

To the Editor

The comments by Dimmitt et al were addressed previously in a response to their referenced letter.(1) In particular, lowering LDL cholesterol more intensively with higher-dose statin therapy has been shown to produce larger reductions in vascular events. With respect to the suggestion that adverse effects (our emphasis) contribute to more than half of patients discontinuing statin therapy, randomised masked trials have demonstrated that patients are no more likely to discontinue statin therapy than placebo; that is, Dimmitt et al confuse attribution with causation (as did Abramson et al (2, 3)). Moreover, as is discussed in our review, 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 et al 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 was designed to assess 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 (4) or on our “intention-to-treat” analysis based on all randomised patients, the observed difference in the muscle pain outcome remains compatible with chance. Thompson’s assertion that STOMP “provides 94.6% certainty that atorvastatin produced myalgia” misunderstands the meaning of P values (5). Furthermore, it is more appropriate to base judgements on the totality of the evidence, rather than – as he does – to single out one particular result in one particular study.

Thompson states that only one trial (CORONA, among 5011 elderly heart failure patients (6)) included in his meta-analysis (7) 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 (8)) and the Heart Protection Study (HPS (9)), which involved more randomised patients (621 and 20,536 respectively) and longer treatment exposure (3.4 and 5.3 years) than STOMP (468 randomised patients for 6 months (4)). Consequently, the trial that Thompson proposes has already been conducted among 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). In a meta-analysis of 26 masked trials (including STOMP, CORONA, OCS and HPS) with an average treatment duration of 3 years (7), 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 Bonnet et al that the availability of additional large-scale evidence from randomised controlled trials among people aged over 75 would be of value in providing more direct evidence about the effects of statin therapy. However, as is discussed in our review, the inverse associations of cholesterol with mortality in observational studies among 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 (10). 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 aged over 75 (11).

With regard to Abramson et al, 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 detail in our review. It also explains 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) may 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 lack of a significant reduction based on the relatively small number of deaths among such individuals considered in isolation).

As was discussed, 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 et al seek to do) when they are associated with subsequent morbidity and mortality. In addition, as was explained in our review, 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 indicates that actual use of an effective statin regimen (eg, atorvastatin 40mg 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 by Figure 3, 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 events 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. However, as 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.

Yours sincerely

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