

Safety and efficacy of statins

The 2016 Review by Rory Collins and colleagues (Nov 19, p 2532),¹ of evidence about the efficacy and safety of statin therapy, claims that the 2012 Cholesterol Treatment Trialists' (CTT) meta-analysis shows that "lowering LDL cholesterol by 2 mmol/L (77 mg/dL) with an effective low-cost statin regimen (eg, atorvastatin 40 mg daily) for 5 years in 10 000 patients would typically prevent major vascular events from occurring in...500 patients (ie, 5% absolute benefit) who are at increased risk but have not yet had a vascular event (primary prevention)". There are major problems with this claim.

First, "major vascular events" (a composite of coronary deaths or myocardial infarctions, strokes, and coronary revascularisation procedures) is twice prohibited by the CTT's 1995 protocol:² it was not a prespecified endpoint, and the CTT meta-analysis applied it to data that had already been unblinded. About a third of the events in this combined endpoint are revascularisation procedures,³ the frequency of which can be influenced by patients' LDL levels—which are lower in patients treated with statins than in those treated with placebo—that effectively unblind treatment allocation and affect diagnostic and treatment decisions.⁴ In the 1995 CTT protocol, total mortality was the first main question to be addressed. Thus, any discussion of "major vascular events" as an endpoint in CTT meta-analyses must be identified as post-hoc and hypothesis-generating only.

Second, projections of benefit are based on an untested 2 mmol/L reduction in LDL. Webtable 3 accompanying the 2012 CTT meta-analysis⁵ shows that among all risk cohorts with <20% estimated 5-year risk of cardiovascular disease, LDL reductions were less than 1 mmol/L compared with placebo. Figure 5 of the 2012 CTT meta-analysis⁵ suggests that 1 mmol/L

reduction in LDL for 5 years would avoid 15 major vascular events per 1000 people in the 5% to 10% risk category (ie, 1.5% absolute benefit).⁵ Furthermore, a third of these events were revascularisation procedures, so the absolute risk reduction in so-called hard events (ie, heart attacks and strokes) is 100 per 10 000 patients, or 1%. In other words, the 2012 CTT meta-analysis shows that 100 patients in this risk category would have to be treated for 5 years to prevent one heart attack or stroke.⁵ Thus, the real benefit shown by the CTT data is 80% lower than that claimed by Collins and colleagues.¹

Finally, the Review cites our 2013 *BMJ* paper,³ but fails to report our primary research finding—that statin therapy does not significantly reduce all-cause mortality (the CTT primary outcome) for patients with less than 10% 5-year risk of cardiovascular disease. This result was upheld by two independent statistical reviews as part of the expert panel review that adjudicated Collins' (unanimously rejected) demand for retraction of our paper. Omission of this crucial finding is misleading.

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We read with interest the Review by Rory Collins and colleagues¹ about the efficacy and safety of statin therapy. The authors state that each mmol reduction of LDL cholesterol is associated with a decrease in major vascular events and mortality, both in primary and secondary prevention of heart attacks and strokes. However, the relationship between cholesterol and cardiovascular events seems to decrease with age. Review of previous large observational cohort studies has even shown a higher all-cause mortality when total cholesterol and LDL-cholesterol levels were in the lowest ranges, particularly with total cholesterol less than 5.5 mmol/L in people older than 80 years.^{2,3} In addition, a review² of results from randomised controlled trials including people older than 75 years did not show any effect of statin therapy on mortality. Similarly, results from meta-analyses have shown that statins significantly reduced the incidence of myocardial infarction and stroke, but not cardiovascular and all-cause mortality among individuals older than 65 years at high cardiovascular risk.⁴ If the goal of prevention is to improve survival and quality of life in elderly people, then we believe that the usefulness of statins remains controversial.

Results from two ongoing controlled trials will provide, after 2020, substantial evidence about the use of statins in the elderly. The STAREE study (NCT02099123) will examine whether atorvastatin 40 mg compared with placebo will prolong overall survival or disability-free survival in healthy elderly people (≥70 years). The



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SITE/SAGA study (NCT02547883) will evaluate the cost-effectiveness ratio of statin cessation in people 75 years and older who are treated in primary prevention with mortality as a primary outcome measure. In the meantime, no doubt many controversial papers will be published about the use of statins in the elderly.

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The concerns of Rory Collins and colleagues in their recent comprehensive Review¹ addressing possible under use of statins, are well received. However, more than half of patients discontinue statin therapy.² Adverse effects seem likely to contribute to this. The clinical trials discussed by Collins and colleagues were industry-sponsored and designed to show efficacy, not safety. These trials did not recruit patients who were previously intolerant of statins or who had complex comorbidities, making it inevitable that adverse effects were substantially under-represented. It seems unreasonable to press patients who are experiencing adverse effects

from statins to comply with treatment. Although clearly valuable, there are now many effective treatments available for coronary prevention besides statins, such as weight loss and antihypertensive and antithrombotic therapy.

Adverse effects from statins, for example cerebral haemorrhage, renal failure, and rhabdomyolysis, are dose-related and sometimes lethal. That toxicity might be reversible after statin cessation is unhelpful because the atheroma benefits would then cease to accrue. Many physicians do not appreciate that all of the reduced mortality and almost all of the reduction in coronary events conferred by statins are already evident³ at around effective dose 50 (ED50—ie, mean population dose known to reduce LDL to half of the maximum possible), which is only about 2 mg for atorvastatin.⁴ At doses higher than this, benefits plateau but adverse effects continue to increase up to 6-times with atorvastatin 80 mg daily,⁵ about 40-times ED50. We are not aware of any other drug treatment that has been shown to be necessary at such high doses. Higher doses increase the potential of interactions of statins with other drugs, with sometimes serious consequences. Proven, lower doses of statins are likely to be much better tolerated and accepted by patients.

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Rory Collins and colleagues¹ conclude that statins do not cause muscle complaints without marked increases in concentrations of creatine kinase because such symptoms are not observed in randomised controlled clinical trials (RCTs). They suggest that such symptoms are imagined or misattributed by patients who have been warned about possible muscle complaints. The STOMP trial² was designed to examine muscle complaints in patients assigned to atorvastatin 80 mg daily or placebo. Participants were queried bi-weekly about muscle symptoms. An outcome of myalgia required resolution of pain with treatment cessation and reappearance on re-challenge. 19 of 203 (9.4%) patients on atorvastatin and 10 of 217 (4.6%) patients on placebo developed myalgia (p=0.054), suggesting that 4.8% of patients develop myalgia because of statin use.² This is a remarkable figure given that subjects were young (mean age=44.1 years), totally healthy, and treated for only 6 months. As pre-planned, we excluded 29 statin and 19 placebo patients who discontinued participation because of time, relocation, or non-muscle symptoms. Collins and colleagues¹ reanalysed our data, including these subjects—yielding myalgia rates of 8.2% for patients on atorvastatin versus 4.2% on placebo (p=0.08)—which is a questionable approach, since we sought to determine symptoms in subjects actually taking the drug. Our p value exceeds the magical 0.05 of significance, but it is very close to this statistical threshold. How could RCTs miss mild symptoms? By not asking. Only one of 44 statin RCTs involved querying participants specifically about muscle symptoms.³ Perhaps