More clarity needed on the true benefits and risks of statins

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The benefits and risks of statins have recently been the subject of much controversy and debate. Dr Malhotra and colleagues argue that selective reporting and publication bias may be overestimating the efficacy and underestimating the side-effects of statins.

A recent paper in *The Lancet* concluded that the benefits of statins significantly outweigh any potential harms.[1] Former medical director of the British Heart Foundation Peter Weissberg described the review as a "masterclass in how evidence should be interpreted".[2] A subsequent *Daily Mail* headline stated: "Statins ARE safe and we should give them to six million more people."[3] But is this true? After closer scrutiny of the evidence, we believe the *Lancet* paper is misleading.

The stated purpose of the *Lancet* review is "to help clinicians, patients and the public make informed decisions about statin therapy for the prevention of heart attacks and strokes." We applaud this goal. Unfortunately, in our opinion the review authors undermined the purpose of their review by relying on a *post hoc* (open to significant bias) composite endpoint they call "major vascular events", which includes heart attack and stroke but adds in revascularisation procedures. These are regarded at best as "soft endpoints" because decisions about diagnosis and treatment are affected by patient low-density lipoprotein (LDL) cholesterol levels – lower in the statin-treated group. Furthermore, coronary stenting for stable disease (the overwhelming majority of revascularisation procedures) does not prevent myocardial infarction or improve prognosis, which makes the inclusion of this endpoint both clinically and scientifically questionable.

With regard to the benefit of statin therapy for healthy people, the *Lancet* review said:

"The absolute benefits of statin therapy depend on an individual's absolute risk of occlusive vascular events and the absolute reduction in LDL cholesterol that is achieved. For example, lowering LDL cholesterol by 2mmol/L (77mg/dL) with an effective low-cost statin regimen (*eg* atorvastatin 40mg daily, costing about £2 per month) for five years in 10,000 patients would typically prevent major vascular events from occurring in about… 500 patients (*ie* 5 per cent absolute benefit) who are at increased risk but have not yet had a vascular event (primary prevention)."[1]

This statement seems to be based on the authors' opinions and belief rather than scientific evidence. The clinical studies included in the Cholesterol Treatment Trialists' (CTT) meta-analysis upon which this claim is based did not achieve even half that level of cholesterol reduction in people whose risk of heart attack or stroke is less than 20 per cent over the next five years.[4] So there is no scientific evidence for the magnitude of benefit of 2mmol/L reduction in a low-risk population; the estimates are based on projections, not fact. The actual data from the 2012 CTT meta-analysis show that the absolute reduction in heart attack and stroke for people in the 5–10 per cent five-year risk group is one-fifth of that stated in the *Lancet* review: 100 people must be treated with a statin for five years to prevent one heart attack or stroke. This small absolute benefit does achieve statistical significance. But from a clinical point of view, there was not a significant reduction in all-cause mortality[5] (the first "main question" prespecified in the protocol for the CTT meta-analysis[6]), and there was no reduction in overall serious illness ("serious adverse events"), so there was no overall net health benefit associated with statin therapy in this population.

Furthermore, it would seem that this re-analysis of the data presented in the 2012 CTT meta-analysis relies on unverified data. The CTT has received patient-level data from most major statin trials that must be held in "strict confidence". Only the drug companies, trialists and CTT have had access to the primary data, meaning medical journal editors, peer reviewers, Cochrane reviewers and even guideline writers have had to rely on unverified analyses of almost exclusively commercially funded clinical trials. The time is long past for the underlying data to be made available for independent analysis, so the public can receive the full benefit of medical science regarding statins and other cholesterol-lowering medication.

Is the cholesterol hypothesis flawed?

Following earlier incidents with the COX-2 inhibitors rofecoxib (Vioxx, which was voluntarily withdrawn from the market in 2004) and celecoxib (Celebrex) (the published results of a key rofecoxib safety study omitted three heart attacks in rofecoxib-treated patients,[7] and the published results of a key celecoxib safety study reported six months of data when the study lasted for 12 months),[8] new clinical trial regulations were implemented by health authorities in Europe and the USA in 2004–2005 in order to bring greater transparency in registering the main features of randomised controlled trials (RCTs), including the dates of initiation and termination. This implies that the published results of RCTs conducted before 2004–2005 are at best selective and therefore may be less reliable.

The cholesterol-lowering medications that have been tested following the 2004–2005 regulations in four RCTs that included a large proportion of patients with cardiovascular disease – namely CORONA, GISSI-HF, AURORA and IMPROVE-IT – all failed to show a clinically significant benefit in secondary prevention despite significant reductions in cholesterol with rosuvastatin or with ezetimibe added to simvastatin. Contrary to popular belief, the well-cited JUPITER trial testing rosuvastatin against placebo in primary prevention revealed no reduction in cardiovascular mortality and the US Food and Drug Administration (FDA) did not allow the small difference in overall mortality to be incorporated into the label.[9]

Failure to replicate data is a red flag that original research findings may be false. Earlier this year, a double-blinded RCT of 12,000 patients was stopped after a novel cholesterol-lowering drug, the cholesteryl ester transfer protein (CETP) inhibitor evacetrapib, failed to improve any cardiovascular outcomes in high-risk patients despite an average reduction in LDL cholesterol of 37 per cent.[10] This was in fact the confirmation of a previous trial (ILLUMINATE) testing another anti-CETP drug added to a statin in secondary prevention. Torcetrapib induced a 25 per cent reduction in LDL cholesterol compared with patients taking the statin only but had no cardiovascular benefits, rather an increased overall mortality rate.[11]

In addition, the lack of improvement in any hard outcomes from dietary RCTs that lowered LDL cholesterol and a lack of an association between LDL cholesterol and cardiovascular disease in those over 60 years in a recent systematic review suggests that the conventional cholesterol hypothesis is fundamentally flawed.[12]

This may be explained by selective reporting and publication bias. Taking many of these points into consideration, one internationally renowned cardiologist and statin expert, Professor Darrel Francis recently openly remarked when he spoke at a CPD-accredited statin debate in BMA House that he didn't know the mechanism for how statins benefited patients, and that their cholesterol-lowering effects "could be a massive coincidence."[13]

Intense controversy over side-effects

The true rate of statin side-effects that interfere with quality of life has been the subject of intense controversy. The recent *Lancet* review concluded that symptomatic adverse effects, *eg* muscle pain or weakness, occur in between 1 in 100 and 1 in 200 patients treated with statins for five years.[1] Its lead author Professor Rory Collins of the University of Oxford launched a very public campaign in 2014 calling for the retraction of two articles published in the *BMJ* questioning the use of statins in people at low risk of heart disease, which he said had overestimated the risk of side-effects "by more than 20 times".[14]

Within just one week of publication of the recent *Lancet* paper, an error in the supporting editorial[15] by its editor-in-chief Richard Horton was pointed out by the *BMJ* in a press release.[16] Horton had suggested that the Committee on Publication Ethics (COPE) had declined to act on a complaint made by Professor Collins regarding the editor of the *BMJ*'s handling of the two papers. In fact COPE carried out a thorough review of the complaint and concluded that the *BMJ* "acted appropriately" in its handling of the articles by Abramson and Malhotra, which had been corrected in reference to the rate of side-effects.[17]

Professor Collins initially raised his concerns in *The Guardian* newspaper stating: "there are only one or two well-documented [problematic] side-effects." Myopathy or muscle weakness occurred in one in 10,000 people, he said, and there was a small increase in diabetes.[18]

Having published several major statin studies and four of the CTT meta-analyses, is the *Lancet* able to be objective? *The Lancet* also published the Heart Protection study in 2002 where 36 per cent of screened patients were excluded before the trial even began.[19] This had the potential to screen out many patients who may have suffered from adverse effects from simvastatin, including muscle symptoms. Professor Collins was the principal investigator.

A *Sunday Times* investigation in September 2016 uncovered that Professor Collins filed a patent in 2009 for a test that identifies a gene that makes patients more likely to suffer muscle pain with statins.[2] The test, branded as StatinSmart, had until recently been sold directly to the consumer in the USA on a website that claimed up to 29 per cent of statin users will suffer muscle pain, weakness or cramps. Although Professor Collins said the 29 per cent figure was "misleading", Boston Heart Diagnostics, the American company granted an exclusive licence for Collins's patent, stood by its claims. It cited a US task force on statins safety that concluded randomised controlled trials "had major limitations" because patients with side-effects were often excluded.[20]

In conclusion, we believe that unless access to the raw clinical trial data is released, any claims about the true efficacy and harms of statins cannot be considered to be evidence based.

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Declaration of interests

Dr Abramson serves as an expert in pharmaceutical litigation, which includes statins. The remaining authors have no relevant interests to declare.

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