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

therapy (n=514). Baseline characteristics were similar. During a mean follow-up of 1.4 years, high-rate therapy and delayed ICD therapy significantly reduced inappropriate therapy compared with conventional therapy—high-rate therapy vs conventional therapy (HR, 0.21; 95% CI, 0.13 to 0.34; p<0.001), delayed therapy vs conventional therapy (HR, 0.24; 95% CI, 0.15 to 0.40; p<0.001)—and reduced all-cause mortality (HR, 0.45; 95% CI, 0.24 to 0.85; p=0.01; HR, 0.56; 95% CI, 0.30 to 1.02; p=0.06; respectively for the same comparisons). The frequency of a first episode of syncope was similar in the 3 treatment groups: high-rate therapy (22), delayed therapy (23), and conventional therapy (23).

Compared with conventional programming, ICD therapies for tachyarrhythmias of 200 bpm or higher, or with a prolonged delay in therapy at 170 bpm or higher are associated with reductions in inappropriate therapy and all-cause mortality during long-term follow-up. Wilkoff [*N Engl J Med* 2012] noted in a related editorial that the value of ICD therapy is greatly influenced and in many ways determined by the programming choices made by the physician. The results of MADIT-RIT call for careful reconsideration of the previously measured effects of ICD therapy on morbidity and mortality. A patient's unnecessary exposure to painful shocks and his or her survival may depend on programming choices.

Serelaxin as a Novel Treatment for Acute Heart Failure: Results of the RELAX-AHF Trial

Written by ***Phil Vinall***

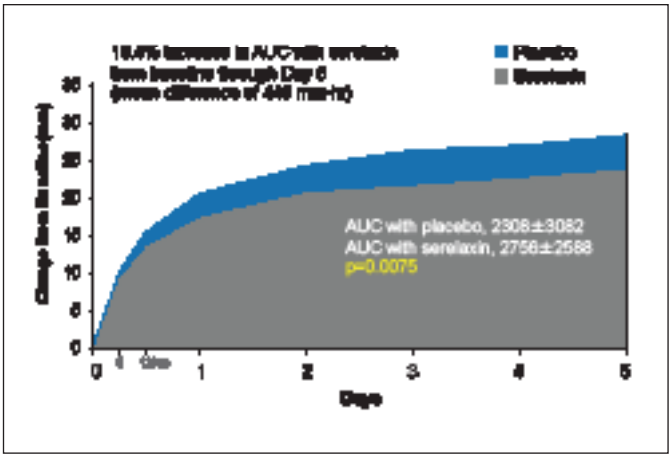
Relaxin, a naturally occurring peptide, is associated with hemodynamic changes as well anti-ischemic, anti-inflammatory, and antifibrotic effects that may offer benefit to patients with acute heart failure (AHF). John R. Teerlink, MD, University of California, San Francisco, California, USA, reported the results of the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure [RELAX-AHF; NCT00520806] trial designed to test the efficacy and safety of serelaxin, a recombinant version of human relaxin-2, in patients with AHF. Serelaxin was associated with relief of dyspnea and reduced hospital stay in patients hospitalized with acute decompensated heart failure.

Patients (n=1161) were enrolled in this international, double-blind, placebo-controlled trial who were aged ≥18 years, weighed <160 kg, and were hospitalized for AHF. All patients had dyspnea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-proBNP), mild-to-moderate renal insufficiency, and systolic blood pressure (SBP) >125 mm Hg. Within 16 hours of presentation, eligible subjects were randomly assigned to standard care plus 48-hour intravenous (IV) infusions of placebo (n=580) or serelaxin 30 µg/kg/day (n=581).

The primary endpoints were change from baseline in the visual analog scale area under the curve (VAS AUC) to Day 5 and the proportion of patients with moderate or marked dyspnea improvement measured by Likert scale during the first 24 hours. Subjects had a mean age of 72 years, SBP of 142 mm Hg and evidence of mild-to-moderate renal insufficiency (with estimated glomerular filtration rate 53.5 mL/min/1.73 m^2), and average NT-proBNP 5064 ng/L. The mean time to enrollment was 8 hours.

There was a 19.4% improvement in VAS AUC with serelaxin from baseline through Day 5, with a mean difference of 448 mm-hr compared with placebo (p=0.0075; Figure 1). However, there was no statistical difference in relief of dyspnea based on Likert scale measurements taken at 6, 12, and 24 hours. The Kaplan-Meier estimate for the secondary endpoint of time to cardiovascular death or HF/renal function rehospitalization at Day 60 was not significantly different between treatment groups (7.5% vs 6.9%; HR, 1.08; 95% CI, 0.70 to 1.66; p=0.73). There was, however, a significant decrease in the exploratory endpoint of cardiovascular death through Day 180 with serelaxin as compared with placebo (9.6% vs 6.1%; HR, 0.63; 95% CI, 0.41 to 0.96; p=0.028; Figure 2) as well as a significant 37% reduction in all-cause death (Figure 3).

Figure 1. Dyspnea Relief (VAS AUC).



AUC=area under the curve; VAS=visual analog scale.

Treatment with serelaxin was associated with improvements in the signs and symptoms of congestion at Day 2 as well as biomarkers of neurohormonal activation and myocyte stress. Use of seralaxin was