Science Advisor's Note: Hospitalization for HF was not reported in the primary EXAMINE publication but was recorded as an exploratory CV endpoint [White WB et al. *Am Heart J* 2011;162:2634-53 (Appendix A)]. Given the results of SAVOR-TIMI 53, further description of this endpoint in EXAMINE will be important in determining whether this is a class effect and clarifying the underlying mechanism.

No Improvement With CRT in Patients With HF and QRS <130 msec

Written by Toni Rizzo

The current 2012 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure (HF) recommend cardiac resynchronization therapy (CRT) for symptomatic HF and a QRS complex ≥120 msec [McMurray JJV et al. *Eur Heart J* 2012]. Although CRT is not currently recommended for HF patients with a QRS complex <120 msec, many such patients have evidence of mechanical dyssynchrony by echocardiography.

The Echocardiography Guided Cardiac Resynchronization Therapy study [EchoCRT; Ruschitzka F et al. *N Engl J Med* 2013] was a prospective, multicenter, randomized, clinical trial designed to evaluate the effect of CRT on morbidity and mortality in patients with symptomatic HF, a QRS complex <130 msec, and evidence of mechanical dyssynchrony. On March 13, 2013, the trial was stopped for futility at the recommendation of the Data and Safety Monitoring Board. The results of the trial were presented by Johannes Holzmeister, MD, University of Zurich, Zurich, Switzerland.

At enrollment, patients had NYHA Class III to IV HF, stable pharmacologic therapy, left-ventricular systolic dysfunction and dilation (ejection fraction ≤35%; left-ventricular end diastolic diameter ≥55 mm), QRS <130 msec, and ventricular dyssynchrony by tissue Doppler imaging and speckle-tracking radial strain on echocardiography. Of the 855 eligible patients, 809 had a successful implantation with a Lumax HF-T CRT-D device and underwent randomization [CRT turned "on" group (n=404); CRT turned "off" group (n=405)].

The primary efficacy endpoint was all-cause mortality or first hospitalization for worsening HF. The primary safety endpoint was freedom from complications due to the CRT-D system at 6 months. Baseline characteristics were similar in both groups, with the exception of chronic kidney disease, which was more common in the CRT group. Utilization of standard HF therapies was very high in both groups (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker 95%, β-blocker 96% to 98%, and aldosterone antagonist 59% to 60%).

The study terminated at a median follow-up of 19.4 months. The primary efficacy endpoint occurred in 28.7% of patients in the CRT group and 25.2% of patients in the control group (HR, 1.20; 95% CI, 0.92 to 1.57; p=0.15; Table 1). Secondary efficacy endpoints including all-cause mortality (Table 2), cardiovascular mortality, and hospitalization for worsening HF occurred more frequently in the CRT group. It is important to interpret the secondary outcomes with caution, especially in the context of the early termination of the trial.

Table 1. Risk of Death or Hospitalization for HF Among All Patients

Endpoint	Control Group (n=405) Number (%) With Event	CRT Group (n=404) Number (%) With Event	Adjusted HR (95% CI) p Value
Primary Endpoint Composite			
Death or WHF hospitalization	102 (25.2%)	116 (28.7%)	1.20 (0.92–1.57); 0.15
Primary Endpoint Components			
WHF hospitalization	90 (22.2%)	99 (24.5%)	1.16 (0.87–1.55); 0.25
All-cause mortality	26 (6.4%)	45 (11.1%)	1.81 (1.11–2.93); 0.02
Other CV Endpoints			
CV hospitalization	137 (33.8%)	147 (36.4%)	1.11 (0.88–1.40); 0.36
CV mortality	17 (4.2%)	37 (9.2%)	2.26 (1.27–4.01); 0.004

CRT=cardiac resynchronization therapy; CV=cardiovascular; WHF=worsening heart failure.

4 deaths in the control group and 1 death in CRT group were after (L)VAD /Transplant and were excluded from analysis; HR (95% CI) from Cox model adjusted for country and p value from stratified log-rank test.

Table 2. All-Cause Mortality Components

Reason	Control Group (n=405) Number (%) With Event	CRT Group (n=404) Number (%) With Event
Cardiovascular/vascular	17 (4.2%)	37 (9.2%)**
Death due to heart failure	10 (2.5%)	17 (4.2%)
Death due to arrhythmic events	4 (1.0%)	14 (3.5%)*
Death due to nonischemic dysrhythmia	0	2 (0.5%)
Death due to symptomatic heart block/bradycardia/PEA	0	4 (1.0%)
Sudden cardiac death	4 (1.0%)	8 (2.0%)
Presumed cardiovascular death	1 (0.3%)	5 (1.2%)
Fatal stroke	1 (0.3%)	1 (0.3%)
Other vascular death	1 (0.3%)	0
Noncardiovascular	9 (2.2%)	8 (2.0%)

CRT=cardiac resynchronization therapy; PEA=pulseless electrical activity.

Statistically significant difference of *p<0.05, **p<0.01; 4 deaths in the control group and 1 death in CRT group were after (L)VAD/Transplant and were excluded from analysis; p value from stratified log-rank test.

The rate of freedom from complications related to the CRT-D system at 6 months was 89.6% for all patients who underwent attempted device implantation. Total serious adverse events (939 vs 732) and CRT-D-system related events (74 vs 32) were higher in the CRT arm.

The results of EchoCRT study confirm that patients with a narrow QRS complex should not receive CRT. Even following current guidelines (QRS ≥120 msec), the rate of "nonresponders" to CRT is very high and further research is needed to better identify those patients with moderate QRS widening (120 and 150 msec) who are most likely to benefit.

Cangrelor Reduces Thrombotic Events Among Patients Undergoing PCI

Written by Nicola Parry

Christian W. Hamm, MD, PhD, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany, presented pooled data from three clinical trials of cangrelor, an intravenous adenosine diphosphate (ADP)-receptor antagonist in patients undergoing percutaneous coronary intervention (PCI) demonstrating significant reductions in thrombotic complications without an increase in major bleeding.

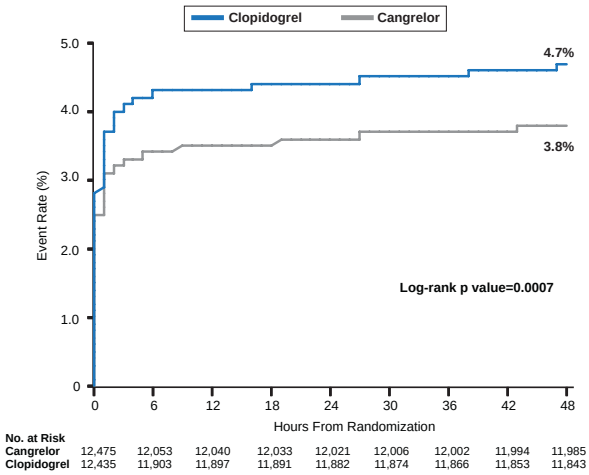
The efficacy of the novel, investigational agent cangrelor, a potent intravenous ADP-receptor antagonist with fast onset and short half-life of 3 to 6 minutes, has been evaluated in three randomized, double-blind, clinical trials against clopidogrel or placebo in patients during and after PCI: CHAMPION PHOENIX [Bhatt DL et al. *N Engl J Med* 2013]; CHAMPION PLATFORM [Bhatt DL et al. *N Engl J Med* 2009]; and CHAMPION PCI [Harrington RA et al. *N Engl J Med* 2009].

Prof. Hamm discussed the results of a meta-analysis of 24,910 patients enrolled in the CHAMPION program. The primary endpoint of the study was the composite of death from any cause, myocardial infarction (MI), ischemia-driven revascularization (IDR), or stent thrombosis (ST) at 48 hours. Secondary endpoints included ST at 48 hours and the composite endpoint of death/MI/IDR at 48 hours. The primary safety endpoint was GUSTO severe bleeding at 48 hours [Steg PG et al. *Lancet* 2013].

The efficacy analysis included patients (72% male; mean age 63 years) undergoing PCI for ST-elevation myocardial infarction (STEMI; 11.6%), non-ST elevation acute coronary syndromes (ACS; 57.4%), and stable coronary artery disease (31.0%) [Steg PG et al. *Lancet* 2013].

Among patients undergoing PCI, cangrelor was associated with a significant 19% relative reduction in the death/MI/IDR/ST at 48 hours compared with control (clopidogrel or placebo; 3.8% vs 4.7%; OR, 0.81; 95% CI, 0.71 to 0.91; p=0.0007; Figure 1) [Steg PG et al. *Lancet* 2013].

Figure 1. Rate of Primary Efficacy Endpoint in Cangrelor Versus Clopidogrel Groups



Reproduced from Steg PG et al. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 2013. With permission from Elsevier.

The rate of ST at 48 hours was reduced by 41% with cangrelor compared with control (0.5% vs 0.8%; OR, 0.59; 95% CI, 0.43 to 0.80; p=0.0008). There was no significant difference in GUSTO severe bleeding, the primary safety endpoint, GUSTO moderate bleeding, or in the rate of blood transfusions between cangrelor and control groups. The rate of GUSTO mild bleeding, however, was increased with cangrelor treatment (16.8% vs 13.0%; p<0.0001) [Steg PG et al. *Lancet* 2013].

Prof. Hamm noted that follow-up was limited to 30 days because this corresponded to data that were available from the CHAMPION PHOENIX study [Bhatt DL et al. *N Engl J Med* 2013]. Despite this minor limitation in the dataset, he concluded that the results of this analysis suggest intravenous cangrelor may represent a viable treatment option to reduce periprocedural thrombotic complications across the range of PCIs, including patients with STEMI, non-ST elevation ACS and stable angina [Steg PG et al. *Lancet* 2013].

Catheter-Based Renal Artery Denervation – Sustained Blood Pressure Lowering With Reassuring Safety at 3 Years

Written by Nicola Parry

Catheter-based renal artery denervation appears to result in sustained blood pressure (BP) reduction with a favorable safety profile in patients through 3 years with consistent benefit across age, diabetes status, and renal function, according to Henry Krum, MBBS, PhD,