Ezetimibe
Rescued by Randomization (Clinical and Mendelian)

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Since its market launch in the early 2000s, ezetimibe has had a stormy history of acceptance and use by the clinical community. Ezetimibe’s initial approval by regulatory bodies was based primarily on its low side effect profile together with its ability to consistently reduce low-density lipoprotein (LDL) cholesterol by \( \approx 20\% \) either as monotherapy or as an additive to statin therapy. Notably, approval was granted despite the absence from ezetimibe’s portfolio of studies, demonstrating reductions in hard clinical cardiovascular outcomes, such as myocardial infarction or stroke. By 2006, ezetimibe accounted for \( >15\% \) of all prescriptions for lipid-lowering medications in the United States, reflecting that era’s stout faith in the reliability of LDL cholesterol as a surrogate marker for clinical end points, together with practitioners’ positive real-world experiences with ezetimibe’s biochemical efficacy and good tolerability. It was tacitly anticipated that the pending cardiovascular outcome studies would be positive, eventually vindicating the early confidence that clinicians placed in the drug.

However, the waters grew rough for ezetimibe in 2008. First, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial conducted for 24 months in 720 patients with familial hypercholesterolemia showed that combined therapy with ezetimibe and simvastatin did not significantly change carotid intima-media thickness when compared with simvastatin alone, despite decreased levels of LDL cholesterol.\(^1\) Next, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial conducted for 52 months in 1873 elderly nondiabetic patients with aortic stenosis showed that ezetimibe plus simvastatin did not reduce the composite outcome of combined aortic valve events and ischemic events.\(^2\) To add insult to injury, the 2009 Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol-6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) study demonstrated that when combined with a statin, extended-release niacin caused a significant regression of carotid intima–media thickness, whereas ezetimibe plus statin had no effect.\(^3\) In retrospect, each of these studies had its weaknesses, but their high profile effectively shifted the discussion from possible benefits of ezetimibe to its potential harms.\(^3\) Some editorialists even concluded that ezetimibe was no more than an expensive placebo.

Within 2 years, the ezetimibe-prescribing rate in the United States dropped by 50%.\(^4\) More importantly, these findings undermined, for many clinicians, the foundational LDL hypothesis in atherosclerosis. The reverberations are felt today, including current clinical practice guidelines that no longer recommend LDL cholesterol targets and discourage the use of nonstatin lipid–lowering therapies\(^5\) and a regulatory climate that no longer automatically accepts LDL cholesterol reduction without accompanying outcome data. However, the tide now seems to be turning in favor of ezetimibe based on the results of 2 recent studies, one is genetic and the other is a randomized clinical trial evaluating cardiovascular outcomes.

The molecular target for ezetimibe is the Niemann-Pick C1-like 1 (NPC1L1) transporter, which is expressed on the apical surfaces of enterocytes and hepatocytes.\(^6\) NPC1L1 increases intestinal cholesterol absorption and decreases cholesterol secretion into bile;\(^7\) disruption of the gene in mouse models and pharmacological inhibition with ezetimibe reduce both of these actions.\(^8,9\) Common single nucleotide polymorphisms (SNPs) in NPC1L1 are associated with variation in both LDL cholesterol concentrations and response to ezetimibe.\(^10,11\) Homozygous carriers of the minor alleles of 5 previously reported NPC1L1 single nucleotide polymorphisms had 2% to 8% higher LDL cholesterol levels and increased risk of coronary artery disease (CAD) events during the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial.\(^12\) These included a synonymous coding variant, rs2072183, identified by the Global Lipids Consortium, whose minor alleles increased LDL cholesterol by 2.0 mg/dL.\(^13\) However, none of these common variants were associated with CAD in the Coronary ARtery DiSease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM)+C4D meta-analysis, using either additive or recessive models of inheritance, perhaps because of their modest effect on LDL cholesterol.

In contrast to common single nucleotide polymorphisms, rare exonic variants generally exhibit greater effects on a given phenotype. For instance, by resequencing NPC1L1 in 512 subjects identified to exhibit low- or high-cholesterol absorption, Cohen et al\(^14\) identified a 5-fold excess of non-synonymous coding variants in low absorbers; these were associated with a 9% decrease in LDL cholesterol concentrations. Now, Stitziel et al\(^15\) on behalf of the Myocardial Infarction Genetics Consortium Investigators, using a...
version of the approach popularly referred to as Mendelian randomization, sequenced NPC1L1 in 7364 patients with CAD and 14,728 controls from 3 ancestral groups. They identified 34 carriers of rare inactivating mutations—non-sense, splice-site, or frameshift—in NPC1L1. One of these rare variants, namely NPC1L1 p.Arg406X, was then genotyped in an additional 22,590 patients with CAD and 68,412 controls. Heterozygous carriers of these loss-of-function alleles had a mean LDL cholesterol level that was 12 mg/dL (=10%) lower than that of noncarriers. From the overall data set of >112,000 total participants, 82 heterozygous carriers of these rare variants were found: the carriers’ odds ratio for CAD was 0.47 (95% confidence interval, 0.25–0.97; P=0.0008). No significant effects on other lipid traits were observed, isolating the association with LDL cholesterol. These findings fall in line with other Mendelian randomization studies for genetic determinants of lifelong reductions in both LDL cholesterol and CAD risk. For instance, the marked reduction in CAD risk associated with a modest difference in LDL cholesterol levels over a lifetime in carriers of NPC1L1 rare variants is similar to that reported for heterozygous carriers of rare LDL cholesterol-lowering alleles within the PCSK9 gene.

The findings of Stitziel et al. thus suggested that attenuating NPC1L1 function will reduce both LDL cholesterol and CAD events. In a remarkable turn of events, publication of that study was followed within a few days by public presentation (on November, 17, 2014) of the results of the long-awaited IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial at the American Heart Association 2014 Scientific Sessions. IMPROVE-IT was the first clinical outcomes trial designed to test the hypothesis that incremental LDL cholesterol reduction using ezetimibe versus placebo added to stable statin therapy would reduce both LDL cholesterol and CAD events. The study enrolled 18,144 patients with either ST-segment-elevation myocardial infarction (n=5192) or unstable angina/non–ST-segment-elevation myocardial infarction (n=12,952) from October 2005 to July 2010. The addition to simvastatin 40 to 80 mg of ezetimibe 10 mg was associated with a 16 mg/dL absolute difference in mean LDL cholesterol compared with placebo: 54 versus 70 mg/dL (1.4 versus 1.8 mmol/L). This LDL cholesterol difference was associated with a significant 10% reduction of the 7-year event rate for the composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio, 0.90; 95% confidence interval, 0.84–0.97; P=0.003), despite the fact that LDL cholesterol control on simvastatin alone was already excellent. This reduction in clinical outcomes, while modest, is consistent with expected effects of reducing LDL cholesterol by 16 mg/dL, as derived from 26 trials of statin therapy. That this LDL cholesterol reduction was achieved by a nonstatin therapy provides clinical and pharmacological validation for the relationship between NPC1L1 inactivation and reduction in both LDL cholesterol and cardiovascular events as predicted by the Mendelian randomization findings of Stitziel et al. The complementary findings of Stitziel et al. and IMPROVE-IT have wider implications. First, they have rescued the reputation of ezetimibe and provide solace for those of us who for more than a decade have prescribed it to dyslipidemic patients because high-dose statins were insufficiently effective or poorly tolerated. Second, they put the LDL hypothesis back on the table and should raise doubts among those holding the opinion that nonlipid or pleiotropic effects of statins supersede the importance of LDL cholesterol in CAD events. Third, these findings should reassure clinicians about the value of combination therapy with nonstatin LDL-lowering agents. Fourth, they are consistent with the idea that lower LDL cholesterol is better and should trigger reconsideration of LDL cholesterol targets in clinical guidelines. Fifth, while not eliminating the need for hard outcome studies of new LDL-lowering agents, such as PCSK9 inhibitors, they might make regulators more comfortable with the idea that LDL cholesterol reduction is a valid surrogate for reduced CAD events.

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**References**


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