Patients with heart failure are at increased risk of developing atrial fibrillation (AF) and other atrial tachyarrhythmias (AF/AT), and their presence is associated with significantly reduced survival.\textsuperscript{3,4} AF has also been associated with attenuation of the benefits observed with proven heart failure therapies, including \( \beta \)-blockers,\textsuperscript{5} implanted cardioverter–defibrillators (ICDs) for primary prevention of sudden death,\textsuperscript{6,7} and cardiac resynchronization therapy (CRT).\textsuperscript{8} AF directly interferes with CRT delivery, by preventing atrioventricular synchronization and by decreasing biventricular pacing percentage.\textsuperscript{9,10} As such, most of the pivotal randomized trials that established the benefit of CRT, except for the Resynchronization/Defibrillation in Ambulatory Heart Failure Trial (RAFT), excluded patients who were in AF at baseline.\textsuperscript{11} In RAFT, randomization was stratified by the baseline presence of permanent AF, and by the investigator’s intention to provide an atrial lead in those randomized to receive a non-CRT ICD. We have previously reported that, in contrast to the overall 25% relative reduction in incidence of death from any cause or hospitalization for heart failure with CRT-D compared with ICD alone, those in the permanent AF stratum did not benefit from CRT-D.\textsuperscript{12}

Whether CRT-D alters the incidence of postrandomization AF/AT and whether postrandomization AF/AT modulate the benefits of CRT-D, remains unknown.

Methods and Results—We studied 972 Resynchronization/Defibrillation in Ambulatory Heart Failure Trial (RAFT) participants without permanent AF, who were randomized to CRT-D (\( n=495 \)) versus nonresynchronization defibrillator (implanted cardioverter–defibrillator; \( n=477 \)) within the predefined stratum eligible for an atrial lead. Occurrence of postrandomization AF/AT was prospectively assessed, and Cox models were used to test the independent association between the postrandomization AF/AT and the RAFT primary composite outcome of all-cause mortality or hospitalization for heart failure. Over 41 (\( \pm 19 \)) months, postrandomization AF/AT occurred in 216 (45.3\%) patients randomized to implanted cardioverter–defibrillator and 249 (50.3\%) randomized to CRT-D. After adjusting for competing risk of death, randomization to CRT-D increased risk of postrandomization AF/AT (hazard ratio, 1.20; 95\% confidence interval, 1.00–1.42; \( P=0.045 \)). Postrandomization AF/AT, which remained paroxysmal in 69.5\%, did not reduce biventricular pacing percentage. In adjusted models, postrandomization AF/AT was not associated with the primary outcome (hazard ratio, 1.04; 95\% confidence interval, 0.84–1.30). However, AF/AT was associated with a borderline decreased risk of mortality (hazard ratio, 0.75; 95\% confidence interval, 0.58–1.00) but increased risk of heart failure hospitalization (hazard ratio, 1.43; 95\% confidence interval, 1.08–1.90).

Conclusions—In RAFT, nearly half of the patients developed postrandomization AF/AT, and those randomized to CRT-D had borderline significant higher risk. Postrandomization AF/AT was associated with risk of heart failure hospitalization, but not with the primary composite outcome.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00251251.

Key Words: atrial fibrillation ▪ cardiac resynchronization therapy ▪ heart failure ▪ mortality ▪ randomized controlled trial
WHAT IS KNOWN

• In the Resynchronization/Defibrillation in Ambulatory Heart Failure Trial cardiac resynchronization therapy with an implantable cardioverter–defibrillator led to improved overall survival and reduced the rate of hospitalization for heart failure compared with implantable cardioverter–defibrillator therapy alone, but these benefits were not observed in the subgroup of patients with permanent atrial fibrillation at baseline.

• In contrast, the impact of postimplantation atrial tachyarrhythmias on clinical outcomes remains unclear.

WHAT THE STUDY ADDS

• In Resynchronization/Defibrillation in Ambulatory Heart Failure Trial, postimplantation atrial fibrillation or atrial tachyarrhythmias occurred in almost half of participants without permanent atrial fibrillation at baseline, with an excess risk in the cardiac resynchronization therapy group.

• These postimplantation atrial arrhythmias remained paroxysmal in over 80% of patients, and in the cardiac resynchronization therapy group were not associated with attenuation in the percentage of biventricular pacing delivery.

• The benefits of cardiac resynchronization therapy were preserved after adjustment for the development of postimplantation atrial arrhythmias.

unresolved questions. Single-center studies and secondary analyses of completed CRT trials have examined the absolute rates of postimplantation AF/AT, the relative risk of postimplantation AF/AT with CRT versus standard care, as well as the prognostic influence of these arrhythmias, yielding contradictory results.13–16 These studies used variable definitions for postimplantation AF/AT and had incomplete AF ascertainment. In this randomized substudy of RAFT participants with continuous atrial rhythm monitoring and without permanent AF at baseline, we compared rates of postrandomization AF/AT with CRT-D versus ICD and studied the influence of these arrhythmias on CRT-D efficacy.

Methods

Study Population

This study is a secondary analysis of data from RAFT, for which the methods and primary results of the have been published.13–17 RAFT tested the efficacy of CRT-D versus ICD, in addition to optimal medical therapy, in 1798 patients with New York Heart Association (NYHA) class II (80%) or III heart failure symptoms, left ventricular (LV) ejection fraction ≤0.30, intrinsic QRS duration ≥120 ms or paced QRS duration ≥200 ms and standard indications for an ICD.

The randomization procedure in RAFT included stratification based on the presence of permanent AF at baseline, and by the local investigator’s intention to provide a dual-chamber or single-chamber ICD in the usual care arm. For this analysis, we excluded patients with permanent AF at baseline because we were interested in postimplantation AF. We also excluded those in the single-chamber ICD stratum to avoid biased ascertainment of device-detected AF, as in this stratum only those randomized to CRT-D received an atrial lead. Thus, this study represents a prespecified randomized subgroup comparison of CRT-D versus ICD in patients without permanent AF who were indicated to receive a dual-chamber device. The institutional review board at each participating site approved study conduct, and all patients provided written informed consent before participation.

Study Procedures, Definitions, and Outcomes

After randomization, patients had in-person follow-up at 1 and 6 months, and then every 6 months for a minimum of 18 months. At each visit, patients underwent standardized history, physical examination, ECG, and interrogation of their CRT-D or ICD, as well as review of between-visit medical encounters. In the ICD arm, devices were programmed to DDI(R) or Medtronic’s managed ventricular pacing mode in those with intact intraventricular conduction, or to DDD(R) with paced and sensed intraventricular delay of 150 ms in those with complete intraventricular block, with a lower rate of 40 to 50 pm per minute. In the CRT-D, arm devices were programmed to maximize biventricular pacing (lower rate, 60–70 per minute; sensed intraventricular delay, 100 ms; and paced intraventricular delay, 130 ms). In both arms, the mode switch rate for atrial high-rate events was set at 175 per minute. Detection and classification of postrandomization AF/AT episodes, including AF, atrial flutter, atrial tachycardias, and supraventricular tachycardia, was prespecified, with active ascertainment of events at each study visit. Postrandomization AF/AT was defined as at least 1 episode of AF lasting at least 30 s, detected clinically by electrocardiography or by identification of atrial high-rate event on device counters, at any time after device implantation. Investigators ascertained symptom–rhythm correlation for all episodes. For this analysis, AT/AF episodes were classified as symptomatic unless all episodes during follow-up were asymptomatic. The pattern of AF was classified as paroxysmal, persistent, or permanent according to the 2006 American College of Cardiology/American Heart Association guideline definitions.18 Percent biventricular pacing was extracted from device diagnostics, and averaged daily.

As in RAFT, the primary clinical outcome for this analysis was a composite of death from any cause or hospitalization for heart failure lasting >24 hours. Secondary outcomes include the components of the primary end point, as well as death from cardiovascular causes, and hospitalization for a cardiovascular cause. A committee whose members were unaware of treatment allocation adjudicated the cause of all primary and secondary outcome events. An additional outcome for this analysis was the occurrence of ischemic stroke, which was recorded as an adverse event in follow-up, but not formally adjudicated. Finally, we assessed the change from baseline to 12 months in quality of life, using the Minnesota Living with Heart Failure Questionnaire (MLWHF), and in 6-minute walk distance (6MWD).

Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. Continuous variables are presented using mean and SDs and compared using the Student t test. Categorical variables are presented using frequencies and percentages and compared using the Fisher exact test.

We compared the time to first occurrence of postrandomization AF/AT between ICD and CRT-D groups using Kaplan–Meier product-limit estimates and the nonparametric log-rank test. Because mortality was influenced by treatment allocation in RAFT, we used a proportional subdistribution hazards model as proposed by Fine and Gray19 to calculate the hazard ratio (HR) for postrandomization AF/AT by treatment group adjusting for death as a competing risk. For the association between postrandomization AF/AT and primary and secondary clinical end points, we calculated HR and associated 95% confidence intervals (CI) with the use of the Cox proportional hazards model. Models were adjusted for baseline characteristics including age, sex, cause of heart failure (ischemic versus nonischemic), NYHA class (III versus II), QRS duration, QRS morphology

Downloaded from http://circpheartjournals.org/ by guest on August 30, 2017
(left bundle branch block versus other), renal dysfunction, and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, β-blockers, and mineralocorticoid receptor antagonists. We verified the proportional hazards assumption with the supremum test. We assessed whether postrandomization AF/AT modified the association between treatment arm and outcomes with the Wald test. There were no missing data for the composite primary outcome or its components. For patients not completing the 12-month assessment because of death, we imputed MLWHF and 6MWD scores to their worst possible values (105 and 0 m, respectively). We used case-wise deletion when follow-up values of these measures were missing for other reasons. All statistical tests were 2-sided, and a P value of <0.05 was used to define significance. We used SAS version 9.4 (SAS Institute, Cary, NC) for analysis.

Results

During a median of 41 months of follow-up, 465 of 972 (47.8%) patients developed at least 1 episode of AF/AT. Postrandomization AF/AT occurred in 216 (45.3%) patients randomized to ICD and in 249 (50.3%) randomized to CRT-D (log rank \( P=0.15 \)). Table 1 compares the baseline characteristics of those who did versus did not experience postrandomization AF/AT, according to randomized treatment group. In the ICD group, those with postrandomization AF/AT were older. Baseline medical treatment was similar, although those with postrandomization AF/AT were slightly less likely to have been prescribed β-blockers in both treatment arms. Baseline 6MWD and MLWHF values were also similar across groups.

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dual Chamber ICD (n=477)</th>
<th>CRT-D (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AF/AT (n=261)</td>
<td>AF/AT (n=216)</td>
</tr>
<tr>
<td>Age</td>
<td>65.1±9.3</td>
<td>67.6±8.9</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>206 (78.9)</td>
<td>176 (82.4)</td>
</tr>
<tr>
<td>Ischemic etiology of heart failure (%)</td>
<td>168 (64.4)</td>
<td>152 (70.4)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II (%)</td>
<td>226 (86.6)</td>
<td>167 (77.3)</td>
</tr>
<tr>
<td>Class III (%)</td>
<td>35 (13.4)</td>
<td>49 (22.7)</td>
</tr>
<tr>
<td>LVEF (mean, SD)</td>
<td>22.7±4.7</td>
<td>23.0±5.0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>115 (44.1)</td>
<td>98 (45.4)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>94 (36.0)</td>
<td>66 (30.6)</td>
</tr>
<tr>
<td>Heart failure hospitalization within 12 mo (%)</td>
<td>66 (25.3)</td>
<td>52 (24.1)</td>
</tr>
<tr>
<td>Intrinsic QRS duration (N, mean, SD)</td>
<td>244, 159.3±24.3</td>
<td>199, 161.3±23.8</td>
</tr>
<tr>
<td>Paced QRS duration (N, mean, SD)</td>
<td>17, 217.3±17.7</td>
<td>17, 211.8±16.8</td>
</tr>
<tr>
<td>QRS pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB (%)</td>
<td>188 (72.0)</td>
<td>157 (72.7)</td>
</tr>
<tr>
<td>Non-LBBB (%)</td>
<td>73 (28.0)</td>
<td>59 (27.3)</td>
</tr>
<tr>
<td>β-Blocker (%)</td>
<td>234 (89.7)</td>
<td>179 (82.9)</td>
</tr>
<tr>
<td>Ei or ARB (%)</td>
<td>253 (96.9)</td>
<td>208 (96.3)</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>103 (39.5)</td>
<td>90 (41.7)</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>78 (29.9)</td>
<td>69 (31.9)</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>61 (23.4)</td>
<td>66 (30.6)</td>
</tr>
<tr>
<td>Aspirin/clopidogrel (%)</td>
<td>209 (80.1)</td>
<td>150 (69.4)</td>
</tr>
<tr>
<td>6MWD, m (mean, SD)</td>
<td>360.1±115.1</td>
<td>344.6±105.3</td>
</tr>
<tr>
<td>MLWHF Score (mean, SD)</td>
<td>38.6±22.4</td>
<td>36.7±22.5</td>
</tr>
<tr>
<td>GFR &lt;60 mL/min per 1.73 m² (%)</td>
<td>127 (49.2)</td>
<td>107 (49.8)</td>
</tr>
</tbody>
</table>

The dual chamber ICD group was randomized to receive an ICD, and it was implanted with a device with right atrial and right ventricular leads. 6MWD indicates 6-minute hall walk distance; ACEi, angiotensin-converting enzyme inhibitor; AF/AT, atrial fibrillation/atrial tachycarrhythmia; ARB, angiotensin II receptor antagonist; CRT-D, cardiac resynchronization therapy-defibrillator; GFR, glomerular filtration rate; ICD, implanted cardioverter–defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living With Heart Failure instrument; and NYHA, New York Heart Association functional class.
Postrandomization Atrial Tachyarrhythmias in RAFT

Figure 1. Kaplan–Meier plots showing the time to first occurrence of postrandomization atrial fibrillation or atrial tachycardia (AF/AT) in those randomized to cardiac resynchronization therapy-defibrillator (CRT-D) versus dual-chamber implanted cardioverter-defibrillator (ICD). After adjusting for the competing risk of death, CRT-D was associated with increased risk of postrandomization AF/AT (hazard ratio, 1.20; 95% confidence interval, 1.00–1.42; \( P=0.045 \)).

Furthermore, 83.6% of initial postrandomization AF/AT episodes were symptomatic, again with no significant between-group differences. By the end of follow-up, among those with at least 1 episode of postrandomization AF/AT, 73 (15.7%) and 69 (14.8%) patients had developed persistent and permanent forms, respectively, with no significant between-group differences (\( P=0.69 \) and \( P=0.13 \)).

Clinical Outcomes

During follow-up, 187 patients (39.2%) in the dual-chamber ICD group and 155 (31.3%) in the CRT-D group experienced a primary clinical outcome event. In unadjusted analyses, occurrence of postrandomization AF/AT was associated with a numerically higher risk of experiencing a primary outcome event in both treatment groups by the end of follow-up, though in the prespecified survival analysis these associations were not statistically significant (Table 3). Examining secondary end points, postrandomization AF/AT not associated with risk of death in either group but was associated with an increased risk of hospitalization for heart failure in both groups: ICD (HR, 1.60; 95% CI, 1.11–2.31; \( P=0.012 \)) and CRT-D (HR, 1.60; 95% CI, 1.05–2.44; \( P=0.03 \)). Occurrence of postrandomization AF/AT was not significantly associated with any other secondary clinical outcomes, including cardiovascular hospitalization, cardiovascular death, or stroke. Only 15 patients had an ischemic stroke, with numerically higher proportions in those with postrandomization AF/AT. There were no statistically significant interactions between postrandomization AF/AT and treatment arm.

Figure 2 shows the multivariable-adjusted HR for the primary end point and its components. Randomization to CRT-D was protective for all 3 end points. Postrandomization AF/AT was not associated with the primary end point (adjusted HR, 1.04; 95% CI, 0.84–1.30; \( P=0.71 \)). This was the result of a borderline significant protective association for mortality (HR, 0.75; 95% CI, 0.56–1.00; \( P=0.047 \)) being offset by a significantly increased risk of hospitalization for heart failure (HR, 1.43; 95% CI, 1.08–1.90; \( P=0.01 \)). In these models, NYHA class III status, mineralocorticoid receptor antagonist use and renal dysfunction were all associated with increased risk of the primary end point, whereas the use of \( \beta \)-blockers was associated with reduced risk. We investigated the apparently paradoxical protective relationship between postrandomization AF/AT and survival by assessing cause-specific mortality, and found that the distribution of adjudicated causes of death, categorized as cardiovascular (including heart failure, sudden death/arrhythmia, stroke, myocardial infarction, and other cardiovascular) versus noncardiovascular, was similar across treatment group and AF/AT status (\( P=0.86 \)).

Additional End Points

In total, 465 (97.5%) patients in the dual-chamber ICD group and 481 (97.2%) patients in the CRT-D group completed MLWHF questionnaires at baseline and 12 months of follow-up. In the dual-chamber ICD group, MLWHF scores improved by a mean of 9.3±20.6 and 8.4±19.7 in those with and without postrandomization AF/AT, respectively (\( P=0.55 \)). A total of 323 patients (67.7%) in the dual-chamber ICD group and 359 patients (72.5%) in the CRT-D group completed 6MWD assessments at baseline
and 12 months of follow-up. In the dual-chamber ICD group, 6MWD increased by a mean of 11.3±42.7% and 12.6±51.8% in those with and without postrandomization AF/AT, respectively (P=0.80), whereas in the CRT-D group, these values changed by 47.6±491.8% and 10.7±33.4%, respectively (P=0.30). Finally, in those randomized to CRT-D, there was no association between postrandomization AF/AT and CRT delivery, measured either as the overall biventricular pacing or by the percent of days with biventricular pacing <95% (Table 4).

**Discussion**

Among RAFT participants without permanent AF at baseline, we report several new and important findings. First, postrandomization AF/AT was extremely common, occurring in 45% of ICD-treated patients and 50% of CRT-D–treated patients. Second, after adjustment for competing risks, patients receiving a CRT-D were 20% more likely to develop postrandomization AF/AT than those receiving a dual-chamber ICD. Third, the development of postrandomization AF/AT was associated

<table>
<thead>
<tr>
<th>Table 3. Association Between Postrandomization AF/AT and Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dual Chamber ICD</strong></td>
</tr>
<tr>
<td>No AF/AT, N=261</td>
</tr>
<tr>
<td>Death from any cause or hospitalization for heart failure (%)</td>
</tr>
<tr>
<td>Death from any cause</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
</tr>
<tr>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>Ischemic stroke</td>
</tr>
</tbody>
</table>

P values from unadjusted Cox HR. AF/AT indicates atrial fibrillation/atrial tachycardia; CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; HR, hazard ratio; ICD, implanted cardioverter–defibrillator; and RAFT, Resynchronization/Defibrillation in Ambulatory Heart Failure Trial.

![Image](http://circep.ahajournals.org/)
with an increased risk of hospitalization for heart failure and an apparently paradoxical decreased risk of death of borderline statistical significance (P=0.047). Finally, randomization to CRT-D remained strongly protective against the primary end point and its components irrespective of the development of postrandomization AF/AT. This finding, which stands in contrast to the neutral effect of CRT-D versus ICD previously reported in the stratum of patients with permanent AF,12,13 may be explained by our observation that postrandomization AF/AT remained paroxysmal in the majority of patients and did not lead to a reduced percentage of biventricular pacing in the CRT-D group.

Does CRT Increase the Risk of AF/AT?
This is the first analysis from a large randomized outcome trial suggesting that CRT-D increases the risk of postrandomization AF/AT compared with an ICD. This finding may seem counterintuitive, as on average, CRT induces positive left atrial (LA) and LV remodeling, reduces severity of mitral regurgitation,20–22 and improves long-term outcomes,23 whereas AF is a marker of adverse prognosis in heart failure.24–26 Indeed, an early nonrandomized study reported reduced AF incidence in CRT recipients compared with matched controls.25 However, reports from subsequent larger randomized trials have tended to suggest a neutral influence of CRT on development of AF. Hoppe et al14 reported incident AF in 14.4% versus 16.1% (P=0.79) in those randomized to medical therapy or CRT in the Cardiac Resynchronization in Heart Failure (CARE-HF) trial. In that study, the diagnosis of AF for comparative purposes was based on ECG alone, although an additional 22% of CRT recipients had asymptomatic AF detected by the device. In an analysis of the left bundle branch block subgroup of the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial, Ruwald et al15 used adjudication of ICD therapies delivered for high-rate ventricular events (>180 beats per minute) to define postrandomization supraventricular arrhythmias, including AF. In that study, the cumulative incidence of such events by 4 years was 10%, with no difference between the ICD and CRT-D groups (P=0.67). The absolute risk of postrandomization AF/AT reported here is higher than in these analyses, likely owing to our more sensitive methods for AF detection. This analysis, which used data from device interrogation coupled with clinical records, maximized detection of AF, and therefore had greater statistical power to detect a difference in risk of postrandomization AF/AT between treatment groups.

Why does not CRT-D decrease the risk of AF compared with an ICD? First, remodeling responses to CRT are variable: depending on the definition applied, between 34% and 91% can be labeled as echocardiographic responders.26 Several studies have reported a relationship between the degree of LV or LA reverse remodeling with CRT and the subsequent risk of AF. In an echocardiographic study, Fung et al27 reported that among 97 patients, the 48.5% classified as LA responders (≥50% relative improvement in LA ejection fraction) had a much lower rate of AF (13% versus 40%) and mortality (17% versus 44%) during long-term follow-up. An analysis from MADIT-CRT reported a strong correlation between positive LV and LA remodeling (R=0.63, P<0.0001), and that CRT-D reduced the risk of AF only in the group with LA response (>20% reduction in LA volume).28 These findings make intuitive sense, but they do not account for the borderline increased risk of AF with CRT-D versus ICD alone observed in this study. Because the baseline characteristics and medical therapy of RAFT patients were balanced between treatment arms, we must consider whether CRT-D device programming can promote AF. Adelstein and Saba28 reported that risk of AF was increased almost 2-fold per quartile of atrial pacing in CRT recipients, similar to findings in patients with sinus node dysfunction.29 However, in the Dual-Chamber and VVI Implantable Defibrillator (DAVID) Trial II, atrial-based pacing did not increase the risk of AF compared with backup ventricular pacing, suggesting that atrial pacing per se may not be causal.30 More likely, potential mechanisms include non-physiological atrioventricular intervals and forced ventricular pacing induced by CRT. Right atrial pacing increases interatrial conduction time to a variable degree,10,31 but LA activation timing is not commonly considered in setting the paced atrioventricular delay. Forcing short atrioventricular times can result in delay of completion of LA mechanical systole until after mitral valve closure, increasing LA pressure, and thereby the risk of incident AF.32 This effect is similar to the proposed mechanism of AF induced by asynchronous right ventricular pacing in patients with atrioventricular block. In RAFT, programmed atrioventricular delay settings were standardized to relatively short intervals in the CRT-D group and to minimize ventricular pacing in the ICD group (DDI or managed ventricular pacing mode), which may in part explain the lack of a reduction in postrandomization AF/AT with CRT-D. Unfortunately, echocardiographic optimization of CRT was not performed, and data on programming changes in follow-up or ventricular pacing burden in the ICD group were not systematically collected, so we are unable to evaluate these potential mechanistic associations.

### Postimplantation Atrial Arrhythmias, CRT Delivery, and Clinical Outcomes

Despite their methodological differences, analyses from CARE-HF, MADIT-CRT, and RAFT are consistent in reporting that the overall benefit of CRT is preserved, despite the development of AF/AT after device implantation. These findings are in contrast to the bulk of the evidence that has accrued in patients with persistent or permanent AF before

| Table 4. Relationships Between Postrandomization AF/AT and Percent Biventricular Pacing in CRT-D Patients |
|------------------|------------------|------------------|
| Percent biventricular pacing at first postimplant study visit | No AF/AT | AF/AT | PValue |
| 90.4±25.3 | 88.1±27.5 | 0.33 |
| Mean percent biventricular pacing during follow-up (%) | 89.7±26.7 | 91.0±21.7 | 0.58 |
| Percent of days with biventricular pacing <95% | 11.5±28.8 | 15.9±32.2 | 0.11 |

Includes data from 490 of 495 (99.0%) cardiac resynchronization therapy (CRT) patients. AF/AT indicates atrial fibrillation/atrial tachycardia.
CRT implantation, suggesting that the benefit of CRT is attenuated or absent. Importantly, AF/AT remained paroxysmal in almost 70% of patients who developed it in our study. Although our data do not allow calculation of the precise burden of postrandomization AF/AT, it is likely that it was relatively low in the majority of patients. Because the principal mechanism by which AF/AT reduce benefit with CRT is thought to be through interfering with the goal of achieving as close to complete biventricular pacing as possible, it is likely that the overall burden of these tachycarrhythmias is relevant to the association between AF and clinical outcomes. Recently, Ousdigian et al. reported on the relationship between AF classification, CRT delivery, and mortality in 54019 US CRT recipients providing data to the Medtronic CareLink system. They found that 24% of patients had ≥1 episode of AF lasting ≥6 hours in the initial 6 months of follow-up, with similar proportions classified as paroxysmal, persistent, or permanent. Although they found that in the paroxysmal AF group the biventricular pacing percentage outside of AF episodes was not statistically different from patients with no/little AF, the proportion achieving ≥98% biventricular pacing overall was reduced. Furthermore, in adjusted analyses, both AF (regardless of classification) and suboptimal biventricular pacing percentage were associated with increased mortality risk. In this study, postrandomization AF/AT was associated with a borderline reduced risk of mortality, but with an increased risk of heart failure hospitalization. These opposing associations may represent a chance finding, given that there was no indication that development of postrandomization AF/AT was linked to cause of death, and most therapies and risk factors studied to date have directionally if not quantitatively similar influences on these end points.

Clinical Implications
The results of this study emphasize important clinical principles. Identification of postimplantation AF in ICD or CRT-D recipients should prompt a thorough review of a patient’s medical therapy and device programming. Device-detected AF has been associated with thromboembolic events, so provision of oral anticoagulation should be strongly considered. Given the association between postrandomization AF/AT and heart failure events, opportunities to optimize medical therapy for heart failure should be sought. Device programming should also be reviewed, to minimize the likelihood of inappropriate shocks related to AF, and potentially to optimize the atrioventricular interval to allow effective LA emptying. Finally, unlike the situation for patients with permanent AF, these and other findings suggest that patients with a history of paroxysmal AF should remain eligible for CRT-D if they meet other accepted implant criteria.

Limitations
History of intermittent AF was not recorded at baseline, so not all patients who had postrandomization AF/AT represent incident cases. The study population was limited to those patients whose physicians determined they were indicated to receive a dual-chamber ICD. The factors leading to this determination were not recorded, and could include some patients with pre-existing atrial arrhythmias or sinus node dysfunction. Also, postrandomization AF/AT episodes were not centrally adjudicated, potentially resulting in some misclassification. Although our definition of device-detected AF/AT (atrial rate >175 per minute for ≥30 s) is relatively specific for true AT versus isolated ectopy or artifact, this threshold is not specific for AF versus atrial flutter or supraventricular tachycardia. However, based on the relative prevalence of these conditions, the majority of device-detected episodes will be paroxysmal AF. This definition was the accepted standard when RAFT was conducted, though more recent studies have required faster rates and longer episodes to identify device-detected AF. All of these factors could inflate the overall absolute risk of postimplantation AF/AT reported here, but there is no reason to think that they were unequally distributed between treatment groups at randomization. Finally, details of changes to device programming during follow-up and results of serial cardiac imaging are not available, limiting our ability to investigate the pathophysiology of postrandomization AF/AT in this cohort.

Conclusions
In RAFT, nearly half of the patients with an atrial lead developed postrandomization AF/AT, with a borderline significant increased risk in the CRT-D group. Development of postrandomization AF/AT was associated with an increased risk of heart failure hospitalization, but not with the RAFT primary end point. However, postrandomization AF/AT did not attenuate CRT-D efficacy. Further investigation of the role of device programming in preventing postimplantation AF is required.

Sources of Funding
The Canadian Institutes of Health Research and Medtronic of Canada funded the Resynchronization/Defibrillation in Ambulatory Heart Failure Trial study. Dr Healey has a personnel award from the Heart and Stroke Foundation, Ontario Provincial office (MC7450).

Disclosures
Dr Wilton received a research grant from St. Jude Medical and consulting fees from Boehringer-Ingelheim and Arca Biopharma. Dr Exner has received research grants and consulting fees from Medtronic Inc, research funding from GE healthcare, research funding from St. Jude Medical, and discloses ownership and patents Analytics for Life. Dr Healey has received research grants and speaking fees from Medtronic, Boston Scientific, and St. Jude Medical. Dr Tang received research grants from Medtronic Inc. The other authors report no conflicts.

References


Frequency and Outcomes of Postrandomization Atrial Tachyarrhythmias in the Resynchronization/Defibrillation in Ambulatory Heart Failure Trial


*Circ Arrhythm Electrophysiol.* 2016;9: doi: 10.1161/CIRCEP.115.003807

*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circcep.ahajournals.org/content/9/5/e003807

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation: Arrhythmia and Electrophysiology* is online at:
http://circcep.ahajournals.org/subscriptions/