Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Expanding treatment options and management of acute ischaemic stroke

1. Summary of the impact

Approximately 152,000 strokes and 49,000 stroke-related deaths occur in the UK every year; of these, 85% are caused by blockage of a blood vessel in the brain (acute ischaemic stroke). The economic burden of stroke in the UK is estimated at £3.75bn with hospital inpatient care accounting for 82% this cost. Since the 1990s advances in thrombolytic treatments (which dissolve blood clots) have limited the extent of damage and subsequent impairment; however their use has been restricted due to ambiguity between stroke onset and stroke symptom presentation. University of Glasgow research has challenged the restrictions associated with thrombolysis treatment which has significantly influenced the wider use and applicability of thrombolytic treatment. This research has influenced new guideline recommendations and emergency stroke care patterns, through the implementation of dedicated acute stroke centres, and contributed to the on-going improvement in stroke survival rates.

2. Underpinning research

Before the late 1990s, no drug treatment was available for acute ischaemic stroke (AIS) and only the resulting complications of this condition were managed. Considerable progress has since been made through the use of thrombolytic agents; these drugs dissolve blood clots and reduce the extent of damage and physical impairment. Nevertheless, use of thrombolysis is restricted depending on i) the time between stroke onset and hospitalisation and ii) the patient's risk/susceptibility of brain haemorrhage. University of Glasgow researchers have been at the forefront of stroke research since the late 1980s, holding central positions (outlined at the end of section 2) in the design, recruitment and management of landmark clinical trials and collaborative research registries of thrombolytic therapy.

Clinical trials confirm the safety, efficacy and treatment window of alteplase

The thrombolytic drug, alteplase, had been shown to be beneficial when used within 3 hours of stroke. Although this drug was licenced in North America for AIS by the late 1990s, concerns remained in Europe regarding the routine use of alteplase owing to the short time-to-treatment window and potential side effects (bleeding within the brain, intracerebral haemorrhage). The European Medicines Evaluation Agency (EMEA) granted a licence for alteplase in 2002; however, this licence was conditional upon the manufacturer implementing an observational safety study and a time-extension trial.[1,2]

Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST; 2002–2006)
SITS is an internet-based, academic-driven, non-profit international collaboration of clinicians that aims to accelerate clinical trials and certify excellence in treatment and prevention of stroke. SITS-MOST was designed to assess the safety profile of alteplase in routine clinical practice within a 3-hour window and offer reassurance that results from other studies conducted internationally could be replicated.[1] University of Glasgow researcher Professor Kennedy Lees took a lead role in the direction and conduct of this 285-centre study. The findings of SITS-MOST confirmed both the safety and efficacy of alteplase. In addition, the results obtained were comparable regardless of the experience level of individual participating centres, establishing the potential for wider use of alteplase in clinical practice.

European Cooperative Acute Stroke Study III (ECASS III; 2003–2007)
ECASS III evaluated whether the time window for alteplase use could be extended beyond the approved 3 hours.[2] Lees was integral to the design of ECASS III, while Professor Matthew Walters led the University of Glasgow participating study centre. ECASS III was the first study to support the safety and efficacy of using alteplase within an extended treatment window (up to 4.5 hours after stroke). A pooled data analysis of several additional trials led by Lees validated the positive risk-benefit ratio of alteplase treatment within this timeframe.[3]

Collaborative international registries advance best practice for stroke care

SITS-International Stroke Thrombolysis Registry (SITS-ISTR; 2000–present)
SITS-ISTR was instituted by the EMEA as part of the conditional licensing procedure for alteplase. As such, SITS-ISTR was instrumental in verifying the safety and efficacy of this drug, leading to the EMEA granting an unconditional licence.[4] SIT-ISTR audits the safety and efficacy of routine therapeutic use of thrombolysis; the registry hosts 1,369 participating centres and holds data on 97,119 patients. Currently, SITS-ISTR supports eight on-going studies.

Virtual International Stroke Trials Archive (VISTA; 2001–present)
VISTA is an academic-led venture that pools data from completed stroke clinical trials internationally; the archive provides access to anonymised data for testing hypotheses and novel exploratory analyses that inform clinical trial design.[5] Lees played a prominent role in a key study, using the VISTA and SITS registries, which examined the efficacy of alteplase among older patients (≥80 years).[6] The study findings confirmed that the association between thrombolysis and improved treatment outcome was maintained in this age group, potentially extending the use of alteplase to include the elderly.

Key University of Glasgow researchers: Kennedy R Lees (Professor of Cerebrovascular Medicine, 1985–present); Matthew R Walters (Senior Lecturer in Medicine, 2003–2008; Reader, 2008–2010; Professor of Clinical Pharmacology, 2010–present); Keith W Muir (SINAPSE Chair of Clinical Imaging, 2008–present).
Key positions held (clinical trials and registries): Kennedy R Lees: Chair, Data and Safety Monitoring Board (ECASS III); Founding and Executive Steering Committee member (SITS-ISTR); Chair (VISTA). Matthew R Walters: Principal Investigator for Glasgow study centre (ECASS III). Keith W Muir: Investigator (ECASS III).
Key research collaborators: SITS-MOST: Nils Wahlgren (Karolinska University Hospital, Sweden) and Gary Ford (Newcastle General Hospital, UK). ECASS III: Werner Hacke (University of Heidelberg, Germany).

3. References to the research

1. Wahlgren N *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; 369: 275–282 doi:10.1016/S0140-6736(07)60149-4.
2. Hacke W *et al.* Thrombolysis with altephase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008; 359: 1317–1329 doi:10.1056/NEJMoa0804656.
3. Lees *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; 375: 1695–1703 doi:10.1016/S0140-6736(10)60491-6
4. Wahlgren N *et al.* Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 2008; 372: 1303–1309 doi:10.1016/S0140-6736(08)61339-2.
5. Weimar C *et al.* The Virtual International Stroke Trials Archive (VISTA): results and impact on future stroke trials and management of stroke patients. *Int J Stroke*. 2010; 5: 103–109 doi:10.1111/j.1747-4949.2010.00414.x.
6. Mishra NK *et al.* Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. *BMJ* 2010; 341: c6046 doi:10.1136/bmj.c6046

4. Details of the impact

University of Glasgow research has exerted marked impact on patient care by improving clinical management and widening access to thrombolytic therapy.

International and national guidelines for AIS

Integral to the EMEA licensing conditions for alteplase, Lees proposed the concept of a time-

window-extension study (ECASS III) to explore the wider use and benefits of alteplase among patients with AIS.[2] This study was instrumental in ensuring that the EMEA extended the approved timeframe for use of alteplase from 3 hours up to 4.5 hours (2011). The SITS-MOST and ECASS III studies are extensively cited as key supporting evidence directly driving clinical guideline recommendations that endorse the safe use of alteplase (*rtPA)*.

- The 2008 ESO guideline[a] states: "*intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke."* (Class I, Level A,; p53).
- The 2009 joint American Stroke Association/American Heart Association (ASA/AHA) Science Advisory[b] recommended that: "*rtPA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke.*" (Class I Recommendation, Level of Evidence B; p2947).
- The UK National Institute for Health Care and Excellence (NICE) 2012 review of Technology Appraisal Guidance 122[c] advised: "*Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults if treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and intracranial haemorrhage has been excluded by appropriate imaging techniques."* (1.1; p20).

Other UK guidelines influencing treatment practice also align with international recommendations on the use of alteplase. For example, the 2008 Scottish Intercollegiate Guidelines Network (SIGN) Guidance 108 recommendation 2.4.1 (p4)[d] and the 2012 Royal College of Physicians National Clinical Guidelines for Stroke recommendations 4.6.1A (xiii) and 4.6.1B (xiv).[e]

University of Glasgow researchers are internationally recognised in the field of acute stroke care. Professor Kennedy Lees has held key positions in clinical trials, including the landmark ECASS III study of alteplase (sections 2 and 3). Furthermore, as founding member of the SITS-ISTR Steering Committee and Chair of VISTA, Lees has driven the creation of patient registries to aid on-going assessment of the clinical benefits and safety of treatments for stroke. Lees currently serves as President elect of the European Stroke Organisation (ESO) and influences European guideline development strategy through chairmanship of this organisation's main committees.

Audit of alteplase use by the NHS

Clinical guidelines represent the best available scientific evidence and are considered the gold-standard in directing clinical practice. The above revisions to the ESO[a] and ASA/AHA[b] guidelines encouraged clinicians to adopt recommendations on the use of alteplase up to 4.5 hours, even though this recommendation was beyond the scope of the alteplase product licence at the time (EMEA only granting an extended use licence in 2011). The National Sentinel Stroke Clinical Audit report[f] confirmed the influence of guidelines to encourage wider use of alteplase. This audit of NHS England, Wales and Northern Ireland showed an increased use of thrombolysis (within 3 hours) from 1.8% in 2008 to 5% in 2010. The Sentinel report also highlighted that levels of alteplase usage could be improved: 14% of eligible patients were sampled, with only 5% actually receiving treatment. Nevertheless, the audit authors predicted that uptake of thrombolysis would increase as more centres provided acute stroke services and with the further education of healthcare professionals and the public. They forecasted that use of alteplase would rise to 16% by increasing the treatment window to 4.5 hours and to 26% if patents older than 80 years proved eligible.

Extending the treatment window for thrombolysis is cost effective

The 2012 NICE Technology Appraisal[c] considered whether giving alteplase within 4.5 hours of stroke was a cost-effective use of NHS resources. Within this assessment, the manufacturer's submission and appraisal committee were in agreement that ECASS III[2] represented the 'the only directly relevant trial' and primary source (respectively) providing evidence on the clinical-effectiveness of an extension of the treatment window from 3 to 4.5 hours – the ECASS III[2] trial is discussed in detail throughout sections 3 and 4 of this document. An economic model containing data from both SITS-MOST[1] (background patient population) and ECASS III[2] (for the 3 to 4.5 hour window effect) showed an incremental cost-effectiveness ratio (ICER, used to evaluate the cost

impact of medical interventions) of £6,272 per quality adjusted life-year (QALY, an indicator of improved health). The NICE appraisal committee agreed that: *"alteplase either dominated standard care or had an ICER below £10,000 per QALY gained depending on the time-to-treatment window considered,"* concluding that treating AIS with alteplase within up to 4.5 hours after onset of stroke symptoms was a cost-effective use of NHS resources (4.10, p20). Therefore, through their key involvement in the ECASS III study, University of Glasgow researchers have directly influenced the expansion of NHS-funded treatment for stroke patients.

Acute stroke care saves lives

The provision of acute stroke care has benefitted patients by reducing the risk of death following an event. The National Sentinel Stroke Clinical Audit found that deaths within the first 30 days after stroke dropped from 24% in 2004 to 17% in 2010, while admissions to a stroke unit rose from 46% to 88% in the same period.[f] The 2013 Scottish Stroke Care Audit states that deaths from stroke among people aged less than 75 years dropped by 60% in the 15 years to 2010, exceeding the original target of 50%.[g] Furthermore, death rates in Scotland have continued to fall, with a 5.7% reduction recorded between 2010 and 2011. NHS Scotland has also set targets to ensure that most stroke patients (90%) are admitted to a stroke unit within 24 hours of being hospitalised. Early access to dedicated stroke care increases the possibility that eligible patients will receive alteplase within the 4.5 window timeframe defined by University of Glasgow research.

Facilitating education and training

The need for appropriately trained healthcare professionals working within specialist acute stroke units and raising of public awareness about stroke were highlighted in the ESO[a] (Class II, Level B p7 and Class I, Level A; p17) and NICE[h] guidelines (1.4.1.1 and 1.4.1.2; p14–15). The University of Glasgow has used its internationally-recognised research knowledge and pivotal roles with global collaborative groups to help foster best practice in stroke treatment to ensure wider adoption of thrombolysis treatment in accordance with guideline recommendations. In collaboration with Professor Gary Ford (Newcastle), Lees developed an education programme for stroke specialist registrars comprising seven thrombolysis training days, as well as master classes to ensure more widespread training of UK healthcare practitioners and to establish thrombolysis treatment as the standard of care. Through consultant training, the University of Glasgow has helped to ensure that every UK hospital offers a specialist stroke service with regional thrombolysis.[f]

5. Sources to corroborate the impact

a. ESO updated guidelines for management of ischaemic stroke and TIA 2008. (Recommendation Class I, Level B p7; education Class I, Level A p17)
b. ASA/AHA Science Advisory on expansion of time window for treatment of acute ischaemic stroke 2009. doi: 10.1161/STROKEAHA.109.192535 (p2947)
c. NICE technology appraisal 264: Alteplase for treating acute ischaemic stroke (review of technology appraisal guidance 122) 2012. (Recommendation 1.1, p20)
d. SIGN 108 guidance on management of patients with stroke or TIA 2008. (Recommendation 2.4.1, p4)
e. RCP national clinical guidelines for stroke 2012. (Recommendations 4.1.6 A and B, pxiii–xiv)
f. National Sentinel Audit for stroke 2010. (Thrombolysis use, p34; specialist stroke centres, p16–52)
g. Scottish Stroke Care Audit, 2013 (p1 and 6)
h. NICE CG68 guidance on diagnosis and initial management of acute stroke and TIA 2008. (Recommendations 1.4.1.1 and 1.4.1.2, p14–15)