Tissue plasminogen activator (tPA) in acute ischaemic stroke: time for collegiate communication and consensus

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It has long been an axiom of mine that little things are infinitely the most important — Arthur Conan Doyle.[1]

STROKE IS A DEVASTATING DISEASE. Nationally, it is the third leading cause of death, but, more importantly, it leaves many survivors permanently disabled. While there have been major advances in stroke prevention over the past half-century, our ability to treat acute stroke has lagged well behind these advances. However, over the past decade, three effective acute stroke therapies have emerged — one for all strokes (organised stroke unit care), one for most strokes (aspirin administered within 48 hours of onset in ischaemic stroke) and one for a select subset of stroke (tissue plasminogen activator [tPA] given within 3 hours of onset in selected ischaemic stroke). Although only a small proportion of stroke patients are eligible to receive tPA, collaborative efforts, with improved organisation of health services, have been shown to increase to 15% the proportion of patients treated with tPA.[2] tPA is the most potent therapy in stroke management, with the number of patients needed to treat being eight to achieve the outcome of minimal or no handicap at discharge from hospital. Thus, the absolute benefit of tPA therapy for ischaemic stroke considerably exceeds that seen for thrombolysis in acute myocardial infarction.[3] For many of us who manage patients with stroke across the continuum of care, all advances in stroke therapy, even if only relevant to a small proportion of patients, are most welcome.

A recent commentary in the Journal on the use of tPA in acute ischaemic stroke[4,5] opened with the remark "why so much has been made of so little". The Australasian Stroke Unit Network (ASUN),[6] the New South Wales Greater Metropolitan Transition Taskforce Stroke Initiative (GMTT Stroke)[7] and the Towards A Safer Culture Stroke Expert Working Group (TASC Stroke)[8] are clinician-based networks involved in the development of effective models of stroke-care delivery. We believe it is necessary to comment on the recent debate to clarify why many clinicians caring for stroke patients in Australasia believe the recent licensing in Australia of tPA for treatment of acute ischaemic stroke is a major advance.

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ABSTRACT

- Systematic reviews of randomised trials of tPA in acute ischaemic stroke indicate a clear benefit of treating selected patients within 3 hours of stroke onset. Moreover, a net benefit remained after adjustment for chance baseline imbalances between subgroups in stroke severity within one of these trials (National Institute of Neurological Disorders and Stroke [NINDS]).
- Rates of favourable outcomes and intracranial haemorrhage comparable with those in randomised trials can be achieved in routine clinical practice; however, translation of net benefit from tPA therapy requires organised and coordinated stroke management across the continuum of care.
- Prerequisites for well organised and coordinated acute stroke care are:
  - ➤ consensus among care providers on the use of tPA;
  - ➤ stroke-care teams spanning the gaps between pre-hospital care, emergency departments and stroke units; and
  - ➤ collegiate relations and effective communication networks between care providers.

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It is important to briefly review the evidence, as the discussion and points of view on the usefulness of tPA in stroke largely revolve around interpretation of clinical trial data.[9,10] An imbalance in stroke severity between treatment and control groups at baseline in the 1995 National Institute of Neurological Disorders and Stroke (NINDS) trial, and the possibility that this imbalance biased the study's outcome, has been the major focus of the discussion.[5,10-12] An important question is: do the imbalances in stroke severity at baseline in the 91–180-minute post-stroke group significantly influence the net difference in outcome between the tPA- and placebo-treated patients? The use of multivariate analysis is a standard approach to adjust for potential confounding in clinical trials. The NINDS Stroke Study Group[10] performed both logistic regression analysis and an analysis excluding the mild stroke subgroup in patients treated within 91–180 minutes. For the outcome of death and dependency, both analyses showed a significant net benefit in favour of tPA. The independent analysis of published group data by Wardlaw et al, adjusting for stroke severity, also indicated a significant benefit in favour of tPA (absolute benefit, 8%).[13] Finally, an independent committee given access to the individual patient data from the NINDS trial[14] found that imbalances in baseline stroke severity did not invalidate the conclusions of the trial, with neither baseline stroke severity

nor time from symptom onset to treatment significantly modifying the tPA treatment effect. Meta-analyses, including the Cochrane review,[15,16] of data on the use of tPA up to 3 hours after stroke onset, although substantially influenced by the NINDS trial dataset, also included data from other trials (ECASS[17,18] and ATLANTIS[19,20]) and provided a clear net benefit in favour of tPA. More recently, pooled analysis of NINDS, ECASS and ATLANTIS data provided further support for the Cochrane and Australian meta-analysis of data for use of tPA less than 3 hours after stroke onset, and suggested a net benefit in some patients receiving tPA up to 4.5 hours after onset.[21] Post-marketing studies, including a recent Australian audit, have shown favourable clinical outcomes and rates of symptomatic intracranial haemorrhage similar to those seen in the NINDS trial.[22,23] Therefore, ASUN supports the decision of the Therapeutic Goods Administration to license tPA for use in appropriately selected patients with acute ischaemic stroke within 3 hours of stroke onset. Overseas, national licensing authorities have also approved the use of tPA in North America, Europe and South America. Furthermore, the use of tPA in appropriately selected patients has been endorsed by professional societies and organisations such as the American Heart Association, the National Institute of Neurological Disorders and Stroke, the European Stroke Initiative, the Canadian Stroke Consortium, the American Academy of Neurology, and the American College of Emergency Medicine.

Additional data are still required for patients over the age of 80 years, but a recent audit from Canada is reassuring, with rates of symptomatic intracranial haemorrhage in those over 80 years being comparable with rates reported in randomised trials.[24] Additional data are also required for assessing the significance of early ischaemic changes on computed tomography (CT) scans, for determining optimal blood pressure management, and for interpreting the heterogeneity among studies in calculating the summary estimate of benefit for the 0–6-hour tPA trials.[15] There are also obvious logistical difficulties in applying a therapy with a narrow time window, emphasising the importance of the keenly anticipated data from current trials evaluating the use of tPA up to 6 hours after stroke onset. However, none of these remaining questions should prevent us from immediately providing the benefit available to patients suitable for treatment with tPA. We recommend that, when there is uncertainty as to the benefit of tPA, clinicians consider entering such patients into one of the ongoing trials of tPA in acute ischaemic stroke (IST-3 <www.ist3.com>; EPITHET <www.astn.org.au/epithet_home.htm>; ECASS III, <www.strokecenter.org/trials/TrialDetail.asp?ref=475&browse=acute>).

Members of ASUN, GMTT Stroke and TASC Stroke strongly believe that communication and collaboration between physicians, emergency physicians and pre-hospital care providers treating acute stroke are essential in developing safe and effective delivery of care. This collaboration is especially important in hospitals opting to use tPA in acute stroke. Our groups will continue to implement and evaluate support systems and infrastructure to facilitate this collaboration and to measure and improve care delivery. Inevitable differences in interpretation of specific aspects of evidence from trials of acute stroke therapy, and variation in the level of healthcare support for stroke management available in the Australian healthcare system, are likely to persist. However, these differences should not prevent a concerted effort to identify common ground in acute stroke management, and the development of consensus and collaboration between members of stroke units, emergency departments and ambulance services. We prefer approaches that minimise differences between clinical groups and promote safer, effective and more efficient acute stroke care systems through communication and collegiality. These are the keys to better organisation across the intersections of care.[25,26] Just as effective anaesthesia eventually led to the development of smooth teamwork extending from the preoperative clinic to postsurgical intensive care, the licensing of tPA for use in acute ischaemic stroke will provide many organisations with an opportunity to promote clinical cooperation in the planning and development of better, safer systems of care for stroke patients. Such an outcome, rather than prompting the comment "Why so much has been made of so little", may lead people to ask, "Why did it take so long?".

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Competing interests

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References

1. Doyle, Arthur Conan. The Adventures of Sherlock Holmes. Adventure III: A case of identity. Available at: doyle.thefreelibrary.com/Adventures-of-Sherlock-Holmes/3-1 (accessed May 2004).
2. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischaemic stroke: Houston experience 1996 to 2000. *Arch Neurol* 2001; 58: 2009-2013.
3. Kaste M. Approval of alteplase in Europe: will it change stroke management? *Lancet Neurol* 2003; 2: 207-208.
4. Hoffman JR. Tissue plasminogen activator (tPA) for acute ischaemic stroke: why so much has been made of so little [editorial]. *Med J Aust* 2003; 179: 333-334.
5. Smith BJ. Thrombolysis for acute ischaemic stroke: revisiting the evidence [letter]. *Med J Aust* 2003; 179: 386-389.
6. Stroke Society of Australasia. Australasian Stroke Trials Network. Available at: www.astn.org.au/SSA/links.html (accessed Apr 2004).
7. NSW Health. Greater Metropolitan Transition Taskforce. Stroke initiative. Available at: www.ppc.health.nsw.gov.au/policy/gap/gmt2/program/chairs.html (accessed Apr 2004).
8. Institute for Clinical Excellence. Towards A Safer Culture (TASC) Program. Available at: www.ice.nsw.gov.au/TASC.htm (accessed Apr 2004).
9. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. *N Engl J Med* 1995; 333: 1581-1587.
10. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000; 55: 1649-1655.
11. Grotta JC, for the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. The NINDS Stroke Study Group response. BMJ rapid response, 2 July 2002. Available at: bmj.bmjjournals.com/cgi/eletters/324/7339/723#23369 (accessed Apr 2004).
12. Mann J. The efficacy analysis of the NINDS trial is flawed. BMJ rapid response, 22 March 2002. Available at: bmj.bmjjournals.com/cgi/eletters/324/7339/723#20720 (accessed Apr 2004).
13. Wardlaw JM, Lindley RI, Lewis S. Thrombolysis for acute ischaemic stroke: still a treatment for the few by the few. *West J Med* 2002; 176: 198-199.
14. Ingall TJ, O'Fallon WM, Louis TA, et al. Initial findings of the rt-PA acute stroke treatment review panel. *Cerebrovasc Dis* 2003; 16 (Suppl 4): 125.
15. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2003; (3): CD000213.
16. Donnan GA, Howells DW, Markus R, et al. Can the time window for administration of thrombolytics in stroke be increased? *CNS Drugs* 2003; 17: 995-1011.
17. Hacke W, Kaste M, Fieschi C, et al, for the ECASS study group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274: 1017-1025.
18. Hacke W, Kaste M, Fieschi C, et al. Randomised double blind placebo controlled trial of thrombolysis with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998; 352: 1245-1251.
19. Clarke WM, Albers GW, Madden KP, et al. The rt-PA (alteplase) 0- to 6-hour acute stroke trial, part A (A0267g): results of a double blind, placebo controlled, multicenter study. *Stroke* 2000; 31: 811-816.
20. Clarke WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (alteplase) for ischaemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study — a randomised controlled trial. *JAMA* 1999; 282: 2019-2026.
21. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. *Lancet* 2004; 363: 768-774.
22. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Ann Neurol* 2002; 52 (Suppl 1): S24.
23. Szoeke CE, 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.
24. Simon JE, Sandler DL, Pexman JH, et al, for the Calgary Stroke Programme. Is intravenous recombinant tissue plasminogen activator (rt-PA) safe for use in patients over 80 years old with acute ischaemic stroke? The Calgary experience. *Age Ageing* 2004; 33: 143-149.
25. Campbell D, Scott I, Anderson J, Greenberg P. Improving clinical practice: what works and what doesn't? *Intern Med J* 2001; 31: 536-540.
26. Committee on Quality Health Care. American Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press, 2001.

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