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Invited commentary

Another clinical evidence straw on the $4 billion ezetimibe camel's back

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The clinical use of ezetimibe began in 2002 when the United States Food and Drug Administration licensed the compound for the reduction of LDL-C either alone or in combination with a statin medication. Since then, clinical use of ezetimibe has grown to levels exceeding annual sales of $4 billion, in parallel with efforts to broadly market the drug to clinicians despite the absence of definitive data on its net benefit on clinical cardiovascular outcomes [1]. Licensing of ezetimibe came under the Prescription Drug User Fee Act program (PDUFA), which required the conduct of clinical trials following licensing [2]. Disturbingly, over the past 9 years, no clinical trials yet support the incremental value of ezetimibe, amid growing concerns over its mechanism of action, and reports of bewildering effects on surrogates of clinical cardiovascular outcomes.

The firestorm over ezetimibe began in earnest with the publication of the ENHANCE trial showing no benefit of the drug on carotid intima media thickness (CIMT) in patients with familial hypercholesterolemia [3]. Criticisms of that trial centered on the selection of a trial population consisting of individuals previously treated with statins, and including some without advanced atherosclerosis. In this issue of the journal Atherosclerosis, West and colleagues, from the University of Virginia, report their findings on the incremental effect of ezetimibe treatment in statin naïve patients with advanced atherosclerosis of the peripheral arteries. The researchers enrolled 67 subjects in 2 different studies: (1) a group of stain naïve patients were randomized to double blind treatment with either statin monotherapy or combination treatment with a statin and ezetimibe; (2) A subset of patients already treated with statin monotherapy received the addition of ezetimibe. All subjects were followed with advanced atherosclerosis imaging of the superficial femoral artery using 1.5 T MRI. In short, they found that ezetimibe showed no benefit when combined with statin monotherapy for the primary endpoint of plaque volume of the superficial femoral artery. In patients already treated with statin, the researchers found evidence of an off-target effect with paradoxically greater progression of atherosclerosis in the setting of greater ezetimibe-induced LDL-C reductions. These data amplify findings from recent atherosclerosis imaging trials of ezetimibe showing no clinical effect of the drug beyond LDL-C reduction [3], and potentially off-target effects [4].

West's study has important strengths and limitations. The endpoint utilized, peripheral arterial MRI, provides a volumetric assessment of atherosclerosis, which appears highly reproducible, however it must be noted that this method, and particularly its use in the superficial femoral artery, has not been validated as a surrogate of clinical cardiovascular outcomes. However, responsiveness of the femoral artery to statin treatment appears comparable to other arterial beds [5,6]. The reproducibility of the imaging technique enabled a small sample size, however this came at a cost of limited statistical power, inability to analyze subgroups for internal consistency of the findings, inability to conduct multivariable adjustment, and the potential confounding from imbalance of baseline or on-treatment variables. As such, MRI imaging micro-trials provide a "demonstration of concept" approach, but their primary strength may lie in their ability to investigate for ancillary atherosclerosis or plaque characteristics. In direct repudiation of the ENHANCE criticism, the authors studied statin naïve subjects with advanced atherosclerosis, and clearly patients with peripheral arterial disease are relevant to the question of therapeutic lipid treatment intensification. Lastly, although the authors provide us with an important evaluation in statin naïve patients, patients previously on statin treatment received ezetimibe in an observational, uncontrolled manner.

In the broader sense, the present study adds to a disturbingly growing list of investigations, which demonstrate bewildering results for a putatively simple drug that modestly lowers LDL-C. A full evaluation of the available literature shows a growing pattern suggesting that there is more to ezetimibe than meets the eye. Eze-

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timibe's effect on lipid particle parameters, endothelial function, and atherosclerosis in humans have shown, at best, mixed results, and most clearly results which cannot be equated to treatment with other LDL-C lowering treatment approaches including diet, statins, and binding resins. Ezetimibe lowers LDL-C, but the effects on qualitative LDL particle profile appear distinct [7–10], and may even lead to a relative increase in the proportion of small, dense LDL particles [8]. In contrast to the effects on statins on non-cholesterol sterol concentrations (reductions in desmosterol [11,12] and lathosterol), ezetimibe leads to an increase in lathosterol, a potentially toxic sterol. The drug has been widely studied for its effects on endothelial function in comparison to statin monotherapy. In 13 different studies, [13–26] a majority (7) have shown [14,16–20,23] that, despite equipotent effects to a statin on LDL-C, ezetimibe does not have comparable effects (and may have no effect) on endothelial function over modest time horizons. West's study on atherosclerosis in humans is now the third such study, each of which either failed to show any effect of ezetimibe over statin monotherapy [3], or to be inferior to alternative forms of combination therapy [4]. Importantly, these data now span a diverse array of patients including patients with severely elevated LDL-C, patients with coronary heart disease or coronary risk equivalents, and now those with peripheral arterial disease. And lastly, data from 2 clinical endpoint trials [27,28] are grossly insufficient with trial designs that were poorly conceived from the perspective of demonstrating the ability of ezetimibe to reduce cardiovascular disease risk, as required under the PDUFA approval.

Lacking definitive proof or disproof of ezetimibe's clinical efficacy, further guidance may derive from the science on ezetimibe's mechanism of action. Ezetimibe's original FDA licensure came amidst uncertainty regarding the drug's mechanism. The compound was originally developed as an acyl-coenzyme A: cholesterol acyltransferase inhibitor, now a demonstrated failed approach to pharmacotherapy of lipids. However, its effect in this regard was weak, yet developers noted its ability to lower LDL-C leading them to seek, and the FDA to grant, a license for clinical use. Subsequently, investigators identified that ezetimibe inhibits the uptake of cholesterol in the enterocyte [29]. Originally described as inhibition of the Niemann-Pick C1 Like 1 receptor, work by independent investigators report that the drug predominately inhibits the scavenger receptor B1 [30–32], involved in intracellular translocation of cholesterol. However, absorbed ezetimibe may lead to an off-target consequence as this same receptor binds to the ligand apoprotein A1, the principal apoprotein component of HDL-C in the process of reverse cholesterol transport. Thus, while many suggest that the simple reduction of LDL-C by ezetimibe should ensure its efficacy to reduce cardiovascular morbidity and mortality, these mechanistic insights serve as a reminder that drugs have both intended and unintended effects, and the balance of these effects require full understanding before a drugs falls into widespread clinical use. In short, ezetimibe likely possesses a combination of beneficial, non-beneficial, and even harmful effects, and the net sum of these is presently nothing if not unclear, and most certainly cannot be simply modeled through a change in LDL-C. Suggestion of this arises again in the study by West showing paradoxically that the further LDL-C was reduced by ezetimibe monotherapy, the greater was the progression of atherosclerosis. This finding, with a bivariate correlation coefficient of −0.38, matches closely and corroborates a similar exploratory finding initially observed in ARBITER 6 ($r = -0.31$). This effect remains counterintuitive to the prevailing understanding that greater reduction in LDL-C yields superior clinical efficacy, and requires explanation. Could the extent to which ezetimibe inhibits SRB1-related cholesterol absorption [33], reflected in the measurable extent of LDL-C reduction, be more than offset by an immeasurable ezetimibe-induced inhibition of other transport mechanisms known to be important in HDL-related reverse cholesterol transport? Which other off-target mechanisms may contribute? Torcetrapib stands as the most recent reminder that the net effects of a lipid drug, and particularly a cholesterol transport inhibitor, cannot be measured solely through its effects on cholesterol concentrations.

Whereas the investigation by West provides no definitive answers, it adds to a growing body of evidence squarely questioning ezetimibe's efficacy, placing another evidence straw on the US $4 billion ezetimibe camel's back. Although a decrease in the use of ezetimibe following negative research reports reflects clinicians' understanding of this controversy, one should reasonably question whether the continued level of use of ezetimibe, a drug with considerable uncertainty awaiting clinical trial evidence development, represents a justifiable allocation of healthcare expenditures. Clinician's should remain open to all possibilities pending completion an ongoing study (www.clinicaltrials.gov; NCT00202878). But, the process of evidence development does not represent evidence. The ongoing trial has significant limitations having been altered several times while in progress including upwards adjustment of the sample size (from 10,000 to >18,000) powering the trial to detect a small as a 9% relative risk reduction (and with it, a minor absolute risk reduction), and what appears to be a broadening of the trial primary endpoints to include soft revascularization events [34]. Most importantly, clinicians will ultimately face significant uncertainty in generalizing results of this trial given its performance in patients with recent acute coronary syndrome, which does not match the majority of clinical scenarios in which ezetimibe use presently occurs. In the interim, regulatory officials in several European Union countries, conscious of rising health care costs and unwilling to accept an uncertain return on investment for an unproven therapy, have sensibly downgraded their recommendations regarding use of ezetimibe in prudent clinical practice.

Conflict of interest

The author reports receiving honoraria from Abbott Laboratories.

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