Institution: The University of Oxford

Unit of Assessment: 2

Title of case study

STATIN THERAPY FOR PREVENTING HEART ATTACKS AND STROKES

Summary of the impact

Studies coordinated by the University of Oxford's Clinical Trial Service Unit (CTSU) within the Nuffield Department of Population Health (NDPH) have strongly influenced the labelling of statin medication internationally, treatment guidelines, and the resulting changes in prescribing have contributed to reductions in mortality and morbidity from heart attack and ischaemic stroke in many countries. CTSU's randomised trials and meta-analyses of trials have shown that lowering low-density lipoprotein (LDL) cholesterol safely reduces the risk of heart attacks, strokes and revascularisation procedures in a wide range of people, and work conducted in collaboration with the NDPH's Health Economic Research Centre has provided clear evidence of cost-effectiveness of statins.

Underpinning research

CTSU's Heart Protection Study (HPS), which commenced in 1994 and included over 20,000 patients, showed that simvastatin 40mg daily reduced the risk of heart attacks, strokes, and the need for arterial revascularisation procedures in a wide range of people at high risk of cardiovascular disease [1]. At about the same time that the HPS began, CTSU set up a collaborative meta-analysis called the Cholesterol Treatment Trialists' (CTT) Collaboration, with the aim of providing more reliable information about the effects of lowering LDL cholesterol on vascular and non-vascular outcomes. The first CTT report in 2005 included data from around 90,000 patients in 14 randomised trials, and provided comprehensive information that has helped to guide the use of statin therapy internationally [2]. It showed that treatment with a statin reduces the risk of heart attacks, strokes and coronary revascularisation procedures, as well as the overall risk of death, in a wide range of patients at risk of cardiovascular disease. It also refuted previous concerns that statin therapy might increase the risk of cancer, and non-cardiovascular causes of death [2].

In 2010, CTSU published the results of its Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH] trial [3] comparing 80 mg versus 20 mg simvastatin daily among 12,000 heart attack survivors. It showed that simvastatin 80mg produced further reductions in major vascular events, but that the risk of myopathy was increased. In tandem with this publication, the CTT published a meta-analysis of the five major trials of intensive versus standard statin regimens (including SEARCH), showing that more intensive regimens yield additional benefits, and that this could be achieved safely with regimens other than simvastatin 80mg. [4]

Recently, there has been controversy over whether statins are effective for the prevention of first heart attacks and strokes in apparently healthy people. In 2012, however, the CTT published a meta-analysis showing definitively that the benefits of statin therapy clearly outweigh the hazards in people at low risk of cardiovascular disease [5].

In addition to its work on the CTT collaboration, CTSU has also provided the first reliable evidence that lowering cholesterol reduces the risk of heart attacks and strokes among kidney patients. Its Study of Heart and Renal Protection (SHARP) was the largest study of its kind, and included over 9000 kidney patients in 380 hospitals from 18 countries. This study showed that lowering cholesterol with the combination of a statin and a drug that blocks cholesterol absorption, ezetimibe can reduce heart attacks and strokes safely by about one quarter in kidney patients [6].

References to the research

[1]. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* **360**, 7–22 (2002). PubMed ID: 12114036. ***Primary paper from the Heart Protection Study, showing that simvastatin 40mg daily reduced the overall risk of death in a wide range of people at high risk of cardiovascular disease.***

[2]. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* **366**, 1267–1278 (2005). PubMed ID: 1621459. ***The first CTT study indicating that statins reduce the risk of heart attacks, strokes and coronary revascularisation. This study also showed that statin therapy does not increase the risk of cancer or non-cardiovascular causes of death.***

[3]. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010; 376: 1658–69. PubMed ID: 21067805. ***This trial demonstrated that larger reductions in cholesterol, with a regimen of 80 mg daily simvastatin, produced worthwhile further reductions in CHD compared with a standard 20 mg daily regimen.***

[4]. Cholesterol Treatment Trialists' (CTT) Collaboration *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* **376**, 1670–1681 (2010). PubMed ID: 21067804. ***A meta-analysis showing that more intensive regimens of statins yield additional benefits without any additional safety concerns.***

[5]. Cholesterol Treatment Trialists' (CTT) Collaborators *et al.* The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380**, 581–590 (2012). PubMed ID: 22607822. ***A meta-analysis showing definitively that the benefits of statin therapy clearly outweigh the hazards in healthy people.***

[6]. Baigent, C. Landray MJ, Reith C, *et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* **377**, 2181–2192 (2011). PubMed ID: 21663949. ***The SHARP study from NDPH provided the first reliable evidence that lowering cholesterol reduces the risk of heart attacks and strokes among kidney patients.***

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Details of the impact

Taken together, the CTSU's Heart Protection Study, Cholesterol Treatment Trialists' Collaboration, SEARCH and SHARP studies have shown that lowering low-density lipoprotein (LDL), or 'bad' cholesterol with a statin regimen, or a statin-based regimen, reduces the risk of heart attacks, strokes and revascularisation procedures in both high-risk and healthy people, and that more

intensive statin regimens lead to further reductions in risk. This work has influenced treatment guidelines and statin medication labelling internationally. Given the known benefits of statins on vascular mortality, and their widespread use, it is likely that CTSU's work has contributed to the continuing decline in vascular mortality that has been observed in developed countries over the past decade.

All the major national and international healthcare policy guidelines on cardiovascular disease prevention have been influenced by CTSU's work on cholesterol-lowering statin therapy. For example, the National Heart Lung and Blood Institute's (NCEP) ATPIII North American guidelines [A], which are the main guidelines used in the US, specifically refer to the Heart Protection Study results. The UK National Institute of Health and Care Excellence (NICE) guidelines on cardiovascular disease and statins [B], and European Society of Cardiology guidelines for the management of dyslipidaemias [C], refer to CTSU's trials (HPS and SHARP) as well as the CTT meta-analyses throughout. By providing unique information about the safety of simvastatin 80mg daily, the SEARCH study significantly influenced both FDA [D] and MHRA [E] guidance on prescription of statins.

The SHARP results provide definitive evidence for the efficacy and safety of a statin-based regimen for the prevention of atherosclerotic events among patients with chronic kidney disease. The Kidney Disease Improving Global Outcomes (KDIGO) group generates internationally recognised guidelines for the care of kidney patients, and a KDIGO Work Group (in which 5 of the 11 members were also members of the SHARP Steering Committee) has recently published updated guidance for the use of statin-based regimens that is based chiefly on the SHARP trial [F]. SHARP has also strongly influenced other guidelines, including the Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidaemia [G], most particularly by helping to identify CKD as an important risk factor for cardiovascular disease.

The NHS reports that there has been a 40% reduction in deaths from heart disease in people under 75 since 2000, and estimates that statins currently save around 7,000 lives a year in the UK [H]. CTSU's work on ensuring that statin therapy is used appropriately widely has undoubtedly contributed to this saving of lives during the REF 2014 period. Indeed, NICE guidance throughout the REF period recommended the HPS regimen of simvastatin 40mg as their first line treatment for cardiovascular disease prevention in high-risk patients [B]. Due to the major public health impacts of CTSU's research into the safety and benefits of statin use, this work has also been featured prominently both on the internet and in print versions of mainstream newspapers. Recent articles include publicity surrounding the CTT's work on the effects of reducing cholesterol among apparently healthy people, for example in the Daily Mail [I] and on the effects of more intensive statin regimens in the Daily Telegraph [J].

Sources to corroborate the impact

[A]. ATP 3 Cholesterol Guidelines, NHLBI. *nhlbi.nih.gov* at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf [Accessed 6th September 2013]
National Heart Lung and Blood Institute's (NCEP) ATPIII North American guidelines on statin use, published in 2002 and still current as of September 2013. See page II-61.

[B]. NICE Guidelines: Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. http://www.nice.org.uk/nicemedia/live/11982/40742/40742.pdf [Accessed 6th September 2013]
UK National Institute of Health and Care Excellence guidelines on lipid modification quote the CTT Lancet meta-analysis widely in their guidance. See pages 147, 168 (HPS), 166, 167, 168, 205, 206, 208 (CTT).

[C]. ESC/EAS Guidelines for the management of dyslipidaemias (2011) http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-dyslipidemias-FT.pdf [Accessed 6th September 2013].

The European Society of Cardiology guidelines for the management of dyslipidaemias. See pages 1792, 1806 (SHARP); 1783 (CTT)

[D]. US Food and Drug Administration website: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm [Accessed 31st October 2013]. ***This FDA guidance specifically refers to the SEARCH results in relation to the risk of muscle injury with high dose statins.***

[E]. Medicine and Healthcare products Regulatory Agency Drug Safety Update Volume 3, Issue 10, May 2010. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085169 [Accessed 31st October 2013]. ***This MHRA update comments on the implications of the SEARCH results.***

[F]. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease Kidney International Supplements (2013) 3, 261; doi:10.1038/kisup.2013.29 http://www.kdigo.org/clinical_practice_guidelines/pdf/LIPIDS/KDIGO Lipid GL.pdf [Accessed 5th November 2013]. ***The KDIGO guidelines are the main guidelines used internationally by nephrologists, and this update is based chiefly on the results of SHARP.***

[G]. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013 Feb;29(2):151-67. doi: 10.1016/j.cjca.2012.11.032. PubMed ID 23351925. ***These guidelines specifically refer to the SHARP results and highlight the important role of CKD as a significant CV risk factor.***

[H]. NHS Choices. Coronary Heart Disease-Treatment. http://www.nhs.uk/Conditions/Coronary-heart-disease/Pages/Treatment.aspx [Accessed 6th September 2013]. ***NHS Choices information page, reporting statistics about reduction in Coronary Heart Disease and statin use in the UK.***

[I]. 'All over-50s should take statins regardless of their health history,' says Oxford professor | Mail Online 2012. *dailymail.co.uk* at http://www.dailymail.co.uk/health/article-2194892/All-50s-statins-regardless-health-history-says-Oxford-professor.html [Accessed 6th September 2013]. ***Daily Mail article about CTSU's statin research featuring an interview with Rory Collins.***

[J]. More potent statins 'could save thousands' - Telegraph 2010. http://www.telegraph.co.uk/health/8117635/More-potent-statins-could-save-thousands.html [Accessed 6th September 2013]. ***Daily Telegraph article about CTSU's statin research featuring an interview with Colin Baigent.***