Institution: University of Oxford

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

Title of case study: Increasing the intensity of cholesterol-lowering treatment to optimise cardiovascular risk reduction in high-risk populations

Period when the underpinning research was undertaken: 2000-2016

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Jane Armitage	Professor of Clinical Trials and Epidemiology	September 1990- present
Colin Baigent	Professor of Epidemiology	October 1991 – present
Louise Bowman	Professor of Medicine and Clinical Trials	September 2000 - present
Rory Collins	Professor of Epidemiology and Medical Statistics	August 1981 - present
Jonathan Emberson	Professor of Medical Statistics and Epidemiology	September 2004 – present
Martin Landray	Professor of Medicine and Epidemiology	November 2000 – present
Christina Reith	Senior Clinical Research Fellow	November 2004 - present

Period when the claimed impact occurred: September 2013 – December 2020

Is this case study continued from a case study submitted in 2014? Yes

1. Summary of the impact

Hundreds of millions of people globally are taking and benefitting from statins to lower their cholesterol. University of Oxford-led research has shown that lowering LDL cholesterol is effective for a wide range of patients, largely irrespective of age, sex, clinical features, and disease history, that 'lower is better', and that the benefits of statins greatly outweigh their known hazards. This work has had a major impact on international guidelines, in which it has informed the use of lower treatment targets for LDL cholesterol, and has led to wider use of statin therapy, including in vulnerable populations, such as those with chronic kidney disease. This has led to changes in prescribing practice internationally. The work has also drawn attention to misinformation about the safety of statins, and this has been widely viewed in news and social media, further enhancing statin uptake and lowered population LDL cholesterol levels.

2. Underpinning research

Over the past two decades, University of Oxford researchers have coordinated large randomised trials and meta-analyses of individual patient data from randomised trials that have collectively demonstrated the efficacy and safety of statin regimens for reducing the risk of cardiovascular disease. Their research strategy has been to extend the evidence on cholesterol-lowering therapy in two ways: first, seeking to provide evidence that 'lower is better' so that, for high-risk patients, an appropriate strategy for reducing risk would be to pursue the lowest possible LDL cholesterol levels; and secondly, seeking to extend the range of high-risk patients for whom cholesterol-lowering therapy is used, thus ensuring that all patients who might benefit from such treatment are able to do so.

i. Evidence that 'lower is better':
Since 1995, the University of Oxford has led the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analyses of statin trials, and a series of major papers has shown that statins

reduce the risk of major cardiovascular events (heart attacks, strokes or revascularisation procedures) in a wide range of high-risk patients, largely irrespective of age, sex, clinical features, and disease history. The earliest CTT analysis showed that the magnitude of the relative risk reduction in cardiovascular events in individual trials of statin versus placebo was proportional to the absolute reduction in LDL cholesterol [1], suggesting that more intensive statin regimens would be more effective in reducing major cardiovascular events for individual patients than standard regimens. In order to test this hypothesis, in a direct randomised comparison, University of Oxford researchers conducted the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial [2], which compared simvastatin 80mg daily with simvastatin 20mg daily, and the subsequent CTT meta-analysis that combined SEARCH with 4 other similar trials [3] confirmed that more intensive statin regimens are more effective in reducing major cardiovascular events than less intensive regimens (that is, 'lower is better') for a wide range of high-risk patients. Their in-depth review in 2016 showed clearly the benefit of statins for a wide range of populations and provided a systematic summary of the available data on the safety of statins from randomised trials, which was reassuring and showed that the benefits greatly exceed the risks [4].

ii. Extending the range of treated patients:
In addition to the work in the CTT, University of Oxford-led collaborations have conducted additional randomised trials to demonstrate that lowering cholesterol is effective in high-risk populations not previously studied [4]. Patients with chronic kidney disease were one such group known to be at increased risk of cardiovascular disease, but where there was uncertainty about the efficacy and safety of cholesterol-lowering. In particular, there was a concern that high statin doses may increase the risk of myopathy in such patients owing to reduced renal drug clearance. University of Oxford researchers were the first to test the concept of maximising the potential LDL cholesterol reduction whilst minimising drug toxicity by combining a standard dose of a statin with the cholesterol absorption inhibitor ezetimibe. The Study of Heart and Renal Protection (SHARP) trial [5] demonstrated conclusively among 9,438 patients with Chronic Kidney Disease (CKD) that this regimen was safe, and that it reduced the risk of major cardiovascular events to the same extent as had been observed in other high-risk populations. In addition to pioneering the use of cholesterol-lowering treatment in neglected and vulnerable patients with CKD, in order to maximise the potential benefit of statin therapy, new research in the CTT has also extended the meta-analytic evidence of efficacy and safety of statin therapy to other populations where there has been therapeutic uncertainty, including in primary prevention, the elderly, and women [6].

3. References to the research

1. Cholesterol Treatment Trialists' (CTT) Collaboration (2005). *3 out of 11 members of the writing committee were from University of Oxford:* **Baigent C, Peto R,** and **Collins R**. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366: 1267-78. DOI: 10.1016/S0140-6736(05)67394-1
2. Cholesterol Treatment Trialists' (CTT) Collaboration (2010). *5 out of 11 members of the writing committee were University of Oxford:* **Baigent C, Emberson J, Reith C, Peto R,** and **Collins R.** 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: 1670–81. DOI: 10.1016/S0140-6736(10)61350-5
3. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group (2010). All 9 members of the writing committee were from University of Oxford, including **Collins R, Armitage J, Bowman L, Parish S, Peto R.** 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* 376: 1658–69. DOI: 10.1016/S0140-6736(10)60310-8

4. **Collins R** et al (*28 authors of which 8 from University of Oxford, also including* **Reith C, Emberson J, Armitage J Peto R** and **Baigent C**) (2016) Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 388: 2532-61. DOI: 10.1016/S0140-6736(16)31357-5

5. **Baigent C** et al (*50 authors, of which 19 from University of Oxford, also including* **Landray MJ, Emberson J, Armitage J, Reith C and Collins R**) (2011). 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* 377:2181-92. DOI: 10.1016/S0140-6736(11)60739-3

6. Cholesterol Treatment Trialists' (CTT) Collaboration (2015). *6 out of 19 members of the writing committee were from University of Oxford, including* **Emberson J, Reith C, Collins R,** and **Baigent C**. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials *Lancet* 385: 1397-1405. DOI: 10.1016/S0140-6736(14)61368-4

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4. Details of the impact

The REF2014 case study described the impact on national and international guidelines on cardiovascular disease prevention from research up to 2011 [1,2,3,5]. New guidelines issued during the REF2021 period continue to draw on this work and be informed further by newer research [4,6], and the effects of these changes have been seen in prescribing practice and service quality standards. In particular, the CTT work has provided a unique and continuously evolving summary of the evidence for additional benefits of lowering cholesterol to very low levels, and as a result has helped to drive target cholesterol levels progressively lower in successive iterations of international guidelines during that period. In Europe, for example, whilst the 2016 guidelines recommended a target of 1.8 mmol/L for LDL cholesterol in very-high-risk patients, the most recent iteration in 2019 [A] lowered this target to 1.4 mmol/L with explicit reference to the work of the CTT.

Change in clinical guidelines

Clinical guidelines have changed substantially based on findings from the Cholesterol Treatment Trialists' (CTT) Collaboration and the Oxford-led randomised trials that higher statin doses yield larger reductions in major cardiovascular events. For example, the 2014 NICE lipid modification clinical guidelines [B] recommended that atorvastatin 20mg daily is used for primary prevention for those with expected risk ≥10% of developing cardiovascular disease (CVD) over 10 years, and atorvastatin 80mg is considered for use in secondary prevention. This compares to the previous NICE recommendation (in 2008, referenced in REF2014 case study) to use simvastatin 40mg daily (which produces less reduction in LDL cholesterol than atorvastatin 20mg daily) in both primary and secondary prevention. Internationally, including in Europe [A] and in the US [C], the evidence that 'lower is better' provided by the CTT over the past decade has resulted in recommendations that high-dose statin regimens are used to meet lower LDL cholesterol targets.

For example, in the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines on the management of dyslipidaemia, the key recommendation for pharmacological LDL-lowering therapy was: *'It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk'* [A] with level of evidence 'A' (that is, supported by meta-analyses of randomised trials, with the 2010 CTT Lancet paper [2] specifically cited).

Similarly, in the 2018 US Guideline on the Management of Blood Cholesterol, the recommendation was: *'In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a*

maximally tolerated statin to lower LDL-C levels by ≥50%' [C]. Throughout that document, the CTT is cited specifically to justify recommendations. For example, on page 1092, it is stated that: '*The writing group used primarily the Cholesterol Treatment Trialists' (CTT) meta-analysis of statin RCTs plus 4 other RCTs*' [2,4], and there are further citations of the CTT to support recommendations for people with diabetes [2] (page 1099), to support recommendations for statins in women [6] (page 1114) and to support recommendations that statins are used for patients with CKD [5] (page 1115).

Altered prescribing practice
There has been a clear shift towards prescribing higher intensity statin therapy in response to more stringent targets. For example, a retrospective cohort study using data from all 8,142 standard NHS general practices in England showed that the proportion of statins prescribed which produced LDL-lowering below the NICE-recommended 40% threshold, fell from 80% in 2011/12 to 45% in 2019 [D]. In the United States, an assessment of trends in statin therapy for secondary prevention of atherosclerotic CVD in US adults reported that the use of high intensity statin therapy approximately doubled over the period 2007-2016 [E].

Effective and safe cholesterol lowering in patients with chronic kidney disease (CKD)
The SHARP trial [5] showed that lowering LDL cholesterol reduces cardiovascular risk in patients with CKD, and remains the sole randomised trial providing evidence for the efficacy and safety of lowering LDL cholesterol in this population. The SHARP trial validated the concept of combination therapy with a statin and ezetimibe in patients for whom the statin dose cannot be increased (whether for safety reasons, or because statins are not tolerated). The SHARP trial was cited as supporting evidence for the National Institute for Health and Care Excellence (NICE) Guidelines on Lipid Modification in 2014 [B]. This brought in a new recommendation that cholesterol-lowering treatment is provided by *"atorvastatin 20mg for the primary or secondary prevention of CVD in people with CKD*", with the guidelines noting that "*the evidence base for the use of statins in people with CKD stages 3b to 5 is the SHARP trial*". This led to a new NICE quality standard in 2017 [F], which stated that all adults with CKD stage 3-5 should be offered atorvastatin 20mg. Within three years of the 2014 change in NICE guidance on statin use in patients with CKD, 69% of such patients were taking a statin [G].

SHARP is also cited as the main source of evidence for cholesterol-lowering in patients with CKD stage 3-5 in the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease - the main guideline followed by nephrologists internationally [H]. Furthermore, SHARP is also cited to support the use of statin therapy in the 2018 US Guideline on the Management of Blood Cholesterol [C].

Reduction in mean population levels of LDL cholesterol
The net effect of wider use of statin therapy worldwide, as well as – in recent years – the increasing use of high-intensity statin regimens and ezetimibe, has been to reduce mean population levels of LDL cholesterol and non-HDL cholesterol. A recent publication [I] estimated that in 2017, high non-HDL cholesterol (which is strongly correlated with LDL cholesterol) was responsible for 3,900,000 deaths from CHD and ischaemic stroke. It also estimated that about half of the reduction in non-HDL cholesterol occurring in high-income countries from 1980 to 2018 was due to the use of LDL-lowering therapy, chiefly statins.

Changing public perceptions and dialogue
The publication of all of CTT's main papers has been accompanied by major media coverage, and University of Oxford researchers have played a major role in informing the public about the efficacy and safety of statins. For example, the publication of the in-depth review [4], which summarised the work of the CTT of statins and provided new data on the safety of statins, was accompanied by major international media coverage and attracted substantial interest from the public – as reflected by over 40 mentions in news media and in over 1,600 mentions in social media [J]. University of Oxford researchers have been prominent in making the case for the safety of statin therapy, and in drawing attention to the negative consequences of misinformation about statin safety deriving from non-randomised and non-blinded studies [K].

5. Sources to corroborate the impact

A. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal* 2020; 41: 111–188. DOI: 10.1093/eurheartj/ehz455

B. NICE Clinical Guideline CG181. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline: Methods, evidence and recommendations. July 2014. https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-pdf-243786637.

C. Grundy SM, Stone NJ, Bailey AL et al. (2018) AHA/ACC/AACVPR/AAPA/ABC /ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 139:e1082–e1143. DOI: 10.1016/j.jacc.2018.11.003

D. Journal article: Curtis HJ, Walker AJ, MacKenna B, Croker R, Goldacre B (2020). Prescription of suboptimal statin treatment regimens: a retrospective cohort study of trends and variation in English primary care. *Br J Gen Pract* 70 (697); DOI: 10.3399/bjgp20X710873.

E. Journal article: Yao X, Shah ND, Gersh BJ et al. (2020) Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Network Open* 3(11):e2025505. DOI: 10.1001/jamanetworkopen.2020.25505.

F. NICE quality standard (QS5) for statins in CKD, (2011, updated July 2017). https://www.nice.org.uk/guidance/qs5/chapter/Quality-statement-3-Statins-for-people-with-CKD

G. National Chronic Kidney Disease Audit: National Report (Part 1) January 2017. https://www.lshtm.ac.uk/files/ckd_audit_report.pdf

H. Kidney Disease: Improving Global Outcomes (KDIGO). Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (CKD) November 2013. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2013-Lipids-Guideline-English.pdf.

I. NCD Risk Factor Collaboration (NCD-RisC). Repositioning of the global epicentre of non-optimal cholesterol. Nature 2020; 582: 73-7 DOI: 10.1038/s41586-020-2338-1

J. PlumX Metrics on *Interpretation of the evidence for the efficacy and safety of statin therapy* (Lancet 2016) https://plu.mx/plum/a/?doi=10.1016/S0140-6736(16)31357-5

K. Examples of media coverage for research on the safety of statin therapy: i) BBC News 08/09/16 ii) The Daily Telegraph 08/09/16 iii) The Guardian 08/09/16 iv) Daily Mirror 08/09/16 v) Daily Mail 09/09/16 vi) Sky News 09/09/16 vii) The Times 09/09/16.