NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Alteplase for the treatment of acute ischaemic stroke (review of TA 122)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Peter Sandercock

Name of your organisation: Association of British Neurologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES (Co-chief Investigator IST-3 trial)**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Current use
Intravenous Alteplase is currently used routinely in the NHS among patients aged under 80 years 3 and increasingly within 4.5 hours. Use among patients aged over 80 varies by region and by hospital within region.

Alternatives
a) ***New iv thrombolytics*** (tenecteplase, desmoteplase) are not currently licensed but are the subject of ongoing RCT's.

b) ***Intra-arterial thrombolysis*** (with or without adjunctive iv thrombolysis and with or without adjunctive mechanical clot retrieval). Two key trial results (IMS-III and SYNTHESIS) comparing standard therapy with IA/clot retrieval will report in 2013.

Advantages of intra-arterial:
- can be used, typically in patients who do not respond to standard iv alteplase therapy, or who have a contra-indication to thrombolytic therapy (eg recent surgery, post-partum stroke, etc)
- may re-open artery if iv therapy has failed.

Disadvantages
- available only to small number of patients with access to the small number of specialised tertiary referral centres with relevant expertise and resources
- procedural complications (arterial dissection, vessel perforation, death)
- high procedural cost (staff and consumables); opportunity cost by diversion of expert staff away from interventions that are known to be effective (endovascular

treatment of ruptured intracranial aneurysms) to treatments for which there no reliable RCT evidence of net clinical benefit (Mechanical clot retrieval).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

- Increasing age and increasing stroke severity are associated with decreasing likelihood of a good prognosis

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology

- Patients treated within 3 hours benefit most[1,2]
- Current indication restricts treatment to patients aged under 80;
- Current spc/indication states that severe stroke as assessed clinically (e.g. NIHSS>25) is a contraindication.
- However, evidence from the recently completed IST-3 trial and the accompanying meta-analysis suggests that older patients (aged over 80) derive no less benefit than younger patients and that severe strokes benefit no less than milder strokes[1,2]

In what setting should/could the technology be used

- Secondary or tertiary care hospitals with appropriate systems for rapid identification of suspected stroke in the community, rapid hospital transfer, fast-track clinical and imaging assessment and the capacity to monitor patients condition carefully over the first 24 hours in the context of a comprehensive stroke care system.

Is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

- Yes, there is variation about overall use and the extent to which it used outside the approved indication. There is increasing use among the over-80's and in patient 3-4.5 hours (chiefly, but not exclusively under 80 in the latter group)

Please tell us about any relevant clinical guidelines

RCP London Guidelines 2008
(http://www.rcplondon.ac.uk/resources/stroke-guidelines). These were developed with appropriate methodology, and an update to the guidelines, to take account of the IST3 trial and updated meta-analysis is due to be published sometime this year.

European Stroke Guideline 2009
http://www.eso-stroke.org/pdf/ESO_Guideline_Update_Jan_2009.pdf
the methodology for this guideline is less robust than the RCPL guideline , but does take account of the data from the ECASS-3 trial, but not IST-3

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The advantages and disadvantages of the technology
The extension of the licence to 4.5 hours will probably not have a major impact on the NHS. It will enable a few more patients to be treated. However, given that benefits are greatest when patients are treated within 3 hours, the priority must be to ensure the NHS reinforces efforts to treat stroke patients at the earliest opportunity and to minimise onset to hospital arrival times shorten and 'door to needle times' to less than the current 1 hour target.

Deciding who to treat/not to treat
The main requirement is for immediate access to plain CT scanning 24/7, with rapid availability of expert interpretation. The role of more advanced imaging (MR DWI/PWI/angiography scanning, CT angiography and perfusion imaging) is being evaluated in research studies. The priority is rapid, non-contrast CT. The IST3 data will provide useful additional information (to be reported in 2013) on the additional value of these more advanced techniques in stroke thrombolytic therapy.

Does the use of the technology under clinical trial conditions reflects that observed in clinical practice.
The evidence from RCT's and audits/observational studies / registries are concordant
- comparable risks of hazard: symptomatic and fatal ICH
- comparable estimates of benefit, overall and in people over 80

Do the circumstances in which the trials were conducted reflect current UK practice,
Yes

What, in your view, are the most important outcomes, and were they measured in the trials?

The following have all been reported by one or more trials
- Major events within 7-10 days of stroke onset: symptomatic intracranial haemorrhage, symptomatic cerebral oedema, major allergic reactions
- Death from all causes: 0-7 days, between 7 days & 6 months, death by 6 months
- Disability at 3-6 months (mRS, OHS)

Only IST-3 has collected data (yet to be published) on
- Survival to 18 months and beyond
- HRQoL (EQ5D)

What is the relative significance of any side effects or adverse reactions?

Symptomatic intracranial haemorrhage (SICH) is the chief cause of death within 7 days. Non-fatal SICH is likely to increase long-term impairment and disability. Management is largely conservative. However, it is . Still difficult to predict which patients are at high risk of SICH – ongoing work from IST3 may help.

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Major allergic reactions (chiefly orolingual oedema) can be life threatening, but is rare. It occurs most commonly on patients treated with ACE inhibitors. It requires urgent treatment as for anaphylactoid reactions, and if severe may require endotracheal intubation

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Not to my knowledge

References

1) Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. The Lancet . 23-5-2012.

(2) IST3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. The Lancet . 23-5-2012.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The IST-3 trial data set

The IST-3 trial has follow up to 18 months for all patients, with data on survival beyond 18 months for patients in the UK, Norway and Sweden. The assessments include disability (OHS version of mRS), HRQoL (EQ5D), placement and other data. The dataset also includes baseline and follow up scan data, assessed blind by an expert neuroradiology panel, and angiography data (450 cases) perfusion data (130 cases). These data are being analysed and will be made publicly available over the next year or so. 18 month outcome data will be reported in mid 2013.

Stroke Thrombolysis Trialists Collaboration

Individual patient data meta-analysis of all i.v. rt-PA RCT's, to update the Lees et al Lancet 2010 pooled analysis. The Protocol and analysis plan are in final draft. The group plan to meet mid 2013 to review preliminary analyses.

Primary analyses

- after what treatment delay is benefit lost or does harm begin,
- do age or stroke severity modify the proportional effect of rt-PA on stroke outcome?

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Stroke Thrombolysis Trialists Collaboration (cont)

Secondary

- Effect of treatment allocation on: death within 90 days, SICH, Symptomatic ischaemic brain oedema
- Effect modification by baseline characteristics

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Implementation to ensure equity of access will require

- Uniform training of ambulance/NHS 24/ NHS 111 staff in detection and appropriate triage of suspected acute stroke
- Regionally targeted Investment in regionally-coordinated systems of acute stroke care to ensure rapid and equitable access to acute stroke care for all in the region
- Uniform inclusion of rapid stroke triage as priority for triage in A&E departments
- NHS management to ensure that

a) job plans for all the consultants involved in acute stroke care include sufficient PA time to provide viable 24/7 acute stroke cover within the region
b) radiology resources sufficient to ensure 24/7 rapid access to immediate brain imaging for all patients with suspected stroke considered a potential thrombolysis candidate, with appropriate radiographer cover and expert radiological input to support diagnosis
c) Adequate day/night nursing support for monitoring patients requiring thrombolysis

- Ongoing training of junior medical, nursing and other staff

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