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Letter to the Editor

Atorvastatin in combination with ezetimibe and carotid atherosclerosis

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Dear Editor,

Luo et al. (2014) reported that the combination of atorvastatin plus ezetimibe decreased carotid intima media thickness (cIMT) significantly more than atorvastatin monotherapy. We would like to add a few comments. The ENHANCE trial (Kastelein et al., 2008) did not compare the effect of atorvastatin plus ezetimibe versus atorvastatin monotherapy on cIMT, as mentioned by Luo et al. (2014). The statin used was simvastatin. As Luo et al. (2014) state, the cIMT in ENHANCE was set too low and could not be reduced further. There are other deficiencies in the ENHANCE trial; these are discussed by us in Paraskevas et al. (2011). Briefly, the latter article also comments on other trials that show that ezetimibe, used together with a statin, decreases cIMT. Furthermore, this article also considers evidence that atorvastatin 80 mg/day did not reduce the cIMT when compared with placebo (CASHMERE study), probably because the cIMT was too low (virtually identical to that in ENHANCE). How-

ever, ENHANCE produced useful information. The C-reactive protein (CRP) level dropped significantly more in the simvastatin plus ezetimibe group compared with the simvastatin monotherapy group (Kastelein et al., 2008). The same pattern was reported by Luo et al. (2014), in which the fall in high sensitivity CRP (hsCRP) level was significantly greater in the atorvastatin plus ezetimibe group compared with the atorvastatin monotherapy group. Indeed as Luo et al. (2014) state, doubling the dose of a statin only results in about 6% further fall in low density lipoprotein cholesterol (LDL-C) levels. A meta-analysis by our group showed that adding ezetimibe to a statin results in an average 23.6% fall in LDL-C levels compared with statin monotherapy (Mikhailidis et al., 2007). This meta-analysis also showed that the addition of ezetimibe to a statin increased the fall in CRP levels. Another meta-analysis showed that adding ezetimibe to a statin is more effective than doubling the dose of the statin (Mikhailidis et al., 2011). Ezetimibe has several potentially useful actions other than altering the lipid profile (Lioudaki et al., 2011). However, it is difficult to assess the contribution of these effects on vascular risk. Other researchers, as well as our group, have observed that high triglyceride levels fall to a greater extent than low levels when ezetimibe is added to a statin (Gazi et al., 2007; Fras and Mikhailidis, 2008; Migdalis et al., 2009; Shigematsu et al., 2012). Therefore, it would be useful to know if the fall in triglyceride levels was greater in the atorvastatin plus ezetimibe group compared with the atorvastatin monotherapy group if only triglyceride levels $\geq$1.7 or $\geq$2.0 mM are considered in the Luo et al. (2014) study. Also, it would be interesting to know if Luo et al. (2014) performed kidney function tests, since there is some evidence that adding ezetimibe to a statin will improve that variable (Gazi et al., 2007; Migdalis et al., 2009). The debate about the evidence supporting the use of ezetimibe to reduce the risk of vascular events continues (Gouni-Berthold et al., 2012). However, the findings of Luo et al. (2014) further support the conclusion that the cIMT results of the ENHANCE trial should not be included in this debate. Secondly, it is relevant that several guidelines mention that the use of ezetimibe is appropriate if LDL-C targets are not reached by statin monotherapy (Catapano et al., 2011; Perk et al., 2012; Teramoto et al., 2013; Anderson et al., 2013; Wanner and Tonelli, 2014; IAS Position Paper, 2014). The recent dyslipidemia guidelines issued by the American College of Cardiology/American Heart Association (Stone et al., 2013) focus on statins and only briefly mentions other lipid lowering options (Mikhailidis et al., 2014).

Conflicts of interest

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