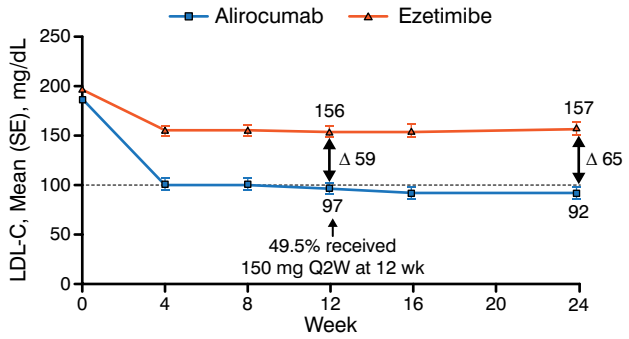
Figure 1. Effect of Alirocumab and Ezetimibe on Low-Density Lipoprotein Cholesterol Over 24 Weeks



LDL-C, low-density lipoprotein cholesterol; Q2W, every other week.
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lipoprotein cholesterol (HDL-C), and triglycerides were 191, 50, and 154 mg/dL, respectively.

In the intention-to-treat population, patients who received alirocumab experienced a significantly greater decrease in LDL-C from baseline at week 24 as compared with patients who received ezetimibe (–45% vs –14.6%; $P < .0001$). The decrease in LDL-C occurred within 4 weeks of treatment and remained steady over the study period (Figure 1). In addition, 42% of patients achieved their LDL-C goal by week 24, compared with 4% in the ezetimibe arm ($P < .0001$). Other lipids—including non-HDL-C, apolipoprotein B, and lipoprotein (a)—demonstrated a greater reduction from baseline in the alirocumab arm versus the ezetimibe arm.

In the safety analysis, a similar number of patients experienced treatment-emergent adverse events (TEAEs), with 18%, 25%, and 25% discontinuing alirocumab, ezetimibe, and atorvastatin, respectively, because of TEAEs. The number of skeletal muscle TEAEs was significantly different between the alirocumab and atorvastatin arms, ($P < .042$) but total discontinuation occurred in 19% of patients, with a similar number occurring in all 3 arms of the study. Common adverse events included myalgia, nasopharyngitis, arthralgia, upper respiratory tract infection, headache, fatigue, muscle spasms, back pain, paresthesia, vomiting, and muscular weakness. The 14-week interim analysis of the open label alirocumab period has indicated that <3% of the patients have dropped out because of TEAEs.

Dr Moriarty concluded that the data from the Odyssey Alternative trial indicate that alirocumab had greater efficacy than ezetimibe at week 24 for the reduction of LDL-C, with fewer TEAEs, including fewer skeletal muscle events. Additionally, the unpredictable nature of patients' intolerance to alirocumab, ezetimibe, and atorvastatin in the 4-week placebo period and 24-week blinded therapy period demonstrates the complexity of diagnosing and treating patients with statin intolerance.

Ezetimibe Plus Statin Reduces CV Events After ACS

Written by Emma Hitt Nichols, PhD

Combination therapy with ezetimibe and simvastatin reduced the rate of cardiovascular (CV) death, myocardial infarction (MI), hospital admission for unstable angina (UA), coronary revascularization, and stroke in patients with acute coronary syndrome (ACS) compared with simvastatin alone. Christopher P. Cannon, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data from the Improved Reduction of Outcomes: Vytorin (Ezetimibe/Simvastatin) Efficacy International Trial [IMPROVE-IT; NCT00202878].

Statins have been demonstrated to reduce morbidity and mortality; however, adding other lipid-modifying therapies to statin treatment has not demonstrated a clear benefit. Ezetimibe causes decreased cholesterol absorption by inhibiting the Niemann-Pic C_1-like$_1$ protein that is located primarily within the brush border of the epithelium of the gastrointestinal tract. The addition of a statin to ezetimibe therapy results in a synergistic decrease of approximately 20% in low-density lipoprotein cholesterol (LDL-C) reduction. The purpose of the IMPROVE-IT trial was to evaluate the clinical benefit of combination therapy with ezetimibe plus simvastatin compared with simvastatin monotherapy in lowering LDL-C levels The design and final baseline characteristics of the IMPROVE-IT trial were previously published [Blazing MA et al. *Am Heart J.* 2014; Cannon CP et al. *Am Heart J.* 2008].

In the multicenter, double-blind, phase 3 IMPROVE-IT trial, 18 144 patients with STEMI and NSTEMI, or UA who were aged ≥ 50 years were randomly assigned to receive simvastatin or ezetimibe plus simvastatin after conventional medical and interventional therapy [Blazing MA et al. *Am Heart J.* 2014]. For inclusion, patients were required to have an LDL-C level of 50 to 125 mg/dL (between 50 and 100 mg/dL if on lipid-lowering therapy) as well as ≥ 1 high-risk feature including new ST changes, positive troponin levels, diabetes mellitus (DM), history of MI, peripheral artery disease, cerebrovascular disease, prior coronary artery bypass grafting (CABG) >3 years ago, and multivessel coronary artery disease. Patients

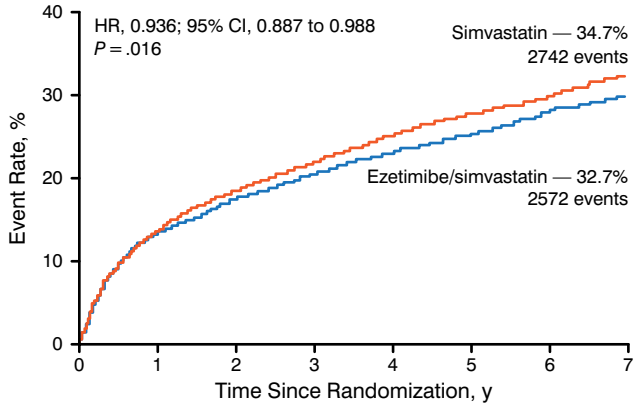
were excluded if they were undergoing CABG, their current statin therapy had potency > simvastatin 40 mg, their creatinine clearance was < 30 mL/min, or they had active liver disease.

The primary end point of the IMPROVE-IT trial was a composite score of CV death, MI, hospital admission for UA, coronary revascularization, or stroke [Blazing MA et al. *Am Heart J.* 2014]. Secondary end points included individual CV end points, as well as various composite scores. At baseline, the mean age was 64 years, 24.5% of patients were female, 27% had DM and 35.5% were on prior lipid-lowering therapy. In addition, the mean LDL-C level at the time of the ACS event was 95 mg/dL.

Treatment with ezetimibe plus simvastatin resulted in a greater decrease in mean LDL-C levels beginning at week 1 after randomization and remained steady up to 96 months. A significantly higher number of patients in the simvastatin monotherapy arm experienced the primary end point (34.7%) compared with patients in the ezetimibe plus simvastatin arm (34.7% vs 32.7%; HR, 0.936; 95% CI, 0.887 to 0.988; $P = .016$) with a number needed to treat (NNT) of 50 (Figure 1). Similarly, significantly fewer patients reached the composite of CV death, nonfatal MI, or nonfatal stroke in the ezetimibe plus simvastatin arm (20.4%) compared with the simvastatin arm (20.4% vs 22.2%; HR, 0.90; 95% CI, 0.84 to 0.97; $P = .003$) with an NNT of 56. In addition, fewer patients experienced the individual end points of MI and ischemic stroke in the combination therapy arm compared with simvastatin monotherapy.

Similar rates of adverse events occurred among both arms, such as elevated liver enzymes, cholecystectomy, gallbladder-related events, rhabdomyolysis, myopathy, and cancer.

Figure 1. Primary End Point of the IMPROVE-IT Trial



IMPROVE-IT, Improved Reduction of Outcomes: Vytorin (Ezetimibe/Simvastatin) Efficacy International Trial.

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In conclusion, Dr Cannon stated that data from the IMPROVE-IT trial suggest that the addition of a nonstatin, LDL-C–lowering agent provides an additional clinical benefit beyond statin monotherapy. In addition, he commented that the results support the LDL hypothesis that lowering LDL-C can reduce the risk of CV events.

Losartan Lacks Benefit in Inherited HCM

Written by Emma Hitt Nichols, PhD

Losartan treatment in patients with hypertrophic cardiomyopathy (HCM) did not alter left ventricular mass from baseline over 12 months compared with placebo. Anna Axelsson, MD, The Heart Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, presented data from the Inhibition of the Renin Angiotensin System With Losartan in Patients With Hypertrophic Cardiomyopathy [INHERIT; NCT01447654] trial.

HCM has a prevalence of 1 in every 500 individuals, making it the most frequently inherited cardiomyopathy, and it results in the fibrosis and hypertrophy of the left ventricle [Green JJ et al. *JACC Cardiovasc Imaging.* 2012]. Data from in vivo studies performed in animal models and humans indicate that angiotensin receptor blockers (ARBs) may have a benefit on diastolic function, left ventricular mass, exercise capacity, and myocardial fibrosis [Shimada YJ et al. *JACC Heart Fail.* 2013; Penicka M et al. *J Mol Diagn.* 2009; Araujo AQ et al. *Am J Cardiol.* 2005]. The purpose of the INHERIT trial was to evaluate the effect of the ARB losartan on morphology and function of the left ventricle in patients with HCM.

In the single-center, double-blind, phase 2 INHERIT trial, 133 adult patients with HCM were randomly assigned to receive losartan 100 mg/d or placebo for 12 months. All patients were in sinus rhythm upon inclusion into the study. Patients were excluded if they had a left ventricular ejection fraction < 50%, significant valvular disease, blood pressure > 140/90 mm Hg, an estimated glomerular filtration rate < 30 mL/min per 1.73 m^2, were currently taking an ARB or angiotensin-converting enzyme inhibitor, or had septal reduction treatment within 6 months. At baseline, the mean age was 52 years and 36% of participants were women. In the study, 64%, 30%, and 6% of patients were classified as having NYHA functional class I, II, and II, respectively. In addition, 43% of patients were identified as having a disease-causing genetic mutation.

The primary end point was change in left ventricular mass as determined by magnetic resonance imaging or computed tomography imaging. Secondary end points