Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: B: Avoiding ineffective statin use in aortic stenosis

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

Impact: Health and welfare; a clinical trial demonstrated that statin therapy is ineffective in aortic stenosis; this informed international guidelines and changed clinical practice.

Significance: Unnecessary statin therapy is avoided in up to 500,000 people in the UK alone, saving the NHS £169M p.a. Known statin side-effects of myalgia or hepatic dysfunction are avoided in 30,000 patients.

Beneficiaries: Patients with aortic stenosis; the NHS and healthcare delivery organisations, the economy.

Attribution: Newby and Boon, UoE, undertook the first investigator-led randomised controlled trial of statin therapy in aortic stenosis: the SALTIRE trial.

Reach: Aortic stenosis affects 2% of people over 65. The SALTIRE trial results informed European and N American guidelines and have impacted the treatment of millions of people globally.

2. Underpinning research (indicative maximum 500 words)

In the late 1990s, Professor David Newby (Professor of Cardiology, UoE, 1995–present), later with Dr Nicholas Boon (Honorary Fellow, UoE, 2005–2013), began investigating the potential association between dyslipidaemia and aortic stenosis. They published preliminary data suggesting that patients with severe aortic stenosis had higher serum cholesterol concentrations [3.1].

Aortic stenosis is the commonest valvular heart disease in the western world. Approximately 2% of people over the age of 65, 3% of people over age 75, and 4% percent of people over age 85 have the condition. Moreover, the prevalence of aortic stenosis is rising in North America and Europe because of aging populations. It is a potentially fatal condition for which the only current clinical management entails surgically replacing the valve at the end-stage of disease. It is the leading indication for valve surgery in North America and Europe; the number of operations is predicted to double over the next 10–20 years.

At the turn of the millennium, there was widespread support for the concept that lipid deposition and an atherosclerosis-like process was responsible for the initiation and progression of the aortic valve disease process, and many observational studies indicated that statins could reduce disease progression. With £185K British Heart Foundation (BHF) funding (2000–2004), and with research infrastructure provided through a £4.4M Clinical Research Infrastructure Initiative (BHF and MRC Programme Grant) and a £7.6M BHF Research Excellence award, Newby and Boon undertook the first investigator-led randomised controlled trial of lipid-lowering therapy in patients with aortic stenosis: the SALTIRE trial. In SALTIRE, 155 people were assigned in 2001–2002 to atorvastatin or placebo and clinically evaluated for up to three years. The trial demonstrated no effect of atorvastatin on disease progression: no decrease in aortic-jet velocity ($P = 0.95$) or valvular calcification ($P = 0.93$) [3.2].

These findings were extremely controversial on a background of increasing enthusiasm for statin therapy in patients with aortic stenosis and many clinicians prescribing statins to these patients based on early observational data. Crucially, and in part because of the contentious nature of the findings of this investigator-led trial, two subsequent randomised controlled trials were initiated — SEAS (2008) and ASTRONOMER (2012) — both of which directly replicated the findings of the

SALTIRE trial.

In the early 2000s, during the conduct of the SALTIRE trial, Newby and Boon made several important and consistent observations of relevance to defining the underlying pathogenesis and natural history of calcified vascular lesions. They demonstrated that the severity of aortic stenosis and degree of valvular calcification were very closely associated and interdependent [3.3] and demonstrated in a randomised controlled trial a lack of effect of high-dose atorvastatin on the progression of coronary artery calcification [3.4].

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

3.1 Chui M, Newby D, Panarelli M, Bloomfield P, Boon N. Association between calcific aortic stenosis and hypercholesterolemia: is there a need for a randomised controlled trial of cholesterol lowering therapy? Clin Cardiol. 2001;24:52–5. DOI: 10.1002/clc.4960240109.

3.2 Cowell S, Newby D, Prescott R,…Boon N. A randomized controlled trial of intensive lipid lowering therapy in calcific aortic stenosis. N Engl J Med. 2005;352:2389–97. DOI: 10.1056/NEJMoa043876.

3.3 Cowell S, Newby D, Burton J,…Boon N, Reid J. Aortic valve calcification on computed tomography predicts the severity of aortic stenosis. Clin Radiol. 2003;58:712–6. DOI: 10.1016/S0009-9260(03)00184-3.

3.4 Houslay E, Cowell S, Northridge D,…Boon N, Newby D. Progressive coronary calcification despite intensive lipid-lowering therapy: a randomized controlled trial. Heart. 2006;92:1207–12. DOI: 10.1136/hrt.2005.080929.

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

Impact on clinical practice

When it was reported in 2005, the results of the SALTIRE trial were highly controversial. Many commentators initially refused to accept the findings such was the widespread belief that statin therapy would be effective in treating aortic stenosis. However, the importance of the study was recognised in an accompanying editorial in N Engl J Med [5.1] and it has since been cited 336 times (Web of Knowledge; Thomson Reuters, 2013). Importantly, two further randomised controlled trials (SEAS [2008] and ASTRONOMER [2012]) corroborated the findings of the SALTIRE trial. The weight of evidence, initially from SALTIRE and supported by the additional two trials, has changed clinical practice internationally, as evidenced by expert commentaries citing SALTIRE on international websites, for example, UK (British Cardiovascular Society) [5.2], USA (Medscape) [5.3] and Argentina (Sociedad Argentina de Cardiologia) [5.4]. Dr KL Chan, lead investigator of the ASTRONOMER trial, stated on TheHeart.org “with three randomized trials…it really means that statins have no role per se in the treatment of aortic stenosis” [5.5] and a 2010 review stated “statins cannot be advocated to patients solely to prevent progression of aortic stenosis” [5.6].

Impact on public policy

The SALTIRE trial was acknowledged as being the first in the field and was cited in 2008 American College of Cardiology/American Heart Association guidelines for the management of valvular heart disease as evidence against the use of statin therapy in these patients [5.7]. Similarly, the 2012 European Society of Cardiology guidelines advise against statin usage as a primary treatment for aortic stenosis [5.8] (SALTIRE cited in the forerunning 2007 version).

Impact on health and welfare and the economy

Approximately 1 million people in the United Kingdom have valvular heart disease and this is predicted by the British Cardiovascular Society (www.statistics.gov.uk) to increase by 50% by 2025. Nearly half of these individuals are accounted for by aortic stenosis, giving an overall prevalence of 400–500,000 people currently in the UK. The SALTIRE findings and their subsequent confirmation have therefore prevented the inappropriate implementation of statin treatment as a disease-modifying drug in the majority of patients with aortic stenosis. Furthermore,

because myalgia and major hepatic dysfunction are associated with statin therapy in 5% and 1% of people, respectively, avoiding statin use has prevented potentially detrimental side-effects in approximately 30,000 people.

In economic terms, based on the prescription cost of atorvastatin, this is calculated to result in cost savings of up to £169M per annum for the UK alone [5.9].

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

5.1 Rosenhek R. Statins for aortic stenosis. N Engl J Med. 2005;352:2441–3. DOI: 10.1056/NEJMe058070.

5.2 Groves S. ASTRONOMER Trial Going where others have been before? (2010). British Cardiovascular Society website. http://www.bcs.com/pages/news_full.asp?NewsID=19709572.

5.3 Intini A, Fang J. Statins for Aortic Stenosis? (2008). Medscape website. http://www.medscape.com/viewarticle/583569. *[Free login required. Available on request.]*

5.4 Roura P. ASTRONOMER trial. Rosuvastatin in the regression of aortic stenosis (2010). Sociedad Argentina de Cardiologia website. http://www.sac.org.ar/web/es/actualizaciones-bibliograficas-1/astronomer-trial--rosuvastatina-en-la-regresion-de-la-estenosis-aortica- (in Spanish).

5.5 TheHeart.org, 'Heartwire' article (2010). ASTRONOMER published: No role for statins in aortic stenosis. http://www.theheart.org/article/1038095.do. *[Free login required. Available on request.]*

5.6 Hermans H, Herijgers P, Holvoet P, et al. Statins for calcific aortic valve stenosis: into oblivion after SALTIRE and SEAS? An extensive review from bench to bedside. Curr Probl Cardiol. 2010;35:284–306. DOI: 10.1016/j.cpcardiol.2010.02.002.

5.7 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2008;118:e523–661. DOI: 10.1161/CIRCULATIONAHA.108.190748.

5.8 The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33:2451–96. DOI: 10.1093/eurheartj/ehs109.

5.9 British National Formulary. www.bnf.org. *[Calculated on the basis of atorvastatin costing £28.21 for 80 tablets; £366.73 per patient per year.]*