Authors' affiliations
H Chung, R R Camejo, D Barnett, National Institute for Health and Clinical Excellence, UK

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Correspondence to: Professor D Barnett, Department of Cardiovascular Sciences, Floor 4 RKCSB, Leicester Royal Infirmary, Leicester LE2 7LX, UK; dbb1@le.ac.uk

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Commentary on NICE guidelines for alteplase for the treatment of acute ischaemic stroke

R I Lindley

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Another important milestone for stroke has been reached with the recent approval by NICE of alteplase for acute ischaemic stroke.[1] This welcome decision provides a much needed boost for those struggling to implement acute stroke intervention, for acute stroke intervention is certainly struggling. The sad truth about alteplase for acute ischaemic stroke is that treatment is still unavailable in a surprisingly large number of large hospitals in the UK and elsewhere.

The decision by NICE was based on a rigorous examination of the randomised controlled trial (RCT) data, and it is reassuring to note that this was based, not on the main positive trial,[2] but on independent systematic reviews of the totality of the data. For those not familiar with these data, the main concern has been that most of the evidence of the effectiveness of alteplase within the 3-hour time window is based on one study—the National Institute of Neurological Disorders and Stroke (NINDS) study.[2] However, concerns about this study have been examined in an independent reanalysis of the NINDS data and the main findings confirmed.[3] The large postmarketing surveillance audit of alteplase in Europe, SITS-MOST, has also been reassuring: provided that alteplase is delivered by doctors trained and experienced in the management of acute stroke, results comparable to the RCT evidence can be achieved.[4]

Interestingly, the economic assessment of alteplase was in the context of treatment being delivered in well-organised stroke centres. It was considered unreasonable to factor in the large costs of stroke reorganisation in the economic modelling. This is reasonable given the impressive evidence that early brain imaging together with organised stroke unit care is the most important intervention in the management of acute stroke.

Implementation of NICE recommendations should follow as: ''The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months…''.[1] However, this deceptively simple sentence hides enormous challenges. A comparison with the successful cardiological implementation of thrombolysis for acute myocardial infarction is instructive. Myocardial infarction is a painful frightening condition which prompts early calls for help and rapid hospital assessment, with coronary care units well established in the 1980s facilitating the completion of a series of coronary ''mega-trials''. The diagnosis of acute ST segment elevation myocardial infarction is relatively straightforward and the risks of cerebral haemorrhage low (3.9 per 1000 treated).[5]

In contrast, stroke is usually painless, and delays in attending hospital common. The diagnosis of stroke is often not straightforward and many doctors find neurological examination skills difficult, and the risk of symptomatic haemorrhagic transformation of infarction, or other intracranial haemorrhage, is high (at least 10-fold the risk compared with acute myocardial infarction). There is no easy equivalent to the ECG. Early CT scanning if often normal, early magnetic resonance scanning is not widely available, many older patients have contraindications to magnetic resonance,[6] and diffusion-weighted abnormalities can be absent even in definite stroke (and can be falsely positive due to non-stroke conditions). Stroke units are still not universally available. As a result of all these barriers, stroke thrombolysis rates in the UK and Australia are still well below 1%. Rates are not much better elsewhere, with USA rates about 2%.[7] Of course, there are exceptions to this appallingly low use, with many stroke centres achieving rates of 10–20%,[8] but these are the exception rather than the rule.

So, what has gone wrong with the implementation of stroke thrombolysis, some 12 years after the publication of the NINDS trial? First, the RCT evidence is inadequate. A mere 5727 patients contribute to the Cochrane Library review, whereas 58 600 subjects were in the 1994 Fibrinolytic Therapy Trialists' overview.[5] The evidence from the cardiological thrombolysis

trials was so convincing that clinical practice changed overnight.[9] The limited data for ischaemic stroke have contributed to the endless debate. As the NICE guidance emphasises, recruitment in the continuing IST-3 (http://www.ist3.com (accessed 18 September 2007)) and ECASS-III trials will establish the effectiveness of alteplase outside the current marketing authorisation (chiefly patients over 80 years of age and those treated after 3 hours of stroke onset). Successful recruitment in these two major studies will do much to end the debate over the RCT data. It is disappointing that there have not been any acute stroke ''mega-trials'' in the past decade. With the advent of stroke units, stroke doctors should collaborate more effectively and ensure treatments with moderate benefits are rapidly evaluated, as is common in cardiological practice.

Second, it is vital that doctors managing acute stroke embrace thrombolysis. Much of neurological practice has become an outpatient specialty, and some have noted the reluctance of neurologists to ''get off their hands''![10] The adrenaline rush of a fast-track stroke assessment is certainly different from usual neurological office practice. The answer is probably to rationalise stroke thrombolysis to larger centres which have a critical mass of stroke doctors to support a 24-hour thrombolysis service. Telemedicine has been successfully employed to support smaller community centres.[11] We also need to ensure that the neurological skills of acute stroke assessment are more widely available in the non-neurological specialties. Generalists should be taught the essentials of the stroke thrombolysis management and new studies have outlined the ''science behind the art'' of the acute assessment of stroke.[12] The major advances in brain imaging have also made stroke assessment more accurate. CT scanning is now extremely quick and cost effective,[13] and the new technology of CT perfusion is likely to be widely available. Training non-neuroradiologists to read a CT scan accurately will improve acute stroke assessment.[14] Advanced magnetic resonance scanning can confirm the ischaemic stroke lesion AND identify the cerebral occlusion.

Finally, public education must be continued to remind people that stroke is a medical emergency.[15] Ambulance staff can implement protocols to identify suspected stroke with high accuracy,[16] and emergency departments also need protocol-driven fast-tracking of patients with suspected stroke.

Overall, the NICE guidance is a great step for stroke medicine, but do not underestimate the difficulty in implementing change. Remember, you need an alteplase treatment rate of about 10% to match the public health benefit of immediate aspirin for acute ischaemic stroke.

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Correspondence to: Dr R I Lindley, Department of Geriatric Medicine, Discipline of Medicine, Westmead Hospital (C24), The University of Sydney, NSW 2006, Australia; richard_lindley@wmi.usyd.edu.au

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