Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: International Carotid Stenting Study influences national and international guidelines on the prevention of stroke resulting from carotid artery narrowing.

1. Summary of the impact

Narrowing of one of the carotid arteries in the neck (carotid stenosis) is an important cause of stroke, a major public health problem. The results of an international multicentre randomised clinical trial, organised and led by Professor Martin Brown at the UCL Institute of Neurology, have been incorporated into national and international guidelines on the treatment of carotid stenosis. The trial evaluated carotid artery stenting (CAS), a new treatment to prevent stroke from carotid stenosis, in comparison to the standard treatment, carotid endarterectomy (CEA) (carotid surgery). The number of patients treated by CAS in England did not increase between 2006 and 2012, whereas the numbers of patients treated by CEA increased by 30%, a finding consistent with a response to the findings of our trials indicating that CEA was safer than CAS.

2. Underpinning research

A 20-year programme of clinical trial research, led by Professor Martin Brown, involved the introduction and evaluation of carotid stenting as a treatment to prevent stroke in patients with carotid artery narrowing (stenosis).

Our first international multicentre trial, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) recruited 504 patients between 1992 and 1997 and followed them for up to 11 years. The trial established the feasibility of carotid angioplasty and stenting, but the results were not definitive **[1, 2]**.

We therefore established a study to produce definitive data concerning the risks and benefits of carotid stenting in comparison to carotid endarterectomy (surgery), known as the International Carotid Stenting Study (ICSS). This was a large multi-centre randomised clinical trial and involved close collaboration with key experts in neurology, vascular surgery and statistics at academic centres including UCL, the London School of Hygiene and Tropical Medicine, University Medical Centre Utrecht, Sheffield Vascular Institute, Newcastle University, Basel University, Erasmus Medical Center Rotterdam, University of Manchester, University of Amsterdam, Leeds University, St George's Hospital Medical School, and Edinburgh University. ICSS included 1,713 patients with recent stroke or transient ischaemic attack caused by carotid stenosis, recruited from 50 centres in Europe, Canada, Australia and New Zealand. Half the patients were randomly assigned to treatment by stenting, and half to surgery. The study was supported by grants from the Medical Research Council, The NIHR-MRC EME Board, the European Union and The Stroke Association. The trial recruited between 2001 and 2008 and followed the patients for up to 10 years until 2011. The interim results were published in the Lancet in 2010 and the long-term results were presented to the European Stroke Conference in 2012 **[3, 4]**. The trial showed that stenting avoids the problems associated with an incision in the neck (e.g. cranial nerve injury), but caused more minor strokes than surgery during the insertion of the stent **[3]**. The long-term risk of disabling stroke or death was similar after the two treatments **[4]**.

A sub-study of ICSS led by Professor Brown and Dr Leo Bonati (UCL and Basel University) in 2010 demonstrated that stenting caused many more small ischaemic lesions in the brain on MRI than endarterectomy **[5]**.

Professor Brown also led a collaboration funded by the Stroke Association with the Chief Investigators from two other smaller European based trials of carotid stenting (Prof W Hacke from Heidelberg University and Prof JL Mas from Paris Descartes University) to establish the Carotid Stenting Trialists Collaboration in 2009. A meta-analysis of individual patient data from the three

trials published in 2010 established that it was older patients in whom the risk of stenting was increased, while in younger patients the risks of stenting and endarterectomy were similar **[6]**.

A collaboration between Professor Brown and Dr R Featherstone from the UCL Institute of Neurology with Dr Bonati and Dr P Lyrer at Basel University led to a systematic review and extraction of new data from all the existing trials of carotid stenting being published in the Cochrane Database in 2012 **[7]**. This meta-analysis confirmed that stenting is associated with an increased risk of peri-procedural stroke or death compared with endarterectomy, but the excess risk is limited to older patients.

3. References to the research

[1] Bonati LH, Ederle J, McCabe DJ, Dobson J, Featherstone RL, Gaines PA, Beard JD, Venables GS, Markus HS, Clifton A, Sandercock P, Brown MM; CAVATAS Investigators. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. Lancet Neurol. 2009 Oct;8(10):908-17. http://dx.doi.org/10.1016/S1474-4422(09)70227-3

[2] Ederle J, Bonati LH, Dobson J, Featherstone RL, Gaines PA, Beard JD, Venables GS, Markus HS, Clifton A, Sandercock P, Brown MM; CAVATAS Investigators. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. Lancet Neurol. 2009 Oct;8(10):898-907. http://doi.org/c94656

[3] International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010;375(9719):985-97 http://dx.doi.org/10.1016/S0140-6736(10)60239-5

[4] Brown MM, Dobson J, Doig D, Featherstone RL, Turner E, for the ICSS collaborators. Primary analysis of the International Carotid Stenting Study: a randomised comparison of the effectiveness of carotid stenting and endarterectomy in preventing long-term stroke in patients with symptomatic carotid stenosis. European Stroke Conference Abstract E-book, page 15-16. See: http://www.esc-archive.eu/lisbon2012/ebook12/index.html#/14/

[5] Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, Macdonald S, Gaines PA, Waaijer A, Stierli P, Jäger HR, Lyrer PA, Kappelle LJ, Wetzel SG, van der Lugt A, Mali WP, Brown MM, van der Worp HB, Engelter ST; ICSS-MRI study group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol. 2010 Apr;9(4):353-62. http://dx.doi.org/10.1016/S1474-4422(10)70057-0

[6] Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, Mali WP, Zeumer H, Brown MM, Mas JL, Ringleb PA. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. Lancet. 2010 Apr;9(4):353-62. http://dx.doi.org/10.1016/S1474-4422(10)70057-0

[7] Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD000515. http://dx.doi.org/10.1002/14651858.CD000515.pub4.

4. Details of the impact

The results of ICSS and the pooled meta-analysis, including data from ICSS, have been incorporated into National Institute for Health and Clinical Excellence (NICE), European,

Australasian and North American guidelines on the treatment of carotid stenosis. They have also influenced public debate and clinical practice.

1. Changes to UK Guidelines: In 2006, the National Institute of Health and Clinical Excellence IPG 191 on Carotid artery stent placement for carotid stenosis, which stated "*Long-term efficacy in terms of prevention of stroke and restenosis is unknown*" and encouraged clinicians "*to enter symptomatic patients into the ongoing International Carotid Stenting Study*". In 2011, NICE updated this guidance (IPG389) stating "*Current evidence on the safety and efficacy of carotid artery stent placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit or research*", quoting the published results of ICSS and our meta-analysis in support of the conclusions **[a]**.

In 2008, the 3rd edition of the National Clinical Guidelines for Stroke, published by the Royal College of Physicians stated "*Carotid angioplasty or stenting should only be carried out in specialist centres where outcomes of these techniques are routinely audited and preferably as part of a randomised clinical trial*." In the 4th edition published in 2012, this changed to read "*Carotid endarterectomy should be the treatment of choice for patients with symptomatic carotid stenosis, particularly those who are 70 years of age and over. Carotid angioplasty and stenting should be considered in patients meeting the criteria for carotid endarterectomy but are considered unsuitable for open surgery*", quoting the results of ICSS **[b]**.

2. Changes to European Guidelines: The Karolinska Stroke Consensus meetings form the platform for revision of the European Stroke Organisation (ESO) Guidelines. In 2008, the consensus statement concerning carotid endarterectomy vs. angioplasty read: "*Until the results of the on-going trials are available for a pooled analysis of safety and long-term effectiveness, stenting should not be routinely offered to patients suitable for carotid endarterectomy*." In 2010, these were changed to read "*CEA is safer than CAS and remains the treatment of choice for patients with symptomatic severe carotid stenosis who are fit for surgery. CAS is an acceptable option for initial therapy for patients younger than 65-70 years with significant symptomatic carotid stenosis in centres with a peri-procedural stroke or death rate similar to that recommended for CEA*", quoting the results of ICCS and our meta-analysis **[c]**.

3. *Changes to Australasian Guidelines:* In 2011, the Australasian Carotid Stenting Guidelines Committee updated its guidelines stating "*CAS should not be performed in the majority of patients requiring carotid revascularization. CAS may be considered for specific high risk patients*" citing ICSS, the ICSS-MRI sub-study and our meta-analysis **[d]**.

4. *Changes to North American guidelines:* In 2011, the Society of Vascular Surgeons in North American updated its guidelines for management of extracranial carotid disease, stating "*CAS should be reserved for symptomatic patients with stenosis of 50% to 99% at high risk for CEA for anatomic or medical reasons*", citing the results of ICSS **[e]**.

5. *Impact on public policy debates:* There has been concern expressed in public debates about the uncontrolled expansion of carotid stenting as an alternative to carotid endarterectomy in the face of the trial evidence. Several recent commentaries and leading articles in prominent medical journals have cited our work **[f-i]**. For example, a commentary in the Lancet by a leading expert neurologist entitled "*Carotid stenting: more risky than endarterectomy and often no better than medical treatment alone*" stated "*This excess risk of stroke is highlighted again in each of the three latest reports: the International Carotid Stenting Study (ICSS), the ICSS imaging substudy, and the Carotid Revascularization Endarterectomy versus Stent Trial (CREST)*" **[i]**.

***6. Impact on clinical practice*:** Individual units have reported a fall in the number of patients treated by carotid stenting after the results of ICSS were published in keeping with the data having a direct impact on the practice of carotid revascularisation **[j]**. Within the English NHS, the numbers of patients treated by CAS did not increase between 2006 and 2012, whereas the numbers of patients treated by CEA increased by 30%, a finding consistent with a response to the findings of

our trials indicating that CEA was safer than CAS **[k]**.

7. Impact on patients: The training, proctoring and supervision in CAS that we introduced as part of the CAVATAS and ICSS trial protocols ensured that patients treated by CAS have the procedure performed as safely as possible. The perioperative risk of stroke or death from CAS fell by 30% from 2001 to 2010 during the course of CAVATAS and ICSS. As a result of our research, patients can now be accurately informed about the current risks of CAS versus CEA, and together with their doctor can make informed choices about which treatment is the most suited to them, resulting in better choice for patients, increased safety and improved long-term outcomes.

5. Sources to corroborate the impact

[a] Link to National Institute for Health and Clinical Excellence Guidance on carotid artery stent placement (2011): http://guidance.nice.org.uk/IPG389/Overview/pdf/English

[b] Intercollegiate Stroke Working Party. National clinical guideline for stroke, 4th edition. London: RCP, 2012, p43: http://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf

[c] Link to Karolinska Consensus Statement re carotid endarterectomy vs angioplasty and recommendation to update the European Stroke Organisation Guideline Committee (2010): http://www.strokeupdate.org/Cons_Carotid%20_stenosis_2010.aspx

[d] The Carotid Stenting Guidelines Committee: An Inter-collegiate Committee of the RACP. Guidelines for patient selection and performance of carotid artery stenting. Intern Med J 2011;41:344-7 http://dx.doi.org/10.1111/j.1445-5994.2011.02445.x

[e] Ricotta JJ, AbuRahma A, Ascher E et al. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. J Vasc Surg 2011;54:e1-e31 http://dx.doi.org/10.1016/j.jvs.2011.07.031

[f] Naylor AR. What is the current status of invasive treatment of extracranial carotid artery disease? Stroke 2011;42:2080-5 http://dx.doi.org/10.1161/STROKEAHA.110.597708

[g] Paraskevas KI, Veith FJ, Riles TS, Moore WS. Is carotid artery stenting a fair alternative to carotid endarterectomy for symptomatic carotid artery stenosis? A commentary on the AHA/ASA guidelines. J Vasc Surg 2011;54:541-3 http://dx.doi.org/10.1016/j.jvs.2011.05.052

[h] Abbott AL, Adelman AA, Alexandrov AV et al. Why the United States Center for Medicare and Medicaid Services (CMS) should not extend reimbursement indications for carotid artery angioplasty/stenting. Brain Behav 2012;2:200-7 http://dx.doi.org/10.1002/brb3.32

[i] Rothwell PM. Carotid stenting: more risky than endarterectomy and often no better than medical treatment alone. Lancet 2010;375 :957-9 http://dx.doi.org/10.1016/S0140-6736(10)60404-7

[j] Web report showing decline in numbers of carotid stenting procedures in one unit between 2010 and 2011: http://www.cedars-sinai.edu/Patients/Quality-Measures/Clinical-Areas/Measuring-Quality-of-Care-and-Outcomes-for-Patients-Undergoing-Stroke-Prevention-Procedures.aspx

[k] Lee AHY, Busby J, Brooks M, Hollingworth W. Uptake of Carotid Artery Stenting in England and Subsequent Vascular Admissions: An Appropriate Response to Emerging Evidence? Eur J Vasc Endovasc Surg 2013;46:282-9 http://dx.doi.org/10.1016/j.ejvs.2013.04.019