Serendipity of post-hoc surrogate marker research

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This editorial refers to ‘Paradoxical progression of atherosclerosis related to low-density lipoprotein reduction and exposure to ezetimibe†, by A.J. Taylor et al., on page 2939

The prerequisites under which 'novel' compounds have to show cardiovascular benefit on top of statin therapy have raised the bar for clinical endpoint studies. B-mode ultrasound measurement of the carotid intima media thickness (cIMT) is the best validated imaging modality and most widely used surrogate endpoint in intervention studies to evaluate treatment efficacy in the progression of atherosclerosis.† In contrast to the overwhelming evidence of epidemiological trials linking increased cIMT to cardiovascular risk, the evidence for a direct relationship between decreasing cIMT progression and lowering cardiovascular risk is, however, less clear.

Taylor and colleagues performed a post-hoc analysis in the Arbiter 6-HALTS trial in which they explored the relationship between treatment effects and cIMT change in 159 patients randomized to ezetimibe.‡ Ezetimibe is a cholesterol absorption inhibitor (CAI) which lowers LDL cholesterol (LDL-c) both as monotherapy (LDL-c reduction 17.2–22.3%) and on top of statin therapy (further LDL-c reduction 5–27%). The Arbiter-6 HALTS study was discontinued prematurely after an interim analysis at 14 months showing that niacin reduced cIMT progression whereas ezetimibe showed no change in cIMT.‡ In a subsequent publication, the authors confirmed a neutral effect of ezetimibe on mean cIMT change (–0.0016 ± 0.0024 mm; P = 0.88) with a hint of a positive relationship between the cumulative ezetimibe exposure (defined as ‘dose × adherence × duration’) and cIMT progression in 161 patients randomized to ezetimibe.† To explore these findings further, an additional subgroup analysis was conducted reporting that, despite a mean LDL-c decrease from 84 ± 23 to 66 ± 20 mg/dl, there was a graded increase in cIMT progression observed across quartiles of increasing LDL-c reduction (P < 0.001). Similarly, a trend was observed between cumulative ezetimibe exposure and cIMT progression (P = 0.051).‡

Although interesting, the observations reported in this small cohort are in contrast to the consistent inverse relationship between the LDL-c reduction and cIMT progression shown in a large number of randomized controlled trials comprising a much larger number of patients (Figure 1).† More importantly, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) researchers reported a positive correlation between LDL-c lowering and cIMT change in 642 patients with familial hypercholesterolaemia, showing that after 24 months a greater LDL-c reduction resulted in less progression of cIMT in the simvastatin–ezetimibe group.‡ The latter is corroborated by data from the Stop Atherosclerosis in Native Diabetics Study (SANDS) study, which also reported cIMT reduction in 499 diabetic patients following 36 months of aggressive lipid-lowering therapy with no difference in cIMT response between ezetimibe vs. non-ezetimibe users.‡ Collectively, the bulk of the data does not support an ezetimibe-induced progression of atherosclerosis as depicted by post-hoc analysis in the Arbiter 6-HALTS study. Besides the paradoxical cIMT progression in the ezetimibe-treated patients, the Arbiter 6-HALTS trial also reported a rapid and highly significant cIMT reduction (–0.0102 ± 0.0026 mm; P < 0.001) in the niacin group.‡ Based on these promising effects of niacin on cIMT, the authors concluded that the Arbiter 6-HALTS results merited strong consideration for the use of niacin in patients with low HDL. However, the AIM-HIGH trial, including 3414 patients, was prematurely discontinued because of a lack of incremental benefit of niacin over placebo with regard to cardiovascular events.§ As a result, we are presently facing a small surrogate cIMT study with results opposite to those of the outcome trial.

What are the consequences of the Arbiter 6-HALTS findings for the choice of surrogate markers in studies on cardiovascular disease? When evaluating surrogate marker studies, one should be aware of potential weaknesses of the study, with a special emphasis on the power of the study, as well as the analytical procedures and choice of endpoints. Imaging studies can then help to guide decisions on phase III trials. In view of this goal, premature discontinuation of a surrogate marker study should be strongly discouraged. Multimodality imaging including magnetic resonance imaging and positron emission tomography—computed...
tomography may show substantial advantages over cIMT, when recognizing that vulnerable plaques are not necessarily those that impinge the vessel lumen. Multimodality imaging can, besides the increase in power, add information on plaque composition, functional aspects, and vessel wall inflammation. Hence, depending upon the study questions, a careful consideration of the optimal imaging technique is warranted.

What are the consequences of the Arbiter 6-HALTS findings for management of patients at increased cardiovascular risk? Above all, the evidence for a clear benefit of intensive LDL-c lowering is robust. Whereas the bulk of evidence concerns statin-induced LDL-c reduction, a benefit of non-statin LDL-c lowering has been generally acknowledged. The latter also holds true for strategies aimed at reducing intestinal cholesterol absorption apart from CAI, such as bile acid sequestrants and ileo-caecal bypass surgery. However, Taylor and colleagues emphasize that ezetimibe may specifically lead to progression of atherosclerosis via non-LDL-related mechanisms, such as adverse effects on key cholesterol transport receptors (ABCA1, SRB1). These adverse effects, however, are not undisputed, whereas similar studies exist on non-LDL-related ‘beneficial’ effects on, for example, post-prandial triglyceride clearance and increased transintestinal cholesterol excretion by ezetimibe. For now, it is reasonable to add ezetimibe on top of statins in high-risk patients with cardiovascular disease not reaching LDL-c target levels despite intensive statin therapy and/or patients intolerant of (higher dosages of) statin therapy.

After all, the proof of the pudding is in the eating. Recently, the Study of Heart And Renal Protection (SHARP) study compared simvastatin plus ezetimibe or placebo in patients with advanced chronic kidney disease, demonstrating a significant reduction of the incidence of major atherosclerotic events by 17% when combining statin therapy with CAI. Although the SHARP trial did not include a simvastatin monotherapy group, the simvastatin–ezetimibe data in the SHARP study compare favourably with previous statin monotherapy trials, in which no significant reduction of the primary endpoint was observed in patients with renal insufficiency.

In support of this, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial reported in a post-hoc analysis that simvastatin plus ezetimibe reduced ischaemic cardiovascular events by 22% compared with placebo. The final answer will be provided by the IMPROVE-IT trial (IMProved Reduction of Outcomes: The Vytorin Efficacy International Trial), a double-blind study on cardiovascular outcomes in patients with an acute coronary syndrome, with results expected mid-2013.

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References