of aspirin for CVD prevention, risks have also been documented [Raju NC, Eikelboom JW. *Curr Opin Cardiol.* 2012]. In addition, the US Food and Drug Administration (FDA) recently stated that current evidence does not support the general use of aspirin for the prevention of CVD [FDA. Use of Aspirin for Primary Prevention of Heart Attack and Stroke. 2014]. The purpose of the JPPP trial was to evaluate if the daily use of low-dose aspirin was effective in reducing the risk of cardiovascular (CV) events in an elderly Japanese population with risk factors for atherosclerosis.

In the prospective, randomized, open-blinded trial, 14 658 Japanese patients aged 60 to 85 years with hypertension, dyslipidemia, or diabetes mellitus were randomly assigned in a 1:1 fashion to receive enteric-coated aspirin 100 mg/d or no aspirin, in addition to their current medication to control underlying disease(s). The median follow-up was 5.02 years. At baseline, the mean age was about 71 years, about 42% were men, the mean body mass index was 24 kg/m^2, and approximately 13% of the patients were current smokers.

The primary end point was a composite of death from CV causes, nonfatal stroke, and nonfatal myocardial infarction (MI). Secondary end points included a composite of the primary end point plus transient ischemic attack, angina pectoris, and arteriosclerotic disease that required intervention. Secondary end points also included individual end points that made up the composite end points and death from causes other than CV events, all-cause mortality, and serious extracranial hemorrhage.

There was no significant difference in the proportion of patients who experienced the primary end point among the aspirin and no-aspirin arms at year 6 (2.77% with aspirin vs 2.96 with placebo; HR, 0.94; 95% CI, 0.77 to 1.15; *P*=.54). The results were consistent among major subgroups. Several secondary efficacy end points reached appeared to be lower with aspirin, including nonfatal MI (HR, 0.53; 95% CI, 0.31 to 0.91; *P*=.02) and transient ischemic attacks (HR, 0.57; 95% CI, 0.32 to 0.99; *P*=.04).

Aspirin treatment resulted in a significantly greater rate of serious extracranial hemorrhage (HR, 1.85; 95% CI, 1.22 to 2.81; *P*=.004). In addition, patients who received aspirin were more likely to experience abdominal discomfort, gastroduodenal ulcer, abdominal pain, heartburn, reflux esophagitis, erosive gastritis, gastrointestinal hemorrhage, and nausea.

Prof Shimada concluded that the data from the JPPP trial suggest that daily low-dose aspirin is not effective in decreasing the risk of CVD in elderly Japanese patients. However, he pointed out that the study was terminated early before statistical power was reached, which may have attributed to the observed lack of benefit for the primary end point.

Alirocumab Has Greater Reduction of LDL-C Than Ezetimibe in Patients With Statin Intolerance

Written by Emma Hitt Nichols, PhD

Treatment of patients who are statin intolerant with alirocumab resulted in a significantly greater reduction in low-density lipoprotein cholesterol (LDL-C) when compared with ezetimibe. Patrick M. Moriarty, MD, University of Kansas Medical Center, Kansas City, Kansas, USA, presented these results from the Study of Alirocumab (REGN727/SAR236553) in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins [Odyssey Alternative; NCT01709513].

In clinical practice, up to 25% of patients are statin intolerant as a result of symptoms and abnormalities in biomarkers [Mancini GB et al. *Can J Cardiol.* 2013; Cohen JD et al. *J Clin Lipidol.* 2012; Bruckert E et al. *Cardiovasc Drugs Ther.* 2005]. However, evidence from well-designed randomized trials is lacking for alternative cholesterol-lowering agents [Guyton JR et al. *J Clin Lipidol.* 2014]. The purpose of the Odyssey Alternative trial was to evaluate the efficacy and safety of the monoclonal antibody alirocumab in patients intolerant of statins.

In the double-blind phase 3 trial, 314 patients with statin intolerance were randomly assigned to receive alirocumab, ezetimibe, or atorvastatin for 24 weeks, followed by 2 years of open-label alirocumab treatment. Statin intolerance was defined as intolerance caused by muscle-related symptoms to a minimum of 2 statin drugs, including 1 at the lowest recommended dosage. All patients received placebo for 4 weeks before randomization. This was 1 of 3 periods of validation for these patients to determine their true intolerance to statins. During this period, 13% of patients dropped out, a majority because of muscle complaints. The patients who finished that section then were randomized into the blinded 24-week therapy section. These patients were blinded to alirocumab, ezetimibe, or atorvastatin for further validation of their intolerance to stains. At week 12, the dose of the study drug was increased if the LDL-C was ≥ 70 or ≥ 100 mg/dL, according to cardiovascular risk. The primary end point was percentage change in LDL-C from baseline in the alirocumab and ezetimibe arms.

At baseline, the mean age among all 3 cohorts was 63 years; slightly more than half were men; mean body mass index ranged from 28 to 30 kg/m^2; and 7% of patients were current smokers. Hypertension was present in 62% of the patients, type 2 DM in 24%, and chronic heart disease in 46%. The mean LDL-C, high-density

Figure 1. Effect of Alirocumab and Ezetimibe on Low-Density Lipoprotein Cholesterol Over 24 Weeks
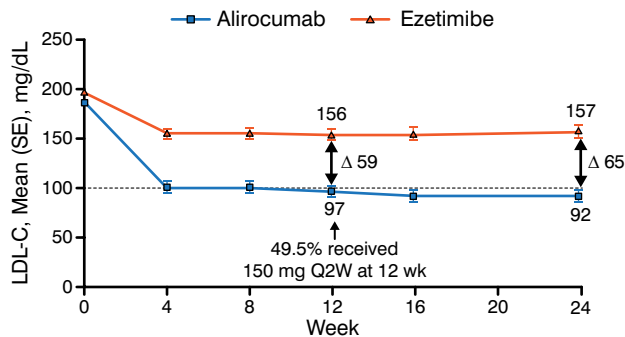
LDL-C, low-density lipoprotein cholesterol; Q2W, every other week.
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lipoprotein cholesterol (HDL-C), and triglycerides were 191, 50, and 154 mg/dL, respectively.

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