South African ischaemic stroke guideline, 2010

To the Editor: We believe the guideline by Bryer *et al.*[1] to be overdue and well constructed, and generally to contain excellent recommendations. However, the authors note that intravenous tissue plasminogen activator (tPA) 'is an accepted therapy' and 'significantly improves outcome'; particular reference is made to the ECASS III trial[2] to justify its use within 4.5 hours of stroke onset. We believe that this is a dangerous and unsupported recommendation.

Most of the initial thrombolysis trials in stroke were negative; some were stopped early due to harm. The ethics that would allow more trials to continue in the light of such existing studies are hard to conceive, but permission was granted and the NINDS trial finally reported a positive outcome.[3] However, NINDS was a relatively small study (312 patients received thrombolytic therapy with tPA), and significantly higher scores for stroke severity in the placebo group could explain the improved outcome attributed to thrombolysis. Others have re-analysed the NINDS data and shown no improvement in outcome.[4] This takes no consideration of the massively increased intra-cerebral bleed rate in the treatment arm (6.4% v. 0.6%). Furthermore, conflicts of interest were not well disclosed; for instance Genentech, the manufacturer of tPA, contributed US$11 million to the American Heart Association, and paid for its national headquarters in Dallas.[5]

There are many flaws in the ECASS III trial.[2] Patients in the treatment group were younger, and had lower stroke severity scores and fewer prior strokes. Although the Modified Rankin Scale was 7% better in the treated group, the rate of symptomatic intracranial haemorrhage was 2.5% v. 0.2%; the 90-day mortality was the same in both groups. Like NINDS, ECASS III was massively funded by the pharmaceutical industry. Previous studies with similar design, such as the ATLANTIS trial, were stopped early due to harm.[6]

There have been over 940 trials of pharmacological treatment for acute ischaemic stroke; 20% (with over 16 000 patients), of which the majority were funded by pharmaceutical companies,[7] have never been reported in full.

The emphasis of the guideline[1] on treating stroke as an emergency, establishing stroke centres, and providing high-quality supportive treatment (to prevent secondary brain injury) is highly commended. 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.

The authors have no conflicts of interest to declare.

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Dr Alan Bryer replies: I thank Wallis and Lahri for their comments on the stroke guideline. A new treatment always requires a balance between potential benefits and harm. However, it was felt that the potential benefits of treatment have been shown to reasonably outweigh the potential harm. Wallis and Lahri alluded to possible collusion between Genentech, which manufactures tissue plasminogen activator (tPA) in the USA, and the American Heart/Stroke Association concerning their recommendation for use of IVI tPA in their stroke guideline and by implication the Food and Drug Administration (FDA) approval of the use of tPA for acute ischaemic stroke. This seems unlikely and would not apply to the other countries and their respective professional bodies or stroke organisations and independent regulatory authorities. Nevertheless I acknowledge and share their concerns about drug company sponsorship in the stroke trials, which is also commonplace in other large clinical trials. Although the ideal would be for all studies to be investigator led without pharmaceutical company involvement, the large trials needed to confirm or refute drug efficacy are difficult to perform without their backing.

Initial thrombolysis studies using streptokinase were stopped because it appeared to cause harm in the doses used. However, evidence for the benefit of tPa within 3 hours of onset of ischaemic stroke is robust. A Cochrane review on thrombolysis for acute ischaemic stroke included 26 trials with data on 7 152 patients testing urokinase, streptokinase, tPA, recombinant prourokinase or desmoteplase with 56% of all data that came from trials testing tPA – 11 trials, 3 977 patients.[1] Overall, tPA significantly reduced the proportion of patients with poor outcomes after stroke and increased the proportion with good outcomes. This benefit at 3 months was apparent despite a non-significant increase in deaths, mostly attributable to intracranial haemorrhage. The authors concluded that the available evidence supported the clinical use of tPA within the existing licence. However, current data are insufficient to determine risks and benefits in certain subgroups of patients, especially those aged 80 years and older.

The European Medicines Evaluation Agency granted licence in 2002 for the use of tPA for treating ischaemic stroke patients within 3 hours of symptom onset on condition of completing: (*i*) a prospective registry of patient treatment experience with tPA given within the 3-hour window from symptom onset (Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST));[2] and (*ii*) a prospective, randomised, placebo-controlled trial of tPA administered between 3 and 4.5 hours after stroke onset, ECASS-III. Under European Union regulations, SITS-MOST was required to assess the safety profile of tPA in clinical practice by comparison with results in randomised controlled trials. A total of 6 483 patients were recruited from 285 centres (50% with little previous experience in stroke thrombolysis) in 14 countries for this prospective, open, monitored, observational study. Primary outcomes were symptomatic (a deterioration in National Institutes of Health stroke scale score of ≥4) intracerebral haemorrhage within 24 hours, and mortality at 3 months. Mortality, the proportion of patients with symptomatic intracerebral haemorrhage as per the Cochrane definition, and functional outcome at 3 months were compared with pooled results from randomised controlled trials. Results from the SITS-MOST study found that intravenous tPA is safe and effective in routine clinical use within 3 hours of stroke onset, even by centres with little previous experience of thrombolytic therapy for acute stroke. They encouraged wider use of thrombolytic therapy for suitable patients treated in stroke centres.

The UK National Institute for Health Care and Clinical Excellence reviewed the Cochrane review and the results of the meta-analysis (including the undue weight of the NINDS trial in the meta-analysis)

and the results of large observational studies such as SITS-MOST and concluded that tPA was effective in the treatment of acute ischaemic stroke.[3] Another pooled analysis of individual data of six tPA trials showed that, even within a 3-hour window, earlier treatment results in a better outcome (0 - 90 minutes: odds ratio (OR) 2.11, 95% confidence interval (CI) 1.33 - 3.55; 90 - 180 minutes: OR 1.69; 95% CI 1.09 - 2.62) and suggested a benefit up to 4.5 hours.[4] The ECASS III trial found tPA to be effective when provided up to 4.5 hours after stroke onset (OR 1.34, 95% CI 1.02 - 1.76, p=0.04). There was a significant increase in symptomatic intracranial haemorrhage (2.7% v. 0.3%), but no significant effect on mortality. In another study the SITS investigators compared 664 patients with ischaemic stroke treated between 3 and 4.5 hours with 11 865 patients treated within 3 hours.[5] There were no significant differences between the 3 - 4.5-hour cohort and the 3-hour cohort for any outcome measures, confirming that tPA remains safe when given between 3 and 4.5 hours after the onset of symptoms in ischaemic stroke patients who otherwise fulfil the European summary of product characteristics criteria. A systematic review of four trials, including ECAS III, confirmed that tPA given between 3 and 4.5 hours after stroke onset is associated with an increased chance of favourable outcome (OR 1.31, 95% CI 1.10 - 1.56, p=0.002) with no significant difference in mortality compared with placebo, thus strengthening the evidence that treatment with tPA in the 3 - 4.5-hour window is beneficial and should therefore be considered for stroke patients who present during this time window.[6]

The recommendation for the use of IVI tPA within 4.5 hours of onset of ischaemic stroke in the new South African guideline is the same as in the guidelines of other countries including the USA, Canada, the European Union, Scandinavia and Australia. The evidence shows that IVI tPA treatment benefits selected patients but should be delivered in well-equipped and skilled emergency units and/or stroke units with adequate expertise and infrastructure for monitoring, rapid assessment and investigation of acute patients. Such patients should be offered treatment with tPA provided the potential risks and benefits are explained to them and their attendant families. Collaboration is recommended between clinicians in pre-hospital services, emergency medicine, neurology and neuroradiology for prompt identification of potentially eligible patients, patient selection, audit and quality improvement initiatives.

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Will National Health Insurance ensure the national health?

To the Editor: The good intentions in the proposed National Health Insurance (NHI) scheme are not doubted, but I suspect that the authorities have not been correctly advised on why the health system is often inadequate.

South Africa's health system provides private health care access to some, but the large majority depends on the state for health services. Private health care appears to offer a better service than state health care because of a lack of adequate state sector infrastructure. However, injecting massive NHI funding into state health will result in a burgeoning bureaucracy and little to improve our citizens' health experience.

Infrastructure, from equipment to health care personnel, is limited in the state health system and patients experience many irritations and inconveniences because of the way it operates.

There is no reason why repeat outpatients cannot have appointments instead of all having to attend the health facility before dawn only to be seen hours later. With appointments the number of patients in a health facility would become more manageable and patients who work would not lose pay by waiting unnecessarily.

Why do patients have to return, often after long journeys, to collect repeat medication instead of accessing it at their nearest state health facility? Private sector prescriptions are on a computer and available at supermarket pharmacies nationwide. State health facilities can use such computer programmes and reduce outpatient and clinic numbers by 30%. And why do supermarkets have better baby-changing facilities than our health facilities, which often do not have any at all?

Patient self-triage is another serious patient-perceived problem. For budgetary and administrative reasons state health services are classified as primary or district, secondary or regional, and tertiary or academic. The family with a sick baby is expected to self-triage the baby into one of these categories. Heaven help them if they appear at a secondary or tertiary hospital with a primary care condition, as they may be denied treatment and referred back. Since when do health facilities turn away patients? Health facilities must recognise that their concept of an emergency differs from that of a lay person and act accordingly!

The state health services have some excellent health practitioners, but there are not enough of them. Most are concentrated in urban areas and medical schools, and although this is unlikely to change, the rural paucity of practitioners could be addressed in part by the following.

Firstly, address the overall numbers of health practitioners in the state services. One cannot buy, but must attract and retain the best personnel. This is not just about money, and the nine provincial health departments and the eight university medical schools must play a role in this joint approach and responsibility. Provinces with medical schools must accept the obligation of providing state-of-the-art equipment and consumables to the teaching environment. It is unacceptable that cardiac procedures be delayed because the budget for stents is insufficient, or that patients should suffer long delays because the prosthetic hips budget is exhausted.

Secondly, as part of their co-responsibility for patients the medical schools must recognise that the health department's responsibility for the patients in a teaching hospital extends throughout the province. In recognising this health and teaching continuum the medical schools should co-operate in outreach programmes throughout and across provinces to take treatment to where the patients live, subject to the provinces meeting their equipment obligations. They must also recognise the medical practitioner needs in South Africa and support the front-line health care disciplines of family medicine and emergency medicine.

The present state health system could be remedied by wise investment in real patient care at less than an NHI would cost, and without creating another bureaucracy.

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