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EDITORIAL COMMENT

Should Nonischemic CRT Candidates Receive CRT-P or CRT-D?*

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Cardiac resynchronization therapy (CRT) in patients with heart failure (HF) with reduced ejection fraction (HFREF) with prolonged QRS intervals has resulted in marked durable benefit (1,2). Improvements in ejection fraction (EF) are associated with a reduction in mortality and appropriate shocks, and occur more often with CRT (3). The debate has been whether patients who meet criteria for CRT also need an implantable cardioverter-defibrillator (ICD) or if a CRT pacemaker (CRT-P) is adequate therapy. This debate has been heightened by the DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial in nonischemic cardiomyopathy (NICM), in which a CRT defibrillator (CRT-D) was not superior to CRT-P (hazard ratio [HR]: 0.91; p = 0.59) (4). In this issue of the *Journal*, Barra et al. (5) compared CRT-Ds versus CRT-Ps in a large registry of 5,307 patients in Sweden, the United Kingdom, and France to try to ascertain if the benefit varied in patients with ischemic cardiomyopathy (ICM) and NICM (5). They found no additional benefit with the addition of an ICD in NICM patients, whereas ischemic patients did have benefit.

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The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial with CRT-Ps showed improvement in EF, quality of life, New York Heart Association (NYHA) functional class, treadmill time, and 6-min walking distance (1). The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial randomized patients to CRT-Ps, CRT-Ds, and guideline-determined medical therapy (GDMT). CRT-Ps reduced mortality 24% (p = 0.059) and predominantly reduced HF deaths, whereas CRT-Ds reduced mortality 36% (p = 0.003), and reduced both HF and sudden cardiac death (SCD) (6,7). The comparison of CRT-Ds versus CRT-Ps in COMPANION had an ~14% all-cause mortality benefit (p = NS). Subsequently, the CARE HF (Cardiac Resynchronization—Heart Failure) trial, with CRT-Ps versus GDMT, reduced all-cause (36%) and HF mortality (~41%), and was one of the few CRT trials to reduce SCD (~24%) (2).

Each GDMT reduces all-cause mortality by ~15% to 35% (**Figure 1A**). However, the impact of GDMT and device therapy on the mode of death varies. Drug therapy and CRT-Ds reduce both HF and sudden death. CRT-Ps reduce both HF death and other deaths (~25%), whereas ICDs reduce only sudden death (**Figure 1B**). The combination of GDMT with a HF device (CRT-P, ICD, or CRT-D) in appropriate patients can reduce mortality by ~60% to 80% (8).

Barra et al. (5) asked if an ICD is necessary for NICM patients who are candidates for CRT-Ps. The investigators found, in unadjusted Kaplan-Meier analyses, that CRT-Ds were superior to CRT-Ps for both ischemic and nonischemic patients (unadjusted HR: ~0.67 for ICM and ~0.63 for NICM). However, after propensity adjustment, the benefit of CRT-Ds versus CRT-Ps remained for ischemic patients (HR: 0.76; p = 0.005), but not for NICM patients (HR: 0.92; 95% confidence interval [CI]: 0.72 to 1.19; p = 0.49).

Should this study change how we approach our patients who are candidates for CRT? The number of propensity-matched NICM patients was relatively

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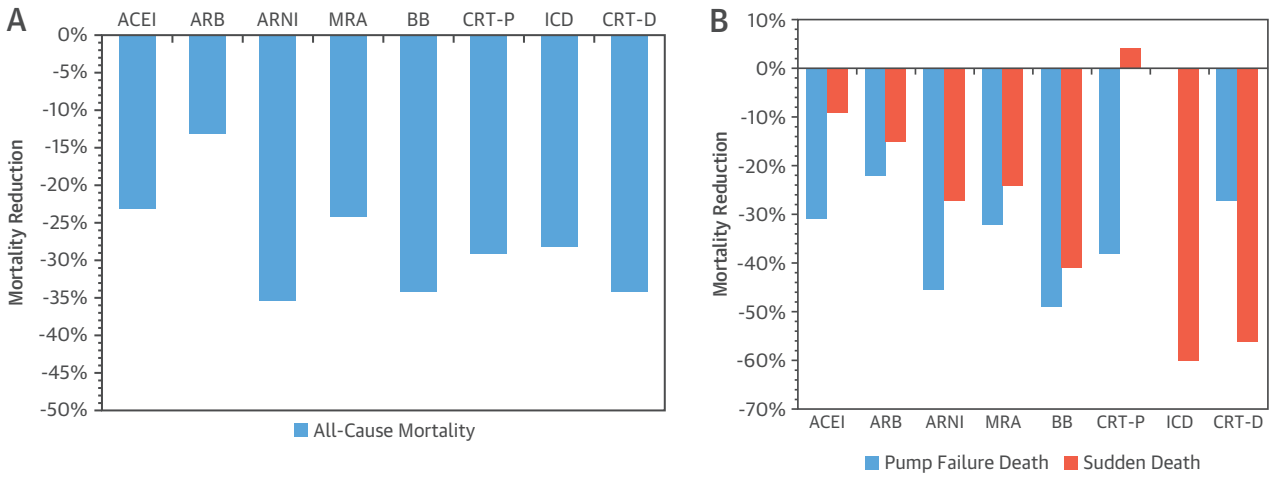
FIGURE 1 Benefit of GDMT and Devices



The benefit of guideline-determined medical therapy (GDMT) and devices on **(A)** all-cause mortality and **(B)** on heart failure and sudden death (2,7-10). The PARADIGM-HF trial was versus angiotensin-converting enzyme inhibitor (ACEI). The observed ARNI benefits were adjusted for ACEI benefit to provide an estimate of angiotensin receptor-neprilysin inhibitor (ARNI) versus placebo (9,10). ARB = angiotensin receptor blocker; BB = beta-blocker; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ICD = implantable-cardioverter defibrillator; MRA = mineralcorticoid receptor antagonist.

low (n = 988), and the study had fewer patients than in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), COMPANION, and MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) trials. Thus, the power to detect an ICD benefit was low, and the CIs were wide. The investigators did not formally test if the HRs for ICM and NICM were statistically different. Most importantly, these results contradict the COMPANION trial, in which the NICM CRT-D subgroup was the only one with a mortality benefit (HR: 0.50; p = 0.015). Patients with NICM who received CRT-Ds had greater benefit versus those who received CRT-Ps (HR: 0.50 and 0.91, respectively), whereas the patients with ICM had no additional benefit from ICDs (HR: 0.73 vs. 0.72). The estimated CRT-D versus CRT-P benefit in the COMPANION trial for NICM was ~0.55 (HR: 0.50 and 0.91, respectively) versus ~1.01 (HR: 0.73 and 0.72, respectively) in the ischemic subgroup. The COMPANION trial, which randomized CRT-D versus CRT-P, found greater benefit in NICM than in ICM (6), which was the opposite of the findings in the registry in study by Barra et al. (5). A recent meta-analysis of CRT-Ds versus CRT-Ps found the ICD benefit for ischemic etiology was greater (HR: 0.70) than that for the NICM etiology (HR: 0.79) (11).

Initial research evaluated CRT-P with a QRS width of any cause of >120 to 130 ms. Subsequent evaluation using a patient-level network meta-analysis in 12,638 patients identified markers of patients who gained the greatest mortality benefit from a CRT device, including left bundle branch block, QRS interval ≥150 ms, women, and age older than 60 years (12). Conversely, ICDs were more effective in men aged younger than 60 years. Ischemic etiology was not a predictor (p > 0.20).

Why are there marked differences in who benefits from an ICD and CRT? These may be due to the proportion of sudden death; the ICD has a greater benefit when the proportion of sudden death is high (>50%), and CRT has greater benefit when the proportion of sudden death is low (<50%). If large HF trials are examined, ~40% of all deaths are sudden, and ~50% to 60% of these may be preventable with the addition of an ICD. However, in CRT-P trials, sudden death is only 23% to 32% in the control subjects, and it was only 35% of all deaths in the DANISH (58% CRT-P) trial (**Figure 2**). This lower proportion of sudden death diminishes the ICD benefit, because the residual sudden death rate approaches the ~20% residual proportion of sudden death seen in patients with CRT-Ds and ICDs (4,7,13).

We have shown that clinical variables can predict the proportion of sudden versus nonsudden death with the Seattle Proportional Risk Model (14). Patients of younger age, male sex, with NYHA functional class I or II, lower EF, no diabetes mellitus, digoxin use, higher body mass index, normal serum

sodium/creatinine, and systolic blood pressure closer to 140 mm Hg have a higher proportion of sudden death (14). Ischemic etiology did not enter the multivariate model, but post hoc testing suggested that the predicted proportion of sudden death would increase by ~3% for ICM versus NICM (i.e., 47% to 50%). Observational ICD trials, in which patients whose primary mode of death was sudden (>50% of all deaths), derived a much greater benefit from an ICD than those with <50% sudden death (15). We suspect the opposite is true with CRT-Ps. In Table 1 in the paper by Barra et al., the NICM patients who received CRT-Ps versus CRT-Ds were 9 years older, 28% more were women, and 8% more had QRS intervals ≥150 ms; these groups had a greater benefit from CRT-Ps, and conversely, less benefit from the addition of an ICD. There was less chronic kidney disease (CKD) in the CRT-P group. These differences between the CRT-P and CRT-D groups were similar in both the ICM and NICM cohorts. Because of the lack of ICD benefit for patients older than 68 years of age in the DANISH trial, and diminished benefit with advancing age for ICDs (16), it should not be surprising that a largely older patient population with CRT-Ps that had a low rate of sudden death (0.4%/year) did not benefit from the addition of an ICD (17). However, these results should not be applied to the larger group of younger patients who received CRT-Ds in clinical trials and in this registry (2,6).

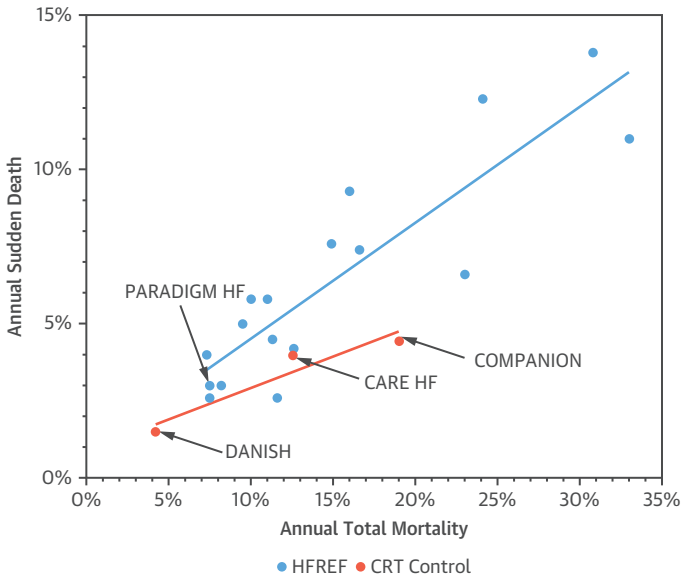
ICDs (CRT-Ds vs. CRT-Ps) provide the greatest benefit in patients with the following:

- High proportion of sudden death (>35%) (15,18);
- Sudden death rate ≥1.2%/year (≥6% over 5 years) (17); and
- Annual mortality of ≤25% (3-year mean survival) (7,18–20).

Patients who do not meet these criteria will not derive a meaningful benefit from an ICD.

This observational cohort does raise the issue of whether patients who are identified to have less ICD benefit should receive a CRT-P versus a CRT-D. Certainly, discussions of goals of care for patients with advanced age or comorbidities are very important (21). Should patients with a CRT-D device, who have never had an ICD shock, a higher EF, older age, CKD, diabetes, cerebrovascular accident, peripheral vascular disease, chronic obstructive pulmonary disease, or cancer, have the device replaced with CRT-P? In younger patients with HFREF who are not in NYHA functional class IV (20), I would continue to place a CRT-D. Further research is needed before changes can be made in guidelines and clinical practice.

FIGURE 2 Annual Sudden Death Mortality Versus All-Cause Mortality for Large HF Trials



Sudden death is ~40% of the total mortality and increases directly proportional to the total mortality. In cardiac resynchronization therapy (CRT)-eligible patients who did not receive CRT, the proportion of sudden death was much lower, in the 25% range (2,7). HF = heart failure. Adapted from Carson et al. (7) and Desai et al. (10).

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