Institution: University of Oxford

Unit of Assessment: 4

Title of case study:

Reduction of Stroke Risk by Risk Stratification and Urgent Intervention after a Transient Ischaemic Attack (TIA) or Minor Stroke

1. Summary of the impact

Research in Oxford by Rothwell and colleagues since 2000 has radically changed how minor strokes and transient ischaemic attacks (TIAs) are managed. First, the risk of a major stroke in days after a minor stroke/TIA was found to be much higher than thought. In consequence, these 'warning' events were rebranded as a medical emergency in clinical guidelines. Second, Rothwell showed that a delay in treating individuals at high risk of major stroke substantially reduced the benefits. Third, the Rothwell group developed a simple risk score ('ABCD system') to triage high-risk individuals, showing that more urgent treatment reduced the 90-day risk of major stroke by 80%. This strategy has been implemented in the National Stroke Strategy and NICE and international guidelines. In the UK it is estimated to prevent 10,000 strokes per year, and to save the NHS £200 million in acute care costs alone.

2. Underpinning research

TIA and minor stroke comprise over 70% of all cerebrovascular events (with major, disabling stroke accounting for the remainder). About 90% of major strokes occur in patients who previously had a TIA or minor stroke. The standard treatments aimed at preventing stroke include surgery to the carotid artery ('carotid endarterectomy') and medical treatments with drugs. Rothwell's research in Oxford since 2000 has focused on TIAs and minor strokes, revealing their significance as precursors to major strokes, and ways to identify and then decrease the risks of these occurring by showing the benefits of earlier intervention.

Minor strokes/TIAs may herald an impending major stroke

Rothwell and colleagues showed that the risk of a major stroke soon after a TIA or minor stroke had been greatly underestimated. They studied the natural history of TIA and minor stroke in Rothwell's Oxford Vascular Study and demonstrated that the 7-day risk of major stroke was about 10% (Coull et al., 2004, cited in Section 3, and several other papers).

Identifying the patients at highest risk of early major stroke

Given this finding, it was important to identify who, amongst the 100,000 referrals with TIA per year, are at highest risk of an early major stroke. Rothwell's group therefore developed the 'ABCD system', a simple clinical tool to identify the high-risk people and to prioritise them for treatment (Rothwell et al., 2005). It was subsequently refined and validated (e.g. Johnston et al., 2007).

Reducing delays in treatment after TIA reduces the risk of major stroke

The above research revealed that there is a significant risk of a major stroke soon after a TIA, and also provided a tool to identify those at highest risk. In addition, Rothwell has shown that success in preventing major strokes in people with TIAs is related to the delay to treatment:

First, the group demonstrated the need for greater urgency in investigation and treatment of TIA and minor stroke in work on the risks and benefits of carotid endarterectomy. Rothwell coordinated a pooled analysis of individual patient data from the European Carotid Surgery Trial and two other large randomised trials of carotid endarterectomy versus medical treatment for symptomatic carotid stenosis (narrowing of the artery). This demonstrated, for the first time, several important interactions between clinical subgroups and treatment effects, notably that the extent to which benefit from surgery falls with delay to intervention (e.g. Rothwell et al., 2004).

Then, to determine the risks and benefits of more urgent treatment of TIA and minor stroke, Rothwell and colleagues performed the EXPRESS Study (Rothwell et al., 2007; See Section 4) - a population-based sequential comparison study of the impact of acute assessment and treatment. As predicted by their previous work, EXPRESS showed that urgent investigation and treatment

reduced the 90-day risk of major recurrent stroke by about 80%. By nesting a prospective "before versus after" study within a rigorous population-based disease incidence study (Oxford Vascular Study), with complete ascertainment and follow-up of all patients with TIA and minor stroke in both phases, a reliable estimate of this effect was obtained, and with good external validity.

Urgent interventions to prevent stroke are cost-effective

Subsequent health-economic analyses by Rothwell and colleagues (Luengo-Fernandez et al., 2009) showed that urgent intervention reduced the risk of disabling stroke and risk of hospitalisation, reducing overall hospital bed-days by over two thirds, generating savings of £624 per patient treated. Rolling the service out across the UK was estimated to prevent about 10,000 strokes per year, saving the NHS up to £200 million annually in acute care costs alone.

3. References to the research

Coull A, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after a transient ischaemic attack or minor stroke: implications for public education and organisation of services. **BMJ** 2004;328:326-328. DOI:10.1136/bmj.37991.635266.44. 279 citations.
One of a series of papers by Rothwell and colleagues from 2000-2007 demonstrating the very high early risk of major stroke after TIA and minor stroke.

Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JNE, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after a transient ischaemic attack. **Lancet** 2005; 366: 29-36. DOI: 10.1016/S0140-6736(05). 259 citations.
Derivation and validation of the first ever risk score to identify patients with TIA who are at high early risk of stroke.

Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. **Lancet** 2007;369:283-92. DOI: 10.1016/S0140-6736(07)60150-0. 350 citations.
Independent validations of the clinical utility of the ABCD risk score.

Rothwell PM, Eliasziw M, Gutnikov S, Warlow C for the Carotid Endarterectomy Trialists Collaboration. Effect of endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. **Lancet** 2004;363:915-24. DOI: 10.1016/S0140-6736(03)12228-3. 555 citations.
Pooled analysis of data from three large randomised trials of carotid endarterectomy versus medical treatment for symptomatic carotid stenosis, demonstrating reliably that benefit from surgery was related to the degree of carotid stenosis and hence the thresholds for intervention. The study also revealed, for the first time, that benefit from surgery falls with delay to intervention.

Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JNE, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJV, Bosch S, Carasco-Alexander F, Silver LE, Gutnikov SA, Mehta Z, on behalf of the Early use of Existing Preventive Strategies for Stroke (EXPRESS) Study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. **Lancet** 2007; 370: 1432-42. DOI: 10.1016/S0140-6736(07)61448-2. 325 citations.
The first demonstration that urgent assessment and treatment of patients with TIA or minor stroke substantially reduces the risk of early recurrent stroke, with an 80% reduction in the 90-day risk.

Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. **Lancet Neurol** 2009;8:235-43. DOI:10.1016/S1474-4422(09)70019-5. 41 citations.
Shows that urgent assessment and treatment of patients with TIA or minor stroke using existing treatments is cost-saving, and assesses the likely health-economic impact across the UK.

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Rothwell was funded as an MRC Senior Clinical Fellow from 2000-5 and HEFC-funded thereafter. *Oxford colleagues include:* Drs Coull, Giles, Schulz, Flossmann, Lovelock, Chandratheva, Geraghty and Marquardt were all Clinical Research Fellows. Dr Luengo-Fernandez is Senior Researcher at Oxford University's Health Economics Research Centre. Dr Silver is Study Coordinator of the Oxford Vascular Study, and Dr Mehta is the Database Manager and Statistician.

4. Details of the impact

This underpinning research, mostly published since 2004, has rapidly and profoundly affected how patients with TIA are viewed, investigated, and treated, both in the UK and internationally.

More urgent assessment and investigation of TIAs

Prior to Rothwell's research, most guidelines suggested that patients should be assessed and treated within four weeks of a TIA. After publication of his research showing that the early risk of stroke after a TIA had been substantially underestimated, guidelines rapidly changed, markedly increasing the urgency with which investigation and treatment was recommended. This was first highlighted in the 2007 Department of Health National Stroke Strategy, which endorsed the "medical emergency" status of TIA and minor stroke (Section 5, Source 1). It was then adopted in the 2008 NICE guidelines for stroke, which remain in force, and also in the latest guideline from the Royal College of Physicians (2012). All now recommend assessment of high-risk patients as an emergency, with completion of initial investigations within 24 hours (Sources 2-5).

More effective identification of high-risk patients

Use of the ABCD system, developed and validated by Rothwell and colleagues to triage and identify patients at highest risk of major stroke after a TIA or minor stroke, is now recommended in all UK guidelines (Sources 2-5). Indeed, the ABCD score is used to define the risk: *'People who have had a suspected TIA who are at high risk of stroke (that is, with an ABCD score of 4 or above)…'*. (NICE stroke guideline CG68, p8; Source 2).

More urgent surgical treatment of TIAs

Rothwell's related work, notably from the EXPRESS study, showing benefits of early intervention in prevention of stroke also rapidly changed clinical guidelines, being included in the National Stroke Strategy and the 2008 NICE guidelines (Sources 1 and 2). The guidelines also stipulate that carotid endarterectomy should be performed within 48 hours or 14 days of the presenting TIA or stroke (depending on its severity). To see whether these recommendations are being met, Rothwell and colleagues set up the UK National Carotid Endarterectomy Audit – an ongoing national audit in collaboration with the Royal College of Physicians and the Vascular Surgical Society. Repeated audits have shown that delays to endarterectomy have been substantially reduced across the UK; for example, in the early 2000s the average delay was over 3 months; by 2009-10 it was 21 days; by 2010-11 it had fallen to 15 days (Royal College of Physicians, 2012 [Source 5]; Mayor, 2012 [Source 6]).

International impacts

The UK impacts affecting clinical guidelines for triage, investigation and treatment are mirrored by similar recommendations from major international guidelines, including the US National Stroke Association (2006, 2011) and the European Stroke Association (2008), both of which remain in force. Both cite Rothwell's work as evidence leading to their guidance (Sources 7-9).

Overall, implementation of the guidelines that have resulted from the work of Rothwell and his team has benefitted groups along the entire healthcare supply chain, resulting in changes to GPs' practice and hospital services through adoption of the NICE guidelines, reducing burden on the NHS for acute care of major recurrent stroke. The findings have also had a similar impact on

clinical guidelines in Europe, USA and many other countries.

5. Sources to corroborate the impact

Impacts on how TIAs/minor strokes are investigated and managed in the UK

1. **Department of Health. National Stroke Strategy 2007**.
   This influential Strategy cites Rothwell's research in several areas: regarding the risks of stroke after a TIA (p22); the reduction in stroke risk which early intervention produces (p23, 25), and the value of identifying high-risk groups (p24). The work forms the Rationale for the quality markers as to how TIAs should be assessed (QM5) and treated (QM6) by the NHS. [The document is no longer on an active website; it has been archived and is available on request].

2. **National Institute for Health and Clinical Excellence: Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA).** NICE clinical guidance 68. http://www.nice.org.uk/nicemedia/live/12018/41363/41363.pdf
   The full version of the guidelines show that Rothwell's work was drawn on heavily (e.g. in showing risks of early stroke, and the value of the ABCD system), and rated as high-quality evidence, in coming to their recommendations about rapid recognition and treatment of TIAs.

3. **Royal College of Physicians Intercollegiate Stroke Working Party. National clinical guideline for stroke**, Fourth edition, 2012. http://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf
   These detailed guidelines cite Rothwell group papers as the basis for their recommendations about initial diagnosis of acute TIA (pp39-40), for management of TIA (pp42-43), for identifying risk factors for subsequent stroke (pp61-62), and for the role of carotid endarterectomy in treatment of TIA (pp72-73).

4. **NHS choices:** www.nhs.uk/NHSEngland/NSF/Pages/Nationalstrokestrategy.aspx
   Public webpage which summarises NICE guidance, noting: *'a TIA is a sign that you may be at risk of a more serious stroke…seek medical help by calling 999 immediately.'*

5. **Royal College of Physicians Clinical Standards Department.** UK Carotid Endarterectomy Round 4 Public Report, 2012. www.rcplondon.ac.uk/projects/uk-carotidinterventions-audit
   Latest of several recent audits, showing that the average delay to carotid endarterectomy is falling in the UK year-on-year, reflecting the recommendations of the National Stroke Survey, and NICE guidelines. It also recommends consideration of closing units with excessive delays.

6. Mayor S. Services with excessive delays in delivering carotid endarterectomy should close, recommends audit. British Medical Journal 2012; 345:e5641. doi: 10.1136/bmj.e5641.
   Brings the above audit and its recommendations to a general medical audience.

International impacts

7. Johnston SC, Nguyen-Huynh MN, Schwarz ME, et al. **National Stroke Association guidelines for the management of transient ischemic attacks.** Annals of Neurology 2006;60:301-313.
   These leading (and current) American guidelines cite Rothwell's studies as being the major or key data underpinning their recommendations in two areas: that TIAs should undergo rapid assessment and investigation, and regarding the use of carotid endarterectomy.

8. Johnston SC, Albers GW, Goerlick PB, et al. **National Stroke Association recommendations for systems of care for transient ischemic attack.** Annals of Neurology 2011; 69: 872-877.
   Linked to the above guideline, these systems-of-care guidelines cite Rothwell's work as underpinning their guidance for the use and organisation of out-patient services for management of TIAs.

9. **European Stroke Organisation. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008.** Cerebrovascular Diseases 2008;25:457-507.
   These guidelines cite references by Rothwell's group as 'important' in their recommendations regarding emergency management of TIAs, and the role of carotid endarterectomy.