Institution: University of Edinburgh

Unit of Assessment: 4

Title of case study: B: Extending the indications for the clot-busting drug alteplase for treatment of acute ischaemic stroke increases patient survival and independent living worldwide

Period when the underpinning research was undertaken: 2000 – 2013

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Peter Sandercock	Chair of Medical Neurology	1987 – present
Joanna Wardlaw	Chair of Applied Neuroimaging	1994 – present
Martin Dennis	Chair of Stroke Medicine	1990 – present
William Whiteley	Senior Research Fellow	2010 – present

Period when the claimed impact occurred: August 2013 – December 2020

Is this case study continued from a case study submitted in 2014? This case study describes both the continued impact of the research described in REF2014/4/J, and new impact from further research on the use of thrombolytics post-stroke leading to broadening of the indications for alteplase use.

1. Summary of the impact

Underpinning Research: The third International Stroke Trial (IST-3), led by Edinburgh Neuroscience researchers, showed that thrombolysis with the 'clot-busting' drug alteplase significantly increased the likelihood of survival without disability after acute ischaemic stroke, regardless of age (when previously it was thought that alteplase would not benefit patients over the age of 80 years) and brain imaging findings.

Significance and Reach of Impact: Since REF2014, the Medicines and Healthcare products Regulatory Agency approved alteplase for acute ischaemic stroke (2015). Leading clinical guidelines from the UK, American Heart Association and the European Stroke Organisation have expanded the indication for alteplase so that it can now be given to several patient groups that were previously excluded, notably patients over the age of 80 and those with subtle early ischaemic changes on imaging. Alteplase was also included in the World Health Organization (WHO) Essential Medicines List in 2019. Thrombolysis by alteplase in eligible patients in the UK increased from 74% in 2013 to 89% in 2020. A worldwide independent audit by the international Safe Implementation of Thrombolysis in Stroke registry showed that the cumulative use of alteplase had gone from 80,000 patients in 2013 to more than 160,000 in 2018. Globally at least 80,000 more people have benefitted from reduced likelihood of disability and better quality of life after acute stroke.

2. Underpinning research

The Challenge: 100,000 strokes in the UK each year

More than 100,000 strokes occur in the UK each year, with approximately 25% of stroke survivors experiencing another stroke within 5 years. Approximately 1/3 of acute strokes occur among people older than 80 years and are caused by clots in the cerebral arteries. Early treatment with intravenous thrombolytics ('clot busting drugs') resolves the immediate problem by breaking up the clot, thus restoring blood flow to the brain and saving brain cells from damage. Timely thrombolysis is essential, as the effectiveness of treatment reduces with the increasing delay between onset of symptoms and treatment, thus increasing the risk of mortality and disability.

Alteplase improves quality of life and survival after stroke

The third International Stroke Trial (IST-3) trial, led by the Edinburgh Neuroscience stroke team between 2000 and 2011, showed that thrombolysis with recombinant tissue plasminogen activator (rt-PA; alteplase) significantly increased the likelihood of survival after acute ischaemic stroke, and provided the first reliable evidence of benefit for patients older than 80 years [3.1; REF2014/4/J]. Prior to IST-3, only one small trial had reported outcomes at 12 months and none reported effects on health-related quality of life.

Specifically, IST-3 demonstrated, for the first time, that for patients treated with alteplase, the odds of surviving to 18 months with less disability were greater than in those not receiving alteplase (p= 0.002), and patients reported better health-related quality of life, less need of help with daily activities and fewer problems in daily life after stroke [3.2; REF2014/4/J]. Patients randomised to alteplase had a 22% lower hazard of death between 8 days and 3 years than those who did not receive alteplase (41% compared with 47%; p=0.007) [3.3; new]. IST-3, therefore, provided the first evidence on the effect of alteplase on long-term health-related outcomes and quality of life. This led to alteplase being widely recommended for thrombolysis in international guidelines, as described in REF2014/4/J. However, several patient groups, including those over 80 and with early ischaemic signs on imaging, were excluded from these.

New analysis of trial data widens pool of alteplase beneficiaries

Since REF2014, new analysis of the brain imaging findings from IST-3 demonstrated that patients with early ischaemic changes on brain imaging, which were previously classified as relative contra-indications to treatment, also benefitted from alteplase [3.4; new]. Notably, patients with early signs of infarction on imaging were not at increased risk of haemorrhagic complications, while those with occlusion of a proximal large artery also benefitted from alteplase, in contrast to prior thinking. In addition, these data highlighted the important contributions of 3 common pre-stroke imaging markers to poorer outcomes after stroke – although, as with the early ischaemic changes, patients with these signs also benefited from alteplase. These results have been verified independently in the ENCHANTED trial (Delcourt et al. 2020 doi: 10.1136/jnnp-2020-323015).

Further verification through systematic reviews and meta-analyses

In 2014, after REF2014 submission, the Stroke Thrombolysis Treatment Collaboration, with key members from Edinburgh Neuroscience, performed a pooled statistical analysis on individual-patient data available from 9 alteplase trials. This demonstrated the consistency of the Edinburgh Neuroscience conclusions described above, i.e. the effect of alteplase across patients with different stroke severities and ages, and the consistency between IST-3 and industry-led trials [3.5; new]. It showed that alteplase resulted in 10% and 5% more patients being disability-free after 3 to 6 months when treated in less than 3 hours, and after 3 - 4.5 hours, respectively. The meta-analysis was essential evidence sought by the Medicines and Healthcare products Regulatory Agency (MHRA) to fully endorse alteplase for the treatment of stroke.

Attribution: The IST-3 trial was led by Edinburgh Neuroscience (Sandercock), with collaborators from University of Sydney (Lindley) [3.6]; the Stroke Thromobolysis Treatment Collaboration was led by University of Oxford (Baigent) with secretariat members from Edinburgh Neuroscience (Sandercock, Wardlaw, Whiteley)

3. References to the research

[3.1] Sandercock P, Wardlaw JM, Lindley RI, et al. 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. Lancet 2012;379:2352–63. doi: 10.1016/S0140-6736(12)60768-5. [**submitted to REF2014**]

[3.2] IST-3 Collaborative Group. Effect of thrombolysis with alteplase within 6h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. Lancet Neurol 2013;12:768–76. doi: 10.1016/S1474-4422(13)70130-3 [**submitted to REF2014**]

[3.3] Berge E, Cohen G, Roaldsen MB, […], Drever J, Wardlaw JM, Lindley RI, Sandercock PA, Whiteley WN; IST-3 Collaborative Group. Effects of alteplase on survival after ischaemic stroke (IST-3): 3 year follow-up of a randomised, controlled, open-label trial. Lancet Neurol 2016;15: 1028–34. doi: 10.1016/S1474-4422(16)30139-9 [**new research article**]

[3.4] IST-3 collaborative group, Wardlaw JM, Sandercock P, et al. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a

randomised controlled trial. Lancet Neurol 2015;14:485–96. doi: 10.1016/S1474-4422(15)00012-5. [**new research article**]
[3.5] Emberson J, Lees KR, […], Cohen G, […], Murray G, […], Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W, STTC. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. Lancet 2014; 384: 1929–35. doi: 10.1016/S0140-6736(14)60584-5 [**new research article**]

Key grants:
[3.6] P. Sandercock, J Wardlaw, M Dennis, "Third International Stroke Trial - IST-3"; UK MRC (sponsored by UoE/LHB/ACCORD) GBP2,878,637 01/04/2005 – 31/03/2010.
Extension grant GBP345,804 01/04/2010-31/03/2012.

4. Details of the impact

Impact on regulatory authority

By REF2014, many national and international stroke guidelines had been revised to recommend thrombolysis with alteplase as a response to Edinburgh Neuroscience's IST-3 trial results (REF2014/4/J). Clinical questions, however, remained about the treatment of patients over the age of 80, with severe or mild stroke, early ischaemic signs on imaging, and the latest time to treatment. In 2015, the MHRA therefore ordered an independent review of the effects of alteplase on acute ischaemic stroke. Evidence from both the IST-3 [3.1-3.3] and the Stroke Thrombolysis Treatment Collaboration [3.5] was vital to the conclusions of the review.

Following the review, the MHRA fully endorsed the conclusions and recommendations of the expert working group that the benefits of alteplase outweighed any risk when used in accordance with the product licence. *"It was considered that the effectiveness of alteplase when given within 4.5 hours of stroke onset did not vary according to stroke severity or age (<80 or ≥80 years)."* [p.2; 5.1]. The European regulatory authorities removed the upper age limit on the use of alteplase in acute ischemic stroke in 2018 based on the combined body of evidence from randomized controlled trials and post-marketing registries [5.2].

Impact on policy and guidelines

Further impact from research reported in REF2014
Since July 2019, alteplase has been listed in the 21st edition of the WHO's Essential Medicines List [5.3a] to be used in specialised diagnostic or monitoring facilities and with specialist medical care [5.3b]. This marks a major step forward to better stroke treatment internationally. Sandercock was 1 of 13 stroke experts assembled by the World Stroke Organization to make the case for submission, and the IST-3 trial is cited repeatedly in the application [5.3c].

Impact from new research since REF2014
Since the last REF submission, Italy [5.4; 2015], the UK [5.5; 2016] and the US (American Heart Association; AHA) [5.6; 2018] have all removed the upper age limit recommendation for thrombolysis treatment, all citing Edinburgh Neuroscience trial data. The Royal College of Physicians (RCP), for example, states: *"Research has established that the current licensed indications for alteplase treatment should be widened. The IST-3 trial and the updated Cochrane systematic review and individual patient meta-analysis published by the Stroke Thrombolysis Trialists' Collaborative Group have added significantly to our understanding of when and to whom intravenous thrombolysis (IVT) should be offered"* [p.40; 5.5]. An independent Evidence Review Group on behalf of the UK's National Institute for Health and Care Excellence (NICE) determined that costs for treatment with alteplase up to 4.5 hours were well below accepted willingness-to-pay thresholds and that alteplase was cost-effective compared with standard treatment [5.7].

In addition, as a result of Edinburgh Neuroscience's s novel imaging work, the previous advice, that patients with early ischaemic changes should avoid alteplase, has now been removed from guidelines. In fact, updated recommendations since REF2014 in national and international

guidelines now include alteplase use in patients with early infarct signs (e.g. RCP 2016; AHA 2018; NICE 2019) [p.40 in 5.5; p. 5 in 5.6; Recommendation 1.4.1 in 5.7]. Significantly, this affects the 25-33% of patients with early ischaemic changes who were being denied alteplase treatment in the belief that they were at increased risk of haemorrhage or would not benefit from treatment since it was too late.

Impact on clinical practice

The Safe Implementation of Thrombolysis in Stroke (SITS) registry audit (2018), which collates thrombolysis use in 1,200 stroke centres in 75 countries, reported that cumulative use of alteplase has gone from 80,000 patients in 2013 to more than 190,000 patients in 2019, i.e. more than doubled the rate of usage since the publication of IST-3 (**Figure 1**) [5.8]. The SITS audit also showed that the median age of alteplase treatment rose from 69 in 2012, to 72 in 2013 and 73 years in 2018, reflecting more patients over the age of 80 receiving alteplase [5.8a]. Indeed, while in 2013 22% of patients over the age of 80 received alteplase, in 2020 29% of them did, reflecting practice change from Edinburgh Neuroscience research since REF2014 [5.8c].

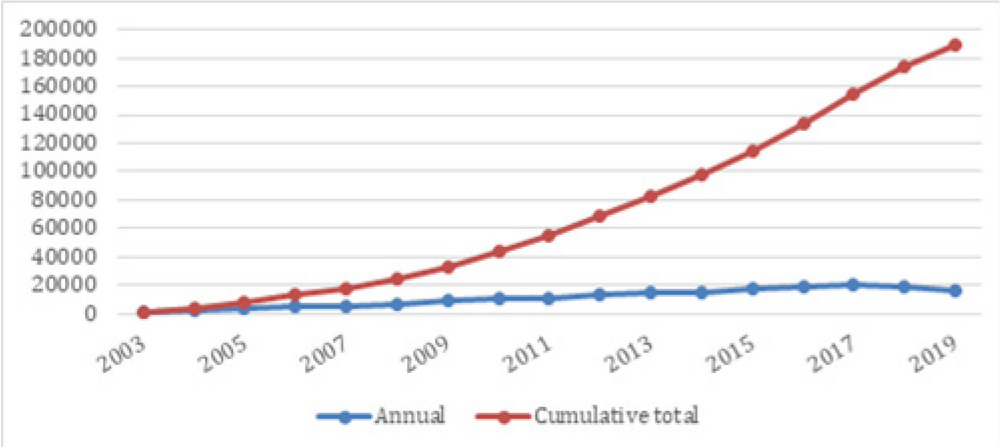

Figure 1. Cumulative and annual registration of patients using IV thrombolysis protocols

In the UK, up to 20% of stroke patients are eligible for thrombolysis. The percentage of eligible patients receiving thrombolysis increased from 74.3% in April 2013 to 89.1% in March 2020 in England, Wales and Northern Ireland [Table 1; 5.9]. The median time between clock start and thrombolysis fell from 58 minutes in 2013 to 52 minutes in 2020 (**Table 1**).

Table 1: Results for all teams for all measures collected in SSNAP for England, Wales and NI. This report covers all admissions and discharges between April 2013 and March 2020 [5.9]

	Apr 13-Mar 14	***Apr 14-Mar 15***	***Apr 15-Mar 16***	***Apr 16-Mar 17***	***Apr 17-Mar 18***	***Apr 18-Mar 19***	***Apr 19-Mar 20***
% of eligible patients[1] given thrombolysis	74.3	80.6	84.9	86.8	87.5	88.6	89.1
% of patients thrombolysed within 1 hour of clock start	53.2	56	58.5	62.2	63.6	62.5	61.2
Median time between clock start + thrombolysis (mins)	58	56	54	52	50	51	53

[1]according to the RCP guideline minimum threshold

In Scotland, the thrombolysis rate increased from 13 per 100,000 of population in 2012 to 19 per 100,000 in 2018 [5.10]. In 2018, 1,033 (12.4%) of all patients with ischaemic stroke received thrombolysis and 60% were thrombolysed within one hour, compared with 915 (11.4%) and 55% in 2016 [5.10]. These rates compare favourably with the rest of the UK and other European countries.

In Germany, the thrombolysis rate for all stroke patients increased from an average of 12.4% in 2013 to 15.9% in 2017, including a 1.5-fold increase in the number of patients older than 80 treated with thrombolysis [5.11]. In Sweden, the number of patients treated with alteplase increased from 2,226 patients to 2,500 between 2013 and 2018 [Riksstroke *pers comm*]. In Austria, alteplase use continuously increased from 9.9% in 2006 to 17.1% in 2010 – 2013 and 21.8% in 2018, with a pronounced increase in alteplase treatments over time in patients older than 80 years, particularly after 2013 [**Figure 1**; 5.12].

5. Sources to corroborate the impact

[5.1] MHRA 2015 Summary of Recommendations; also available on the UK Government website

[5.2] Mortensen JK, Andersen G Editorial: Closing the Age Gap in Acute Ischemic Stroke Treatment Stroke. 2020;51:2279–2280. doi: 10.1161/STROKEAHA.120.030169

[5.3] World Health Organization inclusion of alteplase in their Essentials Medicines List in 2019
a. WHO 21st Essential Medicines List 2019
b. WHO Memorandum confirming listing of alteplase March 2019
c. World Stroke Organization Application form

[5.4] Italian Stroke Organisation (ISO)-SPREAD guidelines 2015

[5.5] RCP National Clinical Guidelines for Stroke 2016 (Section 3.5)

[5.6] American Heart Association 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke (Section 3.5, Table 6)

[5.7] Holmes M, Davis S, Simpson E. Alteplase for the treatment of acute ischaemic stroke: a NICE single technology appraisal; an evidence review group perspective. PharmacoEconomics. 2015;33(3):225-33. doi: 10.1007/s40273-014-0233-z

[5.8] Safe Implementation of Thrombolysis in Stroke (SITS)
a. SITS registry audit 2018 (p.12-16)
b. SITS Thrombolysis data (updated in 2019)
c. Email from SITS re: percentage of patients over 80 who received alteplase, 2013-2020

[5.9] Sentinel Stroke National Audit Programme (SSNAP) National clinical audit results Data used to create Table 1 is available from “Annual Results Portfolio” when the period Apr 2019 – Mar 2020 is selected.

[5.10] Scottish Stroke Improvement Programme (SSCA) 2019 Annual Report (p.25-29)

[5.11] Weber *et al* Age and Sex Differences in Ischemic Stroke Treatment in a Nationwide Analysis of 1.11 Million Hospitalized Cases. Stroke. 2019;50:3494-3502. doi: 10.1161/STROKEAHA.119.026723

[5.12] Marko *et al* Trends of r-tPA (Recombinant Tissue-Type Plasminogen Activator) Treatment and Treatment-Influencing Factors in Acute Ischemic Stroke. Stroke. 2020: doi: 10.1161/STROKEAHA.119.027921