Institution: University of Sheffield

Unit of Assessment: 2 - Public Health, Health Services and Primary Care

Title of case study: Informing national policy to increase prescribing of statins for the prevention of heart disease

1. Summary of the impact

University of Sheffield research which evaluated the clinical and cost-effectiveness of statins for the primary and secondary prevention of cardiovascular events has directly led to an additional 3.3 million people in England and Wales becoming eligible for this treatment. Statins have been shown to reduce the risk of future cardiovascular events, such as heart attacks and stroke.

Guidance on statin prescribing in England and Wales, issued by the National Institute for Health and Care Excellence (NICE) Appraisal Committee in January 2006 was informed by our research report. Following this guidance the number of patients receiving statins has increased year on year with the number of prescriptions increasing by 29% between 2007 and 2011, enabling these patients to benefit from reduced risk of heart attacks and stroke and CVD related deaths.

2. Underpinning research

Researchers at the School of Health and Related Research (ScHARR) at the University of Sheffield undertook a systematic review of the clinical and cost-effectiveness of statins in the primary and secondary prevention of coronary heart disease (CHD) and cardiovascular disease (CVD) in England and Wales. In addition, they developed an economic model to explore the cost-effectiveness of the five statins which were licensed for use in England and Wales in April 2004. The research was undertaken in 2004 and 2005 and was funded by the Heath Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), on behalf of the National Institute for Health and Care Excellence (NICE) in order to compare directly the effectiveness and cost-effectiveness of different statins for the first time and to assess the impact of statins in patients who had not previously experienced a CVD event. The HTA programme commissions research where there are uncertainties surrounding the clinical and cost-effectiveness of interventions used in the NHS.

Statins help lower rates of low-density lipoprotein (LDL) cholesterol in the blood, by reducing the production of LDL cholesterol inside the liver. High levels of LDL cholesterol can lead to hardening and narrowing of the arteries (atherosclerosis) which increase the risk of CVD events such as heart attack and stroke. The systematic review on clinical effectiveness, conducted at ScHARR by Myfanwy Lloyd Jones (at ScHARR between 1996 and 2012) and Abdullar Pandor (at ScHARR since 1999), identified and evaluated all literature relating to the effectiveness of the five statins for the prevention of coronary events. This comprehensive review was unique, looking at the efficacy and safety (including post-market surveillance) of all RCTs (published and unpublished) of the five statins in primary and secondary prevention of CVD. Previous reviews had only focused on secondary prevention, had only considered large trials and had undertaken only a limited review of adverse events.

The review concluded that there was robust evidence to suggest that statin therapy is associated with a statistically significant reduction, as high as 33%, for some events, in the risk of primary and secondary cardiovascular events compared to placebo when assuming a class effect for all statins and doses. The evidence from the placebo-controlled trials indicated that the four statins with hard clinical endpoints of morbidity and mortality (atorvastatin, fluvastatin, pravastatin and simvastatin) demonstrated a very similar beneficial effect. The evidence base for rosuvastatin was less well developed. Limited evidence from direct comparisons between statins suggested that atorvastatin may be more effective than pravastatin in patients with symptomatic CHD. **The review also concluded that** statins were generally well tolerated, with a good safety profile.

A new health economic model was developed by Sue Ward (Senior Operational Research Analyst), Roberta Ara (Operational Research Analyst) and Mike Holmes (Operational Research Analyst) at ScHARR to predict the cost-effectiveness of statin therapy over a patient's lifetime. This was the first economic analysis to compare the five different statins within the same economic model. The model used clinical events to measure effectiveness rather than the surrogate endpoint of cholesterol lowering which had been used in previous models. (NICE guidance section 4.3.6) The effect of statins on the reduction of events was based on relative risks of coronary and cardiovascular outcomes estimated by a pioneering Bayesian meta-analysis. Cost-effectiveness of statins within both secondary prevention (for those who had already experienced a CHD event) and primary prevention (for those at high risk of experiencing a first event) were evaluated within the same model for the first time. For primary prevention the cost-effectiveness was examined on the basis of decreasing risk in a stepwise manner (for example, from a threshold of 3% annual risk to 2% annual risk) to demonstrate the true incremental cost-effectiveness of treating decreasing levels of absolute risk.

The economic modelling work showed that the incremental cost-effectiveness ratios (ICERs) in secondary prevention of CVD increased with age varying between £8,000 and £13,000 per quality adjusted life year (QALY) for ages 45 and 85 respectively and, therefore, statin therapy was likely to be considered cost-effective based on the accepted cost–effectiveness threshold values of £20,000 in England and Wales. In primary prevention, the cost-effectiveness ratios were shown to be dependent on the level of CVD risk and age. At 3% risk the ICERs remain below £17,000 for all ages whereas at 0.5% CHD risk the ICERs reach as high as £50,000. The analysis also suggested that that statin therapy was cost effective in people with diabetes, who have a higher absolute risk of CVD compared to those without diabetes.

This research was used by the NICE Appraisal Committee to inform their guidance on statin prescribing in England and Wales. ([R2 Section 4.3.6 and Appendix B]. The research report was also cited in the subsequent Lipid Modification Clinical Guideline CG67, issued in May 2008.
This research also led to two further high quality research projects in the UK, led by Roberta Ara at ScHARR. Firstly, a Health Technology Assessment on the clinical and cost-effectiveness of ezetimibe in patients with primary hypercholesterolaemia (funded by the NIHR in 2007). This research was used by the NICE Appraisal Committee to inform their national guidance on ezetimibe prescribing in England and Wales. (NICE Technology Appraisal TA132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia Technology appraisals, November 2007). Secondly, a Health Technology Assessment comparing the clinical and cost-effectiveness of potent dose statins versus standard doses in individuals with acute coronary syndrome (funded by the NIHR in 2008).[R3-R6]

3. References to the research

The original work was published as a peer-reviewed Health Technology Assessment monograph. A series of subsequent peer-reviewed publications, and research projects followed directly from the modelling work undertaken as part of the initial project.

R1. **Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A,** Yeo W, **Payne N.** A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 11(14):1-iv Apr 2007.

R2. **NICE guidance. Statins for the prevention of cardiovascular events.** Technology Appraisal 96. January 1996

R3. **Ara R, Pandor A, Stevens J, Rafia R, Ward S, Rees A**, Durrington P, Reynolds T, Wierzbicki A, Stevenson M. Prescribing high-dose lipid-lowering therapy early to avoid subsequent cardiovascular events: is this a cost-effective strategy? *Eur J Cardiovasc Prev Rehabil* 19(3) 01 Apr 2011 doi: 10.1177/1741826711406616

R4. **Ara R, Pandor A, Stevens J, Rees A, Rafia R**. Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation. *Health Technol Assess*

13(34):1-118 Jul 2009

R5. **Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A,** Durrington PN, **Chilcott J** Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 265(5):568-580 May 2009 doi: 10.1111/j.1365-2796.2008.02062.x

R6. **Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, Paisley S, Chilcott J.** Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. Health Technol Assess 12(21):iii-212 May 2008

4. Details of the impact

Impacts on Health and Welfare

The ScHARR research report on statins was submitted to NICE in 2005 and provided the key evidence which shaped new national guidance on statin therapy for England and Wales, *Statins for the prevention of cardiovascular events. Technology Appraisal 96.* (January 1996) [S1]. The guidance resulted in an increase in the number of people benefitting from statin prescribing. Previously statins had been prescribed to people with a history of a CVD event (secondary prevention), but the guidance led to statin prescribing to include "healthy" populations at high risk of future events (primary prevention) [S2], subsequently to diabetics [S3] and to individuals at high genetic risk of coronary disease [S4].

The guidance resulted in an additional 3.3 million people in England and Wales becoming eligible for statin treatment.[S2] In 2006 Professor David Barnett, Chair of the independent NICE Appraisal Committee that developed the TA94 guidance, predicted that "In terms of potential impact this guidance is arguably one of the most significant to have come out of NICE since it started over six years ago."

The volume of statin prescriptions in England has increased year on year since the guidance was issued in 2006, up by 44% between 2005 and 2008 (from 33,772,000 to 48,717,000) and up by 70% (to 57,454,000) between 2005 and 2011 (the latest year for which prescription data are available).[S5] The Health Survey for England (HSE) 2006 reported that use of statins and other lipid-lowering drugs was 73% in men and 65% in women with self-reported doctor diagnosed ischaemic heart disease (IHD) or stroke. [S5] This had increased to 79% of men and 72% of women over 35 with self-reported doctor-diagnosed IHD or stroke, based on the HSE 2011. [S6]

Cardiovascular related mortality rates per 100,000 have reduced from approximately 310 for males (approximately 180 for females) in 2004 to approximately 250 for males (approximately 120 for females) in 2009.[S8] Treatment with lipid lowering drugs, particularly statins, enables effective reduction in LDL, and, therefore, total cholesterol levels, with resulting reductions in CVD incidence and deaths, and overall mortality.[S6] A gradual decrease in mean total cholesterol levels in both sexes between 2006 and 2011 [S6] has occurred. Mean total cholesterol levels have reduced by 4% (from 5.2 and 5.0 mmol/l) in men and by 6% (from 5.4 and 5.1 mmol/l) in women between 2008 and 2011.[S6] Every 1% fall in mean population total cholesterol levels decreases CVD mortality by approximately 2.5%. [S7]

Economic impact

Our research was the first research study to compare directly the five statins available to the NHS in 2004 within the same systematic review and economic model. The systematic review concluded that evidence from the placebo-controlled trials did not indicate any difference between the clinical efficacy of atorvastatin, fluvastatin, pravastatin and simvastatin. The NICE guidance on statins, informed by this research, was, therefore, able to recommend that *"when the decision has been made to prescribe a statin, the therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose)."* [S1] A shift to

prescribing the low cost statin, simvastatin, has been seen in prescribing patterns since the introduction of the guidance in 2006. [S9] Nationally, lower cost statins have increased as a percentage of total statin prescriptions. The impact of this has been to reduce the cost of statin prescribing per patient in the NHS. The NAO reported savings of £323 million achieved by cost effective prescribing of statins in 2009 (relative to a 2005 baseline). [S9]

CVD cost the health care system in the UK around £8.6 billion in 2009. [S10] The cost of hospital care for people who have CVD accounts for 50% of these costs. [S10] Treating people with statins leads to large savings in hospitalisation costs for all vascular events amongst a wide range of high risk individuals. [S11]. For example, statins prescribing has contributed to a fall in the incidence of hospitalised acute myocardial infarction between 2008 and 2010 from 98 to 86 per 100,000 for men and from 138 to 133 per 100,000 for women. [S10]

5. Sources to corroborate the impact

S1. NICE guidance. Statins for the prevention of cardiovascular events. Technology Appraisal 96. January 1996. http://www.nice.org.uk/nicemedia/pdf/TA094guidance.pdf

S2. Millions more to get heart drugs. http://news.bbc.co.uk/1/hi/health/4644828.stm

S3. Statins for all diabetics urged. http://news.bbc.co.uk/1/hi/health/7180733.stm

S4. Genetic cholesterol test warning http://news.bbc.co.uk/1/hi/health/8118804.stm

S5. Health survey for England 2006:https://catalogue.ic.nhs.uk/publications/public-health/surveys/heal-surv-cvd-risk-obes-ad-ch-eng-2006/heal-surv-cvd-risk-obes-ad-ch-eng-2006-rep-v1.pdf

S6. Health Survey for England 2011. Chapter 2 Cardiovascular Disease. http://www.ic.nhs.uk/catalogue/PUB09300

S7. Capewell S and Ford E. Why have total cholesterol levels declined in most developed countries? BMC Public Health. 2011; 11: 641

S8. Scarborough P, Wickramasinghe K, Bhatnagar P, Rayner M. BHF Trends in Coronary heart disease 1961-2011 Available from: http://www.bhf.org.uk/publications/view-publication.aspx?ps=1001933

S9. Department of Health Cost-Effective Prescribing: Better Care Better Value Indicator on Statins. April 2011

S10. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M (2012). *Coronary heart disease statistics 2012 edition.* British Heart Foundation: London.

S11. Medical Research Council. Achievements and Impacts http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Statins/index.htm