Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: L: Pharmacological and interventional therapies for acute coronary syndromes improve patient outcome

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

Impact*:* Health and welfare, policy and clinical practice; randomised trial evidence has changed the management and outcome of acute coronary syndromes (ACS) globally.

Significance*:* Advanced anti-platelet and revascularisation therapies have become standards of care worldwide. There have been large (10–50%) reductions in the death rate from coronary heart disease across Europe. Clopidogrel was the second best-selling drug in the USA in 2011.

Beneficiaries*:* Patients with ACS, clinical practitioners, NHS and healthcare delivery organisations, policy-makers, pharmaceutical companies.

Attribution: Building on prior studies, Fox (UoE) and colleagues led multicentre randomised controlled trials; international trials were co-chaired by Fox with international investigators.

Reach*:* Global; guideline changes in Europe and USA; applies to the up to 5% of the population who have ACS.

2. Underpinning research (indicative maximum 500 words)

Professor Keith Fox (Professor of Cardiology, UoE, 1999–present) and colleagues have defined the evidence base for anti-platelet therapies and coronary revascularisation strategies in acute coronary syndromes (ACS); their implementation as the standard of care worldwide has reduced mortality from coronary heart disease.

ACS refers to any group of symptoms attributed to obstruction of the coronary arteries. It usually occurs as a result of myocardial infarction or unstable angina. ACS affects approximately 5% of men and 3% of women [5.3]. In the UK, about 114,000 patients with ACS are admitted to hospital each year; in the USA, more than 5.5 million patients a year present to an emergency department with chest pain and other symptoms related to ACS. Patients with ACS are at risk of death and re-infarction. In 2008, Fox and colleagues defined the characteristics of patients with ST- and non ST-elevation ACS and their early and late complications [3.1], demonstrating that such complications follow erosion or fissuring of an atheromatous plaque, triggering contact activation of coagulation, platelet aggregation and amplification of the coagulation cascade. Since then, Fox's team has taken an integrated approach to clinical research into pharmacological and interventional methods to inhibit coronary thrombosis in ACS.

<u>Pharmacological strategies: innovations in anti-platelet therapy</u>
In the first ever investigator-led study to test the role of dual anti-platelet therapy (aspirin plus the thienopyridine clopidogrel), Fox, as co-chair with Salim Yusuf (McMaster University, Canada) led the international CURE trial, enrolling 12,562 patients from 28 countries from 1998–2000, and demonstrated a highly significant (21% risk reduction) and sustained improvement in outcome (principally myocardial infarction) [3.2]. However, the clinical responses were not uniform. In later landmark studies in stratified medicine, Fox and colleagues evaluated the impact of the *CYP2C19* genotype on outcomes following clopidogrel treatment and identified the relationship between *CYP2C19* polymorphisms and ischaemic and bleeding outcomes.

In subsequent research, Fox and colleagues have extended their findings in international clinical trials of secondary prevention in stable cardiovascular disease, notably CHARISMA (2002–2003; 15,603 patients) [3.3], and more potent platelet inhibitors in ACS, namely prasugrel in TRILOGY

(2008–2011; 9326 patients from 52 countries) [3.4].

Interventional strategies: coronary revascularisation

Revascularisation procedures (percutaneous coronary intervention [PCI; also known as angioplasty] and coronary artery bypass graft surgery [CABG]) involve physically opening, with a balloon and stent, or surgically bypassing blocked or narrowed arteries. Although revascularisation had been proven to reduce myocardial ischaemia, the long-term effect on recurrent myocardial infarction and mortality was unknown, and practice was highly variable. In a British Heart Foundation-funded study of 1810 UK non-ST-elevation ACS patients (the RITA 3 trial, 1997–2001; Fox Principal Investigator), the team compared an interventional strategy (early coronary angiography followed by revascularisation) with a strategy of conservative management. At 1-year follow-up, rates of death or non-fatal myocardial infarction were similar. However, at 5 years' follow-up, there were fewer deaths or recurrent myocardial infarctions in the intervention group (P = 0.044). The benefits of an intervention strategy were mainly seen in patients at high risk of death or myocardial infarction (P = 0·004), and for the highest risk group, the odds ratio of death or non-fatal myocardial infarction was 0·44 (0·25–0·76) [3.6].

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

3.1 Fox K, Anderson F Jr, Goodman S, et al; GRACE Investigators. Time course of events in acute coronary syndromes: implications for clinical practice from the GRACE registry. Nat Clin Pract Cardiovasc Med. 2008;5:580–9. DOI: 10.1038/ncpcardio1302.

3.2 Yusuf S, Zhao F, Mehta S,…Fox K; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502. DOI: 10.1056/NEJMoa010746.

3.3 Bhatt D, Fox K, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706–17. DOI: 10.1056/NEJMoa060989.

3.4 Roe M, Armstrong P, Fox K, et al; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med. 2012:367:1297–309. DOI: 10.1056/NEJMoa1205512.

3.5 Mega J, Braunwald E, Wiviott S,…Fox K; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366:9–19. DOI: 10.1056/NEJMoa1112277.

3.6 Fox K, Poole-Wilson P, Clayton T, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet. 2005;366:914–20. DOI: 10.1016/S0140-6736(05)67222-4.

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

Impact on health and welfare

Implementation of both anti-platelet and coronary interventional therapies in ACS has led to major improvements in mortality rates. Fox demonstrated a marked improvement in performance measures for reperfusion in ST-elevation myocardial infarction in 2008, across 21 countries in Europe, compared with data from 2006: the number of eligible patients receiving reperfusion therapy in a timely manner increased from 53.1% to 63.5% (P < 0.0001). In parallel, over the 2-year period, in-hospital mortality decreased from 8.1 to 6.6% (P = 0.047) [5.1].

Furthermore, the UK Myocardial Ischaemia National Audit Project public report demonstrated a decline in 30-day mortality for non-ST-elevation myocardial infarction from 12.5% in 2003 to 7% in 2012 [5.2]. The improvements in case fatality and acute outcomes have been independently attributed to the innovations in care following the adoption of guideline recommendations.

The data were corroborated by 2012 British Heart Foundation Coronary Heart Disease statistics

[5.3]. For instance most European countries witnessed a 10% to 50% decrease in death from coronary heart disease from 1998 to 2008 (45% decrease in UK).

Impact on public policy
Clopidogrel was the first anti-platelet agent to demonstrate major improvements in clinical outcome when added to aspirin. Fox and colleagues' landmark study [3.2] changed guidelines in the UK (National Institute for Health and Care Excellence [5.4]), Europe (European Society of Cardiology [5.5]; 55 countries have pledged to implement these guidelines) and North America (American College of Cardiology Foundation/American Heart Association [5.6]). Further to Fox's demonstration of the effect of genetic polymorphisms on the variable clopidogrel metabolism among individuals, the US Food and Drug Administration has, since 2010, recommended consideration of genetic testing for clopidogrel [5.7].

Impact on clinical practice
Dual anti-platelet therapy and coronary revascularisation with PCI has become the standard of care worldwide for all patients presenting with ACS. In 2010, there had been an almost 1000% increase in the number of PCIs in the UK per annum since 1991 [5.3]. This was mirrored by a steady rise in prescription of anti-platelet drugs since their introduction in the late 1980s, up to 40,000 prescriptions in England in 2011 [5.3].

A collaborative meta-analysis led by Fox (2010) confirmed the long-term beneficial impact of interventional revascularisation, demonstrating 2.0–3.8% absolute reductions in cardiovascular death or myocardial infarction in the low- and intermediate-risk groups and an 11.1% absolute risk reduction in the highest-risk patients [5.8].

Impact on commerce
Clopidogrel (marketed as Plavix®) was described as a "blockbuster" drug for its manufacturers Bristol Myers Squibb and Sanofi, generating US$6.5B in sales in the USA in 2011, where it was the second best-selling drug [5.9]. This ranking reduced when the US Food and Drug Administration approved generic versions in 2012, but the drug now generates revenues for multiple manufacturers worldwide (USA, Canada, Europe, India, Australia).

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

5.1 Schiele F, Hochadel M, Tubaro M…Fox K, Gitt A. Reperfusion strategy in Europe: temporal trends in performance measures for reperfusion therapy in ST-elevation myocardial infarction. Eur Heart J. 2010;31:2614–24. DOI: 10.1093/eurheartj/ehq305.

5.2 Myocardial Ischaemia National Audit Report (2012). http://www.ucl.ac.uk/nicor/audits/minap/publicreports/pdfs/minap2012publicreportlowres.

5.3 British Heart Foundation (2012). Coronary Heart Disease Statistics 2012. http://www.bhf.org.uk/publications/view-publication.aspx?ps=1002097.

5.4 National Institute for Health and Care Excellence (March 2010). Unstable angina and NSTEMI The early management of unstable angina and non-ST-segment- elevation myocardial infarction. http://www.nice.org.uk/nicemedia/live/12949/47921/47921.pdf.

5.5 Hamm C, Bassand J, Agewall S, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999–3054. DOI: 10.1093/eurheartj/ehr236.

5.6 Jneid H, Anderson J, Wright R, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2012;126:875–910. DOI: 10.1161/CIR.0b013e318256f1e0.

5.7 US Food and Drug Administration (2010). FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm203888.htm.

5.8 Fox K, Clayton T, Damman P, et al; FIR Collaboration. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. J Am Coll Cardiol. 2010;55:2435–45. DOI: 10.1016/j.jacc.2010.03.007.

5.9 Drugs.com (2013). Plavix sales data. http://www.drugs.com/stats/plavix.