Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Statin Therapy: Patient Selection, Clinical Guidelines and revision of safety labelling

1. Summary of the impact

Over the past ten years, the prescription of cholesterol-lowering statins has soared and they are now the most prescribed drugs in the UK and the US. However, this has raised concerns about inappropriate prescribing. University of Glasgow research has been pivotal in addressing this issue and has triggered revision of major international guidelines to stratify patients in the general population for statin therapy and guide statin use in the rheumatoid arthritis patient population. The identification of a statin-associated risk for diabetes prompted the European Medicines Agency and the US Food & Drug Administration to revise safety labelling for all classes of statins. This risk is now communicated to the 27 million patients in the UK and US who are prescribed statins.

2. Underpinning research

Raised levels of cholesterol are linked to an increased risk of vascular disease, such as heart attack and stroke. The clinical benefit of cholesterol-lowering statins in reducing the risk of vascular disease has been demonstrated through a vast number of randomised clinical trials over the past 20 years. However these trials have been carried out with different patient populations, used different types of statin and yielded variable data relating to side effects. The University of Glasgow metabolic medicine group has expertise in conducting detailed meta-analyses of existing trial and cohort data to answer well-defined and clinically relevant questions.

Lipid levels can be measured non-fasting as a marker of vascular risk

Lipid levels have traditionally been measured in blood taken from patients who have fasted for 12 hours. However, there was widespread uncertainty as to which groups of lipids to assess and whether measuring fasting or non-fasting lipids made a difference to the accuracy of predicting vascular risk. University of Glasgow researchers, Prof Naveed Sattar and Prof Chris Packard were senior investigators in the Emerging Risk Factor Collaboration (ERFC) project, which examined individual records of 302,430 people without initial vascular disease from 68 long-term prospective studies (including two Glasgow trials) linking the results to over 10,000 cardiovascular events. Sattar and Packard provided essential clinical interpretation and analytical input to the results and strongly influenced the final conclusions of the paper. The results, published in *JAMA* in 2009[1], suggested that lipid assessment can be simplified by measuring the levels of either: (i) total cholesterol and a form of cholesterol called high-density lipoprotein cholesterol, or (ii) apolipoproteins (the protein part of the major forms of cholesterol) and that neither required measurement of another blood lipid, triglyceride. The key conclusion of the study was that patients do not need to fast to enable accurate prediction of their cardiovascular risk.

Statins safely lower cholesterol in rheumatoid arthritis patients

With the growing recognition in the mid to late 1990s that certain sub-populations had an increased risk of cardiovascular disease, University of Glasgow researchers Prof Iain McInnes, Prof Naveed Sattar and Prof Ian Ford conceived and undertook the first randomised trial of the use of a statin in patients with rheumatoid arthritis. This patient sub-population is at increased vascular risk because of chronic activation of their immune systems. The trial of atorvastatin in rheumatoid arthritis (TARA) was a double-blind, randomised, placebo-controlled trial that ran from 2000 to 2004 and was published in 2004 in *The Lancet*.[2] The statin not only lowered cholesterol in patients with rheumatoid arthritis, but it did so safely, with no adverse liver effects. In addition, the patients on atorvastatin seemed to experience an improvement in their rheumatoid-associated symptoms.

Statins are associated with a small but dose-dependent risk of diabetes

As trials examining whether statin use was associated with an increased risk of diabetes had provided mixed results, University of Glasgow staff Prof Sattar, Dr David Preiss and Prof Ford

designed and led an exhaustive meta-analysis that was published in *The Lancet* in 2010[3]. The collaborative multi-centre study collated all the available trial data (from 13 trials and more than 91,000 patients) and wrote an original analysis plan for seven of the trials for which new-onset diabetes data had been collected but not examined. The data were analysed to determine diabetes risk and showed that risk did increase with use of statins, albeit modestly (9% increased relative risk)[3]. Preiss and Sattar also led a meta-analysis of diabetes risk in five trials that compared the use of high doses of statins with the use of moderate doses. Published in *JAMA* in 2011, the investigators showed that higher dose statins increased diabetes risk more than statins prescribed at moderate doses, thereby indicating that the increased risk is dose-dependent[4]. Importantly, both studies concluded that the risk of statin-induced diabetes was low compared with the cardiovascular benefits of statins and that this should not affect the clinical practice of prescribing statins to individuals at increased risk of cardiovascular disease or those with existing disease.

Key University of Glasgow researchers: Naveed Sattar (Professor of Metabolic Medicine, 1999-present); Chris Packard (Honorary Professor [clinical biochemistry], 1993-present); Iain McInnes (Professor of Experimental Medicine, 1993-2010; Muirhead Chair of Medicine, 2010–present); David Preiss (Clinical Research Fellow, 2008-2012; Clinical Senior Lecturer 2012-present); Ian Ford (Professor of Biostatistics, 1998-present).
Key collaborators and roles: *ERFC members*: John Danesh (study supervisor), Emanuele Di Angelantonio and Nadeem Sarwar; all University of Cambridge (Sattar and Packard held writing committee positions). *Diabetes risk*: Kausik Ray, University of Cambridge (contributed equally to the study alongside Sattar, Ford and Preiss).

3. References to the research

1. Emerging Risk Factors Collaboration *et al.* Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009; 11;302(18):1993-2000. doi: 10.1001/jama.2009.1619
2. McCarey DW, *et al.* Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *Lancet* 2004; 19;363(9426):2015-21. doi:10.1016/S0140-6736(04)16449-0
3. Sattar N, *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 27;375(9716):735-42. doi:10.1016/S0140-6736(09)61965-6
4. Preiss D, *et al.* Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011; 22;305(24):2556-64. doi: 10.1001/jama.2011.860.

4. Details of the impact

Statins are one of the most widely prescribed medications in the world. In 2011 an estimated 27 million people in the UK and USA alone took statins to control their blood cholesterol levels. Whilst their clinical benefit in reducing the risk of vascular disease is irrefutable, there is a need for improved guidance on which patient populations should be given the drugs and for a better understanding of the side effects associated with statins.

Influencing clinical guidelines to stratify patients for statin therapy

University of Glasgow findings on the accurate assessment of baseline lipid levels, prescription of statins to patients with rheumatoid arthritis and diabetes as a potential side effect of statins (references 1-4 in section 2) have been cited as the leading evidence to support recommendations in a number of international clinical guidelines and consensus statements on statins published since 2008. These include guidelines from some of the most high-profile and influential organisations in the clinical arena, including the European Society of Cardiology (ESC; estimated professional membership of over 80,000), the European League Against Rheumatism (EULAR; encompassing 45 member societies throughout Europe) and the American Diabetes Association (ADA; the leading US diabetes organisation).

- *Cardiovascular risk assessment*: The 2011 joint ESC and European Atherosclerosis Society (EAS) guidelines on the management of dyslipidaemias[a] cite the 2009 ERFC study as the single evidence source to support their recommendation for the potential use of apolipoproteins as alternative markers to total cholesterol (and the high and low density forms) for assessing

cardiovascular risk. However, the paper clearly shows that apoproteins give equal but not superior information to routine lipids, an important clinical interpretation of the result.

- *Rheumatoid arthritis patients:* The 2010 EULAR guidelines on cardiovascular risk management in patients with rheumatoid arthritis[b] cite the 2004 TARA paper as part of the evidence base for recommendation number 7, which promotes the use of statins to address the increased cardiovascular risk in rheumatoid arthritis patients. There are an estimated 3 million adults living with rheumatoid arthritis in Europe and these guidelines form the first set of clinical recommendations in the world to direct statin allocation in this patient group.
- *Diabetes risk:* The ADA 2013 position statement on standards of medical care in diabetes[c], the International Atherosclerosis Society 2013 position paper on global recommendations for the management of dyslipidaemia[d] and the 2011 joint ESC/EAS guidelines on the management of dyslipidaemias[b] all cite the Glasgow 2010 *Lancet* and 2011 *JAMA* papers as the primary sources to acknowledge that statins carry a small, dose-dependent increase in diabetes risk. Each of these statements is in harmony with the Glasgow conclusions in recommending statin use given that the cardiovascular benefit far outweighs the diabetes risk. The impact of these statements highlights the diabetes risk to both physicians (who should now check glycaemia parameters before and after prescribing statins) and patients (who should be told that lifestyle changes will also help mitigate against any increased diabetes risk).

Directly motivating revised statin labelling and product information to inform patients of diabetes risk

In direct response to the 2010 *Lancet* paper, which demonstrated the small, dose-dependent increase in risk of diabetes in patients treated with statins, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both revised the mandatory labelling on all statin drugs.

- *FDA:* In February 2012, the FDA released a drug safety communication[e], noting reports of increased blood sugars and haemoglobin A1 in patients treated with statins with the Glasgow 2010 *Lancet* paper cited in the evidence base. Consequently, the adverse event labelling for statins was revised to include the potential for the drugs to increase the risk of diabetes; this information is distributed within every packet of statins prescribed in the US.
- *EMA:* The Glasgow 2010 *Lancet* paper was the catalyst for a joint EMA, Heads of Medicines Agencies and Pharmacovigilance Working Party review[f] of 130 publications which concluded that:
  '[Statins] may increase the risk of [new onset diabetes] in patients already at risk of developing this disease, but [that] overall the risk-benefit balance remains clearly positive ... A warning should therefore be included in the product information of all [statins] authorised in the EU ... The warning should state that patients at risk (i.e. those with fasting glucose 5.6 - 6.9 mmol/L, body mass index > 30 kg/m^2, raised triglycerides or hypertension) should be monitored both clinically and biochemically according to national guidelines.'
  In March 2012, the EMA formally endorsed these conclusions and implemented changes to add diabetes risk to the adverse reaction section of both the Summary of Product Characteristics (new class warning sections 4.4 and 4.8) and package leaflets (sections 2 and 4) for all statins[g]; the wording is also published on their website. This change in safety labelling is communicated to every recipient of statins in all 27 member states of the EMA.

Both the FDA and EMA qualified these amendments to safety labelling by advising that statins remain the recommended therapy for cholesterol lowering due to their overwhelming benefits on vascular risk reduction.

Informing patients and health professionals regarding statin-related diabetes risk

The changes to statin safety labelling have been communicated to both patients and health professionals via press release statements and media articles that coincided with the revised safety announcements in February 2012. The FDA published consumer safety announcements on their websites to raise patient awareness of the issue[h] and there was significant press coverage,

including that by Reuters and Medscape.[k,l] In the UK, the revisions to safety labelling were highlighted by the Medicines and Healthcare products Regulatory Agency (MHRA)[i] and added as a side effect in the current British National Formulary (BNF) lipid lowering section (2.12) on statins[j] to ensure that clinicians are informing patients appropriately.

Consequently, the slight increase in diabetes risk with statin therapy has highlighted the need for clinicians to monitor blood glucose and haemoglobin A1C levels in patients who are at high pre-existing risk of developing diabetes before and after commencement of statin therapy. Furthermore, it has emphasised the responsibility of patients to maintain lifestyle changes (diet, weight reduction and increased exercise) to mitigate this small risk while taking statins. These messages are now being widely disseminated to the clinical community.[m]

5. Sources to corroborate the impact

Clinical guidelines and consensus statements

a. ESC/EAS guidelines for the management of dyslipidaemias (2011): Recommendation for apolipoprotein measurements as alternative markers (reference 1 in section 2 is cited as reference 42, p1780&1782, Table 5) and recognition of increased diabetes incidence with statins but advocating their use (reference 3 in section 2 is cited as reference 101 in this paper).
b. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis (2010 [Online 2009]). (reference 2 in section 2 is cited as reference 78 on page 4, recommendation number 7*).*
c. ADA Position Statement: Standards of medical care in diabetes - 2013 *Diabetes Care* January 2013 36:S11-S66; Recognition of increased diabetes incidence with statins, while still advocating their use (reference 3 in section 2 is cited as reference 290).
d. International Atherosclerosis Society 2013 Position Paper: global recommendations for the management of dyslipidemia. Recognition of increased diabetes incidence with statins but advocating their use (references 3 and 4 in section 2 are cited on page 9).

Revised safety labelling for statins

e. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. 28 Feb 2012.
f. Pharmacovigilance Working Party. December 2011 plenary meeting. Monthly report issue no. 1112.
g. HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, pitavastatin, rosuvastatin) and safety the risk of new onset diabetes/impaired glucose metabolism. Agreed by PhVWP March 2012.
h. FDA Consumer health information. FDA expands advice on statin risks. Feb 2012
i. MHRA safety update. Statins risk of hyperglycaemia and diabetes. Drug Safety Update 5, issue 6 January 2012.
j. BNF lipid lowering information (login required, PDF available on request)

Media coverage of revised labelling for statins

k. Reuters. FDA adds diabetes, memory loss warnings to statins. Feb 28 2012
l. l. Medscape. FDA adds warnings to statin label Feb 28 2012
m. Goldfine AB. Statins: is it really time to reassess benefits and risks? *N Engl J Med.* 2012; 366(19):1752-5. doi: 10.1056/NEJMp1203020.