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***

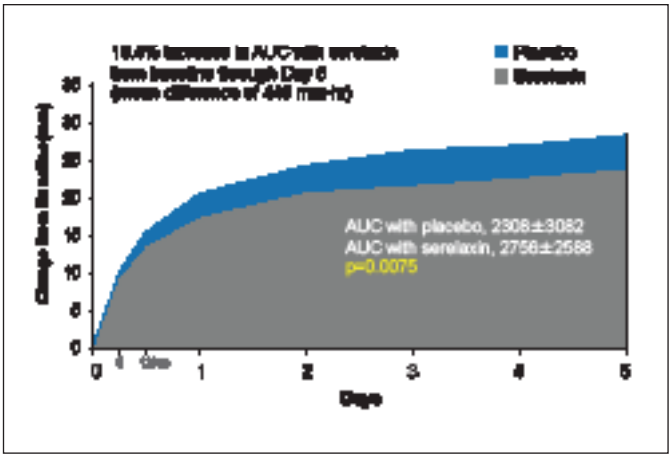
Relaxin, a naturally occurring peptide, is associated with hemodynamic changes as well anti-ischemic, anti-inflammatory, and antifibrotic effects that may offer benefit to patients with acute heart failure (AHF). John R. Teerlink, MD, University of California, San Francisco, California, USA, reported 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).

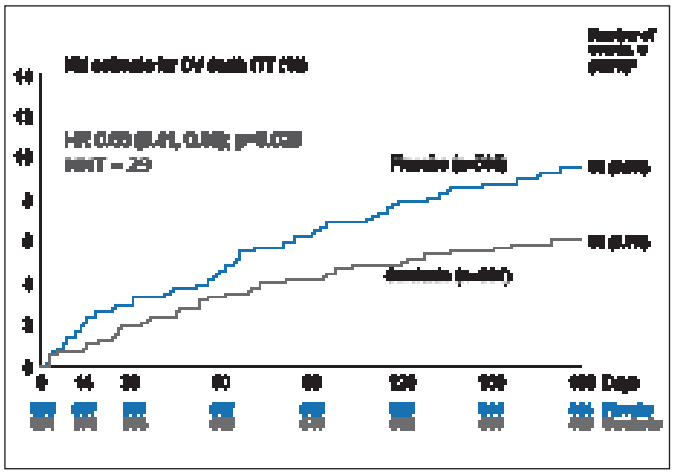


AUC=area under the curve; VAS=visual analog scale.

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

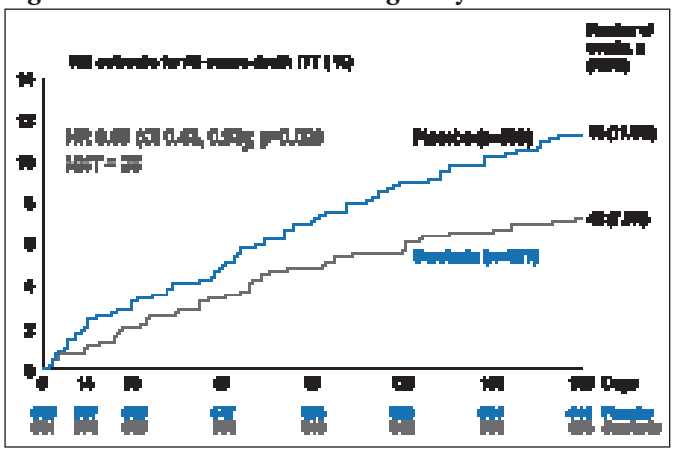
also associated with reductions in resource utilization including intravenous diuretics and length of ICU stay and hospital (p<0.05).

Figure 2. Cardiovascular Death Through Day 180.



CV=cardiovascular; ITT=intention-to-treat; KM=Kaplan-Meier; NNT=number needed to treat.

Figure 3. All-Cause Death Through Day 180.



KM=Kaplan-Meier; ITT=intention-to-treat; NNT=number needed to treat.
Figures 1 through 3 reprinted from *The Lancet* [Epub ahead of print Nov. 7, 2012], Teerlink JR et al. Serelaxin, Recombinant Human Relaxin-2, for Treatment of Acute Heart Failure (RELAX-AHF): A Randomised, Placebo-Controlled Trial. Copyright 2012, with permission from Elsevier.

Adverse events (AEs), including serious AEs, were similar between treatment arms except for renal impairment-related AEs, which occurred significantly (6% vs 9%; p=0.03) less often in the serelaxin arm. Dr. Teerlink concluded that the findings of the RELAX-HF trial suggest some benefit to early treatment with serelaxin in patients with AHF but additional large clinical outcomes studies are needed to further define its role in the management of AHF, the optimal target population, and the cost-effectiveness of therapy [Teerlink JR et al. *Lancet* 2012; Metra M et al. *J Am Coll Cardiol*. In press].

ARCTIC: Randomized Trial of Bedside Platelet Function Monitoring

Written by ***Toni Rizzo***

Responses to oral antiplatelet therapy between patients are variable; thus, bedside assessment has been regarded as an opportunity for individualizing therapy for patients following coronary stent implantation to ensure the optimal platelet inhibition is obtained. The Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation and Interruption Versus Continuation of Double Antiplatelet Therapy [ARCTIC; NCT00827411; Collet JP et al. *N Engl J Med* 2012] trial presented by Gilles Montalescot, MD, PhD, Hôpital Pitié-Salpêtrière, Paris, France, evaluated platelet function testing (PFT) with antiplatelet dose adjustment in suboptimal responders compared with standard of care.

Patients scheduled for planned percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation were randomized to PFT and antiplatelet therapy with dose adjustment for high platelet reactivity (n=1213) versus conventional therapy (n=1227). Patients in both groups then underwent PCI with stent implantation followed by drug and dose adjustment for high platelet reactivity at Day 14 versus conventional therapy. The VerifyNow P2Y12 and aspirin assays were used to estimate the inhibition of platelet aggregation provided by clopidogrel and aspirin. The primary endpoint was death, MI, stroke or transient ischemic attack, stent thrombosis, or urgent revascularization at 12 months. The main secondary endpoints were stent thrombosis or urgent revascularization and major bleeding. The antiplatelet dose adjustment rules used in the study are shown in Figure 1.

Of the total 2440 patients, 20% were women, 37% had a history of diabetes mellitus, and 31% had a history of myocardial infarction (MI). In the PFT group, 7.6% of patients were aspirin poor responders and 35% were thienopyridine poor responders. Among the aspirin poor responders, 85% received on-table aspirin loading. Thienopyridine poor responders received on-table clopidogrel loading (80%), on-table prasugrel loading (3.3%), and on-table GP IIb/IIIa inhibitor loading (80%). Among patients with high on-clopidogrel reactivity at Day 14, 43% had their clopidogrel maintenance increased and 17% were started on prasugrel maintenance dose. Among patients with high on-aspirin reactivity, 46% had their aspirin maintenance dose increased.