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EXPERT OPINION

Letter to the Editor: The ezetimibe 'controversy' is a misunderstanding

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The recent review of the ezetimibe 'controversy' [1] adds to the important misunderstanding of this issue.

The author cites two papers as 'evidence' that ezetimibe raises small dense low-density lipoprotein (LDL), particles in the short term, and calls for longer-term studies. However, one of the papers cited (Rizzo *et al.*, reference 59) only speculated about small-dense LDL, and the other (Berneis *et al.*, reference 60) was only a 14-day study. A six-week study showed [2] that ezetimibe with or without simvastatin reduced small-dense LDL.

The notion that ezetimibe may be harmful to the arteries arose from two studies cited in the paper (ENHANCE, reference 46, and ARBITER, reference 39) that failed to show reduction of carotid intima-media thickness (IMT) despite lowering of LDL cholesterol. Intima-media thickness is not atherosclerosis; it is a different phenotype. Carotid stenosis, plaque and IMT are all different, both biologically and genetically, and must be distinguished from each other. This can be seen by multiple regression analysis with carotid stenosis, IMT, plaque area or plaque volume as the dependent variable, with coronary risk factors as predictors. The proportion of explained variance (R^2) for plaque area or plaque volume is 50 – 52% for plaque area or volume, 15 – 17% for IMT and only 13% for stenosis [3]. For assessing effects of therapy on atherosclerosis, it is necessary to measure carotid plaque area or volume [4]. Indeed, we found that in patients whose plaque was progressing despite statin therapy that was limited by symptoms such as myalgia, addition of ezetimibe resulted in regression of carotid plaque [5].

In my view, this issue is a misunderstanding, not a controversy.

Declaration of interest

The author has received honoraria for lectures from Merck, Sanofi, Pfizer, AstraZeneca, and research grants for investigator-initiated studies from Merck (small) and Pfizer (large).

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Author's response: Which controversy relating to ezetimibe?

The ezetimibe controversy, in my article [1], was that ezetimibe alone, or in the presence of statins, has never been shown to have beneficial effects on cardiovascular clinical end points. Thus, I noted that whereas simvastatin alone reduces cardiovascular mortality, major coronary events, stroke, transient ischemic attacks and claudication; ezetimibe has never been shown to have any of these benefits alone, or in the presence of simvastatin. Thus, my conclusion was "until/unless the use of ezetimibe is clearly shown to improve clinical outcomes, its use should be largely restricted to clinical trials investigating clinical outcomes, and ezetimibe should not be used routinely in everyday practice".

There is presently some preliminary discussion as to whether ezetimibe has harmful effects on atherosclerosis, and this seems to be the 'controversy' that Dr Spence is referring to [2]. Thus, there is a misunderstanding between us over which controversy relating to ezetimibe is discussed in my review. My review was mainly about the lack of beneficial effects of ezetimibe on clinical end points, not any possible harmful effects with ezetimibe. In my review, I briefly considered two possible harms that ezetimibe may have: cancer and the progression of atherosclerosis, and concluded that "Until the long-term safety of ezetimibe is established, regarding cancer and atherosclerosis, questions must be asked about why it is widely used".

I accept, as Dr Spence says in his letter, that carotid stenosis, plaque and intima-media are different. Dr Spence has recently (i.e., after I submitted my review on ezetimibe) shown that the addition of ezetimibe may decrease plaque burden in the carotid arteries of subjects unable to tolerate high doses of statins [3]. In his study, plaque burden was increasing despite the use of statins, and then decreased when ezetimibe was added [3]. However, these subjects were still taking statins, and thus the decrease in plaque burden may be due to a long-term benefit of the statins, especially as there is no control group in this study, that is, a group that continued to take tolerable levels of statins, but were not given ezetimibe. Thus, the study of the effects of ezetimibe on atherosclerosis should continue. However, this should not distract from the ezetimibe controversy, which is that it has not been shown to have beneficial effects on clinical outcomes.

Declaration of interest

The author declares no conflict of interest and has received no payment in preparation of this manuscript.

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