

# CRT Plus ICD Equals Fewer Heart Failure Deaths

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CHICAGO – For the first time, cardiac resynchronization therapy has been shown to offer a survival benefit beyond that provided by an implantable cardioverter defibrillator in patients with mild heart failure, a study has shown.

The addition of cardiac resynchronization therapy (CRT) to an implantable cardioverter defibrillator (ICD) and optimal medical therapy significantly reduced the rates of death and heart failure hospitalization from 40% with an ICD alone to 33% in the multicenter Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT).

The relative risk of death was reduced by 25% among patients who received CRT plus ICD, resulting in an absolute mortality reduction of 6% at 5 years, Dr. Anthony Tang reported at the meeting. Fourteen patients would need to be treated with CRT plus ICD for 5 years to prevent one death.

Significantly fewer CRT-ICD patients were hospitalized for heart failure (19.5%, or 174/894) than ICD-only patients (26%, or 236/904). This meant that 11 patients would need to be treated with CRT plus ICD for 5 years to prevent one heart failure hospitalization, said Dr. Tang, pro-

fessor of medicine at the University of British Columbia, Vancouver.

RAFT enrolled 1,798 patients (mean age, 66 years), who had New York Heart Association class II or III heart failure, a left ventricular ejection fraction (LVEF) of 30% or less, and a wide QRS duration of at least 120 milliseconds or a paced QRS duration of at least 200 milliseconds. Of note, 80% of patients were NYHA class II because during the trial the protocol was changed to include only class II patients.

CRT with or without an ICD is currently indicated only for the treatment of patients with NYHA functional class III or ambulatory class IV heart failure.

The data are likely to change clinical practice, said invited discussant Dr. Clyde W. Yancy, medical director of Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas and immediate past president of the AHA.

He observed that a suite of randomized trials including COMPANION, CARE-HF, MADIT-CRT, REVERSE, and now RAFT demonstrate compellingly that CRT is effective in heart failure.



“The benefit can now be extended to patients who have mild heart failure,” he said.

In the pivotal Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT), however, the use of CRT-ICD therapy decreased the risk of heart failure events, but not the risk of death among NYHA class I or II patients with an ejection fraction of 30% or less and a QRS duration of 130 milliseconds or more (N. Engl. J. Med. 2009; 361:1329-38).

Dr. Yancy observed that CRT plus ICD is used in only about one-third of heart failure patients and suggested that its limited uptake is due to persistent equipoise, postprocedural risks that are not insignificant, an early failure rate of about 5% and a late failure rate of up to 25%, imprecise markers of clinical response, and current guidelines. “We should no longer let equipoise enter into our thought process about the benefits of ICD-CRT in heart failure,” he said.

The improved outcomes, however, did come at the cost of increased adverse events. Within 30 days of device

implantation, significantly more CRT-ICD patients than ICD-alone patients had lead dislodgment (61 vs. 20 patients) and coronary sinus dissection (11 vs. 0), Dr. Tang reported. The CRT-ICD and ICD-alone groups had similar rates of hemothorax or pneumothorax (11 vs. 8 patients), pocket hematoma (14 vs. 11), pocket infection (21 vs. 16), tamponade (1 vs. 2), and device pocket revision (4 vs. 1).

An analysis by NYHA class showed that the majority of positive results held true, Dr. Tang said. The primary composite end point was significantly improved in both NYHA class II and III patients, while death from any cause was significantly improved among class II, but not class III patients.

Also, a post-hoc subgroup analysis of the primary end point suggests that patients with an intrinsic QRS duration of more than 150 milliseconds derive more benefit from CRT-ICD therapy, as do those with left bundle branch block, although the latter finding was weaker, Dr. Tang said.

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## Hyperkalemia Is a Concern

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The use of eplerenone, an aldosterone antagonist, also significantly reduced all-cause mortality by 24%, hospitalization from any cause by 23%, and heart failure hospitalization by 42%.

The benefits were consistent across 20 prespecified subgroups analyzed in the New York Heart Association (NYHA) class II cohort of 2,737 patients.

“We believe that the robustness of these findings, in conjunction with the consistent results from the earlier RALES and EPHESES trials, provides compelling evidence to change medical practice,” said Dr. Zannad, a cardiologist and professor of therapeutics at Henri Poincaré University of Nancy (France).

Current guidelines recommend the use of aldosterone antagonists in moderate to severe heart failure (NYHA class III and IV) and in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

The Randomized Aldactone Evaluation Study (RALES) demonstrated a survival advantage with the aldosterone antagonist spironolactone (Aldac-

tone) plus standard therapy in moderate to severe heart failure patients, while the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESES) did so in the post-MI/heart failure setting.

The current findings have the potential to greatly expand the use of aldosterone antagonists, which are now utilized by fewer than two-thirds of patients with heart failure in the United States with a current indication.

“We have three trials in three distinct groups of heart failure severity which essentially have shown the same results,” Dr. Zannad said in an interview. “This puts this class of drugs on equal ground and if anything, the benefit comes on top of the benefit of angiotensin-converting enzyme inhibitors and beta-blockers.”

The bottom line, he said, is that all patients with a low ejection fraction, provided they have a normal estimated glomerular filtration rate or an EGFR above 30, should be on the three drugs now.

At a press briefing on the study, Dr. Clyde Yancy, immediate past president of the AHA,

### VITALS

**Major Finding:** Eplerenone reduced the risk of cardiovascular death or heart failure hospitalization by 37%, compared with placebo.

**Data Source:** Phase III randomized trial in 2,737 patients with NYHA class II heart failure.

**Disclosures:** EMPHASIS-HF was funded by Pfizer. Dr. Zannad reported receiving grants from and consulting for Pfizer. Two coauthors are Pfizer employees, and several others reported Pfizer grants and consultancy.

said that he was enthusiastic about the potential for these drugs to include patients with mild heart failure, but that his enthusiasm is tempered by the risk of hyperkalemia.

“You need to always watch for the presence of hyperkalemia with these drugs, but having said that, the benefit is not modest,” Dr. Yancy said. “This is a very real benefit. And again, two-thirds of patients with an indication are not getting these drugs, and that is what I hope will change.”

Hyperkalemia was reported in 8% of patients treated with eplerenone, compared with 3.7% given placebo, Dr. Zannad said. Treatment discontinuation due to hyperkalemia was reported in 1.1% of eplerenone patients and 0.9% of placebo patients, with hospitalization due to hyperkalemia occurring in 0.3% and 0.2% of patients.

In all, 171 of the 1,364 patients randomized to eplerenone

and 213 of the 1,373 patients in the placebo group died. Of these, 147 deaths in the eplerenone group and 185 in the placebo group were due to cardiovascular causes.

Invited discussant Dr. Lynne Warner Stephenson, director of the heart failure program at Brigham and Women’s Hospital in Boston, said that EMPHASIS-HF bridges an “awkward gap in our evidence,” but that clinicians need a better understanding of how best to prescribe eplerenone, how the drug works, and how to reduce the life-threatening hyperkalemia associated with these agents before widespread adoption.

She noted that hyperkalemia rates associated with spironolactone in general use have reached 12% in Texas and 10% in Denmark and Norway, and that in Canada the number needed to treat to get one case of hyperkalemia was 13. This led to the recent PEARL-HF tri-

al (Evaluation of RLY5016 in Heart Failure Patients) in which the addition of a new potassium-binding resin (RLY5016) to spironolactone helped lower potassium levels and prevent hyperkalemia in patients with heart failure.

“We have the opportunity and the responsibility to learn from these experiences about how to use aldosterone antagonists safely before we recommend expanding this to the population at risk,” she said.

When asked by reporters whether the data support the use of spironolactone in mild heart failure, Dr. Zannad said that it’s possible to extrapolate the results to spironolactone, but that the findings are limited to eplerenone at a dose of 50 mg in patients with NYHA class II heart failure and an ejection fraction of no more than 35%.

During a panel discussion of the study, Dr. Zannad said now that eplerenone has demonstrated efficacy in all symptomatic patients, the next step will be to evaluate the drug in asymptomatic patients and in those with preserved ejection fractions.

The EMPHASIS-HF results were also published in the New England Journal of Medicine (2010 Nov. 14; doi:10.1056/NEJMoa1009492). ■