A recent widely publicised Lancet review of statin efficacy and safety data generated more controversy than it resolved. \(^1\) Led by Professor Rory Collins of Oxford University, the review claimed that the benefits of statins have been underestimated and the risks exaggerated. Claims of statin intolerance in up to 20% of patients, the review argues, are not supported by large-scale evidence from randomised trials. In fact, Collins et al. claim that statin therapy is no less well tolerated than placebo.

Collins further claimed that the controversy about statin intolerance and myopathy rates emerged only in the past 2 or 3 years as manufacturers began marketing newer and “very expensive” cholesterol-lowering agents, such as, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for patients classified as statin intolerant. He also pointed out that industry has funded reports on statin intolerance, as in the case of the European Atherosclerosis Society’s report\(^2\) which, not only had funding from makers of PCSK9 inhibitors, but also had its meetings coordinated by a commercial entity funded by the manufacturers.

Collins claimed that one could expect that 5 years of a statin regimen that lowered LDL cholesterol by 2 mmol/L would prevent major vascular events in about 1000 of 10,000 secondary-prevention patients and about 500 of 10,000 primary-prevention patients, with a bigger benefit to be expected with lifelong statin use. Moreover, he added, whereas many of the adverse effects (such as myopathy) can be reversed with no residual ill-effects by stopping the statin, the effects of a heart attack or stroke are often irreversible.

Dr Harlan Krumholz (Yale University), commenting on the review in the BMJ,\(^3\) said that while the findings strongly support the benefits of statins in comparison to modest risks, there is little consideration of the limitations of the trial evidence, most notably a lack of robust data on elderly patients, individual trials whose design prevented detection of many relevant harms, and inconsistent methods for adverse event data collection.

A vocal critic of the review, and an author of one of the 2013 BMJ papers,\(^4\) Dr Aseem Malhotra (Lister Hospital, Stevenage, UK) claims that the Clinical Trials Service Unit at Oxford has received hundreds of millions of pounds in funding from statin manufacturers and that Collins’s group has not released raw data on the major statin randomised controlled trials for independent scrutiny. He adds that by using predominantly industry-sponsored trials designed for the purpose of determining the benefits of statins but minimising side-effects, this review simply adds false precision to biased estimates. He also noted that Pfizer’s own patient leaflet on atorvastatin states that common side-effects possibly affecting up to one in 10 people include sore throat, nausea, digestive problems, muscle and joint pains.

Malhotra has also co-authored a recent systematic review revealing that in those patients over age 60, LDL cholesterol is not associated with cardiovascular disease and is inversely correlated with LDL cholesterol.
with all-cause mortality. He is quick to admit that statins have a benefit, but adds that focusing on LDL lowering as if this was the end in itself is counterproductive, especially when insulin resistance is a more important risk factor for myocardial infarction. He concludes that in his view, the Lancet review is a total whitewash, and agrees with the BMJ’s editor-in-chief, Fiona Godlee, who described it as “the trialists making their own homework”.

It turns out that Godlee and Collins have been at odds ever since Collins called on the BMJ to correct and ultimately withdraw the two 2013 studies that repeated claims made in a paper by Abramson et al. that side-effects of statins occur in 18% to 20% of people. The BMJ corrected the statements in the two studies, but Godlee passed the decision, on whether to retract, on to an independent expert panel, which rejected Collins’s request for retraction in June 2014. In October 2014, Collins and other co-authors of the new Lancet review, sent a letter of complaint about the BMJ’s handling of the two papers to the UK’s Committee on Publication Ethics (COPE). In April 2016, COPE determined that the BMJ acted with due diligence and in line with the expectations under the COPE Code of Conduct.

The Lancet editor-in-chief Dr Richard Horton, however, in a comment accompanying the statin review, calls into question the independence of the JOG-appointed panel’s judgement, noting that the chair had previously written critically about statin use among older patients. Horton observed that more than 200,000 patients were estimated to have stopped taking a statin in the 6 months after adverse media coverage following publication of the disputed research, and drew parallels between “this statin scare” and the MMR vaccine scare that began with a now-retracted research paper that had led to widespread vaccine hesitancy.

Horton’s comment about COPE’s conduct prompted Godlee’s rapid response letter of 14th September 2016, that COPE did not decline to act but deliberated on the concerns raised by Collins et al., and on the BMJ’s response, and came to a clear conclusion that the BMJ had acted appropriately. Godlee has also written to England’s chief medical officer asking for an inquiry into the statins saga and for an independent review of the evidence on statins. She claims that an independent third-party scrutiny of the statins trial data remains an essential next step if this increasingly bitter and unproductive dispute is to be resolved.

**Take Home Messages**

1. Apart from the above claims of drug-company funding and dubious research quality, the Lancet review in question, penned by several professors of medicine and cardiology, is flawed for at least another two reasons. One is the fact that all the data is based on routine LDL measurements. Previous instalments in this Synapse series have put forward evidence for LDL having two biologically different sub-fractions – a large light particle LDL and a small dense particle LDL – with only the latter being related to atherosclerosis. Routine LDL measurements do not indicate whether moderately raised LDL is due to a raised large or small sub-fraction. The surrogate marker for a raised small LDL sub-fraction is raised triglyceride (TRG) combined with low HDL – the higher the TRG/HDL ratio, the higher the risk for atherosclerotic disease.

2. Another flaw in the review is the persistent belief that the benefit of statins is via their blood lipid-lowering action. It is now well-established that the essence of atherosclerosis is an inflammatory disease of arteries. Statins are now recognised to be potent anti-inflammatory-cytokine agents, and their clinical benefit is mainly via this anti-inflammatory route. The high-sensitivity C-reactive protein (HsCRP) is the other valuable measurement of possible atherosclerotic inflammatory activity, particularly when combined with the TRG/HDL ratio.

3. As pointed out above by Dr Aseem Malhotra, insulin resistance (chronic hyperinsulinaemia) is a more potent indicator of myocardial infarction risk than LDL. This has been highlighted in a previous instalment of this Synapse series, which also pointed out that the TRG/HDL ratio is a surrogate marker for insulin-resistance/hyperinsulinaemia. Some private laboratories in Malta will be adopting the TRG/HDL ratio and the HsCRP as the main markers of atherosclerotic activity risk.

**References**