Randomized trials have demonstrated that cardiac resynchronization therapy (CRT) improves survival and prevents hospitalizations in patients with sinus rhythm, symptomatic heart failure, a left ventricular ejection fraction $\leq 35\%$, and a QRS width $\geq 120$ ms. $1^{-4}$ Patients with heart failure who have permanent atrial fibrillation (AF) have a reduced survival and more advanced symptoms of heart failure. $5,6$ Many of these patients have a clear indication for an implantable cardioverter defibrillator (ICD), and CRT is perceived as a modest increment in a patient who is undergoing a device implant. However, as atrioventricular (AV) timing may influence response to CRT, $7,8$ it is unclear whether patients without regular, organized atrial activity will derive the same benefit from CRT as was observed in the clinical trials. Furthermore, even moderately rapid ventricular rates during AF may lead to significant reduction in biventricular pacing, further reducing any potential benefit of CRT. $7$

**Background**—Cardiac resynchronization (CRT) prolongs survival in patients with systolic heart failure and QRS prolongation. However, most trials excluded patients with permanent atrial fibrillation.

**Methods and Results**—The Resynchronization for Ambulatory Heart Failure Trial (RAFT) randomized patients to an implantable cardioverter defibrillator (ICD) or ICD+CRT, stratified by the presence of permanent atrial fibrillation. Patients with permanent atrial fibrillation were randomized to CRT-ICD ($n=114$) or ICD ($n=115$). Patients receiving a CRT-ICD were similar to those receiving an ICD: age ($71.6\pm7.3$ versus $70.4\pm7.7$ years), left ventricular ejection fraction ($22.9\pm5.3\%$ versus $22.3\pm5.1\%$), and QRS duration ($151.0\pm23.6$ versus $153.4\pm24.7$ ms). There was no difference in the primary outcome of death or heart failure hospitalization between those assigned to CRT-ICD versus ICD (hazard ratio, 0.96; 95% CI, 0.65–1.41; $P=0.82$). Cardiovascular death was similar between treatment arms (hazard ratio, 0.97; 95% CI, 0.55–1.71; $P=0.91$); however, there was a trend for fewer heart failure hospitalizations with CRT-ICD (hazard ratio, 0.58; 95% CI, 0.38–1.01; $P=0.052$). The change in 6-minute hall walk duration between baseline and 12 months was not different between treatment arms (CRT-ICD: $19\pm84$ m versus ICD: $16\pm76$ m; $P=0.88$). Patients treated with CRT-ICD showed a trend for a greater improvement in Minnesota Living with Heart Failure score between baseline and 6 months (CRT-ICD: $41\pm21$ to $31\pm21$; ICD: $33\pm20$ to $28\pm20$; $P=0.057$).

**Conclusions**—Patients with permanent atrial fibrillation who are otherwise CRT candidates appear to gain minimal benefit from CRT-ICD compared with a standard ICD.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00251251. (Circ Heart Fail. 2012;5:566-570.)

**Key Words:** cardiac resynchronization therapy ■ atrial fibrillation ■ heart failure ■ clinical trial

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Only 1 previous heart failure trial included patients with permanent AF and enrolled only 43 individuals. With the publication of the Resynchronization for Ambulatory Heart Failure Trial (RAFT), randomized trials have now evaluated CRT in 272 patients with permanent atrial fibrillation, which represents 3.6% of all patients in CRT heart failure trials. As a result, current guidelines do not give a class I recommendation for CRT in patients with permanent AF, who are otherwise eligible for this therapy.

The RAFT study evaluated the efficacy of CRT-ICD versus an ICD alone and included more heart failure patients with permanent AF and heart failure than all other published studies combined. It is also the only randomized trial to compare CRT against intrinsic conduction, rather than right ventricular pacing. Because randomization in RAFT was stratified according to the presence of permanent atrial fibrillation, this study has strong methodology for evaluating CRT in this subgroup.

Methods

The methods and main results of the RAFT study have been published. The trial enrolled patients with New York Heart Association class II and III heart failure, with a left ventricular ejection fraction ≤30% and QRS duration ≥120 ms. Enrollment was stratified based on the presence or absence of permanent atrial fibrillation. Permanent AF was defined as no evidence of sinus rhythm nor any plan to restore sinus rhythm. Patients with permanent AF were required to have a resting heart rate of ≤60 beats per minute and ≤90 beats per minute after a 6-minute walk test to be eligible for the study. All patients received optimal medical therapy and were randomized to receive a CRT-ICD or an ICD. Patients and treating physicians were blinded to treatment allocation. Outcomes were adjudicated by a committee that was also blinded to treatment allocation. Patients in the CRT-ICD arm had their lower pacing rate set to 60 beats per minute and had the conducted AF response feature enabled. Patients in the ICD arm had their lower pacing rate set between 40 and 50 beats per minute. The percentage of biventricular pacing was estimated using device diagnostics.

The primary outcome of the RAFT study and this predefined subgroup analysis was the composite of all-cause death or hospitalization for heart failure. Secondary outcomes included cardiovascular mortality and hospitalization for heart failure. Further subgroup analyses were prespecified to examine these outcomes for patients above versus below the median baseline resting heart rate. Other secondary outcomes included the change in 6-minute hall walk distance and Minnesota Living with Heart Failure Questionnaire score between baseline and 12 months.

Continuous variables are presented using the mean and SD and were compared using ANOVA. Categorical variables were compared using Fisher exact test. The effect of adding CRT to ICD therapy on clinical outcomes was estimated using a Cox proportional hazard model and presented using hazard ratios (HR) and 95% CI. Unadjusted survival free of the primary outcome was presented using the Kaplan-Meier method, and groups were compared using the log-rank test. Throughout, a P value <0.05 was used to define significance.

Results

Of the 1798 patients enrolled in the RAFT study, who were followed for a mean of 40±18 months, 229 subjects (12.7%) had permanent AF at baseline and were randomized to receive an ICD (n=115) or a CRT-ICD (n=114) (Table 1). Patients receiving a CRT-ICD were similar to those receiving an ICD in terms of age, left ventricular ejection fraction, New York Heart Association heart failure class, QRS duration, and medications but had significantly poorer Minnesota Living with Heart Failure scores (Table 1). Among patients with permanent atrial fibrillation, there was no difference in the primary outcome of death or heart failure hospitalization between those assigned to receive a CRT-ICD versus ICD (Figure; HR, 0.96; 95% CI, 0.65~1.41; P=0.82). However, this result was not statistically different (P-interaction=0.14) from the strata of patients (n=1569) without permanent AF (HR, 0.708; 95% CI, 0.598~0.837; P=0.0001). In patients with permanent atrial fibrillation, the difference in the primary outcome remained nonsignificant after adjustment for age, coronary artery disease, New York Heart Association class, left ventricular ejection fraction, blood urea nitrogen, and history of heart failure hospitalization (HR, 0.86; 95% CI, 0.60~1.30; P=0.48).

Among patients with permanent atrial fibrillation, cardiovascular death was similar between CRT-ICD and ICD treatment arms (HR, 0.97; 95% CI, 0.55~1.71; P=0.91); however, there was a trend for fewer heart failure hospitalizations (HR, 0.58; 95% CI, 0.38~1.01; P=0.052) with CRT-ICD (Table 2). However, there was, conversely, a trend toward an increase in all-cause hospitalizations in the CRT-ICD group (Table 2).

There was no significant difference in the rate of perioperative complications (within 30 days) between patients assigned to CRT-D and ICD: wound hematoma (2.7% versus 0%; P=0.25); wound infection (0% versus 0.8%; P=NS); and lead dislodgment (3.6% versus 2.7%; P=NS).

Among patients with permanent atrial fibrillation, the effect of CRT-ICD on the primary outcome was similar (P-interaction=0.32) among patients with a baseline resting heart rate above (HR, 0.75; 95% CI, 0.42~1.33; P=0.33) and below (HR, 1.16; 95% CI, 0.67~1.99; P=0.60) the median value of 68 beats per minute (Table 3). Only 1 patient had an AV junction ablation before or within 6 months after randomization. During the first 6 months after randomization, there were 34.3% of CRT-treated patients with ≥95% biventricular pacing and 47.1% with biventricular pacing ≥90% of the time. There was no significant difference in the risk of primary outcome of death or hospitalization for heart failure between CRT-treated patients receiving <90% ventricular pacing versus ≥90% (HR, 0.94; 95%
CI, 0.54–1.64; \( P = 0.83 \)) or those receiving <95% ventricular pacing versus ≥95% (HR, 0.87; 95% CI, 0.49–1.57; \( P = 0.65 \)). CRT-ICD did not significantly reduce the primary outcome in the subgroup of patients with left bundle branch block and a QRS width ≥150 ms (HR, 0.70; 95% CI, 0.32–1.56; \( P = 0.38 \)).

The change in 6-minute hall walk duration between baseline and 12 months (Table 4) was not different between treatment arms (CRT-ICD: 19±84 m versus ICD: 16±76 m; \( P = 0.88 \)). Patients treated with CRT-ICD showed a trend (\( P = 0.057 \)) for a greater improvement in Minnesota Living with Heart Failure score between baseline and 12 months (CRT-ICD: 41±21 to 31±21; ICD: 33±20 to 28±20). However, patients assigned to CRT-ICD had significantly worse baseline scores, and this difference in baseline scores was greater than the difference in change over time (Table 5).

**Discussion**

This prespecified analysis from the RAFT failed to demonstrate a clear improvement in any clinical or surrogate outcome with CRT-ICD in patients with heart failure and permanent atrial fibrillation. However, the trial was not powered to rule out a moderate-sized treatment effect, and there was a trend favoring a reduction in heart failure hospitalizations with CRT-ICD. There was also a clear indication that CRT was suboptimally delivered, because only one third of patients received >95% ventricular pacing.

The Multisite Stimulation in Cardiomyopathies (MUSTIC)-AF trial was the first to evaluate CRT in 59 patients with both permanent AF and a need for ventricular pacing.\(^{10}\) Using a crossover design with a study duration of 6 months, the investigators compared CRT against right ventricular apical pacing and found no difference in the 6-minute hall walk distance between groups.\(^{10}\) However, the study was limited by a 42% drop-out rate, imbalances in patient characteristics between groups, and a lower rate of successful left ventricular pacing than is observed today.\(^{1,10}\) During the duration of MUSTIC-AF, only 1 patient died and 3 were hospitalized for heart failure. The RD-CHF study compared CRT with right ventricular pacing in 44 patients with heart failure, of which 70% had permanent atrial fibrillation; however, a detailed evaluation of the AF subgroup is not available.\(^{15}\) Two other small trials have compared CRT with right ventricular apical pacing in patients with permanent atrial fibrillation, who had undergone AV junction ablation but who did not necessarily have a history of heart failure.\(^{12,16}\) The Post AV-Nodal Ablation Evaluation (PAVE) study followed 184 patients, 88% with a history of symptomatic heart failure, for 6 months and found borderline significant improvements in left ventricular ejection fraction (46±13% versus 41±13%; \( P = 0.03 \)) and improvement in 6-minute hall walk distance (82.9±94.7 m versus 61.2±90 m; \( P = 0.04 \)), both outcomes of borderline statistical significance.\(^{12}\) However, PAVE did not demonstrate an improvement in quality of life or clinical outcomes.\(^{12}\) More recently, Brignole et al\(^{16}\) randomized 186 patients with permanent AF after AV junction ablation to receive right ventricular apical or biventricular pacing and after a mean follow-up of 20 months found a reduction in the primary outcome of death, hospitalization for heart failure, or worsening heart failure.

### Table 2. Clinical Outcomes (With HR and 95% CI for CRT-ICD Versus ICD)

<table>
<thead>
<tr>
<th></th>
<th>ICD, % (n=115)</th>
<th>CRT-ICD, % (n=114)</th>
<th>HR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or heart failure hospitalization</td>
<td>42.6</td>
<td>48.2</td>
<td>0.96 (0.65–1.41)</td>
<td>0.82</td>
</tr>
<tr>
<td>Death</td>
<td>30.4</td>
<td>36.8</td>
<td>1.04 (0.66–1.62)</td>
<td>0.88</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>27.8</td>
<td>19.3</td>
<td>0.58 (0.38–1.01)</td>
<td>0.052</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>20.0</td>
<td>22.8</td>
<td>0.97 (0.55–1.71)</td>
<td>0.91</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>53.9</td>
<td>65.8</td>
<td>1.37 (0.997–1.92)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

\( HR \) indicates hazard ratio; CRT, cardiac resynchronization; ICD, implantable cardioverter defibrillator.
with biventricular (11%) versus right ventricular (26%) pacing (HR, 0.37; 95% CI, 0.18–0.73; P=0.005).

RAFT is the only trial that compared CRT with intrinsic conduction, because all other trials included only patients who had undergone AV junction ablation13,14 or who were otherwise highly dependent on ventricular pacing.10 This is an important distinction, because observational studies suggest that the benefits of CRT are greatest in patients who are paced >95% of the time.7,17 Although RAFT required patients with permanent AF to have good rate control (resting ventricular rate ≤60/min and a ventricular rate ≤90/min after 6-minute walk test) before randomization, only one third of CRT patients received ≥95% ventricular pacing during the first 6 months. Even this may be an overestimate, because Holter monitoring studies have shown that, when device logs indicate ≥90% ventricular pacing in patients with permanent AF but without AV junction ablation, 53% of these paced beats are actually fusion or pseudofusion.14

Table 3. Clinical Outcomes for Patients With Baseline Resting Heart Rate Above Versus Below the Median Value (HR and 95% CI for CRT-ICD Versus ICD)

<table>
<thead>
<tr>
<th>Outcomes, n (%)</th>
<th>ICD (n=115)</th>
<th>CRT-ICD (n=114)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with baseline HF &lt;68/min n=54 n=58</td>
<td>23 (42.6)</td>
<td>31 (53.4)</td>
<td>1.16 (0.67–1.99)</td>
<td>0.60</td>
</tr>
<tr>
<td>Death or HF hospitalization</td>
<td>18 (33.3)</td>
<td>24 (41.4)</td>
<td>1.09 (0.59–2.02)</td>
<td>0.78</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>10 (18.5)</td>
<td>13 (22.4)</td>
<td>1.07 (0.47–2.45)</td>
<td>0.87</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>22 (40.7)</td>
<td>29 (50.0)</td>
<td>1.30 (0.75–2.27)</td>
<td>0.35</td>
</tr>
<tr>
<td>All patients with baseline HF ≥68/min n=61 n=56</td>
<td>26 (42.6)</td>
<td>24 (42.9)</td>
<td>0.75 (0.42–1.33)</td>
<td>0.33</td>
</tr>
<tr>
<td>Death or HF hospitalization</td>
<td>17 (27.9)</td>
<td>18 (32.1)</td>
<td>0.95 (0.48–1.86)</td>
<td>0.88</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>13 (21.3)</td>
<td>13 (23.2)</td>
<td>0.88 (0.40–1.94)</td>
<td>0.75</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>29 (47.5)</td>
<td>25 (44.6)</td>
<td>0.84 (0.49–1.44)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CRT, cardiac resynchronization; ICD, implantable cardioverter defibrillator; HF, heart failure.

This suggests that the standard medical rate control of permanent AF in RAFT was not sufficient to allow effective delivery of CRT therapy.7 AV junction ablation was only used in 1 patient in RAFT; however, emerging evidence suggests that this may be a much better method of rate control in CRT-treated patients with permanent AF.9,17 The pooled results of 3 observational studies suggest that this procedure is associated with a 60% reduction in the rate of nonresponse to CRT.9 As well, in a large observational study of 243 CRT-treated patients with permanent AF, those who had undergone AV junction ablation had a lower mortality rate (4.3% per year) compared with those who did not (15.2% per year; P<0.001). Similar results were seen in another observational study of 154 patients18 and in a recent meta-analysis.19 However, there was bias in these observational series, with a tendency to perform AV junction ablation in healthier patients.17,18 No randomized controlled trials of AV junction ablation versus medical therapy in CRT patients with permanent AF have been conducted to date.

**Conclusions**

RAFT is the largest randomized trial of CRT in heart failure patients with permanent AF and shows no clear reduction in clinical events or improvement in objective surrogate measures. However, there is evidence that despite apparently good rate control before randomization, the delivery of CRT was suboptimal because of a low percentage of biventricular pacing. Further randomized trials in this population are needed, specifically a trial to evaluate routine AV junction ablation.

**Disclosures**

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Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation: Results From the Resynchronization for Ambulatory Heart Failure Trial (RAFT)

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