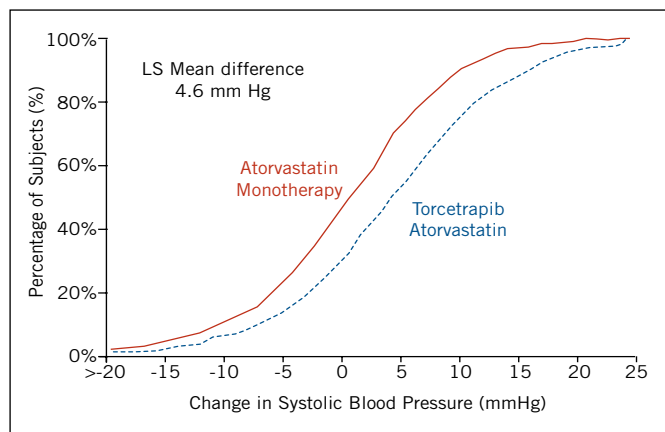**Figure 1. Cumulative Histogram Change in Systolic Blood Pressure.**

Dr. Kastelein presented the results from the RADIANCE 1 and RADIANCE 2 studies. Both studies sought to determine the change in atherosclerosis, using imaging, after treatment with either torcetrapib plus atorvastatin or with atorvastatin alone. RADIANCE 1 was conducted in patients with heterozygous familial hypercholesterolemia (HeFH) and RADIANCE 2 was conducted in patients with mixed hyperlipidemia. These patient populations were selected because they tend to have low levels of HDL-C and high levels of LDL-C. Subjects were treated with atorvastatin to reduce their LDL-C to goal, and then randomly assigned to one of the two treatment arms. The studies were conducted in 8 countries, and scans were centrally read in Europe and the United States. The primary outcome measure of both studies was change in the maximum carotid intima-media thickness (max CIMT).

There was no significant difference in atherosclerotic progression in the torcetrapib/atorvastatin treatment arm (n=450) compared with the atorvastatin monotherapy arm (n=454) despite a 52% increase in HDL-C and a 21% decrease in LDL-C (Figure 2). In addition, the torcetrapib/atorvastatin arm had approximately twice as many serious cardiovascular events when compared with the atorvastatin monotherapy arm (5.3% vs 2.4%, respectively). In the RADIANCE 2 trial, 377 patients were treated with torcetrapib/atorvastatin and 375 patients were treated with atorvastatin alone. There were no differences in any of the arms at any time point. Dr. Kastelein described the graph of the max CIMT of the two treatment arms over time as flat. (Figure 3).
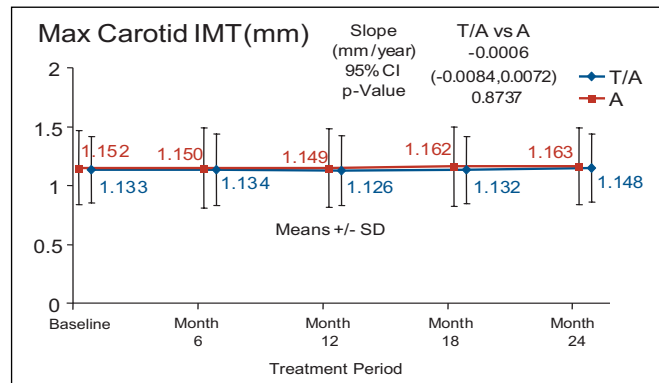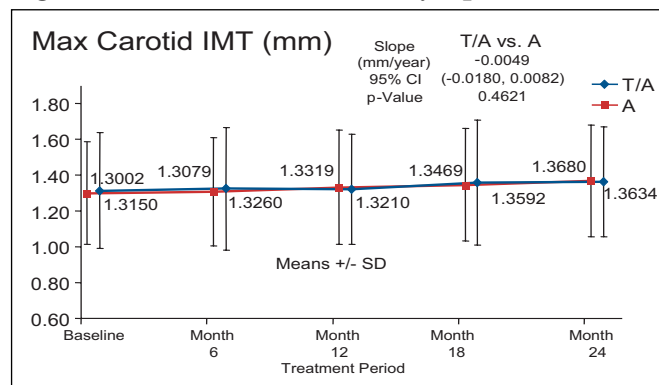
Figure 2. RADIANCE 1 – Heterozygous FH.

Figure 3. RADIANCE 2 – Mixed Dyslipidemia.

Both investigators emphasized that although development has ceased on this particular compound, the class of drugs still holds promise.

Ranolazine Reduces Recurrent Ischemia in Patients with Non-ST Elevation ACS

Ranolazine is an anti-ischemic agent indicated for the treatment of chronic angina. Its effects occur without clinically significant changes in heart rate or blood pressure. However, because ranolazine is associated with a mild prolongation of the QTc interval (mean change approximately 6 ms), it currently is indicated only for patients who have not responded to other therapies. Because of this potentially worrisome prolongation of the QT interval, additional safety data were sought. David Morrow, MD, MPH, of Brigham and Women's Hospital, gave an overview of the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome (MERLIN TIMI 36) study. The study had three main objectives: 1) to

assess acute efficacy of ranolazine in acute coronary syndrome (ACS) by determining the potential for a decrease in major cardiovascular events, 2) to assess chronic efficacy of the drug for secondary prevention and relief of angina and 3) to evaluate the safety of the compound in the acute and chronic setting.

The trial included patients hospitalized with non-ST-elevation ACS with ischemic symptoms at rest and at least one of four features indicating moderate to high risk: 1) an increase in troponin (myocardial infarction limit) or creatinine kinase -MB (upper limit of normal); 2) ST-depression ≥0.1mV; 3) diabetes mellitus, or; 4) a TIMI risk score for unstable angina/non-ST-elevation myocardial infarction ≥3.

A total of 6,550 patients were randomly assigned in a 1:1 ratio to one of two treatment groups: 1) ranolazine IV 200 mg over one hour, followed by 80 mg/hour infusion for up to 96 hours, followed by ranolazine 1000 mg/day PO or; 2) IV and oral placebo given in an identical fashion. Patients were monitored by continuous Holter for one week. The primary endpoint was a composite of cardiovascular death, new/recurrent myocardial infarction (MI), and recurrent ischemia. The primary endpoints were adjudicated by a blinded cardiovascular events committee.

The baseline demographic characteristics were well balanced between the ranolazine (n=3,279) and the placebo group (n=3,281). Primary endpoint analyses indicated no statistically significant difference in the composite of cardiovascular death, MI, or recurrent ischemia between the two groups (p=0.11; Figure 1). In an analysis of the components of the primary endpoint, ranolazine had no effect on cardiovascular death or MI. However, ranolazine was significantly better than placebo in reducing recurrent ischemia (p=0.03; Figure 2).
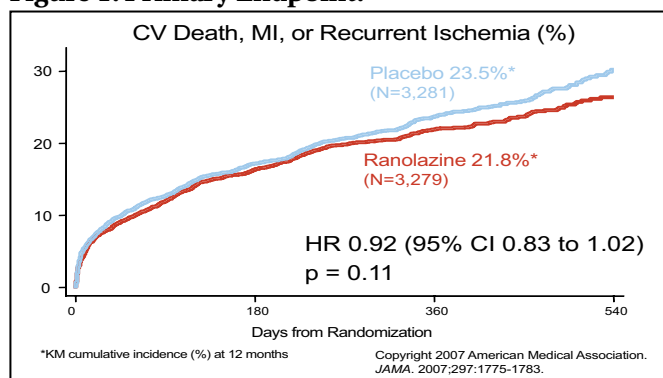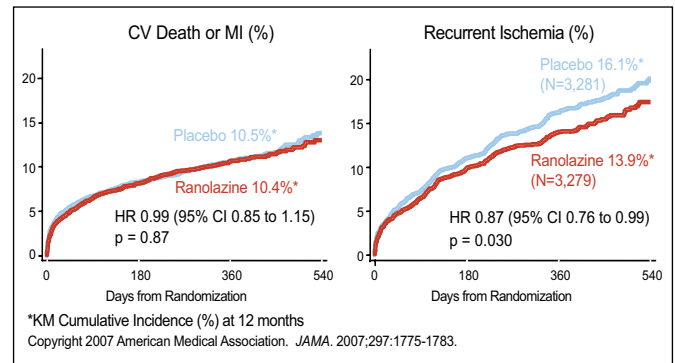
Figure 1. Primary Endpoint.

CV Death, MI, or Recurrent Ischemia (%)

Placebo 23.5%* (N=3,281)

Ranolazine 21.8%* (N=3,279)

HR 0.92 (95% CI 0.83 to 1.02) p = 0.11

Days from Randomization

*KM cumulative incidence (%) at 12 months   Copyright 2007 American Medical Association. *JAMA*. 2007;297:1775-1783.

Figure 2. Components of Primary Endpoint.

CV Death or MI (%)

Placebo 10.5%*

Ranolazine 10.4%*

HR 0.99 (95% CI 0.85 to 1.15) p = 0.87

Recurrent Ischemia (%)

Placebo 16.1%* (N=3,281)

Ranolazine 13.9%* (N=3,279)

HR 0.87 (95% CI 0.76 to 0.99) p = 0.030

Days from Randomization

*KM Cumulative Incidence (%) at 12 months
Copyright 2007 American Medical Association. *JAMA*. 2007;297:1775-1783.

The safety findings indicated no significant differences in death from any cause, sudden cardiac death, death or cardiovascular hospitalization, or symptomatic documented arrhythmia. Significantly more placebo-treated patients experienced a pre-specified set of arrhythmias on Holter (83.1% vs 73.7%, respectively; p<0.001). Dr. Morrow concluded by saying that ranolazine does not add to standard therapy for acute management of ACS. Ranolazine did not reduce cardiovascular death or MI, but was effective as an anti-anginal, with overall safety findings that were reassuring, including potential anti-arrhythmic effects that deserve further study.

The COURAGE Trial: Optimal Medical Therapy Equivalent to PCI

Percutaneous coronary intervention (PCI) is a widely used method of restoring normal blood flow to the myocardium and is lifesaving during acute coronary events. There are little long-term clinical outcome data, however, on the benefits of PCI in patients who have stable coronary artery disease (CAD). William E. Boden, MD, of the Western New York Veterans Affairs Healthcare Network presented the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation (COURAGE) study (*N Engl J Med*. 2007; 356:1503-1516). The objective of this study was to determine if PCI combined with optimal medical therapy (OMT) was more beneficial than optimal medical therapy alone in patients with stable coronary artery disease. The primary endpoint was death from any cause or nonfatal myocardial infarction (MI) during a median follow-up period of 4.6 years.