Misrepresentation of statin safety evidence


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We are writing to draw attention to serious errors in "Concerns about the latest NICE draft guidance on statins", a letter that was sent by Richard Thompson and colleagues to the National Institute for Health and Care Excellence (NICE) and the Secretary of State for Health,[1] and to the media with a press release.[2] The letter[1] was covered extensively in the media and increased confusion about the effects of statins, despite the robust response from NICE.[3] As a consequence, it might well lead patients who are at high risk of heart attacks and strokes to stop statin therapy or not start it, thereby substantially increasing their risks of death and disability.

There are two major types of scientific error in the letter by Thompson and colleagues (see annotated version of the letter).

First, there are errors of interpretation. Much is made in the letter about differences in the rates of adverse events that were recorded in different statin trials. However, it is not scientifically appropriate to make such non-randomised comparisons between trials of the rates of events that are defined very differently in different trials (which also involved different types of patient with different underlying risks of adverse events). For example, the rates of adverse events given as reasons for discontinuation in one trial should not be compared (as was done in the letter[1]) with the rates of all adverse events, or of discontinuations for any reason, in another trial. Moreover, since the results quoted relate to the numbers of events that are recorded during a particular trial (and should more properly be referred to as cumulative incidence rather than rates), they will also be affected by differences in the duration of different trials. By contrast, it would have been entirely appropriate to make direct comparisons of event rates between randomised groups within each trial since these are based

For the **annotated version of the letter** see http://www.ctsu.ox.ac.uk/research/meta-trials/ctt/annotated-thompson-letter-ms-word

on unbiased blinded assessment of events defined in the same way for both the patients allocated active statin treatment and those allocated placebo treatment within any particular trial. The similarity of the rates in the statin versus placebo groups within each of these randomised, blinded, and controlled comparisons reported in the letter[1] provides robust unbiased evidence of an absence of adverse effects of statin therapy on each of these different adverse event measures. This important point is over-looked in the letter by Thompson and colleagues.[1]

Second, there is misrepresentation of the evidence. In the comparisons of rates between trials in section 2 of Thompson and colleagues' letter to NICE,[1] it is not made clear what is meant by "effects" (by contrast with "events" used earlier in their letter), but it seems to be—in view of the rates quoted for some of the trials—something along the lines of adverse events that led to discontinuation of the active or placebo treatment. It is claimed in the letter that these "placebo adverse effect rates range from 2·7% to 80·4%, a thirty fold difference". As noted above, such comparisons are not scientifically appropriate, but the statement is also incorrect. In particular, it is stated[1] that "Total adverse effects" occurred in 80·4% of placebo-allocated patients in the METEOR trial,[4] whereas this is actually the rate of "Total adverse events". It is misleading for Thompson and colleagues to compare the rate of "total adverse events" in METEOR with the rates of subsets of adverse events in the other trials, such as those that led to discontinuation of study treatment (ie, so-called effects). Published results for the rates of the comparable outcome of adverse events leading to discontinuation in METEOR are 11% among those allocated rosuvastatin versus 8% among those allocated placebo, and these results are entirely compatible with the rates reported for similar outcomes in the other trials (especially given that the precise definitions used in the different trials differed, and so too did the types of patient that were included and the duration of study treatment).

Another serious error in Thompson and colleagues' letter[1] relates to their misrepresentation of the results from the WOSCOPS trial.[5] It is stated that "the cumulative incidence of myalgia was 0·06% in the statin arm, and 0·06% in the placebo arm". However, in the paper referenced in support of that claim,[5] it is reported that myalgia was recorded in 20 of the 3302 patients allocated pravastatin and 19 of the 3293 patients allocated placebo: these numbers translate into percentages of 0·6% and 0·6%, respectively (ie, a ten fold error). Moreover, in the same section of the WOSCOPS paper,[5] it was reported that another 97 patients allocated statin and 102 allocated placebo reported other muscle aches, yielding an overall rate of 3·5% and 3·7%, respectively. The METEOR trial classified adverse events using the MedDRA coding system, which includes all muscle aching in the definition of myalgia. Consequently, comparison of the placebo rates of myalgia defined more similarly in METEOR of 12·1% and in WOSCOPS of 3·7% yields a difference that is not 200-fold (as claimed in the letter to NICE), but is only about three fold (ie, more than a 60-fold error).

Errors in the rates quoted by Thompson and colleagues for these and other trials (see supporting material) invalidate their main points about the adverse effects of statins, undermining conclusions that were widely disseminated.

A debate about offering statin therapy to patients who are not at high risk of heart attacks and strokes (as has now been recommended by NICE[6]) is entirely appropriate. However, in making a case against such a strategy, it is not at all appropriate to misrepresent evidence in ways that mislead doctors, patients and the wider public.

For **supporting material** see http://www.ctsu.ox.ac.uk/research/meta-trials/ctt/annotated-thompson-letter-ms-word

The Clinical Trial Service Unit receives grants from the pharmaceutical industry (including manufacturers of statins) for independent research and has a patent for a statin-related myopathy genetic test (http://www.ctsu.ox.ac.uk/about-ctsu/documents/independent-research). It has a staff policy of not accepting any payments directly or indirectly from the pharmaceutical industry, except for reimbursement of the costs of travel and accommodation to participate in scientific meetings (http://www.ctsu.ox.ac.uk/about-ctsu/documents/guidelines).

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1 Thompson R, Gerada C, Haslam D, et al. Concerns about the latest NICE draft guidance on statins. http://www.nice.org.uk/Media/Default/News/NICE-statin-letter.pdf (accessed Sept 17, 2014).
2 Kendrick M, Malhotra A. Leading doctors reject latest statin guidance from the National Institute for Health and Care Excellence. http://www.ctsu.ox.ac.uk/research/meta-trials/ctt/thompson-press-release-pdf (accessed Sept 25, 2014).
3 Haslam D. NICE draft guidance on the use of statins (response to Thompson et al). https://www.nice.org.uk/Media/Default/News/NICE-response-to-statins-letter-June-2014.pdf (accessed Sept 17, 2014).
4 Crouse III JR, Raichlen JS, Riley WA, et al, for the METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis. The METEOR Trial. *JAMA* 2007; **297:** 1344–53.
5 Shepherd J, Cobbe SM, Ford I, et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; **333:** 1301–07.
6 NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE guidelines [CG181], July 2014. http://www.nice.org.uk/guidance/CG181/ (accessed Sept 17, 2014).