*In a recent issue (*MJA *April 7, 2003) we published a series of articles on management of acute stroke in Australia. These have provoked a flurry of vigorous viewpoints. (For editorial comment see* page 333.*)*

Evidence-based care and outcomes of acute stroke managed in hospital specialty units

Charles P Denaro,* Thomas M Ferrier†

* Director of Internal Medicine and Associate Professor, † Physician, Royal Brisbane Hospital, 9th Floor, Ned Hanlon Bldg, Butterfield Rd, Herston, QLD 4029. c.denaro@medicine.uq.edu.au

TO THE EDITOR: We comment on the report by Duffy and colleagues of a study of evidence-based care and outcomes of acute stroke.[1] The Royal Brisbane Hospital contributed 300 patients to this study between September 1999 and May 2001. As our hospital's geographically separate stroke unit did not open until February 2001, it is likely that most, and perhaps all, of these patients were cared for in the Department of Internal Medicine, a general medical service. The study compared 1664 patients treated in four types of unit — stroke, neurological, general medical or geriatric units — and found statistical differences between these units. The authors acknowledged that patients in the stroke units were younger than those in other types of unit and also that there "may be differences . . . in complexity and severity of cases that we did not assess . . .".

Our own experience at the Royal Brisbane Hospital may help readers to interpret this study. Our stroke unit has a defined number of beds and resources. While it tries to accommodate as many patients as possible, it often cannot serve all patients with stroke who come to the hospital. Patients of extreme age or with severe illness, caused by either the stroke or comorbidities, or those with adverse cognitive, social or residential status, are often not accepted into the stroke unit and remain in the general medical service. Thus, baseline characteristics differ markedly between patients in our general medical unit and the stroke unit. We are concerned that similar differences exist at the other institutions that provided data for this study. We see little point in publishing 20 separate χ^2 tests that contrast differences between the four types of services looking after these patients, unless the baseline characteristics of the patients were very similar and statistically identical. In addition, one could also argue that with this number of statistical tests there would be a good chance of a type 1 error.

There is no doubt that stroke units improve outcomes. This makes sense for any acute condition with likely long-term sequelae, as specialty units can provide more resources and a dedicated team of nurses and allied health professionals. However, in our opinion, this study does not provide convincing evidence for the superiority of stroke units over any other type of medical unit, as it is likely that the patients differed significantly between these units.

1. Duffy BK, Phillips PA, Davis SM, et al. Evidence-based care and outcomes of acute stroke managed in hospital specialty units. *Med J Aust* 2003; 178: 318-323. ❑

Paddy A Phillips,* Brendan K Duffy,† Miriam E Vedadhaghi,‡ Stephen M Davis,§ Geoffrey A Donnan¶

* Head, † Cardiology Fellow, Department of Medicine, Flinders University of South Australia, Flinders Medical Centre, Bedford Park, SA 5042; ‡ Project Associate, Servier Laboratories, Hawthorn, VIC; § Director of Neurology, Royal Melbourne Hospital, Melbourne, VIC; ¶ Director, National Stroke Research Institute, Melbourne, VIC. paddy.phillips@flinders.edu.au

IN REPLY: We agree with Denaro and Ferrier that there is selection pressure for admission of different types of patients to different units. This was clearly apparent in our study, with stroke units caring for significantly younger patients.[1] We discussed in our report that, as this study was not a randomised controlled trial, differences in age and other undocumented factors have potential to bias the results.

However, our primary aim was to determine whether current care of patients with stroke in major Australian hospitals accorded with evidence-based strategies. We showed major variations in the use of proven evidence-based strategies in different hospitals and by different specialty units in the real world of Australian healthcare. There were also major and significant variations in outcomes. We believe that all patients with stroke should be cared for in accord with the best evidence available, clinical expertise and their own values[2] to produce the best possible outcomes.

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2. Sackett DL, Straus SE, Richardson WS, et al. Evidence-based medicine: how to practise and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone, 2000. ❑

Thrombolysis for acute ischaemic stroke: revisiting the evidence

Brendon J Smith

Emergency Physician, Bankstown-Lidcombe Hospital, Locked Mail Bag 1600, Bankstown, NSW 2200. brendon.smith@swsahs.nsw.gov.au

TO THE EDITOR: The recent article by Szoeke and colleagues on stroke management expressed the hope that thrombolytic therapy will be licensed for use by specialist units in Australia, based on the "proof" of its benefit demonstrated by the National Institute of Neurological Disorders and Stroke (NINDS) trial.[1]

The NINDS trial was a small, flawed study in which 312 patients received thrombolytic therapy with tissue plasminogen activator (tPA) for stroke.[2] Higher scores for stroke severity in the placebo group could themselves explain the improved outcome attributed to thrombolysis. Further clarification has been thwarted by the investigators' refusal to release the raw data and allow clarification of uncertainty surrounding the results whereby benefit appears confined to those treated at 0–90 minutes after onset, with no benefit in those treated at 90–180 minutes.[2]

Reports of the introduction of thrombolysis with tPA into clinical practice consistently document substantial protocol violations and worse outcomes than without thrombolysis. The study by Szoeke et al documents mortality attributed to thrombolysis given when protocol criteria were not met, as well as a 23% protocol violation rate in a presumed "best practice" setting. It should be highlighted that their finding in an audit of 30 patients that outcomes were

"consistent with reported trial data" means they were also consistent with a worse outcome, although confidence intervals are not presented.

Thrombolysis with tPA is not endorsed as a standard of care in stroke by the Canadian Association of Emergency Physicians, the American Academy of Emergency Medicine or the American College of Emergency Physicians; nor do any of these organisations advocate its introduction into practice outside research trials.[3,4]

In contrast, the American Heart Association upgraded its rating for thrombolysis in stroke from a class IIa to a class I recommendation in its 2000 guidelines without any additional data from randomised trials. Conflicts of interest are substantial and not widely disclosed.[2] Genentech, the manufacturer of tissue plasminogen activator, has contributed US$11 million to the American Heart Association and paid for its national headquarters. Six of the nine panellists responsible for the guidelines had financial ties to Genentech, which were not disclosed.[5] A dissenting panellist had his name removed from the list of contributors, despite previous assurances that his dissenting position would be published.[5]

There are not many areas where so much has been made of so little; it falls a long way short of proof.

1. Szoeke CEI, Parsons MW, Butcher KS, et al. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust* 2003; 178: 324-328.
2. Hoffman JR. Tissue plasminogen activator for acute ischemic stroke: is the CAEP position statement too negative? *Can J Emerg Med* 2001; 3: 183-185.
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4. Lenzer J. Alteplase for stroke: money and optimistic claims buttress the "brain attack" campaign. *BMJ* 2002; 324: 723-729.
5. Hoffman J. Annals supplement on the American Heart Association proceedings. *Ann Emerg Med* 2001; 38: 605.❑

Geoffrey A Donnan,* Stephen M Davis,† Christopher R Levi‡

* Director, National Stroke Research Institute, Melbourne, VIC; † Director of Neurology, Royal Melbourne Hospital, Parkville, VIC 3050; ‡ Neurologist and Conjoint Senior Lecturer, John Hunter Hospital, Newcastle, NSW. stephen.davis@mh.org.au

IN REPLY: The comments of Smith may not reflect the consensus of his emergency medicine colleagues. The broad view of the place of tissue plasminogen activator (tPA) is best appreciated from overviews and meta-analysis of all trials of intravenous tPA in acute ischaemic stroke.[1-3] Overall, tPA is one of the most powerful biological agents in medicine, with a number needed to treat of about eight to benefit one patient.

The integrity of the investigators of the tPA trials is unquestionable. All results were published in journals of the highest repute (including the *New England Journal of Medicine*, the *Lancet* and the *Journal of the American Medical Association*). The National Institute of Neurological Disorders and Stroke (NINDS) trial[4] was investigator-driven and funded by the US National Institutes of Health, the highest standard achievable in trial management.[5] NINDS receives unrestricted grants from the pharmaceutical industry with appropriate ethical guidelines, as do many societies worldwide. To suggest a linkage is certainly extending conspiracy theory to its limits.

Several trial-related issues mentioned by Smith deserve comment. In the NINDS trial, as in many randomised controlled trials, the analysis adjusted for minor baseline imbalances in stroke severity, with no significant impact on outcome. The Melbourne study of Szoeke et al was not a randomised controlled trial, but rather an audit of practice in an expert setting.[6] The protocol violations were all relatively minor, and the rate of 23% is comparable with rates in other Phase IV studies.[7]

Although only a small proportion of stroke patients are eligible for tPA, it is one of the most important advances in stroke medicine. Emergency physicians must play a collaborative role with stroke physicians in delivering this benefit.

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2. Hacke W, Brott T, Caplan L, et al. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. *Neurology* 1999; 53 (7 Suppl 4): S3-S14.
3. Donnan GA, Davis SM. Thrombolytic therapy in ischaemic stroke: do the benefits outweigh the risks? *CNS Drugs* 1996; 6: 257-262.
4. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333: 1581-1587.
5. Donnan GA, Davis SM, Kaste M, for the International Trial Subcommittee of the International Stroke Liaison Committee, American Stroke Association. Recommendations for the relationship between sponsors and investigators in the design and conduct of clinical stroke trials. *Stroke* 2003; 34: 1041-1045.
6. Szoeke CEI, Parsons MW, Butcher KS, et al. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust* 2003; 178: 324-328.
7. Albers GW, Bates VE, Clark WM, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the standard treatment with Alteplase to reverse stroke (STARS) study. *JAMA* 2000; 283: 1145-1150. ❑

Kent R Johnson

Medical Director, Medical Technology Assessment Group (M-TAG), PO Box 5639, Chatswood West, NSW 2067. kjohnson@m-tag.net

TO THE EDITOR: Recent commentators have described the uncertainty surrounding the use of thrombolysis in acute ischaemic stroke.[1,2] Recombinant tissue plasminogen activator (tPA) was first approved in 1996, yet its use in stroke still remains low. One explanation is feasibility, as treatment must begin within 3 hours of stroke onset. However, the evidence itself is being questioned.[3,4] A recent Cochrane meta-analysis advises caution, noting particularly heterogeneity, and concludes that: "In the light of these considerations, some clinicians may wish to use thrombolytic therapy in highly selected patients; others who are concerned about the definite risks may choose not to use the treatment at all."[4] It is worth revisiting the two studies that supplied the preponderance of data for tPA approval — the two parts of the National Institute of Neurological Disorders and Stroke (NINDS) trial.[5]

Firstly, the results at face value cannot be considered particularly robust. The first part of the trial (291 patients) showed no difference in the primary endpoint, "early improvement" (resolution or improvement by at least four units on the 24-hour National Institutes of Health [NIH] Stroke Scale). The second part (333 patients) did show a difference in its primary endpoint, a 3-month global statistic[6] that simultaneously assessed the Barthel Index, modified Rankin Scale, Glasgow Outcome Scale, and NIH Stroke Scale, with the odds ratio for a favourable outcome with tPA being 1.7 (95% CI, 1.2–2.6; $P = 0.008$). However, the two parts of this trial also showed substantial drug toxicity (a combined rate of symptomatic intracerebral haemorrhage of 6.4% with tPA versus 0.6% with placebo) with no improvement in mortality (17% with tPA versus 21% with pla-

cebo; $P = 0.30$). Few would describe these results as robust.

Secondly, the design strategy added uncertainty to the interpretation. The two parts of the trial were sequential, so that the design of the second could profit from lessons learned from the first: an attractive and common strategy. The studies used identical entry criteria and dosing regimens but different primary endpoints and timepoints. Part 1 "test[ed] whether tPA had clinical activity", using "early improvement" as the primary endpoint.[5] It was then extended for 3 months, and those results were used by the Data Safety Monitoring Committee to design an efficient 3-month endpoint for Part 2. In effect, Part 2 was a test of both tPA therapy and of the new endpoint. This endpoint is then entirely conditional on Part 1; there was no prior trial experience with this endpoint. Consequently, the trial's success is less generalisable than if a well-established endpoint had been used, and the two parts together carry less evidentiary weight than if they had been fully independent.

1. Szoeke CEI, Parsons MW, Butcher KS, et al. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust* 2003; 178: 324-328.
2. Mitka M. Tensions remain over tPA for stroke. *JAMA* 2003; 289: 1363-1364.
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4. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke (Cochrane review). The Cochrane Library, Issue 1 2003. Oxford: Update Software.
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Paul M Bailey

Emergency Physician, Joondalup Health Campus, Shenton Ave, Joondalup, WA 6027.

TO THE EDITOR: In their retrospective audit of stroke patients presenting to a Victorian hospital, Szoeke and colleagues present a one-sided view of the usefulness of thrombolysis with tissue plasminogen activator (tPA) in acute stroke.[1]

Proof of the efficacy of tPA in acute ischaemic stroke is far from settled. The National Institute of Neurological Disorders and Stroke (NINDS) trial, in which only 312 patients received thrombolytic therapy, remains the only trial demonstrating benefit from intravenous thrombolysis in a primary outcome measure.[2]

The study design of the NINDS trial required the enrolment of a disproportionate number of patients with very early stroke (within 0–90 minutes of onset). These patients are rarely encountered in everyday clinical practice. Patients in the 91–180 minute group who received placebo were sicker at baseline than those who received tPA, raising significant doubts as to the efficacy of tPA. After further analysis of the results, the NINDS investigators reported that the greatest positive effect of tPA was seen in the 0–90 minute group.[3] The positive effect of tPA in the 91–180 minute group, while not specifically reported, can only have been very small. It is interesting that the median time to treatment in Szoeke et al's study was 2 h 48 min, implying that 50% of patients were treated in the last 12 minutes of the 3-hour window — when benefits of treatment are at their smallest (should they exist at all), but all the risks of therapy remain.

I am also astounded that in the setting of a dedicated stroke unit, with all patients attended to by a team comprising "a stroke neurologist, 'stroke' fellow, registrar and nurse", and a requirement for specific approval for use of tPA to treat stroke in the hospital, that protocol violations occurred in 23% of patients (7/30). That is not the sort of performance that I would want to place in the public domain.

Tiny retrospective "trials" are fraught with potential bias, as non-blinded treatments and outcome measures may reflect the enthusiasm of the authors. In addition, significant publication bias may exist — groups with bad results from thrombolysis may not publish.

I await the publication of further well designed, randomised, placebo-controlled clinical trials, not linked to the manufacturers of tPA, that demonstrate an improvement in a primary outcome measure in patients treated with tPA before deciding that this treatment may have some use outside clinical trials. I will not hold my breath.

1. Szoeke CEI, Parsons MW, Butcher KS, et al. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust* 2003; 178: 324-328.
2. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333: 1581-1587.
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Stephen M Davis,* Mark W Parsons,† Kenneth S Butcher,‡ Cassandra E I Szoeke§¶

* Director of Neurology, † Neurologist, ‡ Neurologist, § Registrar, Royal Melbourne Hospital, Parkville, VIC 3050. ¶ On behalf of the other authors.[1]
stephen.davis@mh.org.au

IN REPLY: Johnson correctly points out that the National Institute of Neurological Disorders and Stroke (NINDS) trial had two parts.[2] Part 1 was designed to test whether tissue plasminogen activator (tPA) had early clinical activity at 24 hours, and Part 2 was designed to assess whether tPA conferred outcome benefits at 3 months. The results of Part 1 of the trial showed a non-significant improvement in neurological score at 24 hours. However, the finding in Part 2 that there was a significant difference in the primary endpoint (a global test statistic at 90 days) was also true for Part 1 and for a combined analysis of Parts 1 and 2.[3] Although there was a substantial increase in symptomatic intracerebral haemorrhage in the thrombolysis group, there was no increase in mortality, and the adverse effects were outweighed by the highly significant benefits at outcome.

Johnson's comment on the choice of endpoints is also of interest. It should be emphasised that the efficacy of tPA in the NINDS trial applied to a range of standard outcome evaluations, including the NIH Stroke Scale, Glasgow Outcome Scale, modified Rankin Scale and Barthel Index, as well as the new global test statistic, which incorporates these scores.[2]

Many of the issues raised by Bailey have been covered by Donnan et al,[4] but some additional comments are warranted. Based on the NINDS trial and meta-analyses of all the intravenous tPA data, this therapy has been licensed for stroke in the United States, Canada, Europe (including the United Kingdom) and many other parts of the world. It is being considered for licensing in Australia. The minor baseline disparities between the tPA and placebo groups have been subject to further

rigorous analysis by an independent review committee commissioned by NINDS. This analysis confirmed the statistically significant benefit of tPA within 3 hours.[5]

The benefits of tPA are indeed time-linked, as shown by further analysis of the NINDS data, but are highly significant right up to the end of the 3-hour window.[6] The odds ratio for favourable 3-month outcome with tPA was 2.11 (95% CI, 1.33–3.35) for treatment at 0–90 minutes and 1.69 (95% CI, 1.09–2.62) for treatment at 91–180 minutes. Furthermore, meta-analysis indicates benefit beyond the 3-hour window,[7] but there is consensus that further trials are needed to extend the current window, and that tPA should not be used after 3 hours, except in clinical trials.

We again emphasise that our audit was not a "trial" and that our protocol violations were generally minor and in line with other expert experience.[1] We do not apologise for emphasising the importance of a well-resourced acute stroke team. This is integral to the expert setting required for tPA administration. In 2003, would anyone suggest that patients with acute myocardial infarction should be treated without optimal resources and expert care? Why should acute stroke patients, with high mortality and disability rates, be the poor relations?

1. Szoeke CEI, Parsons MW, Butcher KS, et al. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust* 2003; 178: 324-328.
2. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333: 1581-1587.
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