality at discharge ranged from 0 to 5.9%.[13,14,16]

It is estimated that <2% of patients with ischaemic stroke in our hospital drainage area received thrombolysis, which seems comparable with data from other developing countries.[15,16] However, our reported thrombolysis rate is an overestimation for the general population, as most patients with acute stroke are managed conservatively at lower level facilities where thrombolysis is not available.

This study was not designed to identify barriers to accessing thrombolysis, but inferences may be drawn from our findings in this regard. Most patients who qualified for tPA used their own transport to hospital, suggesting that delays in the emergency medical services transport system may be a cause for arrival outside of the 4.5 hour window period. A greater proportion of patients who received thrombolysis were employed, and lived in brick houses compared with conservatively managed patients, suggesting that those with higher incomes are more likely to arrive at hospital within the narrow time window required for this intervention. As in other studies,[10,12] low levels of public awareness of stroke may be another barrier to thrombolysis in our setting as reflected by the difference in education levels between the patient groups. Certain quarters in South Africa's emergency medicine community[22] and elsewhere are reluctant to use tPA for stroke,[23] and this may also have contributed to the small numbers of patients referred from secondary level hospitals.

A study limitation is the relatively small number of patients with ischaemic stroke in the GSH cohort that received tPA. Nevertheless, the data indicate that the use of thrombolysis in routine clinical practice in a South African setting has similar safety and early efficacy outcomes to developed and other developing countries. Thrombolysis is specialised and is not available to most South Africans. However, its benefits for reducing disability for stroke

victims should be promoted in the lay and medical community. Implementing an acute stroke response network in the emergency services must be considered to facilitate early arrival and assessment at a designated stroke centre where thrombolysis is available.

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2. SAMJ INSTRUCTIONS TO AUTHORS

Manuscripts

Short items are more likely to appeal to our readers and therefore to be accepted for publication.

Original articles *of 3 000 words or less, with up to 6 tables or illustrations, should normally report observations or research of relevance to clinical medicine. References should preferably be limited to no more than 15. Original articles must be accompanied by a structured abstract not exceeding 250 words, with the following recommended headings: Background, Aims, Methods, Results, and Conclusion.*

Manuscript Preparation

Refer to articles in recent issues for guidance on the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org.

Manuscripts must be written in UK English.

Qualification, affiliation and contact details of ALL authors must be provided with submissions.

Abbreviations should be spelt out when first used in the text and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl (Note: litres is denoted with a lowercase l as in 'ml'). Units should be preceded by a space (except for %), i.e. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e. 'females >40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 400 000, 22 160, etc. Dates must not contain spaces, e.g 2001, 2012, etc.

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round brackets (parentheses) should be used in the text and not square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General Formatting

The manuscript must be in Microsoft word of RTF document format. Text must be single-spaced; in 12-point Times New Roman font; employ italics and bolding rather than underlining; and be free of unnecessary formatting (e.g. text in boxes, with the exception of Tables).

Figures - see ILLUSTRATIONS below. Figures must be numbered (1,2,3...) and must be referred to in the text e.g. 'Refer to Fig. 1'. Figures legends must appear as such: 'Fig. 1. Brief history of the development of...'

*Tables - may be embedded in the manuscript file or provided separately as 'supplementary files'. Tables must be numbered in Roman Numerals as such: Table I, Table II, etc. Footnotes must be indicated with the use of the following symbols (in order): * † ‡ § ¶ || then ** †† ‡‡ etc.*

Illustrations

Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s).

Please note: All illustrations/figures/graphs etc. must be of high resolution/quality: 300 dpi or more is preferable but images must not be resized to increase resolution. Raw (unformatted/uncompressed) images must be attached as 'supplementary files' upon submission, and not embedded in the accompanying text document. TIFF and PNG formats are preferable. JPEG is accepted but authors must be wary of image

compression. Figures may also be provided in high-quality uncompressed PDF format. For figures/graphs prepared in Microsoft powerpoint/excel, the original workbook must be provided.

References

Authors are responsible for verifying references from the original sources. Only complete, correctly formatted reference lists will be accepted. Reference lists must be generated manually and not with the use of reference manager program add-ons.

References should be inserted in the text as superscript numbers following the punctuation marks completing the phrases or sentence to be referenced.

All references should be listed at the end of the article in numerical order (not alphabetical order) - i.e. in order of appearance in the text.

References should be set out in the Vancouver style and approved abbreviations of journal titles must be used; please consult the List of Journals in Index Medicus for these details.

Names and initials of all authors should be given unless there are more than six authors, in which case the first three names should be given followed by et al. First and last page numbers, and volume and issue numbers should be given.

Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

Unpublished observations and personal communications may be cited in the text, but not in the reference list. For personal communications please provide the full name of the source person: e.g. '(Prof. Michael Jones, personal communication)'

3. PTC-DRC APPROVAL

Division of Clinical Pharmacology
Department of Medicine
K45, Old Main Building, Groote Schuur Hospital
Observatory 7925
South Africa

Prof Karen I Barnes

Tel: +27 (0) 21 406 6758
E-mail: karen.barnes@uct.ac.za

5 August 2011

Dear Dr Wasserman

Re: MMed Research Project Protocol:

Title: Early outcomes of thrombolysis for acute ischaemic stroke in a South African tertiary care centre.	
Registrar:	Dr Sean Wasserman
Student number:	WSSSEA001
Degree:	Masters in Medicine (Internal Medicine)
Supervisor:	Prof Alan Bryer

I am pleased approve this proposal on behalf of the Department of Medicine Postgraduate Training Committee and the Department of Medicine Research Committee. Two reviewers evaluated the proposal and confirmed its scientific merit, its likely impact on the safety and well-being of potential participants and the feasibility of its completion within the limited time available to registrars for this purpose.

If this research project is successfully completed as proposed, we believe it should be suitable for publication in a peer-reviewed journal, and should meet the research project (Part III) requirements of the College of Medicine of South Africa and the Health Professions Council of South Africa for registration as a specialist in South Africa.

Once your protocol has been approved by the UCT Human Research Ethics Committee (HREC), and if needed by the Provincial Governemnt of the Western Cape, you will be eligible for a departmental research grant of up to R 5000 towards the direct costs of your research project. A brief motivation and budget should be submitted, together with a copy of the HREC approval, to Rukshana Champion (Rukshana.Champion@uct.ac.za) to facilitate the disbursement of these funds.

To assist other registrars in drafting feasible research proposals, we would like to post approved proposals on the Medicine Registrars VULA website. Please let me know if you object to this posting.

Congratulations on the progress you have made to date towards the successful completion of your research project.

Yours sincerely,

KBarnes
Karen I Barnes (Prof)

MMed (Internal Medicine) Part III Convenor
Department of Medicine Research Committee
Department of Medicine Postgraduate Training Committee

4. HREC APPROVAL

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

25 August 2011

HREC REF: 386/2011

Dr S Wasserman
c/o Prof A Bryer
Medicine

Dear Dr Wasserman

PROJECT TITLE: EARLY OUTCOMES OF THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE IN A SOUTH AFRICAN TERTIARY CARE CENTRE.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 28 August 2012.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

Wesley Brockman

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
PP
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

s.thomas

5. PROTOCOL

(As submitted to and approved by the UCT human research and ethics committee)

Early outcomes of thrombolysis for acute ischaemic stroke in a South African tertiary care centre

By:

Dr Sean Wasserman

Student Number: WSSSEA001

Supervisor:

Prof Alan Bryer

Submitted to the University of Cape Town for proposed research as partial fulfilment of the requirements for the degree:

Masters in Medicine (Internal Medicine)

Faculty of Health Sciences

University of Cape Town

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Project title

Early outcomes of thrombolysis for acute ischaemic stroke in a South African tertiary care centre.

1.2 Purpose of the study

The primary objective of this project is to evaluate the early outcomes and safety of thrombolysis for acute ischaemic stroke in routine clinical practice in a South African public healthcare setting. In order to determine this, we will analyse data prospectively entered into the UCT Stroke Database over the past 11 years. Our findings will be compared with published results of trials and large observational studies from developed countries as well as with those from open-label use in developing regions. We also hope to identify potential factors that limit the application of this therapeutic option and ways in which it may be improved.

1.3 Background

It has been estimated that 355 000 stroke deaths occurred in sub-Saharan Africa in 2001 [Connor, 2007], with an overall prevalence ranging from 0.07 to 0.3% [Dalal, 2011]. That year the SASPI study group documented an age-specific prevalence of 598 per 100 000 at the Agincourt site in rural Limpopo province, which is similar to that recorded in developed countries [Connor, 2004].

Morbidity and mortality of stroke in sub-Saharan Africa is high. Sixty six percent of stroke survivors from the Agincourt district site required assistance with at least one activity of daily living [Connor, 2004]; much higher compared to stroke survivors from a New Zealand community, only 22% of whom required help with self-care activities [Bonita, 1997]. In three Tanzanian sites the 15 to 64 years age-adjusted stroke mortality rates were statistically higher than in England and Wales [Walker, 2000]. An observational study performed at a rural site in Kwazulu-Natal showed an overall mortality of 30% at 3 months after stroke, much higher than the all stroke fatality of 20% in high-income countries. Most of the strokes suffered resulted in

severe disability, placing a burden on family carers in a poor socio-economic environment [Wasserman, 2009].

An extended follow-up of the Agincourt community over the period 1995 to 2005 found that deaths due to stroke, ischaemic heart disease, and hypertension had increased by 65% (1.65 [0.99 - 2.76]; p = 0.056) in adults aged over 65 [Tollman, 2008], providing evidence that cerebrovascular disease is a growing problem in South Africa. Connor et al concluded from a systematic review that although the prevalence of stroke is lower than in high-income regions, disabling stroke prevalence may be at least as high in sub-Saharan Africa [Connor, 2007]. This is consistent with a so-called bipolar health transition where infectious and non-communicable diseases co-exist and both contribute significantly to chronic illness [Frenk, 1989]. There is evidence that hypertension and obesity are highly prevalent in rural and urban [Rayner, 2010] areas in South Africa, and this, together with increasing rates of non-communicable disease, represents the early phase of a health transition in the region. Data from the SASPI study also demonstrated the presence of considerable sub-clinical atheroma in a rural population [Thorogood, 2007], an indication of progression to later phases of the transition characterised by complications of atherosclerotic disease. South Africa may thus be facing an emerging epidemic of vascular disease which may potentially place a significant economic burden on the country.

A number of studies have been conducted in South Africa with the aim of identifying factors to be included in a model of stroke care for both rural and urban communities. In rural areas the development of more effective home-based care and training of family carers may be important interventions [Wasserman, 2009], but it is indisputable that the management of patients in a dedicated stroke unit (SU) reduces mortality and disability after acute stroke. The latest Cochrane review published in 2007 showed a 14% reduction in death (OR 0.86; 95% CI 0.76 to 0.98; p = 0.02) at a median time of one year after acute stroke. This analysis also demonstrated that patients treated in SUs are more likely to be alive and independent (OR 0.82; 95% CI 0.73 to 0.92; p = 0.001) and to return home (OR 0.82;

95% CI 0.73 to 0.92; p = 0.0006) compared with controls from 31 trials involving almost 7000 patients [Stroke Unit Trialists' Collaboration, 2007]. A local study demonstrated that improved outcomes can be achieved by managing patients in a multidisciplinary SU without the requirement of additional funding and staff [de Villiers, 2009].

Thrombolysis with recombinant tissue plasminogen activator (t-PA, alteplase) is the only effective specific treatment for acute ischaemic stroke. The landmark trial in 1995 demonstrated that patients receiving this intervention were 30% more likely to survive with minimal disability giving a 12% absolute increase in the proportion having excellent functional outcomes at 3 months [NINDS, 1995]. Subsequent large observational trials and meta-analyses have provided robust evidence for the efficacy and safety of alteplase for treatment of acute ischaemic stroke. The latest Cochrane review included 26 placebo-controlled trials with a variety of thrombolytic agents and ranges of times from stroke onset to treatment involving 7152 patients [Wardlaw, 2009]. Over half of the data was from trials testing tPA. They found that treatment within three hours of stroke significantly reduced the proportion of patients who were dead or dependent (mRS ≥3) 3 to 6 months after stroke (OR 0.71, 95% CI 0.52 to 0.96).

The benefits of thrombolysis have been consistently reproduced when used in routine clinical practice across different patient populations. The CASES study [Hill, 2005] collected data on stroke patients from 60 Canadian centres over the period February 1999 to June 2001. A total of 1135 patients were thrombolysed with tPA, with 36.8% achieving the pre-defined excellent outcome (adjusted mRS of 0 to 1) at 3 months. The SITS-MOST study included 6483 patients from 285 European centres between the years 2002 and 2006. Complete recovery at 3 months was seen in 38.9% (95% CI 37.7 to 40.1) of patients in SITS-MOST compared with 42.3% (95% CI 37.8 to 47.0) in randomised controlled trials. At the time of discharge the median NIHSS score had fallen to 4 (IQR 1 – 11). There were no significant differences in the rates of complete recovery or symptomatic intracranial haemorrhages between experienced and new centres [Wahlgren, 2007].

Although its use comes at a cost of increased rates of intracranial haemorrhage, thrombolysis has no impact on overall disability or mortality. The 2009 Cochrane review of thrombolysis trials demonstrated no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86 to 1.48). The overall benefit of tPA was achieved despite an increased risk of symptomatic intracranial haemorrhage (SICH) which occurred in 7.7% of patients receiving thrombolysis versus 2.1% of those allocated to control (OR 3.49, 95% CI 2.81 to 4.33). Although there was a trend towards higher mortality in the first ECASS trial, these patients were treated with a higher dose of alteplase up to 6 hours after stroke onset and the deaths occurred mainly in those with major early infarct signs on CT [Hacke, 1995]. In the subsequent ECASS II trial using a tPA dose of 0.9mg/kg, there was no difference in overall mortality at both 7 days and 3 months (10.3% in the alteplase group) compared with control, despite a 2.5 fold excess in SICH with alteplase [Hacke, 1998]. In the CASES study SICH occurred in 4.6% (95% CI 3.4 to 6.0), while in SITS-MOST the proportion of patients with SICH according to the NINDS/Cochrane definition was 7.3% (95% CI 6.7 to 7.9) compared with 8.6% (95% CI 6.3 to 11.6) in the pooled data from controlled trials, demonstrating that there is no increased risk of SICH with thrombolysis used in routine clinical practice.

The efficacy of thrombolytic therapy has a clear inverse association with the interval between onset of stroke symptoms and administration of treatment. An analysis of the NINDS study data showed a significant improvement of outcomes at both 24 hours and at 3 months in the group given alteplase between 0 and 90 minutes of stroke onset-to-treatment (OTT) compared with those thrombolysed at 91 to 180 minutes [Marler, 2000]. Similar findings were demonstrated in a pooled analysis of 2775 patients from 6 randomised trials of tPA given over a range of OTTs from 3 to 6 hours [Hacke, 2004]. The benefit of tPA was shown to extend beyond 3 hours with demonstration of an odds ratio of 1.40 (95% CI 1.05 to 1.85) for favourable outcome for those treated within 181 to 270 minutes. Although SICHs were seen more frequently in the tPA group (5.9% versus 1.1% $p < 0.0001$) and in older patients (median age 72, IQR 65–76), they were not associated with OTT ($p = 0.71$).

This led to ECASS III, a randomised placebo-controlled trial designed to test the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of acute ischaemic stroke [Hacke, 2008]. In this study 821 patients from 130 European sites were randomised between July 2003 and November 2007 to receive either alteplase 0.9mg/kg or placebo between 3 and 4.5 hours after stroke onset. Compared with placebo, significantly more patients in the alteplase group achieved a favourable outcome (52.4% versus 45.2%; OR 1.34 (1.02 - 1.76), p = 0.04). This represented an absolute improvement of 7.2%, and translates into 1 patient having a favourable outcome for every 14 patients treated in the extended time window. Despite the significantly higher rates of total (27.0% vs. 17.6%; OR 1.73 (1.24 - 2.42) p = 0.001) and symptomatic intracranial bleeding (2.4% vs. 0.2%; OR 9.85 (1.26 - 77.32) p = 0.008) in the patients who received thrombolysis, there was no difference in 3 month mortality between the two groups: 7.7% versus 8.4% for placebo; OR 0.90 (0.54 - 1.49), p = 0.68. An updated pooled analysis incorporating data from 8 trials (including ECASS III) and 3670 patients published in 2010 confirmed that benefit is seen with tPA up to 4.5 hours after onset of stroke symptoms [Lees, 2010].

As a result of the above evidence, the South African Stroke Society officially endorsed thrombolysis with recombinant tissue plasminogen activator (tPA) within 4.5 hours of symptom onset as the standard of care for acute ischaemic stroke [Bryer, 2010].

tPA thus represents a major therapeutic breakthrough in the treatment of stroke. However, its impact on the general population has been limited, mainly by the narrow time window allowed for administration, but also as a result of the various other restrictions. The CASES study estimated that only 1.4% of 90200 patients with ischemic stroke received thrombolysis over the 2.5 year study period [Hill, 2005]. Others have estimated that only between 1.8 to 3.0% of all ischaemic stroke patients are treated with tPA in the United States [Qureshi, 2005; Kleindorfer, 2008]. In an analysis of 495186 ischemic stroke admissions in the USA between the years 2005 and 2007, only 2.4% received tPA [Kleindorfer, 2009]. A systematic review of studies from 1990 to 2001 that assessed barriers to delivery of thrombolysis for acute stroke

found that in European studies the proportion of patients arriving within 3 hours of stroke onset ranged from 25 to 61%, in the USA/Canada 30 to 56%, and in Asia 24 to 50%. Delay to treatment over 3 hours or unknown onset time was the commonest reason (up to 94%) for tPA ineligibility. The most consistent pre-hospital barrier was the patient's or family's poor knowledge of stroke symptoms [Kwan, 2004]. Another US review also identified lack of public knowledge of stroke symptoms and tendency not to seek immediate care as major factors in treatment delay [Bambauer, 2006]. The fear of emergency physicians about the increased risk of intracerebral bleeds and perceived lack of efficacy with tPA is another obstacle limiting its use. A survey found that 40% of emergency department physicians would not use alteplase for acute stroke, with 65% citing risk of intracerebral haemorrhage as the reason for not using tPA, and 23% of physicians citing perceived lack of benefit [Brown, 2005]. This view also seems to be prevalent in South Africa. The head of the emergency medicine department at UCT recently published a letter claiming that "there is no compelling evidence to support the use of tPA in stroke; its use beyond 3 hours is dangerous, and it should not form part of national guidelines"[Lahri, 2001].

Because of the potential problems of cost and limited availability of required facilities, there have been concerns that thrombolysis may not be a viable option for treating stroke in developing countries. This treatment option is only available in a minority of developing countries including Brazil, Argentina, Senegal, Iran, Pakistan, China, Thailand, and India; and even in the places where it is offered, the number of patients receiving alteplase for stroke is very low [Durai Pandian, 2007].

However, despite limited experience with this agent, there is growing evidence of its comparable efficacy and safety when used in these settings. A hospital in the low income and densely-populated Indian region of Uttar Pradesh was able to thrombolyse 32 of 584 patients (≈5%) with acute stroke over a 3 year period from September 2004. At 48 hours 65.6% had improved their NIHSS score by 4 or more points. There was only 1 symptomatic intracerebral haemorrhage and 1 death unrelated to treatment. At one month follow-up a favourable Barthel index score of 75 was documented in over three quarters of the patients [Sharma, 2008]. A larger

study from New Delhi of 54 patients with comparable baseline characteristics showed similar positive results. None of these patients suffered symptomatic intracranial bleeds and there were no mortalities at discharge; 65% had significantly improved NIHSS scores by 48 hours [Padma, 2007].

The safety outcomes of 21 patients thrombolysed at two tertiary hospitals in Karachi were less reassuring. In this group the mean age was 62 (range 27 to 77) years, the mean time delay from stroke onset to tPA infusion was 169 minutes (95 to 200), but stroke severity was not reported. A total of 4 patients (19%) died, 3 of a fatal intracranial haemorrhage. There were protocol violations for all patients who had complications [Wasay, 2010]. The small numbers and retrospective design were major limitations, and the findings of this study should be interpreted in this context.

The largest published cohort of stroke patients receiving tPA in Asia is from three referral hospitals in Ho Chi Min City, Vietnam. Prospective data was collected on 121 patients, representing 2% of the total number of patients who presented with acute ischaemic stroke over the period 2006 to 2009. Just over 40% of the patients could not afford a second ampoule of alteplase and were treated with a lower dose, mean 0.62mg/kg. In the lower dose group 56.3% had achieved functional independence (mRS 0 to 1) by 3 months, the proportion in the standard dose group was 34.2%. The rate of symptomatic intracranial haemorrhages was higher in the standard dose group at 5.5% versus 2.1% in those receiving lower dose tPA. There were a total of 10 deaths in the cohort (8.3%), only 2 (1.7%) resulting from bleeding complications [Nguyen, 2010].

The results of two prospective studies of tPA in Thailand showed comparable results to published trials from developed countries. The first reported 34 cases of severe stroke (median NIHSS score 20) thrombolysed over the period 2001 to 2004. Significant neurological improvement was achieved by 70.6%, with only 2 cases (5.9%) having symptomatic intracranial bleeds resulting in 1 death [Suwanwela, 2006].

The second Thai study evaluated the introduction of an acute stroke support network in a community-based hospital. The network covered 25 rural, 2 regional, and 2 provincial hospitals, all located within 80 km of the referral centre. After arrival at their local hospital, usually by private transport, patients are immediately screened by trained clerks and nurses using a modified Cincinnati pre-hospital stroke screen. If acute stroke with onset less than 3 hours is suspected, the stroke fast track is activated whereby patients are immediately sent to the emergency department for baseline investigations, insertion of IV lines and urgent transfer arranged to the referral centre for CT scanning and assessment for thrombolysis. Over a 16 month period from October 2007, 458 patients were admitted with acute ischaemic stroke. A high proportion (21%) received IV t-PA, and of these 100 patients, 59 had been transferred from a hospital in the acute stroke referral network. A total of 41% of the referred patients were thrombolysed, and the mean OTT was 160 minutes (range, 60-270 minutes). At 3 months 42% of patients had achieved excellent recovery (mRS 0-1) with a mortality rate of 14%. Only 2% of patients had symptomatic intracerebral bleeding [Muengtaweepongsa, 2010].

These data indicate that integration of an acute stroke referral network into a protocol of IV thrombolysis for acute stroke is feasible in a developing country, and helps to increase the rate of tPA use.

There are no published data on thrombolysis for acute ischaemic stroke in Africa. We therefore seek to investigate whether tPA can be safely used in routine practice at a tertiary stroke referral centre in South Africa, and if this results in the early neurological improvement seen with its use in other settings.

2. METHODOLOGY

2.1 Study design

Review of data captured prospectively over the period January 2000 to February 2011 for patients receiving tissue plasminogen activator (tPA) for acute ischaemic stroke at Groote Schuur Hospital (GSH).

2.2 Characteristics of the study population

GSH is a tertiary referral centre in the Western Cape, but also provides secondary level care for patients living in its direct drainage areas; it thus receives referrals from other centres as well as self-referrals. The hospital supports a community of predominantly low to middle socio-economic status from an urban environment. In this population there appears to be a high prevalence of risk factors for cardiovascular disease: 26% of general medical admissions at Groote Schuur have an underlying diagnosis of diabetes, hypertension, ischaemic heart disease, chronic kidney disease or previous stroke (Peter Raubenheimer, personal communication, unpublished data from GSH database). With few exceptions, every patient presenting with acute stroke is initially assessed in the Emergency Department (ED) and subsequently referred to either the general medical ward or stroke unit for admission and further care.

Patients are selected for thrombolysis on the basis of clinical eligibility criteria defined by the Stoke Unit Protocol (Appendix F). Men and women between the ages of 18 and 75 years with a clinical diagnosis of acute stroke and certain time of onset within the preceding 3 hours are potential candidates. Deviations from this protocol are allowed for selected patients over the age of 75 years. This is based on recent data from Germany and Canada showing no increase in severe intracranial haemorrhage in very old patients [Berrouschot, 2005; Mateen 2010]. After publication of the ECASS III trial in 2008 the OTT window was extended to include patients presenting within 4.5 hours. The completion of specifically-designed consent form by the patient or a legally-competent representative is required prior to the administration of tPA.

2.3 Recruitment and enrolment

This analysis will include all patients who received tPA at GSH over the period January 2000 to March 2011. Patients are recruited by virtue of being selected to receive thrombolysis according to the Stoke Unit Protocol criteria, and their clinical details are prospectively captured in the UCT Stroke Database. Eligibility for intravenous thrombolysis is assessed by the neurology or 'stroke' registrar on call in

consultation with an attending neurologist. Patients receiving intra-arterial tPA are also included in the analysis, and the decision to use this route of administration is made in each case by a neurologist together with a neurosurgeon.

Exclusion criteria are clearly defined by the existing GSH Stroke Unit guidelines which are based on those used in the NINDS-tPA trial. Contraindications to thrombolysis broadly include any evidence of intracranial haemorrhage on brain imaging, depressed level of consciousness or rapidly improving symptoms, a history of stroke within the preceding 3 months, and a high risk of bleeding (the detailed criteria are included in Appendix F).

2.4 Treatment protocol

Those eligible for intravenous (IV) thrombolysis are given alteplase at a dose of 0.9mg/kg (maximum 90mg) with 10% of the dose given as a bolus followed by the remainder given as an infusion over 60 minutes. The administration of anticoagulants or anti-platelet agents is not allowed within 24 hours of thrombolytic treatment. Initial monitoring takes place in the ED and thereafter patients are transferred to either the SU or a high-care environment for 24 hours. Safety monitoring is performed by regular clinical examinations with the aim of detecting bleeding or neurological deterioration. Follow-up CT scans are done routinely on all patients at some time before discharge and after any clinical suspicion of intracranial haemorrhage.

2.5 Research procedures and data collection methods

Patient data is captured by the attending doctor at the time of discharge from the SU on a specifically designed proforma (Appendix A). All doctors involved in the assessment of thrombolysis patients have received some training on how to administer the various scoring systems and are given detailed guidelines on their use.

Study numbers are assigned automatically by the database and the following information is recorded for each patient:

- Demographic details
    - Hospital folder number
    - Date of birth
    - Gender
    - Relationship
    - Housing
    - Education
- Risk factors for stroke including co-morbid medical conditions
- Time intervals between symptoms, presentation, and infusion of tPA
- Referral sources
- Stroke subtype according to TOAST classification (Appendix C):
    - Large vessel atherothromboembolic (probable/possible)
    - Cardioembolic (probable/possible)
    - Small vessel/lacunar (probable/possible)
    - Acute ischaemic stroke of other aetiology (probable/possible)
    - Acute ischaemic stroke of unknown cause (single or more than one likely aetiology)
- Baseline functional and neurological deficits using standardised scoring systems:
    - Modified Rankin Scale (mRS) as a measure of functional disability (Appendix D)
        - Mild = 0 to 1
        - Moderate = 2 to 3
        - Severe = 4 to 5
    - National Institute of Health Stroke Scale (NIHSS) as a measure of neurological impairment (Appendix E)
        - Mild = 0 to 7
        - Moderate = 8 to 14
        - Severe ≥ 15
- Details of investigations and management
- Route of administration of tPA

- Outcomes at discharge measured using mRS and NIHSS scores
    - Functional independence is defined as an mRS score of 0 to 2
    - Significant neurological improvement is defined as an improvement on the NIHSS scale of 4 or more points
- Any complications resulting from the administration of tPA
    - Symptomatic intracranial haemorrhages
        - Defined according to the NIHSS trial and Cochrane review as any haemorrhage detected on CT or MRI scanning accompanied by a deterioration in neurological function of 4 or more points on the NIHSS scale
    - Asymptomatic intracranial haemorrhage
    - Any extracranial bleeding
    - Other complications such as angioedema or hypotension
- Deaths from all causes
    - mRS score of 6 is death
- Duration of hospital stay
- Discharge destination

2.6 Data analysis

The UCT Stroke Database was established in the year 2000 in order to collect clinical information from all patients with a diagnosis of stroke admitted to the stroke unit (SU), including the details of any patient receiving tPA. Faculty of Health Sciences Human Research Ethics Committee approval was obtained for this (REC Ref 189/2002) and is valid until 15 July 2012. All data is entered into a pre-designed Microsoft Access Stroke Unit Database and coded for further analysis. For the purpose of this study, each patient data form will be checked for completeness and any missing information recovered by a retrospective folder review by the investigators. Data will be analysed using 1-way ANOVA and paired student's t-test using GraphPad Prism V5.0 software (GraphPad Software, San Diego, CA, USA).

3. ETHICAL ISSUES

3.1 Description of risks and benefits

The use of tPA for thrombolysis in selected patients with acute ischaemic stroke is considered to be standard of care, and has been endorsed in recently published stroke management guidelines by the South African Stroke Society [Bryer, 2010]. This survey does not involve randomisation or control substances, and patients are informed of the risks and benefits of the intervention during the consent process. Participation in this observational study is dependent on the patient consenting to the treatment on its own merits and in no way influences the management decisions taken with regard to individual patients. The alternative to this intervention includes the same stroke care provided to those patients who do not otherwise qualify for thrombolysis. The harm: benefit ratio of tPA for stroke is described in section 1.3.

3.2 Informed consent process

In all cases informed consent for the use of tPA is obtained before the therapy is administered. In cases where the patient lacks capacity to consent, consent is obtained from a suitable relative as per standard hospital guidelines. The consent process is performed by the clinician administering the treatment, and is documented on a specifically designed form which also includes an explanation of the risks and benefits of the intervention (Appendix B).

3.3 Privacy and confidentiality

Personal and medical information of the participants is only accessible to the attending doctors and the study investigators. All names are erased and variables have been coded in the dataset used for statistical analysis. The UCT Stroke Database is only accessible to the investigators.

3.4 Conflicts of interest

The investigators report no conflicts of interest. The study received no external funding.

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5.1 Appendix A: Data sheet

UCT STROKE DATABASE

Hospital:

Surname: _____ First name: _____

Hospital folder number: _____ Sex: ☐ Male ☐ Female

Date of Birth | | | | | | | Age: _____

Ethnic Group: ☐ White ☐ Black ☐ Coloured ☐ Indian-Asian

Address: _____

Telephone: Home: _____ Work: _____ Cell: _____

Date of admission: | | | | | | | DATE of STROKE: | | | | | | | Time of STROKE: ____h__

Awoke with deficit: ☐ yes ☐ no Onset unknown: ☐ yes ☐ no

Duration of interval between stroke onset and hospital medical assesment:

Referral to hospital: ☐ self ☐ GP ☐ Day hospital ☐ Secondary hospital ☐ other: _____

Medical insurance: ☐ yes ☐ no

Marital Status ☐ Married / Common-law ☐ Single ☐ Widowed ☐ Divorced

Sole Bread Winner ☐ yes ☐ no

If Yes then state number of financial dependents including partner:

Housing:
- ☐ House / Flat
- ☐ Serviced Shack (toilet plus tap)
- ☐ Unserviced Shack
- ☐ Dormitory / Hostel / single room
- ☐ Other - Specify: _____

Number of people living in dwelling:

Number of rooms used for sleeping in the dwelling:

Education:

Years of schooling passed:

Years of tertiary education passed:

Employment:

Employed:
- ☐ professional/managerial
- ☐ middle management
- ☐ manual foreman/skilled artisan
- ☐ farmer - large farm
- ☐ subsistence farmer
- ☐ clerical / semi-skilled
- ☐ unskilled/informal sector trader

Unemployed:
- ☐ looking for work
- ☐ unemployed by choice e.g. home maker
- ☐ full time student
- ☐ social pensioner - on disability grant or old age pensioner

Risk factors - known prior to stroke

Past Hypertension	☐ yes	☐ no	pregnancy	☐ yes	☐ no
Known diabetes	☐ yes	☐ no	trauma	☐ yes	☐ no
periph vasc disease	☐ yes	☐ no	oral contraception	☐ yes	☐ no
previous TIA	☐ yes	☐ no	cancer	☐ yes	☐ no
previous stroke	☐ yes	☐ no			
hyperlipidaemia	☐ yes	☐ no	specify:		
recent infection	☐ yes	☐ no	specify:		
coagulopathy	☐ yes	☐ no	specify:		
collagen vascular disease	☐ yes	☐ no	specify:		
other arteriopathy	☐ yes	☐ no	specify:		
substance abuse	☐ yes	☐ no	☐ dagga	☐ mandrax	other:
Smoking	☐ never	☐ ex smoker > 1 year		☐ present smoker	
	number smoked per day: ☐				
Alcohol	☐ never/hardly ever		☐ ex-drinker > 1 yr		☐ drinks
	amount af alcohol: ☐ g/week				
	[100ml wine(1glass), or 30 ml spirits (1 tot), or 250ml beer, all = to 10g alcohol]				
Cardiac disease:	☐ none	☐ ischaemic	☐ valvular	☐ atrial fibrillation	
	☐ cardiomyopathy	☐ other:			

Neurologic deficit:

	Adm	1 week	discharge
pyrexia			
comatose			
decreased LOC			
motor weakness			
sensory deficit			
cerebellar signs			
dysphasia			
impaired swallowing			
other cortical signs (apraxia, visual deficit, cortical sensory)			
Rankin Score			
NINDS Stroke Score			
Scandinavian Stroke Score			
Barthel Score			

BP on admission: ☐

Complications:

pneumonia:	☐ yes	☐ no
UTI	☐ yes	☐ no
DVT or PE	☐ yes	☐ no
seizures	☐ yes	☐ no
depression	☐ yes	☐ no
bedsores	☐ yes	☐ no
worsening stroke (symptoms and signs evolve over hours)	☐ yes	☐ no
Recurrent new stroke	☐ yes	☐ no

Other:

Type of Stroke

- ☐ TIA
- ☐ Haemorrhage
- ☐ Ischaemic infarct
- ☐ Uncertain (no CT)

Localisation of ischaemic stroke:

- ☐ complete anterior circulation
- ☐ partial anterior
- ☐ posterior
- ☐ lacunar
- ☐ uncertain

Localization of haemorrhage

- ☐ cortical lobar
- ☐ deep capsular-ganglionic
- ☐ brainstem
- ☐ cerebellar
- ☐ ventricular

Lateralization:

- ☐ right
- ☐ left
- ☐ multiple
- ☐ unknown

Investigations:

Bloods:

FBC:		☐ normal	☐ abnormal - specify:_____
ESR or blood viscosity:		☐ normal	☐ abnormal - specify:_____
Urea/creatinine/elecs:		☐ normal	☐ abnormal - specify:_____
Blood glucose (on admission):		☐ normal	☐ abnormal - specify:_____
HIV:	☐ not done	☐ negative	☐ positive
VDRL:	☐ not done	☐ negative	☐ positive
hypercoag screen:	☐ not done	☐ negative	☐ positive - specify:_____
antiphospholipid Ab:	☐ not done	☐ negative	☐ positive - specify:_____
collagen screen:	☐ not done	☐ normal	☐ abnormal - specify:_____
lipids:	☐ not done	☐ normal	☐ abnormal - specify:_____

CSF:	☐ not done	☐ normal	☐ abnormal - specify:_____
ECG:	☐ not done	☐ normal	☐ abnormal - specify:_____

Radiology:

CXR:	☐ not done	☐ normal	☐ abnormal - specify:_____
CT head:	☐ not done	☐ normal	☐ abnormal - specify:_____
cerebral angio:	☐ not done	☐ normal	☐ abnormal - specify:_____
MRI head:	☐ not done	☐ normal	☐ abnormal - specify:_____
MRA head:	☐ not done	☐ normal	☐ abnormal - specify:_____

Carotid duplex dopplers: ☐ not done ☐ normal ☐ abnormal - specify :
_____ % occlusion left _____ % occlusion right
dissection: ☐ yes ☐ no

transcranial dopplers ☐ not done ☐ normal ☐ abnormal - specify :_____

Cardiac echo: ☐ not done ☐ normal ☐ abnormal - specify:
(Transthoracic) ☐ intracavity clot ☐ dyskinetic segment ☐ R to L shunt
☐ valvular lesion other:_____

Transoesophageal ☐ not done ☐ normal ☐ abnormal - specify:
Cardiac echo: ☐ intracavity clot ☐ dyskinetic segment ☐ R to L shunt
☐ valvular lesion other:_____

Other relevant investigations:

Medication prior to stroke:
☐ antiplatelet ☐ heparin ☐ warfarin
☐ antihypertensive ☐ statin

Was patient independent on ADL prior to admission? ☐ yes ☐ no
Modified Rankin before this event:_____

Aetiology of ischaemic stroke :

- ☐ Large vessel atherothromboembolic: ☐ probable ☐ possible
- ☐ Cardioembolic: ☐ probable ☐ possible
- ☐ Small vessel (lacunar): ☐ probable ☐ possible
- ☐ Acute Ischaemic stroke of other aetiology- **specify:**_____
- ☐ Acute Ischaemic stroke of unknown cause (incomplete workup)
- ☐ Acute Ischaemic stroke of unknown cause (no probable aetiology despite complete workup)
- ☐ Acute ischaemic stroke of unknown aetiology (more than one likely aetiology and a single likely aetiology cannot be determined) **specify:**_____

Aetiology of intracerebral haemorrhage:_____

Treatment:

- ☐ Aspirin ☐ aspirin + dipyridamole ☐ ticlopidine ☐ clopidogrel
- ☐ Heparin prophylactic dosage ☐ heparin full dosage
- ☐ Warfarin
- ☐ Oxygen ☐ Antibiotics ☐ Antipyretics ☐ Insulin ☐ Antihypertensive meds
- ☐ Surgery:_____
- ☐ **Thrombolysis** - specify thrombolytic agent:_____ total dose:_____
  - Route of administration: ☐ intravenous ☐ intra-arterial
  - Time interval (stroke onset to infusion):_____
  - Complications: ☐ symptomatic intracerebral haemorrhage ☐ asympt intracerebral haemorrhage ☐ extracranial haemorrhage other:_____
- ☐ **Neuroprotective agents:** specify agent:_____ total dose:_____
  - Route of administration: ☐ oral ☐ IVI ☐ IMI
  - Time interval (stroke onset to infusion):_____
  - Complications:_____

Duration of hospitalization:

- ☐ admission ward - duration:_____
- ☐ ICU - duration:_____
- ☐ Medical ward - duration:_____
- ☐ Stroke Unit - duration:_____
- ☐ Other ward - duration:_____

TOTAL duration of hospital stay:_____

Death: ☐ yes ☐ no cause of death:_____

Assessment by professions allied to medicine:

- ☐ physiotherapy
- ☐ Speech therapy
- ☐ Occupational therapy
- ☐ Community liason
- ☐ Social worker
- ☐ dietician
- ☐ psychologist

Special case: ☐ Yes ☐ No

Comments:

DATE OF DISCHARGE: |_|_|_|_|_|_|

discharge to: ☐ home care ☐ rehabillitation centre ☐ other:_____

Home carer available: ☐ no ☐ yes - if yes specify: ☐ partner ☐ other:_____

Interviewer name: **date:**

5.2 Appendix B: Consent form

CONSENT FORM TO RECEIVE THROMBOLYTIC TREATMENT WITH TISSUE PLASMINOGEN ACTIVATOR (TPA) FOR ACUTE ISCHAEMIC STROKE

I understand that my doctors believe that I have suffered a stroke. They also believe that I may benefit from treatment with TPA.

Recent medical research suggests that some patients will benefit significantly from this treatment. Specifically, patients receiving TPA have a 30% better chance, three months after their strokes, of having minimal or no disability.

I understand that TPA treatment has risks. Research indicates a 6.4% chance of brain haemorrhage in patients receiving this treatment as compared to 0.6% of patients not receiving this treatment. Brain haemorrhage, if it occurs can result in a significant worsening of my stroke symptoms, may increase my ultimate disability, and may result in my death. TPA can also cause haemorrhaging elsewhere in the body, such as the intestines, kidneys or other organs.

I have read the above information and understand the potential risks and benefits of TPA therapy for my condition. I wish to proceed with TPA treatment as described by my physician.

.....

.....

.....

Patient or Representative **Date**

.....

Physician **Date**

.....

.....

.....

.....

.....

5.3 Appendix C: TOAST classification

TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

5.4 Appendix D: Modified Rankin Scale (mRS)

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____
Rater Name: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out 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

TOTAL (0–6): _____

5.5 Appendix E: NIHSS score

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert;** but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. **Extinction and Inattention (formerly Neglect):** Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

5.6 Appendix F: Stroke Unit thrombolysis inclusion and exclusion criteria

RECOMMENDATIONS FOR THE USE OF INTRAVENOUS t-PA FOR TREATMENT OF ACUTE ISCHAEMIC STROKE UCT STROKE UNIT

PATIENT SELECTION CRITERIA:

Inclusion Criteria:

1.	Age > 18 and < to 75.	Yes	No
2.	Clinical diagnosis of acute ischaemic stroke causing a new measurable deficit defined as impairment of motor function, language, cognition and/or gaze, vision or neglect.	Yes	No
3.	Time of onset well established to be less than 270 minutes before treatment would begin.	Yes	No
4.	CT Scan or MRI Scan performed and read.	Yes	No
5.	Bloods drawn and lab results reviewed (Full Blood Count, Glucose and Electrolytes, PT, PTT, INR).	Yes	No

Exclusion

1.	Patient has: (a) only minor symptoms of stroke (NIH stroke score < 4)	Yes	No
	(b) major symptoms that are rapidly improving by the time of onset of treatment	Yes	No
2.	Patient is comatose.	Yes	No
3.	CT Scan shows (a) evidence of intracranial haemorrhage (of any degree or location)	Yes	No
	b) Coincidental or causal intracranial tumours (except small meningiomas).	Yes	No
	(c) ischaemic infarcts with significant mass effect with midline shift	Yes	No
4.	Patient has a clinical presentation that suggests subarachnoid haemorrhage even if the initial CT Scan is normal.	Yes	No
5.	Patient known to have aneurysm, or arteriovenous malformation.		
6.	Patient is female and lactating or known or suspected to be pregnant.	Yes	No

7.	The patient has:			
	(a)	Currently is taking oral anticoagulants.	Yes	No
	(b)	A known haemorrhagic diathesis.	Yes	No
	(c)	Platelet Count less than 100,000	Yes	No
	(d)	Prothrombin time greater than 15 seconds or INR >1.7	Yes	No
	(e)	Received Heparin within 48 hours and has an elevated partial thromboplastin time (greater than the upper limit of normal for laboratory, i.e. greater than 1,5 x normal).	Yes	No
8.	Patient has had:			
	(a)	Major surgery, biopsy of a parenchymal organ, or serious trauma (excluding head trauma) in the previous 30 days	Yes	No
	(b)	Serious head trauma in the previous 90 days.		
9.	Patient has a history of gastro-intestinal or urinary tract haemorrhage.		Yes	No
10.	Patient has had:			
	(a)	An arterial puncture at a non-compressible site in the previous 7 days.	Yes	No
	(b)	A lumbar puncture in the previous 7 days.	Yes	No
11.	On repeated measurement, patient has systolic blood pressure greater than 185 or diastolic blood pressure greater than 110 at the time treatment is to begin.		Yes	No
12.	Patient has a history of stroke in the previous 3 months.		Yes	No
13.	Patient has ever had an intracranial haemorrhage or subarachnoid haemorrhage at any time in the past.		Yes	No
14.	Patient has a septic embolism.		Yes	No
15.	Patient has a serious medical illness that outweighs treatment benefit.		Yes	No
16.	Patient has abnormal Blood Glucose (< 2.7mmol/l or > 22.2mmol/l).		Yes	No
17.	The patient has:			
	(a)	Clinical presentation consistent with acute myocardial infarction.	Yes	No
	(b)	Clinical presentation suggesting post myocardial infarction pericarditis.	Yes	No
18.	Patient has had a seizure at onset of stroke.		Yes	No
19.	Patient has severe liver disease including hepatic failure, cirrhosis, portal hypertension, and active hepatitis		Yes	No

5.7 Appendix G: SYNOPSIS *(prepared for lay persons as per UCT HREC requirements)*

Project title

Early outcomes of thrombolysis for acute ischaemic stroke in a South African tertiary care centre

Background and rationale for study

Stroke is a growing problem in sub-Saharan Africa and is a leading cause of disability and death in the region. Until recently there has been no specific cure for stroke, and the management has focused on prevention and supportive care. Ischaemic-type strokes are caused by sudden obstruction of an artery in the brain by a blood clot, called a thrombus. These clots either arise from distant sites such as the heart or carotid arteries in the neck, or form in situ on an already diseased cerebral artery. There are certain drugs that have the ability to dissolve newly-formed thrombi, a process known as thrombolysis. These thrombolytic drugs work by mimicking and exaggerating the physiological process of clot dissolution. It was hypothesised that they could be used early in the course of ischaemic strokes to open the occluded artery in order to re-perfuse and salvage affected downstream brain tissue. However, thrombolytic agents are usually administered intravenously and their site of action is not specific. They thus have the potential to cause life-threatening bleeding both at distant sites and intracranially, a feared and real complication of their use.

Thrombolytic therapy for acute ischaemic stroke has been thoroughly tested in both controlled and open-label trials which have consistently shown benefit for its use up to 4.5 hours after the onset of stroke symptoms. The only drug approved for this is a recombinant tissue plasminogen activator (tPA) called alteplase. Patients receiving alteplase are 30% more likely to survive with minimal disability and have a 12% absolute greater chance of achieving excellent functional outcomes at 3 months. Although this intervention does come at the cost of significantly increased risk of intracranial bleeding compared with placebo, thrombolysis has no impact on overall disability or mortality.

There are a number of limitations to the widespread use of thrombolysis. Firstly, all patients require a CT scan prior to treatment to ensure that there is no pre-existing intracranial bleeding. Second, the benefits of alteplase are inversely related to the time of infusion after stroke symptom onset, and its administration beyond 270 minutes may be harmful. Thus potential candidates need to arrive at an equipped hospital early after their stroke in order to access this treatment. These inherent limitations impose significant barriers to thrombolysis, especially in resource-poor developing countries.

Despite the above concerns, a number of studies have demonstrated equivalent safety and efficacy of thrombolysis in developing countries. However, there is no published data on the feasibility of this important intervention in an African setting. We therefore seek to investigate whether tPA can be safely used in routine practice at a tertiary stroke referral centre in South Africa, and if this results in the early neurological improvement seen with its use in other settings. In order to determine this, we will analyse efficacy and safety outcome data prospectively entered into the UCT Stroke Database over the past 11 years. Our findings will be compared with published results of trials and large observational studies from developed countries as well as with those from open-label use in developing regions. We also hope to identify potential factors that limit the application of this therapeutic option and ways in which it may be improved.

Patients, recruitment and eligibility

This analysis will include all patients who received alteplase at Groote Schuur Hospital (GSH) over the period January 2000 to March 2011. GSH is a tertiary referral centre in the Western Cape, but also provides secondary level care for patients living in its direct drainage areas; it thus receives referrals from other centres as well as self-referrals. The hospital supports a community of predominantly low to middle socio-economic status from an urban environment. In this population there appears to be a high prevalence of risk factors for cerebrovascular disease, such as diabetes and hypertension, as well as chronic infectious diseases related to HIV.

Patients are recruited by virtue of being selected to receive thrombolysis according to the Stoke Unit Protocol criteria, and their clinical details are prospectively captured in the UCT Stroke Database. Men and women between the ages of 18 and 75 years with a clinical diagnosis of acute stroke and certain time of onset within the preceding 4.5 hours are potential candidates. Eligibility for intravenous thrombolysis is assessed by the neurology or 'stroke' registrar on call in consultation with an attending neurologist. Patients receiving intra-arterial tPA are also included in the analysis, and the decision to use this route of administration is made in each case by a neurologist together with a neurosurgeon.

Exclusion criteria are clearly defined by the existing GSH Stroke Unit guidelines (protocol appendix F) which are based on those used in the NINDS-tPA trial. Contraindications to thrombolysis broadly include any evidence of intracranial haemorrhage on brain imaging, depressed level of consciousness or rapidly improving symptoms, a history of stroke within the preceding 3 months, and a high risk of bleeding.

Informed consent and privacy

The use of tPA for thrombolysis in selected patients with acute ischaemic stroke is considered to be standard of care, and has been endorsed in recently published stroke management guidelines by the South African Stroke Society. This survey does not involve randomisation or control substances, and patients are informed of the risks and benefits of the intervention during the consent process. Participation in this observational study is dependent on the patient consenting to the treatment on its own merits and in no way influences the management decisions taken with regard to individual patients. The alternative to this intervention includes the same stroke care provided to those patients who do not otherwise qualify for thrombolysis.

In all cases informed consent for the use of tPA is obtained before the therapy is administered. In cases where the patient lacks capacity to consent, consent is obtained from a suitable relative as per standard hospital guidelines. The consent process is performed by the clinician administering the treatment, and is

documented on a specifically designed form which also includes an explanation of the risks and benefits of the intervention (included in protocol Appendix B).

Personal and medical information of the participants is only accessible to the attending doctors and the study investigators. All names are erased and variables have been coded in the dataset used for statistical analysis. The UCT Stroke Database is only accessible to the investigators.