Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Global adoption of statins for cardiovascular disease prevention

1. Summary of the impact

More than half of UK adults aged over 45 years have high cholesterol levels, the major modifiable risk factor for cardiovascular disease (CVD). Over the past 20 years, University of Glasgow researchers have led numerous landmark clinical trials establishing the benefits of statins for CVD prevention. High-profile international clinical guidelines on lipid lowering cite these studies in the key evidence base for recommendations to guide statin use, demonstrating the considerable influence this work exerts on current clinical practice and public health. This has driven the global uptake of statins and provided the evidence-base for CVD risk assessment and prevention strategies that are now implemented worldwide. The use of statins has transformed patient care, provided a cost-effective prevention strategy for healthcare providers and made major contributions to the falling CVD mortality rates across Europe and the US.

2. Underpinning research

WOSCOPS establishes the effectiveness of statins for primary prevention of CVD

A University of Glasgow research team (see below) conceptualised and led the ground-breaking West of Scotland Coronary Prevention Study (WOSCOPS). Published in 1995, the innovative WOSCOPS study was a clinically driven *primary prevention* randomised controlled trial (RCT): the researchers purposely targeted individuals with no history of heart attack who were apparently healthy yet were hypothesised to be at a high risk of having a heart attack in the near future based on their cholesterol levels.

Drawing on a wealth of experience in cholesterol metabolism research, the University of Glasgow team randomised 6,595 men (aged 45–64 years) with raised low-density lipoprotein cholesterol (LDL-C) levels (two consecutive measurements ≥4 mmol/L, one ≥4.5 mmol/L and one ≤6 mmol/L) to treatment with pravastatin or placebo and participants were followed for an average of 5 years. WOSCOPS showed that pravastatin reduced the risk of a first-time heart attack (myocardial infarction, MI) or death from coronary heart disease (CHD) by 31% and, importantly, the risk of death from any cause by 22%.[1] In contrast to previous cholesterol-lowering drugs, pravastatin was well tolerated. WOSCOPS therefore set the stage for statins as a safe primary prevention therapy for reducing CHD risk and provided conclusive evidence in support of the hypothesis that a raised blood cholesterol level is a modifiable risk factor for CVD. In testament to the importance of this study, the publication has received over 6,100 citations (Scopus, November 2013).

Statins provide long-term protective effects

A subsequent seminal study published by the University of Glasgow team in 2007 reported on the long-term benefits ('legacy effects') of pravastatin.[2] Follow-up of the WOSCOPS survivors 10 years after the completion trial revealed that the risk of heart attack or death from CHD remained lower in the pravastatin treated population. The results suggested that 5 years of statin therapy during the trial had slowed disease progression and resulted in on-going CVD risk reduction over the entire 15-year follow-up period.

Statins confer primary and secondary prevention among elderly populations

Whereas primary prevention seeks to reduce risk before disease develops, the goal of *secondary prevention* is to limit further episodes after an initial event has occurred. The pravastatin in elderly individuals at risk of vascular disease study (PROSPER, 2002) was a collaborative RCT led by the University of Glasgow.[3] The trial enrolled 2,804 men and 3,000 women aged 70–82 years who either had a history of CVD or were at increased risk of CVD due to raised cholesterol levels. Participants received pravastatin or placebo for 3 years. Pravastatin reduced the risk of the primary end point (coronary death, non-fatal stroke, non-fatal MI) by 15% thereby prompting the extension of prevention strategies with statins to include elderly individuals.

Statins are cost effective for primary prevention

The University of Glasgow extension of the WOSCOPS follow-up categorised the cause-specific reason for hospital admission and number of events in the 10 years post-trial to show the cost effectiveness of statin therapy (saving the NHS £710,000 over 15 years per 1,000 patients treated with pravastatin for 5 years).[4] By retrospectively assigning trial participants into three categories

based on their pre-trial CHD risk, the analysis revealed that statin therapy was beneficial and cost effective even among patients with the lowest pre-existing risk. The study further confirmed the protective legacy effect and long-term safety of statins in primary prevention.

Benefits of statins extend to other clinical scenarios

University of Glasgow investigators have gone on to further define the clinical utility of statins through major contributions to landmark multi-centre statin RCTs in patients without raised cholesterol. The ASCOT-LLA trial (2003; Professor Gordon McInnes, steering committee) examined the effect of atorvastatin in patients with high blood pressure, demonstrating a 36% reduction in coronary death and non-fatal MI in the atorvastatin group.[5] Furthermore, the JUPITER trial (2008; Professor James Shepherd, steering committee) demonstrated the value of statins in patients with elevated C-reactive protein (CRP) and no history of CHD. Patients treated with rosuvastatin showed a 54% reduction in MI and a 20% reduction in death from any cause[6], thereby confirming the benefit of statins in primary prevention as shown by WOSCOPS. Finally, the 2005 TNT trial (Shepherd, steering committee) randomised 10,001 men and women with a history of CHD to either 10 or 80 mgs/day of atorvastatin. The trial not only demonstrated that higher doses of atorvastatin were safe but that more intensive lipid lowering (80 mg/day) reduced CVD events by 22% versus conventional lipid lowering strategies (10 mg/day).

Key University of Glasgow researchers: WOSCOPS[1,2] – James Shepherd (Honorary Professor of Clinical Biochemistry [1977–present]); Stuart Cobbe (Walton Chair of Medical Cardiology [1985–2008], Honorary Senior Research Fellow [2008–present]); Ian Ford (Professor of Statistics/Biostatistics [1992–present]); Peter Macfarlane (Professor in Medical Cardiology [1991–1995]; Professor of Electrocardiology, [1996–2010]; Honorary Research Fellow [2010–present]); James McKillop (Muirhead Chair of Medicine [1974–2011]); Christopher Packard (Honorary Professor of Clinical Biochemistry [1993–2011]). PROSPER[3] – Shepherd and Packard (as above). Cost-effectiveness study[4] – Ford, Packard and Cobbe (as above); Alex McConnachie (Assistant Director of Biostatistics [2010–present]). ASCOT-LLA[5] – Gordon McInnes (Professor of Clinical Pharmacology [1980–2011]). JUPITER[6] and TNT – Shepherd (as above). ***Key collaborators:*** Members of the PROSPER, ASCOT-LLA, JUPITER and TNT Steering Committees; see original articles for details.

3. References to the research

1. WOSCOPS study group Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995; 333: 1301–1307 doi: 10.1056/NEJM199511163332001.
2. Ford I *et al.,* for the WOSCOPS Group. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med.* 2007; 357: 1477–1486 doi: 10.1056/NEJMoa065994.
3. PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360: 1623–1630 doi: 10.1016/S0140-6736(02)11600-X.
4. McConnachie A *et al.* Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J.* 2013 (published online Jul 9) doi:10.1093/eurheartj/eht232.
5. Sever PS *et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003; 361:1149–1158 doi:10.1016/S0140-6736(03)12948-0.
6. Ridker PM *et al.*, for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359: 2195-2207 doi: 10.1056/NEJMoa0807646.

4. Details of the impact

Statins are the preferred lipid-lowering drugs to prevent CVD

Current estimates suggest that more than 7,000 European and US adults die of CVD each day. Internationally recognised clinical trials conducted by the University of Glasgow have provided the cornerstone of the evidence base supporting lipid lowering as a strategy to reduce CVD risk. This landmark research drove the global adoption of statins as the first-line medical option for prevention of CVD and continues to shape modern day lipid-lowering guidance and practice worldwide, with associated benefits for patients and healthcare systems. Statins offer major

benefits for patient outcomes, including reduction in mortality and major CVD events.

Clinical guidelines support prevention strategies with statins

The University of Glasgow led/steering committee involvement in RCTs on lipid lowering[1,2,3,5,6] dominate the evidence base in current, high profile clinical guidelines on lipid lowering including the joint European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) and the American Association of Clinical Endocrinologists (AACE). These guidelines recommend statins as the cholesterol-lowering drug of choice.

2011 ESC/EAS guideline on the management of dyslipidaemias[a]

These state that '*not only should those at high risk be identified and managed; those at moderate risk should also receive professional advice regarding lifestyle changes, and in some cases drug therapy will be needed to control their plasma lipids*.' The guidelines also underscore the need to promote primary prevention efforts.

- Recommendations for the use of statins among patients who have been stratified according to CVD risk (*via* assessment with the ESC Systematic Coronary Risk Evaluation [SCORE] algorithm) and LDL-C level - WOSCOPS[1], PROSPER[3], ASCOT-LLA[5], JUPITER[6] and TNT are cited in the evidence base; Table 3 (p1780). In summary the ESC/EAS recommends immediate lipid-lowering intervention for all individuals at high risk (SCORE >5 but <10) with LDL-C levels ≥2.5 mmol/L or at very high risk (SCORE ≥10; LDL-C ≥1.8 mmol/L). Lipid-lowering may be considered in both groups at lower LDL-C levels and among low-risk and moderate-risk individuals with LDL-C levels uncontrolled by lifestyle intervention.
- ASCOT-LLA[5] and JUPITER[6] are two of three papers cited to support the following recommendation on primary prevention "*statin therapy should be considered for reducing the risk of ischaemic stroke and other CV events in accordance with the recommendations given in Table 3.*"

2012 AACE guideline on the management of dyslipidaemia and prevention of atherosclerosis[b]

- 'Lipid goals recommended for patients at risk of coronary artery disease' - PROSPER and ASCOT-LLA underpin five of these seven key recommendations including lowering LDL-C to less than 100 mg/dL (2.6 mmol/L) for all adults and below 70 mg/dL (1.8 mmol/L) for patients at very high risk (Grade A recommendation); p13-14 and Table 12.

Taken together, the ESC/EAS and AACE lipid management guidelines advise that adults with a 20% chance of developing CVD within a 10-year timespan should be offered a statin for primary prevention. Furthermore, statins are unequivocally recommended for individuals considered to be at very high risk; namely, patients with diabetes (if aged over 40 years), chronic kidney disease or peripheral arterial disease, as well as those who have previously experienced a CVD event. These recommendations on lipid lowering are also aligned in the major European and American guidelines on CVD prevention reinforcing the value of lipid lowering in disease prevention.

Cochrane Systematic Review

Despite the fact that there have been many subsequent clinical trials investigating statin use, the validity and profile of the seminal University of Glasgow studies in driving best practice for patient care remain undiminished. These trials are regularly included in meta-analyses, such as the Cochrane Systematic Reviews, which evaluate primary clinical research and are recognised as the gold standard for providing an evidence base for changing clinical practice. For example, a meta-analysis conducted by the Cholesterol Treatment Trialists (CTT) Collaboration, which was published in 2010 and utilised the University of Glasgow studies, was instrumental in changing the recommendations of the Cochrane Systematic Review on the use of statins for primary prevention of CVD (2013).[c] The 2013 evidence review stated: "*our previous conclusion urging caution in the use of statins in people at low risk of CV events is no longer tenable in light of the CTT Collaboration findings … these new findings counter earlier opinion that the evidence is insufficient to support use of statins in primary prevention for women or in older men.*" The 2013 Cochrane Systematic Review also cited WOSCOPS[1] and JUPITER[6] in the evidence base supporting this conclusion, with JUPITER[6] identified as one of four new studies included in the analysis.[c]

Primary prevention with statins provides benefits for patients

Reduced mortality

The WOSCOPS follow-up study[2] showed that primary prevention with statins exerted durable, long-term reduction in death rates. US estimates revealed that deaths as a result of CVD declined by approximately 33% from 1999 to 2009.[d] The 2013 American Heart Association heart disease and stroke statistics report[d] cites evidence that lipid lowering prevents or postpones around 24% of all deaths from CHD, equivalent to an 8.2% drop in deaths during the period 1999–2009 in the US.

Indicators of quality care

The Quality and Outcomes Framework (QOF) is an incentive scheme for GP practices in England providing financial rewards for patient care across multiple disease domains. Several of these QOFs focus on primary and secondary prevention with statins. For example, 74% of diabetes patients, 73% of patients with CHD and 68% of stroke patients received a statin to achieve total cholesterol levels at or below 5 mmol/L (April 2011–March 2012).[e] The fact that cholesterol levels are one of the best adhered to targets is testament to the community acceptance of the benefits of this approach.

Health checks

University of Glasgow research demonstrated that lipid lowering prevention strategies are valid tools for public health and initiatives are now in place worldwide to promote heart health. For example, the US Million Hearts programme (launched September 2011) has a stated goal to ensure effective implementation of lipid-lowering treatment on a population basis, from a baseline of 33% in 2011 to 65% by 2017.[f] Since March 2009, vascular risk assessment has been implemented in England through NHS Health Check. All adults aged 40–74 years without diagnosed CVD are invited for a health check once every 5 years for assessment of risk factors including cholesterol level. Personalised primary prevention advice based on the risk assessment is provided. In the period 2012–2013, around 1.3 million eligible adults attended assessments.[f]

Emergence of generic statins drives down cost of primary prevention

The detailed extension of the WOSCOPS follow-up[4] demonstrated that CVD prevention with statins had saved money for healthcare providers even at levels below the 20% risk of CVD listed in current clinical guidelines. The economic viability of statin use shown by this analysis attracted extensive media coverage, raising public awareness of this strategy.[g] More than 60 million statin prescriptions were dispensed in England alone in 2012, and the global statin market was valued at $20.5 billion in 2011. However, the increasing availability of generic formulations of statins is predicted to eat into this market.[h] Consequently, use of statins will become even more prevalent and cost effective for healthcare organisations.[4]

5. Sources to corroborate the impact

a. ESC/EAS guideline, 2011 WOSCOPS (ref 19), PROSPER (ref 26), ASCOT-LLA (ref 28), TNT (ref 33) and JUPITER (ref 37) cited in Table 3 (Section 3.2, p1779–1780) as 5 of 27 Level A evidence studies. Also cited on p1790 (section 7.1); p1802 (Section 10.4); p1805 (Section 10.7); and p1809 (Section 10.12)

b. AACE guideline, 2012. WOSCOPS[1] (ref 463), WOSCOPS follow-up[2] (ref 505), PROSPER[3] (ref 38), ASCOT-LLA[5] (ref 39) and JUPITER[6] (ref 338) cited. See Executive Summary (p13–14); Tables 12, 18, 20 and 21; and the evidence base (p22/23, 28/29, 32/34/39, 44/45/47/48 and 52)

c. Update to Cochrane Systematic Review, 2013. Cites CTT 2010 and CTT 2012a (p3–4, 13–14 and 87–94 [feedback summary]); WOSCOPS (p8, 12–13, 44 and 52–80); and JUPITER (p8, 11–13, 39 and 52–80)

d. American Heart Association heart disease and stroke statistics, 2013 (p110 and 187; reference, Table 2)

e. Quality and Outcomes Framework, 2011–2012. See diabetes (DM17) and coronary heart disease (CHD8) and stroke (STROKE8)

f. Health checks: Million Hearts (USA) and NHS Health Check (England)

g. Media coverage of primary prevention economic benefit: Herald, Reuters, Express, Scotsman

h. Media coverage of generic statins, 2011–2013: Cardiovascular Business, Forbes, Crain's New York Business, Philly.com