

Impact case study (REF3b)

Institution: University of Leicester
Unit of Assessment: UoA1 Clinical Medicine
Title of case study: Heart attacks: improving therapeutic options for patients through the development of life-saving medical techniques and devices
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Every year in the UK, 150,000 heart attacks are caused by coronary artery occlusion (blockage); worldwide, the figure is 17 million, according to the World Health Organization (WHO). Since 1993, the Leicester Interventional Cardiology group has been at the forefront of research to determine how best to manage such patients. Its findings have been incorporated into official UK (2008), European (2008, 2012) and US (2008) guidelines and have helped to change the way coronary heart disease and heart attacks are treated, with the number of patients treated with primary angioplasty doubling between 2008 and 2011. By guiding service provision, supporting industrial innovation and informing clinical practice, the Unit has contributed to improved healthcare and outcomes for thousands of heart patients. Overall, one-month mortality according to European figures has fallen from 15% to 4% between 2008 and 2013.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Leicester has a long history of pioneering work in the treatment of coronary artery occlusion, initially in the era of thrombolytic ('clot-busting') drugs to proactively unblock the coronary arteries attenuating heart attack outcomes. Professor David deBono was the first in the UK to treat a heart attack patient with a thrombolytic, while Professor Tony Gershlick was the first to deploy a drug-eluting stent (bare-metal stents or 'scaffolds' coated with a drug to reduce inflammation or cell proliferation). DeBono and Gershlick were foremost in the European Cooperative working group (with Arnold AE, Simoons ML, Serruys PW (Rotterdam), Van de Werf F (Belgium) and Lubsen J (Switzerland) publishing on optimal delivery of thrombolytics, with seminal studies showing benefit from mechanical balloon angioplasty (opening an artery mechanically using a balloon and stent), thus improving the outcomes when used in conjunction with thrombolysis. Between 1993 and 2000, their basic lab science (1, 2) allowed for optimising of thrombolysis at cellular levels: these studies were combined with clinical trials including first-in-man designed to improve outcomes following angioplasty and delivery of anti-thrombotic/lytic drugs by coronary stents.</p> <p>Testing the efficacy and safety of different drug-eluting stents</p> <p>During this period and between 2005 and 2007, the group led the field in research on drug-eluting stent development, with studies assessing benefits in animal models of anti-platelet/anti-thrombotic eluting stents (3, 4). This work highlighted that thrombolytic agents were limited and could open only 65% of occluded arteries. The 'open artery hypothesis' proposed that the earlier and more complete the artery could be opened, the better the outcomes (with a reduction in mortality >60% for those with maximal flow). Between 2005 and 2010, Gershlick was UK PI for a number of studies which tested the efficacy and safety of different drug-eluting stents. These included: REDUCE (Low molecular weight heparin, Reviparin, in the prevention of restenosis after PTCA) in 1998, CLASSICS (Clopidogrel in subacute stent thrombosis) in 2000, RENO (European surveillance with the Novoste Beta Cath System) in 2000, E-SIRIUS (European Rapamycin trial) from 2001-2003, e-CYPHER (Real world Registry 15 000 patients) from 2002-2005, and ELUTES International (Drug Eluting Stent) trial from 2001-2003. This was combined with national leadership to develop and evolve angioplasty as a treatment for heart attack victims (British Cardiovascular Intervention Society, NICE and National Infarct Angioplasty Programme (NIAP)).</p> <p>REACT UK trial</p> <p>A question arose early on as to whether thrombolysis could be combined with angioplasty in heart attack victims and, if so, in which cohort. In the late 1990s, Gershlick devised the British Heart Foundation (BHF)-funded multi-centre REACT UK trial to determine which of three commonly and empirically used strategies (a second dose of the thrombolytic agent, or transport to the catheter</p>

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lab for angioplasty as soon as possible, or just managing the patient conservatively) was superior in those patients in whom thrombolytic drugs failed to establish full flow. This study established that viewing of the ECG 90 minutes after the thrombolytic treatment to see if the changes (indicating a myocardial infarction) had resolved, was a good way of determining whether the vessel had been opened by a thrombolytic agent. This is still used worldwide. REACT also showed, with a hazard ratio of around 0.5 (a 50% reduction in the primary endpoint of the study - death, stroke and heart attack), that those patients whose ECGs had not normalised at 90 minutes post-thrombolytic did much better in terms of major adverse cardiac events, including death, with angioplasty (5).

International comparisons

Although it has become clear that angioplasty for heart attacks appears better than thrombolytic (since it is mechanical opening of the artery), not all patients in the UK and elsewhere are able to receive it in a timely fashion. An international study devised by Gershlick has addressed the circumstances in which angioplasty may not be deliverable because of time delays in getting patients to hospital, particularly in rural areas where transfer of patients for angioplasty is delayed beyond the time considered in the Guidelines as beneficial (6).

The STREAM trial (2009 -2012) (7) of 1,850 patients compared angioplasty for myocardial infarction with a strategy of thrombolytic plus REACT-based angioplasty, and showed that these were equivalent. This has enabled better outcomes for the 20% of patients in areas where there are geographical challenges to delivery of angioplasty for heart attacks.

Key staff: Professor A H Gershlick (1989–present); Dr D Adlam (2011–present); Dr Elved Roberts (2009–present); Professor N Samani (1985–present); Professor David deBono, Foundation BHF Professor (1989–1998).

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

1. Underwood MJ, More RS, **Gershlick AH, de Bono DP**. Effect of locally applied tissue-type plasminogen activator on venous fibrinolytic activity: in vitro and in vivo investigations. *Cardiovasc Res*. 1993 Dec;27(12):2270-3.
2. Aggarwal RK, Ireland DC, Azrin MA, Ezekowitz MD, **de Bono DP, Gershlick AH** Antithrombotic potential of polymer-coated stents eluting platelet glycoprotein IIb/IIIa receptor antibody. *Circulation*. 1996 Dec 15;94(12):3311-7.
3. Chitkara K, Hogrefe K, Vasa-Nicotera M, Swanson N, **Gershlick AH** Eptifibatide-eluting stent as an antiproliferative and antithrombotic agent: in vitro evaluation. *J Invasive Cardiol*. 2006 Sep;18(9):417-22.
4. **Gershlick A**, De Scheerder I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, Reifart N, Missault L, Goy JJ, Brinker JA, Raizner AE, Urban P, Heldman AW. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaluation of paclitaxel Eluting Stent (ELUTES) trial. *Circulation*. 2004 Feb 3;109(4):487-93. Epub 2004 Jan 26.
5. **Gershlick AH**, Stephens-Lloyd A and Hughes S, *et al*. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med*. 2005 **353**: 2758–2768.
6. Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention? **Gershlick AH**, Banning AP, Myat A, Verheugt FW, Gersh BJ. *Lancet*. 2013 Aug 17;382(9892):624-32.
7. Paul W. Armstrong, M.D., **Anthony H. Gershlick**, M.D., *et al*. Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction. *N Engl J Med* 2013; 368:1379-1387 April 11, 2013 DOI: 10.1056/NEJMoa1301092.

Grant income over the past decade exceeds £5 million, including: BHF Complete v Lesion-only Primary PCI (CVLPRI) 2010: **£250,530**; McCann Dr G CO-PI Gershlick A NIHR Complete V Lesion-only Primary PCI - Cardiac MRI substudy (CVLPRI-t-CMR) 2011-2013: **£386,323**; EC-Cooperation Research PRESTIGE-PREvention Late Stent Thrombosis by an Interdisciplinary Global European effort 2010-2014: **£446,243.00**; NIHR MRC Randomized Controlled Trial Intracoronary Administration Adenosine or Sodium Nitroprusside v Control for Attenuation of Microvascular Obstruction During PPCI 2011-2013: **£484,993.00**

Impact case study (REF3b)**4. Details of the impact** (indicative maximum 750 words)

Coronary heart disease is the narrowing of the coronary arteries as a result of deposition of atherosclerotic plaque (hardening of the arteries), accounting for nearly 125,000 deaths per year. As a result of pre-clinical and initiation of trials in the area of stent technology, the work of the Leicester team, together with others' global efforts, has resulted in the recurrence after stenting being reduced from 35% to 5%. The first drug-eluting stent (releasing agents that inhibit the inflammatory over repair response) deployed in the UK was by Gershlick at UHL, as was the first drug-eluting absorbable stent.

Underpinning guidance on management of heart attack patients

Translational and clinical research based in Leicester has contributed to angioplasty and coronary stenting becoming a mainstream standard clinical procedure. The Unit's research has allowed stenting to evolve into an effective and safe procedure by testing the efficacy, safety and cost-efficiencies of stent designs and the drugs on them.

The REACT trial was the first definitive study to show the absolute clinical benefit of angioplasty in the 35% of patients whose occluded artery had failed to be re-opened following the use of clot-busting drugs (thrombolysis). Across the world, patients are now managed according to a protocol that states that, if they receive thrombolysis, the ECG should be reviewed after 90 minutes and if the changes due to the heart attack have not resolved then they should have rescue angioplasty.

The following national and international guidelines, underpinned by the Unit's research, directly influence how patients with heart disease are treated in the UK, Europe and the US:

- In July 2008, NICE updated its guidance on drug-eluting stents. The Unit's research is cited in the assessment report for the appraisal prepared by University of Liverpool (Drug-eluting stents: a systematic review and economic evaluation, November 2005), the literature review which underpins the 2008 guidance (Technology Appraisal 152). (1) Gershlick represented the British Cardiovascular Society (BCS) as Medical Expert presenting data to NICE.
- In 2008 and 2012, European Society of Cardiology published guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Gershlick was co-author on the European Guideline Writing Committee on STEMI. (2)
- In 2008, the American College of Cardiology and American Heart Association issued a "focused update" of their 2004 guidelines for the management of ST-segment elevation myocardial infarction (STEMI). (3)

The results of the STREAM trial were presented at the late-breaking session at The American College of Cardiology meeting in April 2013, with simultaneous publication in New England Journal of Medicine, and had an immediate impact on clinical practice, particularly in parts of the world with geographical challenges to delivery of angioplasty for heart attacks. Editorial accompanying the NEJM article stated: "The findings of this trial could have a major effect on clinical practice." (4)

Influencing national service provision

The UK Government's National Service Framework (NSF) for coronary heart disease was a 10-year strategy launched in 2000 to reduce coronary heart disease and stroke-related deaths by 40% by March 2010. The original NSF proposal was inter-hospital transfer of patients for PCI, with the journey time between hospitals should not exceed 30 minutes. (5.5) Work on stents and representations to NICE, underpinned by the Unit's research into angioplasty and stenting and Gershlick's representation on the British Cardiovascular Intervention Society (BCIS), has resulted in the development of network systems and also the devolution of stenting to all hospitals judged as angioplasty capable (BCIS visits).

The driving force behind the roll-out of angioplasty as standard care was a joint project launched in 2005 between the Department of Health and the British Cardiac Society. The National Infarct Angioplasty Project (NIAP) was set up to test the feasibility of implementing a countrywide angioplasty service for heart attack victims. Gershlick was a founder member of the NIAP Academic Group. The final report was used to inform commissioners, cardiac networks and service

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providers in their discussions on the configuration of acute services and to feed into the development of primary care trust (PCT) annual operating plans. A recent Department of Health report indicates that >90% patients in the UK now receive primary PCI. Charting the change, the report shows that in the third quarter of 2008, just 46% of those STEMI patients in England who received reperfusion treatment were being treated by primary angioplasty while the remaining 54% were treated with thrombolysis. By the second quarter of 2011, 94% of patients were treated with primary angioplasty.(6)

Guiding the development of new pharmaceutical therapies and drug-eluting stents

Since the 1990s, Gershlick has worked with medical device and drug manufacturers to guide the design of drug-eluting stents. He has been involved in comparative trials of different drug-eluting stents including steering and Data and Safety Monitoring Board committees which have assessed the efficacy of stents and drug treatments for heart patients. Such studies were precedents in the development of drug-eluting stents which are used in over two million patients worldwide.

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

1. NICE guidelines on Drug Eluting Stents: <http://www.nice.org.uk/ta152>
2. The European Society of Cardiology Guideline documents for: Acute Myocardial Infarction in patients presenting with ST-segment elevation http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/Guidelines_AMI_STEMI.pdf
3. American College of Cardiology and American Heart Association update of 2004 guidelines [http://www.ncbi.nlm.nih.gov/pubmed/18519158?log\\$=activity](http://www.ncbi.nlm.nih.gov/pubmed/18519158?log$=activity)
4. New England Journal of Medicine editorial: <http://www.nejm.org/doi/full/10.1056/NEJMe1302670>
5. National Service Framework for Coronary Heart Disease: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/198931/National_Service_Framework_for_Coronary_Heart_Disease.pdf
6. Department of Health report showing the increase in patients treated with primary angioplasty by 2011. <http://www.improvement.nhs.uk/LinkClick.aspx?fileticket=PWttejHG45M%3d&tabid=63>