hypothesized to combine favorable actions on lipoproteins with insulin-sensitizing and glucose-lowering affects that might translate into a reduction in adverse CV outcomes, explained Dr. Lincoff.

In a Phase 2 trial, aleglitazar was associated with greater reductions in HbA1C and blood levels of triglycerides, and a greater increase in high-density lipoprotein cholesterol (HDL-C) than either placebo or the PPAR-γ agonist pioglitazone [Henry RR et al. *Lancet* 2009].

In AleCardio, 7226 patients with T2DM who were hospitalized with a recent acute coronary syndrome were randomly assigned in a double-blind fashion to aleglitazar 150 µg/day, or placebo in addition to standard care. The trial was conducted at 720 sites in 26 countries. Patients could be randomized up to 12 weeks after discharge to allow clinical stabilization or completion of planned revascularization. The primary endpoint of the study was the composite of time to CV death, nonfatal myocardial infarction, and nonfatal stroke. The anticipated follow-up duration to achieve 950 primary endpoints was ~2.5 years.

At baseline, patients were a mean age of 61 years. About two thirds were taking metformin, one third were on a sulfonylurea, and ~30% were being treated with insulin. More than 90% were on aspirin and a statin.

The Data Safety Monitoring Board recommended early termination of the trial due to a higher incidence of heart failure in the aleglitazar arm. The trial was terminated after a median follow-up of 104 weeks.

The primary composite endpoint occurred in 344 patients (9.5%) in the aleglitazar group and 360 patients (10.0%) in the placebo arm (Table 1), for an HR of 0.96 that was not significant (p=0.57).

Heart failure occurred more frequently in the aleglitazar arm compared with the placebo arm (4.7% vs 3.8%; HR, 1.24; p=0.06). Peripheral edema also developed significantly more often in the aleglitazar arm (14.0% vs 6.6%; p<0.001). By Month 24, mean serum creatinine increased by 0.11 mg/dL in the aleglitazar arm and by 0.01 mg/dL in the placebo arm (p<0.001), a difference that was reversible by 4 weeks after discontinuation of aleglitazar. Gastrointestinal hemorrhage was also significantly more common in the aleglitazar group (HR, 1.44; p=0.03).

HbA1C was significantly lower among patients assigned to aleglitazar compared with placebo, with the mean change from baseline being –0.99% in the aleglitazar arm and –0.36% in the placebo arm. At 3 months, HDL-C levels increased from baseline by 26.9% in the aleglitazar arm and 8.4% in the placebo arm. Triglyceride levels increased in the placebo arm and decreased by 23.9% in the aleglitazar arm. The level of low-density lipoprotein cholesterol increased in both groups, but more so in the aleglitazar arm.

The adverse effects associated with aleglitazar highlight the difficulties in developing PPAR-activating drugs where gene modulation can result in complex metabolic effects and unpredictable therapeutic profiles, concluded Dr. Lincoff.

Table 1. Cardiovascular Efficacy Endpoints

	No. of Patients (%)			
	ALE n=3616	Placebo n=3610	HR (95% CI)	p Value
Primary composite: CVD, MI, stroke	344 (9.5)	360 (10.0)	0.96 0.83–1.11)	0.57
CV death, MI, stroke, UA hospitalization	441 (12.2)	488 (13.5)	0.90 (0.79–1.02)	0.11
Death, MI, stroke	373 (10.3)	392 (10.9)	0.95 (0.83–1.10)	0.51
Death from any cause	148 (4.1)	138 (3.8)	1.08 (0.85–1.36)	0.54
CV death	112 (3.1)	98 (2.7)	1.15 (0.87–1.50)	0.32
Nonfatal MI	212 (5.9)	239 (6.6)	0.89 (0.74–1.07)	0.22
Nonfatal stroke	49 (1.4)	50 (1.4)	0.98 (0.66–1.45)	0.92
UA hospitalization	118 (3.3)	155 (4.3)	0.75 (0.59–0.96)	0.02
Unplanned revascularization	397 (11.0)	496 (13.8)	0.79 (0.69–0.90)	<0.001

ALE=aleglitazar; CV=cardiovascular; CVD=cardiovascular disease; MI=myocardial infarction; UA=unstable angina.

Early CRT Improves Long-Term Survival in Mild Heart Failure (MADIT-CRT)

Written by Toni Rizzo

The Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT; Moss AJ et al. *N Engl J Med* 2009] trial evaluated the effect of CRT with biventricular pacing on the combined endpoint of death from any cause and nonfatal heart failure (HF) events in 1820 patients with mild HF. Eligible patients had ischemic or nonischemic cardiomyopathy with NYHA Class I or II symptoms, an ejection fraction of ≤30%, and a QRS duration of ≥130 msec. At a median follow-up of 2.4 years, the primary endpoint occurred in 17.2% of patients who received a CRT plus an implantable cardioverter defibrillator (ICD) compared with 25.3% of patients who received an ICD alone (HR, 0.66; 95% CI, 0.52 to 0.84; p=0.001). The benefit of a CRT plus ICD (CRT-D) was driven by a 41% reduction in the risk of nonfatal HF events and was observed only in patients with left bundle-branch block (LBBB) [Zareba W et al. *Circulation* 2011].

Because a survival benefit was not demonstrated for CRT-D during the MADIT-CRT trial, the aim of the long-term follow-up analysis [Goldenberg I et al. *N Engl J Med* 2014], presented by Ilan Goldenberg, MD, University of

Rochester Medical Center, Rochester, New York, USA, was to prospectively assess the effect of CRT-D on long-term survival.

All of the surviving MADIT-CRT trial patients (n=1691) participated in Phase 1 of the long-term follow-up until September 10, 2010. Of these, 854 were included in the Phase 2 registry and followed until September 30, 2013. The primary endpoint was all-cause mortality from MADIT-CRT enrollment until post-trial follow-up. Secondary endpoints included nonfatal HF events and a combined endpoint of a nonfatal HF event or death. The analyses were performed on an intention-to-treat basis and by LBBB status at enrollment.

Overall after 7 years of follow-up, 292 patients (16%) had died and 442 patients (24%) had experienced a nonfatal HF event. Among patients *with* LBBB, the all-cause mortality rate among was 18% in the CRT-D group compared with 29% in the ICD-only group (adjusted HR, 0.59; 95% CI, 0.43 to 0.80; p<0.001; Table 1). Patients in the CRT-D group also had a significantly lower probability of nonfatal HF events than the ICD-only group (adjusted HR, 0.38; 95% CI, 0.30 to 0.48; p<0.001) and the composite endpoint of HF or death (adjusted HR, 0.45; 95% CI, 0.37 to 0.56; p<0.001).

Among patients *without* LBBB, CRT-D provided no benefit (possibly harm) over ICD-only for all-cause mortality (adjusted HR, 1.57; 95% CI, 1.03 to 2.39; p=0.04), nonfatal HF events (adjusted HR, 1.13; 95% CI, 0.80 to 1.60; p=0.48), and the combined endpoint of HF or death (adjusted HR, 1.27; 95% CI, 0.94 to 1.73; p<0.001).

No subgroup with LBBB demonstrated worse survival when treated with CRT-D versus CRT alone. Patients with LBBB benefited from CRT-D regardless of QRS duration (QRS 130 to <150 msec or ≥150 msec), while those without LBBB did not benefit from CRT-D regardless of QRS duration.

Dr. Goldenberg concluded that early intervention with CRT-D compared with ICD-only is associated with a significant long-term survival benefit in patients with mild HF symptoms, left ventricular dysfunction, and LBBB. However, early CRT-D intervention does not benefit patients without LBBB and may be harmful.

Minimal MI Risk With Undetectable hs-cTnT and No ECG Ischemia in ED Patients With Chest Pain

Written by Toni Rizzo

Approximately 15 to 20 million patients visit hospital emergency departments (EDs) in Europe and the United States for chest pain each year [Thygesen K et al. *J Am Coll Cardiol* 2012; Nawar EW et al. *Adv Data* 2007; Goodacre S et al. *Heart* 2005]. However, only 10% to 20% of patients hospitalized for chest pain are diagnosed with myocardial infarction (MI) [Body R et al. *J Am Coll Cardiol* 2011; Than M et al. *Lancet* 2011; Pope JH et al. *N Engl J Med* 2000]. MI is characterized by cardiac troponin elevation in the presence of symptoms, ischemic electrocardiogram (ECG) changes or diagnostic imaging (eg, coronary angiography, echocardiogram) [Thygesen K et al. *J Am Coll Cardiol* 2012]. Traditionally several cardiac troponin measurements are required over hours in order to detect injury indicative of myocardial infarction. Recently developed high-sensitivity cardiac troponin assays, however, can detect increased troponin concentrations hours earlier than older generation assays potentially establishing a diagnosis with a single measurement.

To explore this hypothesis the investigators performed the Undetectable High Sensitivity Cardiac Troponin T Level in the Emergency Department and Risk of Myocardial Infarction study [Bandstein N et al. *J Am Coll Cardiol* 2014], which was presented by Nadia Bandstein, MD, Karolinska University Hospital, Stockholm, Sweden. The investigators hypothesized that all patients presenting with chest pain who have a first undetectable high-sensitivity cardiac troponin T (hs-cTnT), independent of symptom duration, and no signs of ischemia on ECG may be safely discharged from the ED.

The study population included all patients aged ≥25 years who visited the Karolinska University Hospital ED for chest pain and who had at least one hs-cTnT level analyzed between December 10, 2010, and December 31,

Table 1. Multivariate Analysis of Survival Benefit with CRT-D by LBBB Status

			LBBB		No LBBB		
Endpoint	No. of Events	No. of Patients	HR (95% CI)	p Value	HR (95% CI)	p Value	p Value for Interaction
All-cause mortality	267	1681	0.59 (0.43–0.80)	<0.001	1.57 (1.03–2.39)	0.04	<0.001
Nonfatal HF event	405	1681	0.38 (0.30–0.48)	<0.001	1.13 (0.80–1.60)	0.48	<0.001
Nonfatal HF event or death	530	1681	0.45 (0.37–0.56)	<0.001	1.27 (0.94–1.73)	0.12	<0.001

HF=heart failure; LBBB=left bundle branch block; results adjusted for age at enrollment, serum creatinine ≥1.4 mg/dL, smoking, diabetes, etiology of cardiomyopathy, left ventricular end systolic volume, QRS duration ≥150 msec, NYHA Class >II at 3 months prior to enrollment.