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LETTERS

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STATINS FOR EVERYONE?

Authors' reply to Huffman and colleagues

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We thank the Cochrane review authors for their thoughtful comments (highlighted in quotes below), which give us the opportunity to clarify unresolved issues about the benefits and harms of statins in low risk people.[1]

> "This article predated by three weeks the publication of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol treatment guidelines (12 November 2013), but statements were made about 'proposed standards' without full knowledge of these guidelines."

The "proposed standards" that we referred to in our article were not the yet to be published 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on cholesterol treatment.[2 3] Rather, they were the 2013 update of the Cochrane review on statins for the primary prevention of cardiovascular disease,[4] which had incorporated the findings and recommendations of the 2012 Cholesterol Treatment Trialists' (CTT) meta-analysis.[5]

The 2012 CTT meta-analysis reported that statins significantly reduce major vascular events in people "with 5-year risk of major vascular events lower than 10%." It concluded that the current major guidelines—ATP-III in the US, the European Society of Cardiology task force, and the National Institute for Health and Care Excellence guidelines in the UK—"might need to be reconsidered."

The 2013 Cochrane review stated: "in light of new evidence derived from the CTT Collaboration on primary prevention, there is a need to update existing cost-effective analysis."

We based our comments about "proposed standards" on these calls to update existing recommendations. Although we had no advanced knowledge of the contents of the forthcoming ACC/AHA cholesterol treatment guidelines, we anticipated that these findings and recommendations would be influential.

> "Abramson and colleagues state: 'Under the proposed 2013 standards, however, no level of risk would preclude statin therapy'"

The 2012 CTT meta-analysis concluded: "The present report shows that statins are indeed both effective and safe for people with 5-year risk of major vascular events lower than 10% and, therefore, suggests that these guidelines might need to be reconsidered." No lower limit of benefit is suggested in this meta-analysis.

The 2013 Cochrane review then stated, "Our previous conclusion urging caution in the use of statins in people at low risk of cardiovascular events is no longer tenable in light of the CTT Collaboration findings." Again, a lower limit of risk for the benefit of statins was not specified.

> "Abramson and colleagues state: '. . . raising the question whether all people over the age of 50 should be treated.' Neither the Cochrane review nor the ACC/AHA cholesterol guidelines proposed treatment for everyone over the age of 50 years."

The 2012 CTT meta-analysis reported a significant reduction in major vascular events for patients with less than a 10% five year risk—an average of 2.6% five year risk for major coronary events.

Two editorials that accompanied publication of the 2012 CTT meta-analysis commented on the benefit of statin therapy found in low risk people in the 2012 CTT meta-analysis. One cautioned about the increased risk of new onset diabetes, but stated "a good case could be made for treatment of individuals with an absolute risk of a cardiovascular event of less than 5% during 5 years with statins."[6]

The other editorial, entitled "Statins for all by the age of 50 years?," discussed the translation of the CTT findings into practice: "Because most people older than 50 years are likely to be at greater than 10% 10-year risk of cardiovascular disease,

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it would be more pragmatic to use age as the only indicator for statin prescription." Both authors of this editorial were members of the Cochrane Heart Group.[7]

The 2013 Cochrane review to which we refer concluded: "The individual patient data meta-analyses now provide strong evidence to support [statin] use in people at low risk of cardiovascular disease." No lower limit of benefit was indicated.

The ACC/AHA cholesterol guidelines, issued three weeks after our Analysis article was published in the *BMJ*, recommend statin therapy for people with a 7.5% or more 10 year risk of cardiovascular disease, with the option of statins for those whose 10 year risk is 5-7.4%. This strengthens the argument presented in the 2012 editorial that the decision to prescribe statins could be made more cost effectively simply on the basis of age. A 50 year old American man with all values entered into the AHA risk calculator[8] at the 50th centile has a 6% 10 year risk of cardiovascular disease. A 55 year old American man with risk factors at the 50th centile has a 10% 10 year risk of cardiovascular disease.

> "The updating of the evidence base resulted in an expected narrowing of confidence intervals, and the addition of the JUPITER trial added important evidence on diabetes risk."

The addition of clinical trial data would be expected to narrow the confidence intervals. However, the effect of statin therapy on cardiovascular risk did not change, so there was no evidence for the Cochrane review to radically change its recommendation from 2011 to 2013. Furthermore, we question the validity of the JUPITER trial data given that the trial was prematurely stopped at a time when there was no difference in cardiovascular mortality or serious adverse events between the rosuvastatin and control groups. In addition, the unrealistically low mortality rate (8.8%) associated with myocardial infarction in the control group, compared with a 29% case fatality rate in the rosuvastatin group, raised questions about bias in event ascertainment.[9]

> "The authors consider that for statins to have a place in primary prevention in people in lower strata of cardiovascular disease risk these drugs should reduce total mortality, and they estimate a relative risk of 0.95 (95% confidence interval 0.86 to 1.04). However, the authors included people with and without previous vascular disease in this estimate."

The "main results" of the 2013 Cochrane review reported: "Recent findings from the Cholesterol Treatment Trialists study using individual patient data meta-analysis indicate that these benefits are similar in people at lower (<1% per year) risk of a major cardiovascular event." The table in our Analysis article deals with this issue. As stated in our article, statin therapy does not significantly reduce overall mortality for the population of low risk patients included in the clinical trials.

In considering the effect of statin therapy on the low risk population, no clinical logic supports the removal of low risk patients diagnosed with cardiovascular disease from this calculation. Inclusion of these patients would be expected to increase rather than decrease the efficacy of statins. The discrepancy between the effects of treatment on the primary prevention population and the low risk population as a whole results from a statistical quirk in the clinical trial data. This was that overall mortality was not reduced in people at low risk (<20% 10 year risk) with a history of vascular disease (relative risk of overall mortality associated with statin therapy for <5% risk=1.04 and for ≥5% to <10%=1.00).[10] "Slicing and dicing" the data for overall mortality in the low risk group exploits the removal of these data to increase the estimated effect of statins.

Although the title of our article was correct, we agree that the précis beneath the title incorrectly points readers toward the effect of statin therapy in the primary prevention population rather than the low risk population as a whole.

> "The number of total deaths was small (1% of control group participants dying over four years) and non-cardiovascular disease causes of death exceeded deaths from cardiovascular disease by more than 2:1 . . . No strong evidence of benefit for total mortality was seen because other causes of death make up a greater proportion of total deaths, and it is unlikely that taking statins influences these non-cardiovascular disease deaths."

We agree that, in the lower risk groups, by definition, cardiovascular causes of death will constitute a smaller proportion of total mortality. However, among low risk patients included in the CTT meta-analysis, statins failed to reduce overall mortality or serious adverse events, so no "net" or overall health benefit can be claimed.

> "We disagree with Abramson and colleagues' statement that the 'best indication of the net effect of a treatment on overall health is the total number of serious adverse events—which include deaths from all causes, hospital admissions, prolongations of admission, cancer, or permanent disability.'"

We agree with this criticism. This sentence should read: "After overall mortality, the best indication of the net effect of a treatment on overall health…"

> "While criticising the randomised controlled trials, the authors use low quality evidence from observational studies to support their statements about the hazards associated with statins, even though the risk of bias is likely to be high in such studies."

We agree that observational studies provide a lower level of evidence than well conducted randomised controlled trials. Unfortunately none of the clinical trials included in the CTT meta-analysis compared drug therapy with lifestyle intervention to answer the question of how to reduce the burden of cardiovascular disease most effectively and efficiently in the low risk population. Thus, we relied on the best available information.

A recently published meta-epidemiological study included randomised controlled trials that compared the effectiveness of exercise and drug interventions in the reduction of mortality for the secondary prevention of coronary heart disease, stroke, prediabetes, and congestive heart failure.[11] Results showed that exercise and statins were equally effective in patients with coronary heart disease, and exercise was 90% more effective than anticoagulants and antiplatelet drugs for patients with stroke.

A publicly funded randomised controlled study comparing statin, lifestyle intervention, and both for the prevention of cardiovascular disease in low risk patients would provide important comparative effectiveness information.

> "They also conflate muscle pain (myalgias), an important side effect of statins, with myopathy, a rare and more serious problem."

This is a semantic criticism, with which we disagree. From a practical point of view, statin induced myopathy includes:

myalgia (muscle symptoms without raised creatine kinase), myositis (raised creatine kinase, with or without muscle symptoms), and rhabdomyolysis (creatine kinase >10 times the upper limit of normal).[12] Furthermore, histopathological findings of myopathy occur in patients with or without muscle symptoms and normal creatine kinase levels.[13 14 15]

> "They cite studies that identify adverse events associated with statin therapy but fail to cite systematic reviews that show no increased risk of psychological outcomes, fractures, acute renal failure, arthritis, or venous thromboembolism."

To narrow this concern, we did not comment on the association between statins and the risk of fractures, arthritis, or venous embolism. In fact, an article we cited, based on 225 000 new users of statins in England and Wales, showed no significant association between statins and these three adverse events.[16] The same article did, however, show a significantly increased risk of acute renal failure associated with the use of statins. Because of under-ascertainment of the adverse effects of statins in clinical trials, epidemiological data, such as data from general practices in England and Wales and the data on psychiatric adverse reactions from the New Zealand Center for Adverse Reactions Monitoring, must be heeded as substantial warnings of potential adverse events.[17] The problem of under-ascertainment of adverse events in clinical trials is exemplified by a 2006 meta-analysis of clinical trials involving statins that reported no increase in the risk of myalgia.[18] We agree that a more extensive review of the literature about each of these potential adverse reactions should include the full range of published articles.

> "Finally, Abramson and colleagues set up a false dichotomy, stating: 'Rather than being compelled by guidelines to prescribe statin therapy for people at low risk of cardiovascular disease, doctors would provide a far greater service by explaining the magnitude of the benefits and uncertainty about the harms of statins together with discussion of the epidemiological evidence showing that behavioural risk factors—including tobacco use, lack of physical exercise, and unhealthy diet—are responsible for 80% of cardiovascular disease.' If they (and the BMJ editors) had awaited the publication of the 2013 ACC/AHA cholesterol guidelines, they would have been directed to the companion lifestyle guidelines, which aim to deal with these topics."

We agree that the 2013 ACC/AHA cholesterol guidelines include guidance on positive lifestyle modification—as did the preceding guidelines. But once again, it is the expanded criteria for prescribing statins that is getting the attention, not the fundamental importance of lifestyle modification. The proforma nature of the lifestyle recommendations is seen in an editorial written by a vice chair of the expert panel responsible for the 2013 ACC/AHA guideline on the treatment of blood cholesterol: "Despite decades of exhortation for improvement, the high prevalence of poor lifestyle behaviors leading to elevated cardiovascular disease risk factors persists, with myocardial infarction and stroke remaining the leading causes of death in the United States. Clearly, many more adults could benefit from evidence-directed use of statins for primary prevention."[19] Once again, doctors are implored to "get real"—stop hoping that efforts to help their patients and communities adopt healthy lifestyle habits will succeed, and start prescribing more statins. This is a self fulfilling prophecy. Note that the author of these comments disclosed receipt of funding from 11 drug companies, at least four of which produce or are developing new classes of cholesterol lowering agents,[20] which are projected to achieve annual sales of up to $10bn (£6bn; €7.3bn) a year.[21]

Our response to the Cochrane reviewers' comments would not be complete without mentioning the evidence on which they relied. The review adhered to strict standards of data collection and analysis, evaluating data for risk of bias, examining heterogeneity, sensitivity analysis, and so on. However, there is no evidence they were granted access to the fundamental clinical evidence that prevents bias: patient level data from the clinical trials. The references section of the 2013 Cochrane review shows that the source of data for every study included in the review was "published data only."[4] Unlike the Cochrane review, the Cholesterol Treatment Trialists Collaboration has been granted access to and relies on patient level data for every study incorporated into its meta-analyses.

In 2009, when the Cochrane reviewers of neuraminidase inhibitors for the prevention and treatment of influenza in healthy adults were unable to gain access to primary data from the manufacturer's clinical trials of oseltamivir (Tamiflu),[22] they withdrew previous reviews.[23 24] Access to patient level data is also necessary for Cochrane reviewers of statin therapy to be able to perform a thorough and independent evaluation. At the very least, analyses of prespecified outcome measures could be performed independently, and the question of whether statins reduce the incidence of serious adverse events across all trials could be investigated.

If the Cochrane reviewers have requested and been denied access to the patient level data from the statin studies, we believe they should do what the reviewers of oseltamivir have done: publicly declare their inability to perform a responsible evaluation and retract conclusions that are based on published data only. The entire world is relying on third party representations of data that the manufacturers should make readily available to Cochrane reviewers and other academic researchers.

Competing interests: JDA and NJ serve as experts for plaintiffs' attorneys in litigation involving the drug industry (including a statin). JDA has received payment for lectures from several universities, medical schools, and non-profit organisations. He was formerly executive director of health management for Wells Fargo Health Solutions.

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