Institution: The University of Edinburgh

Unit of Assessment: 4

Title of case study: A: Reducing the global burden of stroke by using aspirin and avoiding heparin use in the treatment of acute stroke

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare; saving lives by determining that aspirin is an effective treatment for acute stroke and that heparin anticoagulation is ineffective.

Significance: In the UK, treating all acute stroke patients with aspirin and avoiding heparin means 1800 people avoid death or disability each year; aspirin is also highly cost-effective.

Beneficiaries: Stroke patients, the NHS, the economy.

Attribution: Sandercock, UoE, designed, led and reported the International Stroke Trial, and was on the steering committee of the Chinese Acute Stroke Trial.

Reach: Up to 15M stroke patients annually affected by guideline changes worldwide, encompassing Europe, North America and Australasia; educational events by the World Stroke Academy promote aspirin use.

2. Underpinning research (indicative maximum 500 words)

Each year, worldwide, about 15 million people suffer a stroke, of which one third will die, and one third will survive in a disabled state.

1. Benefit of aspirin in acute stroke. Professor Peter Sandercock (Professor of Medical Neurology, UoE 1987–present) led the International Stroke Trial (IST) group (Dr Richard Lindley (Honorary Senior Lecturer, UoE until 2004; then University of Sydney), Professor Martin Dennis (Professor of Stroke Medicine, UoE, 1990–present), Professor Joanna Wardlaw (Professor of Applied Neuroimaging, UoE, 1994–present) and Professor Charles Warlow (Professor of Neurology, now Emeritus, UoE, 1987–2008)). IST was a randomised controlled trial in patients with acute ischaemic stroke within 48 hours of stroke onset, evaluating the safety and efficacy of aspirin, heparin, both or neither. The study, funded by grants of £1.2M from the UK Medical Research Council, UK Stroke Association and the European Union Biomedicine and Health Programme (BIOMED)-1, recruited 19,453 patients from 1991–1997. IST, organised and led from Edinburgh, showed that for every 1000 patients treated immediately with aspirin, 10 patients avoid early recurrent stroke or death, and at 6 months after stroke onset, 13 more were alive and independent [3.1].

2. Confirmatory evidence. Sandercock was a member of the Steering Group of the Chinese Acute Stroke Trial (CAST; 1993–97) with Dr Chen (University of Oxford). The trial design was modelled on IST but did not include the heparin component. Sandercock and Chen published an individual patient data meta-analysis of the two trials to confirm the benefits of aspirin [3.2].

3. **Lack of benefit from heparin.** IST showed that patients allocated to heparin had a lower risk of early recurrent ischaemic stroke and pulmonary embolism, but a higher risk of intracranial haemorrhage and extracranial bleeding so, overall, heparin had no effect on the likelihood of death or of being alive and independent [3.1].

4. **Updating of Cochrane systematic reviews**. Other antiplatelet (ticlopidine and the glycoprotein IIb/IIIa inhibitor abciximab) and anticoagulant agents (heparinoid, low-molecular-weight heparin and direct thrombin inhibitors) have been tested elsewhere. Sandercock updated two Cochrane reviews in 2003 and 2008, to determine whether the new evidence altered the

conclusions from IST and CAST. To date, aspirin reduces the number of deaths and remains the agent of choice [3.3] and there is no evidence to support the routine use of any form of anticoagulation therapy [3.4], as confirmed in the Edinburgh group's 2013 individual patient data meta-analysis of the large trials of heparin in stroke [3.5].

Estimated health gain. Warlow estimated in 2008 [3.6] that for a typical European population of 1 million people, in 1 year, 2260 people would have a stroke and, by one year afterwards, 700 will have died and 1240 will be dead or dependent. The effect of giving early aspirin to the 85% of the patients whose stroke is ischaemic and who have no contraindication to or intolerance of aspirin would be to reduce stroke deaths at 3 months by 15 out of 520; i.e., 3%, and the number of patients who are either dead or dependent by 29 (2%).

3. References to the research (indicative maximum of six references)

3.1 Sandercock P, Collins R, Counsell C, et al; International Stroke Trial Collaborative Group. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet. 1997;349:1569–81. DOI: 10.1016/S0140-6736(97)04011-7.

3.2 Chen Z, Sandercock P, Pan H et al.; the CAST and IST collaborative groups. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the Chinese acute stroke trial and the international stroke trial. Stroke. 2000;31:1240–9. DOI: 10.1161/01.STR.31.6.1240.

3.3 Sandercock P, Counsell C, Gubitz G, Tseng M. Antiplatelet therapy for acute ischaemic stroke. Cochrane Database Sys Rev. 2008;3:CD000029. DOI: 10.1002/14651858.CD000029.pub2.

3.4 Sandercock P, Counsell C, Kamal A. Anticoagulants for acute ischaemic stroke. Cochrane Database Sys Rev. 2008;4:CD000024. DOI: 10.1002/14651858.CD000024.pub3.

3.5 Whiteley W, Adams H, Bath P,…Sandercock P. Targeted use of heparin, heparinoids, or low-molecular weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. Lancet Neurol 2013;12:539–45. DOI: 10.1016/S1474-4422(13)70079-6.

3.6 Warlow C, Van Gijn J, Dennis M, Wardlaw J, et al. Stroke: Practical Management. 3rd edition. Oxford: Blackwell Publishing, 2008, sections 18.3.1–2. [Available on request.]

4. Details of the impact (indicative maximum 750 words)

Pathways to impact
The above articles by Sandercock et al. have been cited over 1250 times and together with the Cochrane reviews have been cited in the stroke guidelines of the Royal College of Physicians, and the National Institute for Health and Care Excellence stroke guidelines in the UK, the European Stroke Organisation, the American Stroke Association, Canadian Best Practice Guidelines, and Singaporean, Australian and New Zealand national guidelines. Sandercock has given lectures and conference presentations on these findings in 18 different countries (1997–2013).

Impact on public policy
Aspirin is now strongly recommended, and high-dose heparin is 'not recommended', for routine use as part of standard treatment for acute ischaemic stroke worldwide in UK [5.1], European [5.2], North American [5.3] and Australasian [5.4] guidelines.

Impact on clinical practice
The guideline statements have led to implementation of appropriate health policy and quality improvement and audit programmes. In the UK, the administration of aspirin within 24 hours is a

quality standard against which services are judged nationwide. The National Stroke Strategies in England and Scotland state that aspirin should be administered as soon as possible after onset of stroke. The UK-wide National Sentinel Audit has set the proportion of patients with acute stroke started on aspirin within 48 hours of stroke onset as one of its nine key quality indicators. A 2010 National Sentinel Audit of Stroke in England showed that 92% of patients received aspirin within 48 hours (up from 65% in 2001) [5.5], and in Scotland in 2010, 73% of ischaemic stroke patients were prescribed aspirin by one day after admission (up from 41% in 2005) [5.6]. As regards heparin use, the evidence of lack of benefit and the risks of significant bleeding with anticoagulants have led to a decline in the use of heparin. While some local registry data have shown a decline in heparin use, the only nationwide quality improvement effort on heparin has been in Sweden. The Swedish Riks-Stroke quality improvement programme clearly demonstrates a dramatic decline in the use of full-dose heparin in acute stroke, from 7.5% in 2001 to 1.6% in 2008 [5.7]; quality improvement programmes in other countries have yet to focus on efforts to minimise the unnecessary use of heparin and other anticoagulants in stroke.

Impact on health

Warlow estimated that in a population of 1 million people, routine use of two weeks aspirin therapy for all eligible stroke patients would avoid 15 deaths and result in 29 more people being alive and independent each year [3.6]. For the UK population of 62 million, this would translate to 930 fewer deaths each year and 1800 more people alive and independent. The avoidance of heparin likewise will reduce the number of treatment-related disabling and fatal cerebral haemorrhages.

Impact on the economy

In the UK, the estimated cost to health and social services of a dependent stroke survivor is £11,292, and the annual cost of an independent survivor £876; the avoidance of post-stroke dependency therefore can save the UK health care system substantial amounts. Warlow estimated that the 2008 treatment cost per patient with acute stroke of the two-week treatment course with aspirin was £0.50, the annual cost of treating all eligible patients in a population of 1 million was £955, the cost per death avoided was £62.50, and the cost per death or disability avoided was £33.50 [3.6]. Routine use of aspirin in acute stroke is therefore highly cost-effective.

Maximising global impact

The World Stroke Organisation (Sandercock is a member of the Board of Directors) established the World Stroke Academy (Sandercock is a member of the Steering Committee) [5.8], which seeks to improve stroke education on a global scale. It has a programme of educational events that is being delivered in several countries in Europe (Greece, Hungary), but also in China (2006), South Africa (2006), Vietnam (2009) [5.9], Korea (2010), Brazil (2012) and West Africa (2013; jointly with the European Federation of Neurological Sciences) to implement affordable evidence-based stroke care that includes implementing aspirin and avoiding heparin.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE. 2008 http://www.nice.org.uk/nicemedia/live/12018/41363/41363.pdf. *[UK guidelines.]*

5.2 Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack European Stroke Organization (2008). http://www.eso-stroke.org/recommendations.php?cid=9. *[European guidelines.]*

5.3 Jauch E, Saver J, Adams H, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2013;44:870–947. DOI: 10.1161/STR.0b013e318284056a. *[North American guidelines.]*

5.4 Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE et al. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. Chest. 2012 February 1;141(2

suppl):e601S-e636S. DOI: 10.1378/chest.11-2302. *[Australasian guidelines.]*

5.5 National Sentinel Stroke Audit (2010). http://www.rcplondon.ac.uk/sites/default/files/national-sentinel-stroke-audit-2010-public-report-and-appendices_0.pdf. *[Confirms numbers of patients in England receiving aspirin.]*

5.6 Scottish National Stroke Care Audit, 2012 National Report. http://www.strokeaudit.scot.nhs.uk/Downloads/2012_report/SSCA-annual-report-2012-web.pdf. *[Confirms number of patients in Scotland receiving aspirin.]*

5.7 Eriksson M, Stecksen A, Glader E, et al; Riks-Stroke Collaboration. Discarding heparins as treatment for progressive stroke in Sweden 2001 to 2008. Stroke. 2010;41:2552–8. DOI: 10.1161/STROKEAHA.110.597724. *[Corroborates decline in heparin use.]*

5.8 World Stroke Academy website. http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%292051-333X.

5.9 Brainin M, Norrving B. WSO Stroke Education Program in Vietnam 2008–2011: 8596 hospital doctors attended in 58 cities and received a certificate from the WSO and the Ministry of Health. Int J Stroke. 2013;8:148–9. DOI: 10.1111/ijs.12083. *[Corroborates World Stroke Academy educational events in Vietnam.]*