Data were pooled from the 2 studies (n=135) for this analysis. LDL-C and TC decreased <15% in the placebo, and 0.25 mg/kg and 1 mg/kg RN316-dose groups, with reductions in LDL-C of 46% and 56% with 3- and 6-mg/kg doses of RN316, respectively (p<0.001). For the 3- and 6-mg/kg doses of RN316, there were also significant reductions in TC (30% and 37%, respectively [p<0.001]) and significant increases in HDL-C (7% and 11%, respectively [p<0.05]; Figure 1). There was no significant change in triglyceride levels. More than half of the subjects in the 3- and 6-mg/kg dose groups had at least 1 interrupted dose (19 [59.4%] and 12 [70.6%], respectively). Without dose interruption, overall LDL-C lowering at Week 12 would have been similar to maximal LDL-C lowering observed at Week 4, as confirmed by the sustained LDL-C lowering of 75% in the 6-mg/kg dose subgroup that had no dose interruption.

Figure 1. Mean LDL-C Percent Change from Baseline.
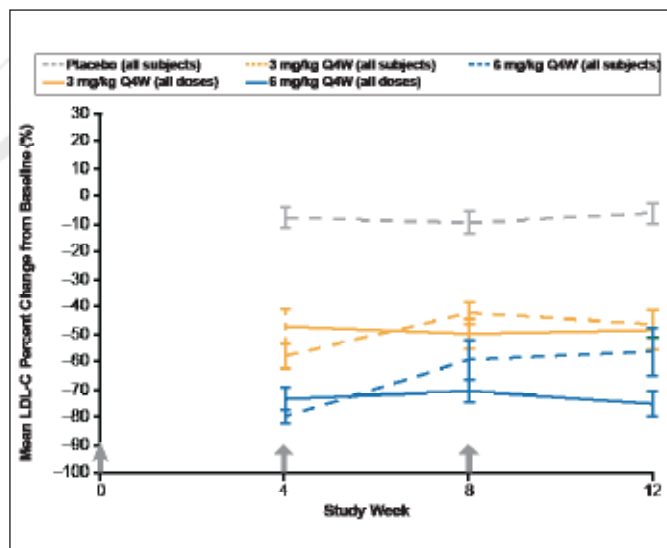
Values are mean ± SE; B1481005 and B1481012 data combined, modified ITT results; results include subjects who had dosing interrupted for LDL-C ≤25 mg/dL; * p<0.05; **p<0.001
Reproduced with permission from B Gumbiner, MD.

Approximately two thirds of all subjects experienced adverse events (AEs) that were mild in nature and resolved without intervention; Dr. Gumbiner said that majority these were reported by the investigators as not likely to be related to the study drug. Overall AEs were balanced between the randomization groups. The development of antidrug antibodies (non-neutralizing) occurred in 5% of subjects receiving RN316, but there were no hypersensitivity reactions. Dr. Gumbiner concluded that overall RN316 appeared to be efficacious, safe, and well tolerated at the doses studied.

Dalcetrapib in Patients with Recent Acute Coronary Syndrome

Written by Toni Rizzo

Observational studies have suggested that spontaneously higher high-density lipoprotein cholesterol (HDL-C) levels are associated with lower cardiovascular (CV) risk; however, it is uncertain whether raising HDL-C by a pharmacologic approach reduces the risk. The cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib raised HDL-C by approximately 30% in Phase 2 trials [Lüscher TF et al. *Eur Heart* 2012; Fayad ZA et al. *Lancet* 2011] without affecting blood pressure (BP) or neurohormones. The objective of the Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome [dal-OUTCOMES; NCT00658515; Schwartz GG et al. *N Engl J Med* 2012] presented by Gregory G. Schwartz, MD, PhD, VA Medical Center and University of Colorado School of Medicine, Denver, Colorado, USA, was to compare the effects of dalcetrapib versus placebo in patients with recent acute coronary syndrome (ACS).

Following a single-blind placebo run-in period of 4 to 12 weeks, patients with recent ACS were randomized to dalcetrapib (n=7938) versus placebo (n=7933) in addition to evidence-based background therapy. Patients with triglycerides >400 mg/dL or under treatment with niacin, fibrates, or bile acid sequestrants were excluded. The primary composite endpoint was time to first occurrence of coronary heart disease death, nonfatal myocardial infarction (MI), ischemic stroke, hospitalization for unstable angina, and cardiac arrest with resuscitation. Secondary endpoints were all-cause mortality and coronary revascularization. The study was terminated for futility at the second prespecified interim analysis (median follow-up 31 months) with 1135 primary endpoint events (71% of projected) since the probability of demonstrating a benefit with dalcetrapib was <20%.

Baseline characteristics, concurrent treatments, and baseline lipid levels were well balanced between the treatment groups. Dalcetrapib raised HDL-C from 43 mg/dL to 59 mg/dL compared with only a slight increase from 43 mg/dL to 45 mg/dL in the placebo group. Low-density lipoprotein cholesterol (LDL-C) averaged 76 mg/dL at baseline in both groups and differed minimally between groups during the study. Despite the effect of dalcetrapib on HDL-C, there was no significant difference in the cumulative percentage of patients reaching the primary endpoint with dalcetrapib (3-year event rate 9.2%) versus placebo (9.1%; HR, 1.04; 95% CI, 0.93 to 1.16; p=0.52).

There were no significant differences in the dalcetrapib versus placebo group in any of the individual components of the primary composite outcome or in the secondary outcomes (Table 1).

Table 1. Primary and Secondary Endpoint Events.

Event	Dalcetrapib (% at 3 Years)	Placebo (% at 3 Years)	Hazard Ratio (95% CI)	p Value
Primary composite	9.2	9.1	1.04 (0.93–1.16)	0.52
CHD death	1.6	1.8	0.94 (0.73–1.21)	0.66
Nonfatal MI	5.9	6.0	1.02 (0.89–1.17)	0.80
Unstable angina	1.3	1.3	0.91 (0.68–1.22)	0.54
Resuscitated cardiac arrest	0.2	0.1	1.41 (0.63–3.18)	0.40
Ischemic stroke	1.4	1.0	1.25 (0.92–1.70)	0.16
All-cause mortality	3.1	3.4	0.99 (0.82–1.19)	0.90
Coronary revascularization	9.5	9.6	1.00 (0.90–1.11)	0.97

CHD=coronary heart disease ; MI=myocardial infarction.
Adapted from Schwartz GG et al. Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome. *N Engl J Med* 2012; 367:2089-2099.

Analysis of the annualized event rates relative to baseline or on-treatment HDL-C levels showed that there was no association between baseline HDL-C and risk of the primary endpoint. Mean systolic BP was 0.6 mm Hg higher in patients treated with dalcetrapib versus placebo (p<0.001). After 3 months on assigned treatment, the median high sensitivity C-reactive protein (hs-CRP) level was 0.2 mg/L higher in the dalcetrapib versus placebo group (p<0.001).

In this study dalcetrapib raised HDL-C by about 30% with a minimal effect on LDL-C, but had no effect on the risk of major CV events in patients with recent ACS. HDL-C concentration did not predict risk in this study population. Slightly higher systolic BP and CRP caused by dalcetrapib might represent adverse effects of CETP inhibition. This is now the second large trial with a CETP inhibitor that failed to show benefit (see *MD Conference Express Coverage* of AHA 2007 Issue coverage of the ILLUMINATE trial). The REVEAL-HPS 3/TIMI 55 trial continues to test anacetrapib, which has more robust LDL-C lowering in addition to its HDL-C raising effects, in an ongoing trial of 30,000 patients with established vascular disease.

Together with the recently terminated AIM-HIGH study in which niacin raised HDL-C by approximately 15% but had no effect on CV events [The AIM-HIGH Investigators. *N Engl J Med* 2011], the dal-OUTCOMES study challenges the long-held assumption that raising HDL-C concentration favorably modifies CV risk. However, HDL-C concentration may not reflect HDL function, such as reverse cholesterol transport from tissues to liver. It remains to be determined whether measures of HDL function bore a relationship to risk in dal-OUTCOMES and/or were affected by dalcetrapib treatment.

MADIT-RIT: ICD Programming Change Reduces Inappropriate Therapy and All-Cause Mortality

Written by Rita Buckley

Arthur J. Moss, MD, University of Rochester Medical Center, Rochester, New York, USA, presented findings from the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy [MADIT-RIT; NCT00947310] that were simultaneously published in the *New England Journal of Medicine* [Moss AJ et al. 2012].

Inappropriate therapy delivered by implantable cardioverter-defibrillators (ICDs) is defined as ICD therapies that are triggered by nonventricular tachyarrhythmias. These errors occur frequently despite sophisticated device-related detection algorithms designed to differentiate supraventricular from ventricular tachyarrhythmias [Moss AJ et al. *N Engl J Med* 2012]. Activations that fail to make this distinction can have potentially life-threatening consequences [Daubert JP et al. *J Am Coll Cardiol* 2008].

MADIT-RIT was a global, prospective, randomized, nonblinded, 3-arm, multicenter clinical investigation performed at 98 hospital centers in the United States, Europe, Canada, Israel, and Japan from September 15, 2009, through trial termination on July 10, 2012. The study assessed specific programming features for reducing inappropriate therapy in patients with ICDs.

The primary objective was to determine whether programmed high-rate therapy (with a 2.5-second delay before the initiation of therapy at a heart rate of ≥200 beats per minute [bpm]) or delayed therapy (with a 60-second delay at 170 to 199 bpm, a 12-second delay at 200 to 249 bpm, and a 2.5-second delay at ≥250 bpm) was associated with a decrease in the number of patients with a first occurrence of inappropriate antitachycardia pacing or shocks compared with conventional programming (with a 2.5-second delay at 170 to 199 bpm and a 1.0-second delay at ≥200 bpm). The secondary endpoints were death from any cause and the first episode of syncope.

A total of 1500 patients were randomized to high-rate therapy (n=500), delayed therapy (n=486), or conventional