Cardiac resynchronization defibrillators have been demonstrated to reduce both mortality\(^1\) and heart failure\(^2\) in patients with significant ventricular dysfunction and widened QRS. The influence of cardiac resynchronization therapy (CRT) on ventricular arrhythmias, however, is less certain. A systematic review of randomized controlled trials of more advanced heart failure populations with New York Heart Association class III-IV raised the concern that CRT may increase arrhythmia deaths,\(^4\) yet the CARE-HF trial (the Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure) demonstrated a reduction in mortality, including a reduction in sudden death\(^5\) in patients treated with CRT pacemakers. Small series and case studies have reported potential proarrhythmia related to biventricular pacing,\(^7\) and mechanistic and clinical studies have proposed potential mechanisms for a proarhythmic effect of CRT.\(^8\) Nonetheless, both MADIT-CRT (the Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events trial) and REVERSE Cardiac Resynchronization Therapy Reduces Ventricular Arrhythmias in Primary but Not Secondary Prophylactic Implantable Cardioverter Defibrillator Patients Insight From the Resynchronization in Ambulatory Heart Failure Trial John L. Sapp, MD; Ratika Parkash, MD; George A. Wells, PhD; Elizabeth Yetisir, MSc; Martin J. Gardner, MD; Jeffrey S. Healey, MD; Bernard Thibault, MD; Laurence D. Sterns, MD; David Birnie, MD; Pablo B. Nery, MD; Soori Sivakumaran, MD; Vidal Essebag, MD, PhD; Paul Dorian, MD; Anthony S.L. Tang, MD

Background—The RAFT (Resynchronization in Ambulatory Heart Failure Trial) demonstrated that cardiac resynchronization therapy (CRT) reduced both mortality and heart failure hospitalizations in patients with functional class II or III heart failure and widened QRS. We examined the influence of CRT on ventricular arrhythmias in patients with primary versus secondary prophylaxis defibrillator indications.

Methods and Results—All ventricular arrhythmias among RAFT study participants were downloaded and adjudicated by 2 blinded reviewers with an overreader for disagreements and committee review for remaining discrepancies. Incidence of ventricular arrhythmias among patients randomized to CRT-D versus implantable cardioverter defibrillator (ICD) were compared within the groups of patients treated for primary prophylaxis and for secondary prophylaxis. Of 1798 enrolled patients, 1764 had data available for adjudication and were included. Of these, 1531 patients were implanted for primary prophylaxis, while 233 patients were implanted for secondary prophylaxis; 884 patients were randomized to ICD and 880 to CRT-D. During 5953.6 patient-years of follow-up, there were 11278 appropriate ICD detections of ventricular arrhythmias. In the primary prophylaxis group, CRT-D significantly reduced incidence ventricular arrhythmias in comparison to ICD (hazard ratio, 0.86; 95% confidence interval, 0.74–0.99; \(P=0.044\)). This effect was not seen in the secondary prophylaxis group (hazard ratio, 1.14; 95% confidence interval, 0.82–1.58; \(P=0.45\)). CRT-D was not associated with significant differences in overall ventricular arrhythmia burden in either group.

Conclusions—CRT reduced the rate of onset of new ventricular arrhythmias detected by ICDs in patients without a history of prior ventricular arrhythmias. This effect was not observed among patients who had prior ventricular arrhythmias.

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

(Circ Arrhythm Electrophysiol. 2017;10:e004875. DOI: 10.1161/CIRCEP.116.004875.)

Key Words: cardiac resynchronization therapy ■ congestive heart failure ■ heart failure ■ implantable cardioverter-defibrillator ■ ventricular arrhythmia
WHAT IS KNOWN
- Cardiac resynchronization defibrillator implantation reduces mortality and heart failure hospitalization for patients with functional class II or III heart failure and left bundle branch block in comparison to implantable defibrillator alone.
- Cardiac resynchronization reduces new-onset ventricular arrhythmias in those with no history of arrhythmias who obtain or are likely to obtain hemodynamic response.

WHAT THE STUDY ADDS
- Cardiac resynchronization was found to significantly reduce new-onset and first recurrences of ventricular arrhythmias for patients who have not experienced prior ventricular arrhythmias.
- For patients with a history of ventricular arrhythmias, there was a statistically insignificant trend to increased ventricular arrhythmias with cardiac resynchronization pacing.

Methods

Study Population
The design, protocol, and results of the RAFT trial have been previously published.1-16, it was approved by the research ethics boards at all participating institutions, and all participants provided written informed consent. The trial included patients with New York Heart Association functional class II or III heart failure symptoms, despite optimal medical therapy with left ventricular ejection fraction ≤30% with intrinsic QRS duration ≥120 ms (or paced QRS duration ≥200 ms), with either a primary or secondary prophylactic indication for ICD implantation. Patients were enrolled from January 2003 to February 2009 within 34 centers. Among 1798 patients enrolled, 1787 had an ICD or CRT-D implanted; 1764 had device-download information available for review. In the RAFT study, in which randomized patients with implantable cardioverter defibrillator (ICD) or CRT-D device downloads throughout a long follow-up period were available for analysis.

Device Programming and Data Acquisition
Patients were implanted with defibrillators (Medtronic, Minneapolis, MN) programmed according to prespecified evidence-based guidelines.1,16,17 In brief, devices were programmed with ventricular tachycardia (VT) detection at 150 beats per minute (or less if slower clinical VT had been documented), requiring 16 intervals for initial detection. Fast VT and ventricular fibrillation (VF) intervals were specified, as well as standardized discriminator algorithms. Anti-tachycardia pacing was programmed in all zones. Patients were seen in follow-up at 1 month after implantation and every 6 months throughout the trial. At each visit, the ICD was interrogated to capture all arrhythmia events detected by the device since implantation, and the data were saved and transmitted to a core laboratory. Data from each device interrogation were concatenated for each patient, and arrhythmia events were uploaded to a web-based electrogram/event review database (WebEGM, Medtronic Inc).

Event Adjudication
All spontaneous events detected by the ICD as sustained ventricular arrhythmias were reviewed using a web-based adjudication system by an experienced ICD technician and a Cardiac Electrophysiologist investigator. Arrhythmia event reviewers were blinded to clinical data, although the presence of embedded electrogram data precluded complete blinding of the reviewers to presence or absence of a left ventricular lead. Adjudicators determined accuracy of arrhythmia detection and categorized by type (monomorphic VT had stable morphology, polymorphic VT had unstable morphology with mean cycle length ≥240 ms, and VF had unstable cycle length or morphology with mean cycle length ≤240 ms). If there was uncertainty by the investigator or disagreement between the first 2 reviewers, the event was reviewed by a third reviewer, blinded to the prior adjudications. If there was disagreement between either investigator reviewers, or remaining uncertainty, the event was reviewed by the entire committee and adjudicated by consensus. Device event logs and totals from implant to final follow-up were reconciled with electrogram and event data available for review. In the case of events with missing electrograms, the clinical event record (blinded to treatment allocation) was examined, and the event was adjudicated if there was clear ECG evidence to classify the event. In the absence of clear clinical documentation, events without electrograms were classified as appropriate if the patient had an adjudicated VT episode with cycle length within 40 ms or inappropriate if the patient had an adjudicated supraventricular tachycardia episode with cycle length within 40 ms. If the

Figure 1. Patient enrollment is shown; 11 patients were excluded because an implantable cardioverter defibrillator (ICD) was not implanted. A further 23 patients were excluded because no ICD download data were available for blinded review.
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Primary Prophylaxis Indication (n=1531)</th>
<th></th>
<th>Secondary Prophylaxis Indication (n=233)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD (n=772)</td>
<td>ICD+CRT (n=759)</td>
<td>P Value</td>
<td>ICD (n=112)</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>66.0±9.4</td>
<td>65.9±9.3</td>
<td>0.76</td>
<td>66.6±9.7</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>630 (81.8)</td>
<td>642 (84.6)</td>
<td>0.13</td>
<td>86 (76.8)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>142 (18.4)</td>
<td>117 (15.4)</td>
<td>0.18</td>
<td>26 (23.2)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>497 (64.4)</td>
<td>514 (76.7)</td>
<td>0.18</td>
<td>77 (68.8)</td>
</tr>
<tr>
<td>Nonischemic heart disease, n (%)</td>
<td>275 (35.6)</td>
<td>245 (32.3)</td>
<td>0.55</td>
<td>35 (31.3)</td>
</tr>
<tr>
<td>NYHA class II, n (%)</td>
<td>663 (82.0)</td>
<td>613 (80.8)</td>
<td>0.55</td>
<td>84 (75.0)</td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
<td>139 (18.0)</td>
<td>146 (19.2)</td>
<td>0.97</td>
<td>28 (25.0)</td>
</tr>
<tr>
<td>LV ejection fraction, %, mean±SD</td>
<td>22.7±5.0</td>
<td>22.6±5.5</td>
<td>0.07</td>
<td>22.4±5.0</td>
</tr>
<tr>
<td>Atrial tachyarrhythmia, n (%)</td>
<td>99 (12.8)</td>
<td>96 (12.7)</td>
<td>0.94</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Single chamber</td>
<td>341 (44.2)</td>
<td>331 (43.6)</td>
<td>0.84</td>
<td>40 (35.7)</td>
</tr>
<tr>
<td>Dual chamber</td>
<td>431 (55.8)</td>
<td>428 (56.4)</td>
<td>0.28</td>
<td>72 (64.3)</td>
</tr>
<tr>
<td>CV risk factors, n (%)</td>
<td></td>
<td></td>
<td>0.27</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>334 (43.3)</td>
<td>336 (44.3)</td>
<td>0.72</td>
<td>53 (47.3)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>272 (35.2)</td>
<td>246 (32.4)</td>
<td>0.26</td>
<td>29 (25.9)</td>
</tr>
<tr>
<td>Smoking</td>
<td>105 (13.6)</td>
<td>89 (11.7)</td>
<td>0.28</td>
<td>21 (18.8)</td>
</tr>
<tr>
<td>RBBB</td>
<td>82 (10.6)</td>
<td>58 (7.6)</td>
<td>0.24</td>
<td>11 (9.8)</td>
</tr>
<tr>
<td>LVBB</td>
<td>540 (70.0)</td>
<td>553 (72.9)</td>
<td>0.17</td>
<td>91 (81.3)</td>
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<tr>
<td>NICVD</td>
<td>91 (11.8)</td>
<td>89 (11.7)</td>
<td>0.89</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Ventricular paced</td>
<td>59 (7.6)</td>
<td>58 (7.6)</td>
<td>1.00</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Conducted QRS duration, ms, mean±SD</td>
<td>158.0±23.9 (n=713)</td>
<td>158.6±23.7 (n=701)</td>
<td>0.35</td>
<td>161.0±24.5 (n=109)</td>
</tr>
<tr>
<td>Paced QRS duration, ms, mean±SD</td>
<td>210.4±18.8 (n=59)</td>
<td>209.1±21.2 (n=58)</td>
<td>0.73</td>
<td>216.7±22.3 (n=3)</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td>689 (89.3)</td>
<td>691 (91.0)</td>
<td>0.27</td>
<td>99 (88.4)</td>
</tr>
<tr>
<td>ACEI–ARB use</td>
<td>754 (97.7)</td>
<td>732 (96.4)</td>
<td>0.17</td>
<td>105 (93.8)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>330 (42.8)</td>
<td>321 (42.3)</td>
<td>0.88</td>
<td>40 (35.7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>654 (84.7)</td>
<td>641 (84.5)</td>
<td>0.89</td>
<td>85 (75.9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>280 (36.3)</td>
<td>263 (34.7)</td>
<td>0.52</td>
<td>31 (27.7)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>91 (11.8)</td>
<td>93 (12.3)</td>
<td>0.81</td>
<td>29 (25.9)</td>
</tr>
<tr>
<td>Statin</td>
<td>521 (67.5)</td>
<td>514 (67.7)</td>
<td>0.96</td>
<td>82 (73.2)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>262 (33.9)</td>
<td>273 (36.0)</td>
<td>0.42</td>
<td>28 (25.0)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>116 (15.0)</td>
<td>108 (14.2)</td>
<td>0.67</td>
<td>26 (23.2)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>69 (8.9)</td>
<td>87 (11.5)</td>
<td>0.11</td>
<td>12 (10.7)</td>
</tr>
<tr>
<td>ASA</td>
<td>526 (68.1)</td>
<td>489 (64.4)</td>
<td>0.13</td>
<td>81 (72.3)</td>
</tr>
<tr>
<td>Other antiarrhythmia drugs</td>
<td>6 (0.8)</td>
<td>8 (1.1)</td>
<td>0.60</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CRT, cardiac resynchronization therapy; CV, cardiovascular; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LV, left ventricle; NICVD, nonspecific intraventricular conduction delay; NYHA, New York Heart Association; and RBBB, right bundle branch block.
cycle length matched both or neither, but was part of a cluster (within 48 hours) of similar events with electrograms available for adjudication, it was classified the same. In the absence of this evidence, the event was adjudicated as unknown.

**Study Outcomes**

The primary outcome of this study was incidence of ventricular arrhythmia after randomization to ICD or CRT-D in patients without previous ventricular arrhythmia (primary prophylaxis device indication) and in patients with previous ventricular arrhythmia (secondary prophylaxis device indication). Secondary study outcomes included mean numbers of ventricular arrhythmias and ICD therapies per patient and number of patients affected with ventricular arrhythmias and ICD therapies.

**Statistical Analysis**

All analyses were performed according to the intention-to-treat principle. Continuous data are presented as mean±SD. Differences in baseline demographic variables and among the primary and secondary prophylaxis groups were compared using t tests for continuous variables and the χ² or Fisher exact test for categorical variables. We used survival analysis techniques to compare CRT-D versus ICD with respect to survival free of ventricular arrhythmias in both the primary and secondary prophylaxis device indication patients. Survival was summarized with the use of Kaplan–Meier curves and compared using log-rank tests. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. Because duration of follow-up was longer among patients treated with CRT-D (who had a survival advantage), analysis of arrhythmia burden was performed using counts of events per person-year at risk, and rates were compared using a zero inflated Poisson model. In addition, to account for the competing risk of death and the occurrence of ventricular arrhythmia, a multistate model was used to estimate the time to the occurrence of first ventricular arrhythmia or death and subsequent ventricular arrhythmia episodes.

**Results**

Among 1798 patients enrolled in the trial, 1787 had ICD or CRT-D implanted, and 1764 (99%) had device-download data available for review (Figure 1) and comprise the study group. Device counters were reconciled with event logs and electrograms. Of 15103 device-detected events, 14515 (96.1%) had event-specific data available; 10373 (71.5%) were adjudicable by electrogram review, and 4142 (28.5%) were classified by cycle length and temporal proximity to electrogram- adjudicable events. Baseline characteristics are shown in Table 1. The majority of patients in the RAFT trial were included in this study, and no differences in baseline variables were observed between ICD and CRT-D randomization groups among either the primary prophylaxis or secondary prophylaxis groups (Table 1). There were no major differences in baseline ejection fraction, etiology of cardiac dysfunction, sex, age, QRS morphology, or pharmacological therapy.

The mean follow-up was 40.7±19.2 months, with a total follow-up of 5953.6 patient-years. A total of 871 (49.4%) patients had ventricular arrhythmias detected, 448 (50.7%) in the ICD group and 423 (48.1%) in the CRT-D group (HR, 0.90; 95% CI, 0.7–1.03; P=0.13). There were 11 278 events adjudicated to be appropriate detections of ventricular arrhythmias (8096 adjudicated by electrogram review and 3182 by cycle length and temporal proximity to adjudicated events). There were 3183 events adjudicated as inappropriate detections of ventricular arrhythmia (2277 by electrogram review and 906 by cycle length and temporal proximity to adjudicated events) and 54 events adjudicated as unknown. Patients experienced 11 278 ventricular arrhythmias during follow-up, including VF, polymorphic VT, and monomorphic VT. Of patients with a primary prophylaxis indication, 47.5% of patients experienced ventricular arrhythmia as compared with 61.8% of those with a secondary prophylaxis indication (P<0.0001).

**Effect of CRT on Ventricular Arrhythmias**

Among primary prophylaxis patients, there is a trend to fewer patients implanted with CRT-D, 344 (45.3%) patients experiencing ventricular arrhythmia during follow-up than patients implanted with ICD, 383 (49.6%; P=0.10; Table 2). The time to the occurrence of ventricular arrhythmia was significantly prolonged in the CRT-D patients in comparison with the ICD patients (HR, 0.86; 95% CI, 0.74–1.00; P=0.044). However, among secondary prophylaxis patients, there was no difference in the number of patients who developed ventricular arrhythmia between the 2 groups, 79 (65.3%) patients implanted with CRT-D and 65 (58.0%) patients implanted with ICD, P=0.28; the time to occurrence of ventricular arrhythmia between CRT-D patients and ICD patients was no different (HR, 1.14; 95% CI, 0.82–1.58; P=0.45; Figure 2). When primary and secondary prophylaxis patients were combined, there was a trend to prolongation of time to the occurrence of ventricular arrhythmias among patients treated with CRT (HR, 0.90; 95% CI, 0.79–1.03; P=0.13), but it was not statistically significant.

### Table 2. Patients Experiencing Ventricular Arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>Primary Indication</th>
<th>Secondary Indication</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD (n=772)</td>
<td>CRT-D (n=759)</td>
<td>ICD (n=112)</td>
</tr>
<tr>
<td>Patients with ventricular arrhythmia</td>
<td>383 (49.6%)</td>
<td>344 (45.3%)</td>
<td>65 (58.0%)</td>
</tr>
<tr>
<td>Patients with mono VT</td>
<td>357 (46.2%)</td>
<td>326 (43.0%)</td>
<td>61 (54.5%)</td>
</tr>
<tr>
<td>Patients with poly VT</td>
<td>52 (6.7%)</td>
<td>34 (4.5%)</td>
<td>9 (8.0%)</td>
</tr>
<tr>
<td>Patients with VF</td>
<td>28 (3.6%)</td>
<td>22 (2.9%)</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Patients with appropriate ATP</td>
<td>347 (45.0%)</td>
<td>318 (41.9%)</td>
<td>60 (53.6%)</td>
</tr>
<tr>
<td>Patients with appropriate shock</td>
<td>172 (22.3%)</td>
<td>148 (19.5%)</td>
<td>35 (31.3%)</td>
</tr>
</tbody>
</table>

P values calculated using zero inflated Poisson model. ATP indicates antitachycardia pacing; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation; and VT, ventricular tachycardia.
Similar trends were seen for each arrhythmia subtype, including monomorphic VT, polymorphic VT, and VF (Table 3). Within the primary prophylaxis patients, CRT-D was associated with trends toward reduced monomorphic VT (HR, 0.85; P=0.085), VF (HR, 0.76; P=0.34), appropriate antitachycardia pacing (HR, 0.88; P=0.099), and appropriate shock (HR, 0.82; P=0.082), as well as a significant reduction in polymorphic VT (HR, 0.64; P=0.041). In contrast, within the secondary prophylaxis patients, randomization to CRT-D was associated with trends to increases in monomorphic VT (HR, 1.23; P=0.23), polymorphic VT (HR, 1.30; P=0.55), and VF (HR, 1.49; P=0.52) along with increased appropriate antitachycardia pacing (HR, 1.19; P=0.31) and appropriate shock (HR, 1.2; P=0.34).

Effect of CRT on Recurrent Episodes of Ventricular Arrhythmias: Multistate Model

With adjustment for the competing risk of death, a multistate model analysis demonstrated that for the patients without prior ventricular arrhythmia at entry to the study (primary prophylaxis), the time to the first occurrence of ventricular arrhythmia in patients implanted with CRT-D was significantly longer than in those with ICD (HR, 0.86; 95% CI, 0.74–0.99; P=0.039). For patients with prior ventricular arrhythmia at entry to the study (secondary prophylaxis), the result was different. The time to the first occurrence of ventricular arrhythmia in patients implanted with CRT-D was not longer than in those implanted with ICD (HR, 1.15; 95% CI, 0.83–1.60; P=0.40). The same observation was
During longer term follow-up (Figure 4), patients in the secondary prophylaxis group experienced significantly more frequent ventricular arrhythmias than those in the primary prophylaxis group (median, 0.37; interquartile range [IQR], 0–2.07 versus median, 0; IQR, 0–0.71 episodes per person-year at risk; P<0.0001), including more frequent monomorphic VT (median, 0.33; IQR, 0–1.83 versus median, 0; IQR, 0–0.67 episodes per person-year at risk; P<0.0001) and more frequent polymorphic VT or VF (mean±SD, 0.07±0.40 versus 0.070±0.47; median, 0; IQR, 0–0 versus median, 0; IQR, 0–0 episodes per person-year at risk; P=0.0099). Similarly, the secondary prophylaxis group experienced more frequent appropriate antitachycardia pacing (median, 0.28; IQR, 0–1.65 versus median, 0; IQR, 0–0.57 per person-year at risk; P<0.0001) and more frequent appropriate shocks (mean±SD, 0.82±2.95 versus 0.32±1.68; median, 0; IQR, 0–0.37 versus median, 0; IQR, 0–0 per person-year at risk; P<0.0001). Randomization to CRT-D was not associated with a significant change in mean number of arrhythmia episodes nor mean number of appropriate therapies experienced, except for a significant increase in episodes of polymorphic VT or VF associated with CRT-D randomization in the primary prophylaxis group (mean±SD, 0.073±0.51 versus 0.067±0.43; median, 0; IQR, 0–0 versus median, 0; IQR, 0–0 episodes per person-year at risk; P=0.023).

The number of ventricular arrhythmias experienced by each group is shown in Figure 5. The distribution demonstrates higher numbers of ventricular arrhythmias experienced in the secondary prophylaxis groups, but no consistent trend associated with CRT-D randomization.

**Discussion**

This study demonstrated that CRT reduced ventricular arrhythmia only in patients without prior ventricular arrhythmia (primary prophylaxis), but for patients with prior ventricular arrhythmia (secondary prophylaxis), CRT was not associated with a reduction in ventricular arrhythmia, but may even have been associated with an increase.

CRT has brought important benefit to patients with heart failure. Standard cardiac pacing from the right ventricular apex is a highly effective treatment for bradycardias, but is associated with an increased risk of ventricular dysfunction and may increase the risk of ventricular tachyarrhythmias. It should, therefore, be no surprise if CRT, which can improve ventricular function, has complex effects on ventricular arrhythmias. Some studies have suggested that it can suppress ventricular arrhythmias, while others have raised concern...
about an increase in ventricular arrhythmias in case reports and series.\textsuperscript{7,8,20,25–28} The MADIT-CRT trial\textsuperscript{1} enrolled patients without a history of ventricular arrhythmias\textsuperscript{14} and found that CRT reduces the risk of new-onset ventricular arrhythmias (faster than 180 beats per minute), particularly in patients with left bundle branch block conduction pattern, without a significant reduction on subsequent arrhythmia risk. It also showed a trend to an increase in recurrences of ventricular arrhythmias among patients with non–left bundle branch block conduction patterns.\textsuperscript{12} The MADIT-CRT trial also demonstrated that the reduction in ventricular arrhythmia risk was seen among patients with a significant hemodynamic response to CRT.\textsuperscript{13,14} This finding has been further confirmed in a meta-analysis.\textsuperscript{29}

This study represents the largest adjudicated database of ventricular arrhythmias in patients treated with CRT-D and ICD and includes more than double the number of patients experiencing ventricular arrhythmias reported in prior studies. The population treated with CRT in the RAFT study experienced reductions in both heart failure hospitalization and mortality, with the largest reductions seen in patients without atrial fibrillation and with left bundle branch block conduction abnormalities, particularly among those with the most prolonged QRS durations.\textsuperscript{30} In this study, we observed that in the overall population, there was no significant influence of CRT on either new-onset ventricular arrhythmias or recurrent arrhythmias. Nonetheless, there was a trend to reduce new-onset ventricular arrhythmias among the entire study group and a significant reduction in new-onset ventricular arrhythmia and recurrent arrhythmias in the primary prophylaxis group. Among patients who had already experienced ventricular arrhythmias (secondary prophylaxis group), the trend was reversed, with a slight increase in the point estimate of risk of

Figure 4. Mean number of ventricular arrhythmias or implantable cardioverter defibrillator (ICD) therapies per person year at risk. The effect of cardiac resynchronization therapy (CRT-D) on the patient experience of ventricular arrhythmias is shown, normalized per patient year at risk (because of differential mortality rates between the groups). Significant differences are indicated (*). Among the primary prophylaxis group, the number of arrhythmias experienced was similar between CRT-D and ICD. The most frequent arrhythmias were monomorphic ventricular tachycardia (VT), treated most frequently by antitachycardia pacing (ATP). The secondary prophylaxis group experienced more frequent arrhythmias than the primary prophylaxis group, most frequently monomorphic VT treated by ATP. Among the secondary prophylaxis group, treatment with CRT-D was associated with significantly more appropriate detections of ventricular arrhythmias. VF indicates ventricular fibrillation.
ventricular arrhythmias. This is in keeping with and extends
the observations in MADIT-CRT, which included patients
implanted for primary prophylaxis.14

This study does not provide a clear mechanistic explana-
tion for the contrasting findings that CRT reduced ventricu-
lar arrhythmia in patients without prior ventricular arrhythmia but
appeared to increase ventricular arrhythmia in patients with
prior ventricular arrhythmia. One might speculate that CRT-D
provides favorable hemodynamic benefits to patients without
a ventricular arrhythmia history that delays progression of
arrhythmogenic substrate, but that once this substrate is pres-
ent, the hemodynamic benefit is no longer antiarrhythmic.
Further, it is possible that imposing continuous left ventricu-
lar epicardial pacing with CRT might carry a slight increased
proarrhythmic risk once the arrhythmogenic substrate is pres-
ent. Our observation that numbers of ventricular arrhythmias
experienced by patients randomized to CRT-D were not sig-
ificantly different (although they tended to be more frequent)
from those randomized to ICD in either primary or secondary
prophylaxis groups would be consistent with this hypothesis
of competing (antiarrhythmic) hemodynamic protection with
a proarrhythmic risk in patients with the necessary substrate.

Limitations
Although this study is large and includes a large number of
ventricular arrhythmia events, there are some factors that limit
interpretation. Use of amiodarone was significantly higher
within the secondary prophylaxis group, which might have
an unpredictable influence on the effect of CRT-D on ven-
tricular arrhythmias. Randomization was stratified by center
and by whether patients were to receive single versus dual-
chamber ICD, but not by primary versus secondary prophy-
laxis indication. Further, we do not have comprehensive data
on postrandomization ejection fraction to reliably classify
patients’ clinical response to CRT-D. This limits interpreta-
tion of potential mechanisms for the observations. The sec-
ondary prophylaxis group, although large in comparison to
prior studies, included only 233 patients and may have been
underpowered to detect a significant influence of CRT on
ventricular arrhythmias. Finally, analysis of recurrent events
in the multistate model was curtailed after first recurrences
because interventions (antiarrhythmic drugs or catheter abla-
tion) would complicate interpretation.

Conclusions
CRT reduced the rate of onset of new ventricular arrhythmias
detected by ICDs in patients without a history of prior ventricu-
lar arrhythmias. This effect was not observed among patients
who have experienced ventricular arrhythmias.

Sources of Funding
Funding for this study was provided by a grant from the Heart and
Stroke Foundation of Canada. Dr Birnie is supported by a Mid-Career
Investigator Award from the Heart and Stroke Foundation of Ontario.
Dr Essebag is supported by a Clinical Research Scholar Award from
the Fonds de Recherche de Quebec-Sante. Dr Healey is supported
by the Population Health Research Institute Chair in Cardiology
Research, and a Heart and Stroke Foundation of Ontario Mid-Career
Award (MC7450).

Disclosures
Dr Sapp reports receiving modest lecture fees from Medtronic. Dr
Healey reports receiving research grant support from Medtronic and
St Jude Medical. Dr Thibault reports receiving research support from
Medtronic and St Jude Medical, as well as modest speaker fees from St
Jude Medical. Dr Sivakumaran reports receiving modest travel expenses
from St Jude Medical. Dr Essebag reports receiving modest speaker fees
from Medtronic, St Jude Medical, and Boston Scientific. Dr Tang re-
ceived a research grant from Medtronic. The authors report no conflicts.

References
1. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S,
Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau
JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial
Investigators. Cardiac-resynchronization therapy for mild-to-moder-
NEJMoa1009540.
AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heat
Failure (COMPANION) Investigators. Cardiac-resynchronization therapy
with or without an implantable defibrillator in advanced chronic heart fail-
NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon

Figure 5. Number of ventricular arrhyth-
rias experienced by patients. The
distribution of number of appropriate ven-
tricular arrhythmia detections per person
is shown. Fewer secondary prophylaxis
patients experienced zero ventricular arrhyth-
rias, but more experienced >5 episodes. CRT indicates cardiac resyn-
chronization therapy; and ICD, implant-
able cardioverter defibrillator.


Cardiac Resynchronization Therapy Reduces Ventricular Arrhythmias in Primary but Not Secondary Prophylactic Implantable Cardioverter Defibrillator Patients: Insight From the Resynchronization in Ambulatory Heart Failure Trial

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Circ Arrhythm Electrophysiol. 2017;10:
doi: 10.1161/CIRCEP.116.004875

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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