Collins and colleagues should perform a larger STOMP-like RCT to make sure they are right before concluding that statin myalgia does not exist.

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Authors' reply

The comments by Simon Dimmitt and colleagues have already been addressed in a response to a previous letter from them.[1] In particular, lowering LDL cholesterol more intensively with higher-dose statin therapy has been shown to produce larger reductions in vascular events than with smaller LDL reductions. With respect to the suggestion that adverse effects contribute to more than half of patients discontinuing statin therapy, results from randomised masked trials have shown that patients are no more likely to discontinue statin therapy than placebo; that is, Dimmitt and colleagues confuse attribution with causation (as did John Abramson and colleagues[2,3]). Moreover, as is discussed in our Review,[4] many of these trials were started before statin therapy was being widely used, so few of the patients would have been previously exposed to a statin and excluded because of having had problems with it. Dimmitt and colleagues state that it is "unreasonable to press patients experiencing adverse effects from statins to comply". We agree; however, it is also important that patients are not encouraged to stop statin therapy if they experience adverse events that are not actually caused by the statin.

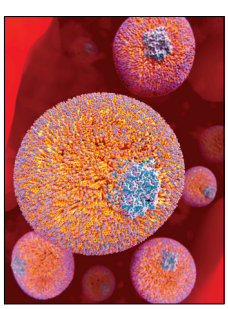
The STOMP trial[5] involved multiple comparisons of several different muscle-related measures: there were no apparent effects of statin therapy on muscle strength or endurance, aerobic performance, or physical activity, and, whether emphasis is put on the on-treatment analysis reported by the investigators[5] or on our intention-to-treat analysis based on all randomly assigned patients,[4] the observed difference in the muscle pain outcome remains compatible with chance. The assertion by Paul Thompson and Beth Taylor that the "p value exceeds the magical 0·05 of significance, but it is very close to this statistical threshold" represents a misunderstanding of the meaning of p values.[6] Moreover, rather than single out one particular result in one particular study, it is more appropriate to base judgments on the totality of the evidence.

Thompson and Taylor state that only one randomised trial (CORONA,[7] of 5011 elderly patients with heart failure) included in their meta-analysis[8] specifically sought information about muscle symptoms. However, this is incorrect: patients were also asked about such symptoms at each follow-up visit in (at least) the Oxford Cholesterol Study (OCS)[9] and the Heart Protection Study (HPS),[10] which involved more patients (621 and 20 536, respectively) and longer treatment exposure (3·4 and 5·3 years, respectively) than STOMP (468 patients for 6 months[5]). Consequently, the trial that Thompson and colleagues propose has already been done in large numbers of people with comorbidities.

Moreover, as discussed in our Review, randomised masked trials are able to detect differences that exist in the incidence of adverse events even if they are not sought specifically (eg, the small excess of diabetes with statin therapy[4]). In a meta-analysis of 26 masked trials (including STOMP, CORONA, OCS, and HPS) with an average treatment duration of 3 years,[8] muscle problems were reported by 14 000 patients but there was little difference between the treatment groups: 12·7% of participants assigned statin versus 12·4% of those assigned placebo; an absolute excess of 0·3% (95% CI 0–0·7; p=0·06). Thompson asserts that we concluded that "statin myalgia does not exist", but we did not. Instead, we concluded that the annual excess of muscle-related problems actually caused by (rather than being attributed to) statin therapy is no more than about 10–20 cases per 10 000 treated individuals, with only about one of those cases associated with substantial elevations in creatine kinase concentrations (ie, myopathy) and requiring statin therapy to be stopped.

We are in agreement with Fabrice Bonnet and colleagues that the availability of additional large-scale evidence about the effects of statin therapy from randomised controlled trials in people aged over 75 years would be of value. However, as is discussed in our Review, the inverse associations of cholesterol with mortality in observational studies in older people appear to reflect a failure to take account of reverse causality (which becomes increasingly important with age as more people experience chronic disease). By contrast, Mendelian randomisation studies indicate that the strength of the association of LDL cholesterol with coronary heart disease continues unchanged into older ages.[11] Consequently, until additional evidence becomes available, it remains reasonable to extrapolate from the evidence among younger individuals to the use of statin therapy in people older than 75 years.[4,12]

With regard to the comments by Abramson and colleagues, the many misrepresentations of the evidence in their previous paper (including the claim, subsequently withdrawn, that statins cause side-effects in one-fifth of treated patients[2,3]) are dealt with in



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detail in our Review. We also explained that analyses based on a composite outcome for which the direction and magnitude of the effects of treatment on the separate components are similar (as is the case with statin therapy and major vascular events) can allow reliable evidence to emerge about the effects in different circumstances, because they are based on much larger numbers of events than for any of the separate components. So, for example, combination of the beneficial effect of statin therapy on vascular mortality overall and the definite reduction in major vascular events among lower-risk patients provides support for concluding that statin therapy reduces the risk of death among lower-risk patients (despite the absence of a significant reduction in the relatively small number of deaths among such individuals considered in isolation).

As was discussed in our Review, the use of such composite outcomes does not mean that equal weight should necessarily be given to the different components of the composite in deciding whether or not to use the treatment. However, nor should effects on some types of major vascular events be dismissed entirely, as Abramson and colleagues seek to do, when they are associated with subsequent morbidity and mortality.

Additionally, it is a mistake not to recognise that intention-to-treat analyses tend to under estimate the effects of actually taking a treatment. Table 3 in our Review[4] indicates that actual use of an effective statin regimen (eg, atorvastatin 40 mg daily) would reduce LDL cholesterol by at least 2 mmol/L in individuals who present with concentrations of 4 mmol/L or more (estimated to be about half of the European or North American population in the absence of statin therapy). As shown in figure 3,[4] the reductions in the risks of major vascular events were larger in trials in which there were larger reductions in LDL cholesterol, and more intensive statin therapy produced larger reductions in risk than lower dose regimens (without good evidence of higher rates of side-effects other than myopathy).

Consequently, it is appropriate to base the estimated magnitude of benefit that can be achieved by the use of an effective statin regimen on the LDL reduction that is likely to be achieved (rather than on the risk reduction per mmol/L): that is, lowering LDL cholesterol by 2 mmol/L for 5 years in 10 000 patients would typically prevent one (or more) major vascular event from occurring in about 1000 patients (ie, 10% absolute benefit) with pre-existing occlusive vascular disease (secondary prevention) and in 500 patients (ie, 5% absolute benefit) who are at increased risk but have not yet had a vascular event (primary prevention). Figure 5 provided estimates for the absolute benefits that would be achieved with different LDL reductions.[4] However, because statin therapy reduces vascular disease risk during each year that it continues to be taken, the absolute benefits would be even larger with more prolonged therapy.

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Lessons from the controversy over statins

Jane Armitage and colleagues, led by senior author Rory Collins, (Nov 5, p 2237)[1] and Richard Horton (Nov 5, p 2237)[2] appear to believe that retraction of an article from *The BMJ* will end the debate about statins and primary prevention. Even were there grounds for retraction, I fear they would be disappointed. Questions about the evidence base for statins continue to emerge from many quarters: how strong is the evidence, how large is the benefit for individuals at lowest risk of heart disease, how well did the trials record common minor side-effects, how representative were the trials of women and the elderly,

For **questions about the evidence base for statins** see http://blogs.bmj.com/bmj/2016/09/12/richard-lehman-where-next-with-statins/