Institution: University of Oxford		
Unit of Assessment: 4 – Psychology, Psychiatry and Neuroscience		
Title of case study: Urgent secondary prevention after transient ischaemic attacks and minor stroke		
Period when the underpinning research was undertaken: 2000 – 2018		
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 M Rothwell	Professor of Neurology	1996 – present
Ziyah Mehta	Senior Medical Statistician	1997 – Aug 2003, Jan 2004 – Nov 2018
Sergei Gutnikov	Programmer	1997 – present
Ramon Luengo-Fernandez	Health Economist	2003 – 2020
Zhengming Chen	Professor of Epidemiology	2006 – present
Louise Silver	Research Coordinator	April 2002 – present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research at the University of Oxford's Stroke Prevention Research Unit (SPRU), led by Professor Peter Rothwell, radically changed how transient ischaemic attacks (TIAs) and minor strokes are managed. It led to these 'warning' events being rebranded as a medical emergency in all clinical guidelines, including NICE, re-emphasis in international guidelines and the National Stroke Strategy mandating the rapid implementation of urgent treatment . Approximately 70,000 strokes have been prevented since 2013 in the UK alone saving the NHS GBP200,000,000 per year in acute stroke care costs, and further improvements in management. In addition, the University of Oxford SPRU research found that the substantial benefit of urgent investigation and treatment was due primarily to the early use of antiplatelet drugs. Aspirin was shown to more than halve the risk of a subsequent major stroke, leading to the recommendation of *immediate* aspirin *prior to* specialist assessment in clinical practice guidelines and public / patient information sources. Finally, the University of Oxford algorithm for identifying individuals at particularly high risk of stroke after a TIA (the ABCD2 score) enabled planning of health services while clinical resources were scarce and has led to new guidelines on the targeted use of dual antiplatelet therapy.

2. Underpinning research

TIA and minor stroke comprise 70% of all acute cerebrovascular events. Research at the University of Oxford's Stroke Prevention Research Unit (SPRU) since 2000, led by Rothwell, has identified the high early risk of major stroke and demonstrated the very considerable benefits of urgent intervention.

Minor strokes/TIAs often herald an impending major stroke: Oxford SPRU research showed that the risk of a major stroke in the days after a TIA/minor stroke had been greatly underestimated. In the Oxford Vascular Study (2003 to 2010), the risk of major stroke in the 7 days after a TIA/minor stroke was found to be about 10% [1].

Identifying the patients at highest risk: Given 100,000 referrals with TIA/minor stroke per year in the UK alone, Rothwell developed a simple risk prediction tool (ABCD system, first published in The Lancet, 2005) to prioritise assessment/treatment of high-risk cases until clinical capacity could be increased to meet demand, and to target more intensive antiplatelet treatment. This research validated the score against 2,893 patients diagnosed with TIA in the UK and US and refined it further to include diabetes as a factor in predicting very early stroke risk [2] to form the 'ABCD2' score.

Reducing delays in treatment prevents major stroke: Having highlighted the risk of major stroke soon after a TIA/minor stroke, Rothwell then showed that urgent treatment was very effective in preventing major strokes.

First, the Oxford SPRU identified the need for much greater urgency in treatment of TIA/minor stroke due to carotid artery disease. Rothwell led the Endarterectomy Triallists' Collaboration, analysing individual patient data from three large randomised trials of carotid endarterectomy versus medical treatment for symptomatic carotid stenosis. This showed important interactions between clinical characteristics and treatment effects, most notably the rapidity with which benefit fell with delay to surgery [3].

Second, to determine the risks and benefits of more urgent medical treatment of TIA/minor stroke more generally, Rothwell led a large team at the Oxford SPRU in the EXPRESS Study [4]. EXPRESS showed that urgent investigation and treatment reduced the 90-day risk of major recurrent stroke by about 80% - one of the most effective interventions in medicine. The intervention (daily urgent clinic service with immediate treatment) was rolled-out across the NHS in the 2008 National Stroke Strategy. The SPRU team's subsequent health-economic analyses showed that the EXPRESS Study intervention reduced hospital bed-days by over two thirds, generating savings of GBP624 per patient treated [5].

The benefit of urgent preventive treatment was due to aspirin alone: The EXPRESS Study treatment was multifactorial, including aspirin, other antiplatelet drugs, BP-lowering drugs and statins, and it was uncertain what had reduced stroke risk. Aspirin was given to all patients, but the effect on recurrent stroke risk had long been considered modest, based on trials in acute major stroke and in long-term prevention after TIA/minor stroke. By detailed analysis of individual patient data from these trials, working closely with their lead investigators at other institutions, Rothwell showed that the acute benefits of aspirin in TIA/minor stroke had been considerably underestimated, showing that aspirin alone reduced the 90-day risk of disabling recurrent stroke by 80% and of all stroke by 60% [6].

3. References to the research (Oxford authors in bold)

1. **Coull A, Lovett JK, Rothwell PM**, on behalf of the Oxford Vascular Study (2004). 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* 328:326-328. DOI:10.1136/bmj.37991.635266.44
2. Johnston SC, **Rothwell PM**, Nguyen-Huynh MN, **Giles MF**, Elkins JS, Bernstein AL, Sidney S (2007). Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 369:283-92. DOI: 10.1016/S0140-6736(07)60150-0. 1,535 citations.
3. **Rothwell PM**, Eliasziw M, **Gutnikov S**, Warlow C for the Carotid Endarterectomy Trialists Collaboration (2004). Effect of endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. *Lancet* 363:915-24. DOI: 10.1016/S0140-6736(04)15785-1. 1,486 citations.
4. **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 Study (2007). Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 370:1432-42. DOI: 10.1016/S0140-6736(07)61448-2. 1,249 citations.

5. **Luengo-Fernandez R, Gray AM, Rothwell PM** (2009). 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* 8:235-43. DOI: 10.1016/S1474-4422(09)70019-5. 228 citations

6. **Rothwell PM**, Algra A, **Chen Z**, Diener HC, Norrving B, **Mehta Z** (2016). Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* 2016; 388: 365-75. DOI: 10.1016/S0140-6736(16)30468-8. 211 citations

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4. Details of the impact

There are over 13,700,000 new strokes worldwide each year, with a lifetime risk of 20%. Prior to the Oxford research, most guidelines had suggested that patients should be assessed and treated within four weeks of a TIA or minor stroke. After the University of Oxford team's research showed that the early risk of stroke after a TIA had been substantially underestimated, guidelines rapidly changed, markedly increasing the urgency with which assessment, investigation and treatment of minor stroke and TIA is recommended. Prior to the start of this REF period, this recommendation had been adopted in the 2007 Department of Health National Stroke Strategy (NSS), the NICE guidelines for stroke (2008), and by the European Stroke Association (2008) [A(i)], US National Stroke Association (2011) [A(ii)] and UK Royal College of Physicians (2012). Similarly the identification of urgent intervention in prevention of stroke [3] had been included in the 2007 NSS and 2008 NICE guidance. Both research and impact have broadened since the REF2014 case study that presented those outcomes.

During the current REF period, the updated versions of the Royal College of Physicians guideline (2016) [B, section 2.3] and the NICE guideline (2019) [C(i)] reaffirmed this recommendation. In coming to recommendations about rapid recognition and treatment of TIAs, the detailed version of the revised NICE guideline draws heavily on Rothwell's work (e.g. [6] showing benefits of urgent treatment with aspirin [Cii]), and rates it as high-quality evidence. In addition, the 2014 US Guideline on the prevention of stroke after TIA [D] recommends early carotid surgery on the basis of the Oxford research in [3]. The other prior guidelines [A] remain active.

Health service changes and benefits resulting from guideline recommendations
Repeated UK national audits showing improvements between 2006 and 2014 in provision of acute services for TIA and minor stroke and in urgent carotid imaging were sustained in the current REF period. The median delay from TIA or minor stroke to assessment in a specialist clinic in the UK had fallen from 12 days in 2006 to 2 days in 2012. The 2014 and 2016 audits showed this maintained at 2 days [E]. Rolling the service out UK-wide was shown to prevent about 10,000 strokes per year [5], thus approximately 70,000 over this REF period, continuing to save the NHS up to GBP200,000,000 annually in acute care costs alone. Equivalent benefits in stroke prevention and reduced healthcare costs are considered to have resulted from recommendations outside the UK.

The improved guidelines on management of TIA and minor stroke has also driven further improvements in patient care during the current period. For example, NHS service provision has continued to improve, with the proportion of hospitals that provide a 7-days a week service able

to see, investigate and treat 'high-risk' patients on the day of referral increasing: for inpatients from 60% in 2014 to 71% in 2016 and similarly 45% increasing to 52% for outpatients [E].

Rothwell's findings on carotid endarterectomy [3] led to guidelines that stipulated it should be performed within 14 days of a TIA/stroke, with continued inclusion in the 2016 Royal College of Physicians guideline [B, section 5.3] and the 2019 NICE guideline [C(i)]. The ongoing UK National Vascular Registry showed that median delay to carotid surgery (approx. 5,000 operations per year) fell from over 3 months in the early 2000s to 12 days in 2018, with the upper quartile cut falling from 28 days in 2015 (2016 report) to 23 days in 2018 (2019 report) [F]. The UK national stroke audit has also shown that the proportion of hospitals that are able to provide same-day carotid imaging 7-days a week for 'high-risk' patients has continued to increase: from 42% in 2014 to 50% in 2016 [E].

Advice to clinicians and the public on immediate aspirin use after TIA/minor stroke
Rothwell's finding of the substantial reduction in early risk and severity of major stroke after TIA and minor stroke with aspirin alone [5] led subsequent UK guidelines to recommend *immediate use of aspirin even prior to specialist assessment/investigation* (Royal College of Physicians 2016 [B, section 3.1]; NICE 2019 [C(i)]). In particular, the Evidence Review for the 2019 NICE Guideline [C(ii)] recommended that aspirin is offered immediately for suspected TIA, requiring that first-line healthcare professionals (e.g. paramedics, NHS 111, GPs, nurses, ED physicians) advise aspirin, and that general practices have adequate supplies to enable treatment, and cited [3] and [5] as two of its three key papers. The 2017 Australian guidelines made a 'Strong recommendation' for the use of antiplatelet therapy in all people with TIA or ischaemic stroke, citing [6]. [G, Chapters 3 & 4].

The recommendation for immediate use of aspirin prior to specialist assessment/ investigation is also now supported in online advice to patients and the public, including the NHS website [H]. which states in a section encouraging prompt action to seek medical advice, '*If a TIA is suspected, you should be offered aspirin to take straight away. This helps to prevent a stroke*.' This change was called for by Rothwell and colleagues in their 2016 paper [6] and was shown to be necessary by their further work on continuing delays in patients seeking medical attention. As immediate aspirin reduces the risk of disabling stroke by 80% [6], any increase in aspirin self-medication has benefits by reducing early recurrent stroke.

Identification of high-risk patients
Use of the Oxford Team's ABCD2 system [2] to triage patients at high risk of stroke after TIA wass recommended in international guidelines [A,D,G,I]. Use of the score in the UK was recommended until 2019 whilst clinical services were under-resourced and needed to be expanded to meet demand. It was used as a Key Performance Indicator (KPI) to identify 'high risk' patients in the 2014 and 2016 UK national stroke audits [E].

The ABCD2 score also underpins the eligibility criteria for TIA (usually ABCD score >4 or 5) in all recent major international randomised trials of acute antiplatelet treatment (CHANCE trial NEJM 2013; SOCRATES trial NEJM 2016; POINT trial – NEJM 2018; THALES trial; NEJM 2020) and hence for treatment recommendations based on the results of these trials. Use of the ABCD2 score to identify high-risk TIA patients for dual antiplatelet treatment is recommended in the most recent Australian [G] and Chinese guidelines [I] and was used by the European Stroke Organization (ESO) in the formulation in 2020 of its updated guidelines for management of TIAs [J]. The latter cites [1,4,6] and was submitted in October 2020 for public release in 2021.

5. Sources to corroborate the impact

A. Earlier clinical guidelines:
(i) **European Stroke Organisation**. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovascular Diseases* 2008;25:457-507. DOI: 10.1159/000131083
(ii) 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. DOI: 10.1002/ana.22332

B. **Royal College of Physicians** Intercollegiate Stroke Working Party. National clinical guideline for stroke, October 2016. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines

C. **National Institute of Clinical Excellent (NICE)** Guideline NG128 (May 2019):
(i) Published guideline: Stroke and transient ischaemic attack in the over 16s: diagnosis and initial management. http://www.nice.org.uk/guidance/ng128
(ii) Intervention Evidence Review: Aspirin for suspected transient ischaemic attack (TIA) https://www.nice.org.uk/guidance/ng128/evidence/a-aspirin-pdf-6777399566

D. Clinical guidelines: **American Heart Association / American Stroke Association:** Kernan WN, Ovbiagele B, Black HR et al. Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke* 2014; 45:2160-2236. https://doi.org/10.1161/STR.0000000000000024

E. **Sentinel Stroke National Audit Programme (SSNAP)** Acute Organisational Audit report. Intercollegiate Stroke Working Party. Biennial reports (2014; 2016; 2019). https://www.strokeaudit.org/

F. Annual report**: National Vascular Registry**: Waton S et al. (2019), for The Royal College of Surgeons of England (November 2019). https://www.vsqip.org.uk/reports/2019-annual-report/

G. **Australian Stroke Foundation** Guidelines (downloaded 8/10/2020) https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management

H. Patient information**: NHS Website,** Transient ischaemic attack (TIA**)** (downloaded 25/10/2020) https://www.nhs.uk/conditions/transient-ischaemic-attack-tia

I. Clinical guidelines: Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association** guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke & Vascular Neurology* 2020;5. DOI: 10.1136/svn-2020-000378.

J. Clinical guidelines: Fonseca AC, Merwick A, Dennis M et al. **European Stroke Organisation** (ESO) guidelines on management of transient ischaemic attack. *European Stroke Journal* (Submitted 4 October 2020, published online 16 March 2021). DOI: 10.1177/2396987321992905