discontinuation of therapy [Zhang H et al. *Ann Intern Med* 2013; Mancini GB et al *Can J Cardiol* 2011]. Reduced adherence to, and discontinuation of, statins adversely affect survival in both the primary and secondary prevention settings [Chowdhury R et al. *Eur Heart J* 2013; Perreault S et al. *Eur J Clin Pharmacol* 2009; Rasmussen JN et al. *JAMA* 2007]. Further therapeutic efforts are therefore needed to lower low-density lipoprotein cholesterol (LDL-C) in this setting. Evolocumab, a fully human monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9), reduced levels of low-density lipoprotein cholesterol (LDL-C) to a greater extent than ezetimibe in hypercholesterolemic patients who could not tolerate effective doses of statins.

Erik Stroes, MD, Academic Medical Center, Amsterdam, The Netherlands, presented the results from a double-blind multicenter Phase 3 Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects 2 study [GAUSS-2; Stroes E et al. *J Am Coll Cardiol* 2014] in which 307 patients with hypercholesterolemia who were statin intolerant were randomized on a 2:2:1:1 basis to evolocumab, 140 mg Q2W or 420 mg QM plus daily oral placebo, or subcutaneous placebo (Q2W or QM) plus 100 mg/day of oral ezetimibe. The study was designed to build on the Phase 2 experience with evolocumab, which demonstrated potent LDL-C lowering in hypercholesterolemic patients intolerant to at least one statin [Sullivan D et al. *JAMA* 2012].

Participants qualified for the study if they were unable to tolerate effective doses of ≥2 statins because of myalgia, myopathy, myositis, or rhabdomyolysis that resolved with statin discontinuation [Stroes E et al. *J Am Coll Cardiol* 2014]. Their mean LDL-C at baseline was ~195 mg/dL. The coprimary endpoints were the mean percent change from baseline in LDL-C at Week 12 and the mean at Weeks 10 and 12.

Mean age of patients ranged from 60 to 63 years in the four treatment groups. More than 90% were white and the distribution between males and females was fairly equal. About 60% of patients qualified as high risk under the National Cholesterol Education Program risk category system. An additional 15% were classified as moderate risk. More than half of the patients were intolerant to at least three statins. Seventy eight percent to 88% had myalgia as their worst muscle-related side effect to statins.

Compared with ezetimibe, patients randomized to evolocumab Q2W had a 37% reduction in LDL-C at a mean of 10 and 12 weeks, and a 38% reduction at 12 weeks. Patients randomized to monthly evolocumab had a 39% reduction in LDL-C at a mean of 10 and 12 weeks and a 38% reduction at 12 weeks as compared with ezetimibe (p<0.001 for all comparisons). Compared with baseline, the mean reductions in LDL-C at 12 weeks were 56% with Q2W evolocumab and 53% with monthly dosing. Of evolocumab-

treated patients at high risk, >75% achieved LDL-C <100 mg/dL compared with <10% of ezetimibe-treated patients (Figure 1).

Figure 1. LDL-C Goal Achievement at Week 12
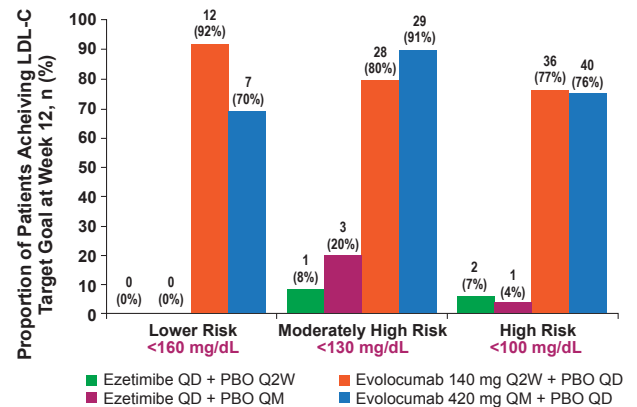


LDL-C=low-density lipoprotein cholesterol.

Reproduced from Stroes E et al. Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients with Statin Intolerance: The GAUSS-2 Randomized, Placebo-controlled Phase 3 Clinical Trial of Evolocumab. *J Am Coll Cardiol* 2014 doi: 10.1016/j.jacc.2014.03.019. With permission from Elsevier.

Both dosing frequencies of evolocumab also significantly reduced levels of apolipoprotein B and lipoprotein (a) and increased levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I.

The rate of adverse events was generally balanced across treatment groups. The most common adverse events (>5% in evolocumab combined group) were headache (8% with evolocumab vs 9% with ezetimibe), myalgia (8% vs 18%), pain in extremity (7% vs 1%), and muscle spasms (6% vs 4%).

Dr. Stroes noted that the robust LDL-C lowering and good tolerability suggests that evolocumab is a promising therapy for high-risk hypercholesterolemic patients.

# Dual PPAR Agonist Fails to Improve CV Outcomes After ACS (AleCardio)

Written by Wayne Kuznar

A dual agonist of peroxisome proliferator-activated receptors (PPARs) did not reduce adverse cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus (T2DM) Findings from the Phase 3, multinational, AleCardio study [Lincoff AM et al. *JAMA* 2014] were announced by A. Michael Lincoff, MD, Cleveland Clinic, Cleveland, Ohio, USA.

Aleglitazar is a PPAR agonist with balanced affinity for the PPAR-α and PPAR-γ subtypes. The primary effect of agonists of PPAR-α is to improve the plasma lipid profile, and the primary effect of agonists of PPAR-γ is to improve insulin sensitivity. A dual PPAR agonist, therefore, was

hypothesized to combine favorable actions on lipoproteins with insulin-sensitizing and glucose-lowering affects that might translate into a reduction in adverse CV outcomes, explained Dr. Lincoff.

In a Phase 2 trial, aleglitazar was associated with greater reductions in HbA1C and blood levels of triglycerides, and a greater increase in high-density lipoprotein cholesterol (HDL-C) than either placebo or the PPAR-γ agonist pioglitazone [Henry RR et al. *Lancet* 2009].

In AleCardio, 7226 patients with T2DM who were hospitalized with a recent acute coronary syndrome were randomly assigned in a double-blind fashion to aleglitazar 150 µg/day, or placebo in addition to standard care. The trial was conducted at 720 sites in 26 countries. Patients could be randomized up to 12 weeks after discharge to allow clinical stabilization or completion of planned revascularization. The primary endpoint of the study was the composite of time to CV death, nonfatal myocardial infarction, and nonfatal stroke. The anticipated follow-up duration to achieve 950 primary endpoints was ~2.5 years.

At baseline, patients were a mean age of 61 years. About two thirds were taking metformin, one third were on a sulfonylurea, and ~30% were being treated with insulin. More than 90% were on aspirin and a statin.

The Data Safety Monitoring Board recommended early termination of the trial due to a higher incidence of heart failure in the aleglitazar arm. The trial was terminated after a median follow-up of 104 weeks.

The primary composite endpoint occurred in 344 patients (9.5%) in the aleglitazar group and 360 patients (10.0%) in the placebo arm (Table 1), for an HR of 0.96 that was not significant (p=0.57).

Heart failure occurred more frequently in the aleglitazar arm compared with the placebo arm (4.7% vs 3.8%; HR, 1.24; p=0.06). Peripheral edema also developed significantly more often in the aleglitazar arm (14.0% vs 6.6%; p<0.001). By Month 24, mean serum creatinine increased by 0.11 mg/dL in the aleglitazar arm and by 0.01 mg/dL in the placebo arm (p<0.001), a difference that was reversible by 4 weeks after discontinuation of aleglitazar. Gastrointestinal hemorrhage was also significantly more common in the aleglitazar group (HR, 1.44; p=0.03).

HbA1C was significantly lower among patients assigned to aleglitazar compared with placebo, with the mean change from baseline being –0.99% in the aleglitazar arm and –0.36% in the placebo arm. At 3 months, HDL-C levels increased from baseline by 26.9% in the aleglitazar arm and 8.4% in the placebo arm. Triglyceride levels increased in the placebo arm and decreased by 23.9% in the aleglitazar arm. The level of low-density lipoprotein cholesterol increased in both groups, but more so in the aleglitazar arm.

The adverse effects associated with aleglitazar highlight the difficulties in developing PPAR-activating drugs where gene modulation can result in complex metabolic effects and unpredictable therapeutic profiles, concluded Dr. Lincoff.

**Table 1. Cardiovascular Efficacy Endpoints**

| | No. of Patients (%) | | | |
|---|---|---|---|---|
| | ALE n=3616 | Placebo n=3610 | HR (95% CI) | p Value |
| Primary composite: CVD, MI, stroke | 344 (9.5) | 360 (10.0) | 0.96 0.83–1.11 | 0.57 |
| CV death, MI, stroke, UA hospitalization | 441 (12.2) | 488 (13.5) | 0.90 (0.79–1.02) | 0.11 |
| Death, MI, stroke | 373 (10.3) | 392 (10.9) | 0.95 (0.83–1.10) | 0.51 |
| Death from any cause | 148 (4.1) | 138 (3.8) | 1.08 (0.85–1.36) | 0.54 |
| CV death | 112 (3.1) | 98 (2.7) | 1.15 (0.87–1.50) | 0.32 |
| Nonfatal MI | 212 (5.9) | 239 (6.6) | 0.89 (0.74–1.07) | 0.22 |
| Nonfatal stroke | 49 (1.4) | 50 (1.4) | 0.98 (0.66–1.45) | 0.92 |
| UA hospitalization | 118 (3.3) | 155 (4.3) | 0.75 (0.59–0.96) | 0.02 |
| Unplanned revascularization | 397 (11.0) | 496 (13.8) | 0.79 (0.69–0.90) | <0.001 |

ALE=aleglitazar; CV=cardiovascular; CVD=cardiovascular disease; MI=myocardial infarction; UA=unstable angina.

# Early CRT Improves Long-Term Survival in Mild Heart Failure (MADIT-CRT)

Written by Toni Rizzo

The Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT; Moss AJ et al. *N Engl J Med* 2009] trial evaluated the effect of CRT with biventricular pacing on the combined endpoint of death from any cause and nonfatal heart failure (HF) events in 1820 patients with mild HF. Eligible patients had ischemic or nonischemic cardiomyopathy with NYHA Class I or II symptoms, an ejection fraction of ≤30%, and a QRS duration of ≥130 msec. At a median follow-up of 2.4 years, the primary endpoint occurred in 17.2% of patients who received a CRT plus an implantable cardioverter defibrillator (ICD) compared with 25.3% of patients who received an ICD alone (HR, 0.66; 95% CI, 0.52 to 0.84; p=0.001). The benefit of a CRT plus ICD (CRT-D) was driven by a 41% reduction in the risk of nonfatal HF events and was observed only in patients with left bundle-branch block (LBBB) [Zareba W et al. *Circulation* 2011].

Because a survival benefit was not demonstrated for CRT-D during the MADIT-CRT trial, the aim of the long-term follow-up analysis [Goldenberg I et al. *N Engl J Med* 2014], presented by Ilan Goldenberg, MD, University of