The Epidemic of Inadequate Biventricular Pacing in Patients With Persistent or Permanent Atrial Fibrillation and Its Association With Mortality

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Background—We classified patients’ atrial fibrillation (AF), assessed its impact on biventricular pacing (BIVP%), and determined whether AF classification or BIVP% independently correlate with mortality in cardiac resynchronization therapy defibrillator patients.

Methods and Results—Cardiac resynchronization therapy defibrillator patients were classified as permanent (daily mean AF burden ≥23 hours), persistent (≥7 consecutive days of AF ≥23 hours/d), paroxysmal (≥1 day with AF ≥23 hours), or no/little AF (all others) using device-detected AF during the 6 months postimplant. We evaluated subsequent all-cause mortality using a multivariable Cox proportional hazard regression. Among 54019 patients (age, 70±11 years; 73% male; follow-up, 2.3±1.2 years), 8% of patients each had permanent (N=4449), persistent (N=4237), and paroxysmal AF (N=4219). A high proportion of patients with permanent (69%) and persistent (62%) AF did not achieve high BIVP (>98%). Relative to no/little AF, patients with AF had increased mortality after adjusting for age, sex, BIVP, and shocks (permanent: hazard ratio=1.28 [1.19–1.38]; P<0.001; persistent: hazard ratio=1.51 [1.41–1.61]; P<0.001). Relative to patients with BIVP >98%, patients with reduced BIVP had increased mortality after adjusting for age, sex, AF, and shocks (90%–98%: hazard ratio=1.20 [1.15–1.26]; P<0.001; <90%: hazard ratio=1.32 [1.23–1.41]; P<0.001). High BIVP% was associated with the greatest mortality improvement in permanent AF among the AF classifications.

Conclusions—High BIVP% was not achieved in two thirds of 8686 patients with persistent or permanent AF, and these patients had an increased risk of death. A shift toward more aggressive rate control and more pacing may be necessary in patients with AF to maximize the benefits of cardiac resynchronization therapy. (Circ Arrhythm Electrophysiol. 2014;7:370-376.)

Key Words: atrial fibrillation ■ cardiac resynchronization therapy ■ heart failure ■ heart rate ■ mortality

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ardiac resynchronization therapy defibrillators (CRT-Ds) have been proven to significantly reduce hospitalizations and all-cause mortality in heart failure patients.1 Unfortunately, 30% to 40% of these patients do not realize an improvement in their symptoms and are often referred to as nonresponders.2 Rapid conduction of atrial fibrillation (AF) interferes with CRT delivery and has been implicated as a reason for nonresponse to CRT therapy.3 Current means of controlling AF in CRT-D recipients, thereby increasing the percentage of biventricular pacing (BIVP), include sinus rhythm management with medications or AF ablation, or controlling the ventricular rate during AF (VRAF) via medications or atrioventricular (AV) node ablation.

Clinical Perspective on p 376

AF is common in patients with heart failure with an estimated prevalence of ≈5% in those with New York Heart Association class I to ≈50% in those with class IV symptoms.4 The majority of studies looking at AF in patients with heart failure have small sample sizes or highly variable assessments of AF burden which can lead to a potential sampling bias and imprecise reporting of AF.5 In addition, studies have consistently shown that increased BIVP is associated with better clinical outcomes. Koplan et al6 reported reduced mortality in patients who had >92% BIVP. A more recent report from Hayes et al7 suggests that the goal for BIVP should be as close to 100% as possible because the lowest mortality risk was found in patients with >98% BIVP. However, neither study used a continuous AF detection algorithm, stored daily data on AF and VRAF, categorized the patients by AF classification, or adjusted for shocks.

The deidentified Discovery Link database overcomes many of the limitations described above by using a continuous AF detection algorithm with high accuracy and storing data...
that includes daily measurements of AF burden, VRAF, and BIVP%. The aim of our study was to determine how device-derived AF classification impacts BIVP% and whether AF classification and BIVP% independently predict mortality in CRT-D patients.

### Methods

#### Data Collection

Data collection from implanted CRT-D devices was obtained through remote telemetry from the patient’s place of residence, permitting frequent and accurate transfer of the stored, programmed, and diagnostic data to the Medtronic CareLink data server. The deidentified Discovery Link database was created from the stored data of devices implanted in the United States. Parameters included in the analysis were age, sex, device shocks, CRT-D programming, premature ventricular contractions (PVCs), daily device-detected AF cumulative duration (ie, burden), daily mean VRAF, and BIVP%.

#### Study Patients

We performed a retrospective, observational analysis using the Discovery Link database. Patients were included if they had all of the following: CRT-D device with the required monitoring capabilities, a transmission between 3 and 12 months postimplant, an atrial lead for AF diagnostics, and their device appeared to be programmed with the intent to achieve BIVP. The latter was defined as pacing right ventricle→left ventricle or left ventricle→right ventricle and (1) pacing mode DDD or DDDR with paced AV ≥250 ms, (2) pacing mode DDI or DDIR with lower rate ≥40 beats per minute and paced AV <250 ms, or (3) pacing mode VVI or VVIR with lower rate ≥40 beats per minute.

#### CRT-D Programming and Diagnostics

CRT-Ds were programmed at the discretion of the implanting physician. We evaluated programming at the transmission nearest in time to the 6 months postimplant transmission. The frequency of remote CRT-D data transmissions was determined by clinicians and patients. All devices recorded the total time spent in AF each day along with the mean VRAF on days when AF was present. Throughout the article, the term AF, when used to describe the device diagnostics, includes any atrial tachyarrhythmias when the atrial-ventricular pattern was ≥1:1 for ≥32 ventricular events and the median atrial rate was fast (nominally >171 beats per minute). Using device-stored electrograms and Holter monitor recordings, the AF detection algorithm has been previously shown to have 100% sensitivity for identification of AF duration with a specificity of 99.99% for detecting non-atrial tachycardia/AF rhythms. Similar to the intent of the AF guidelines, we categorized patients based on AF diagnostics as having permanent AF if the mean daily AF burden was ≥23 hours over the entire evaluation period, persistent AF if there was ≥7 consecutive days of AF ≥23 hours/d, or paroxysmal AF if there was ≥1 day with AF ≥26 hours. All other patients were classified as having no/little AF.

The BIVP% was calculated from the ventricular pacing and sensing histograms. We divided the BIVP% data into 3 groups using an upper threshold of 98% because that identified a significant change in mortality in prior work, and a lower threshold of 90% was chosen because that is the threshold of a notification in the devices used in this study. Therefore, the 3 BIVP groups were high BIVP (>98%), moderate (90%-98%), and low (<90%).

PVCs were recorded by the devices, and the average number of PVCs per hour was computed. A PVC was defined as a sensed ventricular event that directly follows any other ventricular event with no atrial event between them, and the period of the ventricular event was <69% of the mean of the last 4 ventricular events.

### Statistical Analysis

We sought to understand if AF classification and BIVP% in the period before 6 months postimplant correlated with subsequent mortality (Figure 1). Mortality data were obtained by cross-referencing the Social Security Death Index with the device registry. The data were censored 6 months before freezing the database to allow adequate time for death reporting.

Kaplan–Meier methods were used to analyze mortality. A multivariable Cox proportional hazard regression model was used to adjust for AF classification and BIVP% and for the following variables that were chosen a priori: sex, age, and presence of any implantable cardioverter defibrillator (ICD) shock. Proportions were compared with the χ² test. χ² test was also used for the categorical variables in the Table, and Kruskal–Wallis was used for continuous variables. An ANOVA was used for comparisons in Figure 2. P values <0.05 were considered statistically significant. Statistical software from SAS, Inc (Version 9.2) was used.

### Results

#### Patients

Overall there were 61,135 patients with adequate data and intent to BIVP. Of those, 7116 were excluded because of the lack of an atrial lead, resulting in 54,019 patients from ≥2645 centers in the United States being included in this analysis. Patients had an average follow-up of 2.3±1.2 years from the date of implant resulting in a total of 124,497 patient-years of follow-up. The patients were predominantly male (73%) and had an average age of 70±11 years at baseline (Table).

#### AF, VRAF, and Shocks

Approximately one quarter (24%) of the 54,019 patients had ≥1 day with ≥6 hours of AF during the initial 6-month diagnostic evaluation phase including 8% each in the paroxysmal, persistent, and permanent classifications (Table). These patients with AF were significantly older, and higher proportions were male. The patients with permanent AF were more likely to be programmed to a nontracking mode (DDI/R or VVI/R) with higher lower rates near the 6-month transmission. The daily AF burden during the initial 6 months was dramatically different between the 4 AF groups ranging from a median of 0.0 hours/d in the no/little AF to 0.3 hours/d in paroxysmal AF to 10.4 hours/d in persistent AF and ≤24 hours/d in permanent AF. In addition to the 24% of all patients who had ≥1 day with ≥6 hours of AF in the initial 6 months, 11% developed AF during the remaining follow-up (5.1% paroxysmal, 5.6% persistent, and 0.1% permanent). Therefore, during the entire follow-up of 2.3 years, 35% of the CRT-D patients in this cohort had ≥1 day with AF ≥6 hours. Of the patients who had paroxysmal AF during the initial 6 months, 28% developed persistent AF, 2% developed permanent AF, and 37% returned to no/little AF post 6 months. Nearly one third (32%) of the patients with initially persistent AF progressed to permanent AF, 40% remained persistent, 10% improved to paroxysmal, and 19% returned to no/little AF. The patients...
with permanent AF initially continued to have high AF burden and reduced pacing during the remaining follow-up (average burden 23 hours/d and 69% of patients had ≤98% BIVP like in the initial period).

The patients with paroxysmal AF had higher VRAF with more variation than the patients with persistent and permanent AF, although their time in AF was minimal (Figure 2A). The risk of an all-cause shock was highest in patients with persistent AF (14%) compared with each other group (all P<0.001). Patients with paroxysmal AF (11%) also had an elevated risk of shock compared with either the no/little AF (5%) or the permanent AF (4%) patients (P<0.001).

BIVP% by AF Classification
The BIVP% outside of periods of AF was similarly high in the patients with no/little AF, paroxysmal AF, and persistent AF (Figure 2B). Similar to their uncontrolled ventricular rates during AF, the patients with paroxysmal AF had less BIVP and more variation during the brief periods when they were in AF. Nearly half (47%) of the patients with persistent AF had <90% BIVP during AF. The BIVP of patients with persistent AF dropped an average of 13% (SD, 19%) from sinus rhythm to AF. Despite slightly better rate control in the permanent AF group, nearly a third (31%) had low BIVP during their continuous AF. The reduced pacing during AF had less of an impact on the total BIVP% (in and out of AF) in the patients with paroxysmal AF. The no/little AF group had 35% of patients without high total BIVP%, compared with 46% of the paroxysmal AF group, 62% of the persistent AF group, and 69% of the permanent AF group. BIVP% decreased inversely proportional to PVC burden in the patients with no/little AF (BIVP group: median PVCs/h; high: 4; moderate: 40; low: 94; P<0.001).

Mortality
Patients with paroxysmal, persistent, or permanent AF had increased mortality rate relative to the no/little AF group before (Figure 3A) and after adjusting for age, sex, CRT-D shock, and BIVP% (Figure 4). Relative to the no/little AF group, patients with paroxysmal AF had a 32% increase in mortality rate (hazard ratio [HR]=1.32; 95% confidence interval [CI]: 1.22–1.42; P<0.001), whereas persistent AF had a 51% increase in mortality rate (HR=1.51; 95% CI, 1.41–1.61; P<0.001), and permanent AF had a 28% increase (HR=1.28; 95% CI, 1.19–1.38; P<0.001) in the multivariable analysis. All AF groups had increased mortality relative to the no/little AF group in each of the 3 BIVP patient groups (P<0.001).

Patients not receiving high BIVP had an increased mortality rate relative to those with high pacing before
Our CRT-D recipient cohort had an AF prevalence of 24% during the initial 6 months and 35% during 2.3 years. Persistent and permanent AF patients who have the highest burden of uncontrolled AF had the highest reduction of total BIVP. A high PVC burden often accounts for these findings in these low AF burden groups, and Cheng et al found non-optimal programming (eg, paced or sensed AV interval) also resulted in reduced BIVP. These findings further underscore the importance of rigorously following patients and the need for expertise in recognizing various factors that affect CRT delivery.

Impact of AF Classification on BIVP%

Our study of 54,019 CRT-D patients found that all 3 AF groups had an increased risk of mortality relative to the patients with no/little AF after adjusting for age, sex, CRT-D shocks, and BIVP%. The impact of AF in patients with ICDs/CRT-Ds has been limited by relatively small sample sizes. A study by Santini et al included 122 CRT-D patients with persistent AF and 33 with permanent AF. They also found that patients with persistent or permanent AF had a higher risk of the combined end point of heart failure hospitalization or death. Wilton et al also found that patients with a history of AF had an increased mortality risk relative to the patients without a history of AF in their meta-analysis.

There is a paucity of prospective randomized trials showing that CRT-D improves outcomes in patients with AF. The CARE-HF (Cardiac Resynchronization in Heart Failure) trial showed that patients with AF had increased mortality compared with patients without AF; however, AF patients who received CRT realized a similar outcome benefit as the patients without AF who received CRT.2 The Resynchronization for Ambulatory Heart Failure Trial (RAFT) study stratified patients with permanent AF to ICD (N=115) versus CRT-D (N=114).13 They reported that CRT did not improve death or the combined end point of death or heart failure hospitalization. RAFT required these patients to have good rate control (≤90 beats per minute during 6-minute walk test); however, only 34.3% (N=39 patients) of the patients with permanent AF received ≥95% BIVP during the initial 6 months, and only 1 patient received an AV nodal ablation before or within the 6 months after randomization. Two meta-analyses have looked at the impact of CRT in patients with AF, and both concluded that CRT provides functional improvements or outcome benefits in patients with AF.12,14 We also observed lower mortality in patients who received more CRT therapy (ie, BIVP%) irrespective of their AF classification.

Impact of BIVP% on Mortality

Our study found that high (>98%) BIVP% was associated with decreased risk of mortality independent of age, sex, AF classification, or ICD shocks. Prior registry and clinical studies have evaluated BIVP% and found a mortality benefit with higher percentages of BIVP, but cutoff values have varied. Koplan et al reported a mortality and heart failure hospitalization benefit with >92% BIVP. Hayes et al reported an incremental decrease in mortality as the percentage of BIVP...
increased with greatest benefit observed in patients having >98% pacing.

All of the large studies that have investigated BIVP%, including ours, were limited because they were only able to report device-measured BIVP%. These larger studies have not been able to report on effective BIVP capture (ie, pacing into excitable tissue and thereby avoiding pseudo fusion). In a small study using Holter and device data, Kamath et al\textsuperscript{15} showed that effective BIVP capture percent is typically lower than device-measured BIVP% in patients with permanent AF and, therefore, is more clinically important (ie, better predicts CRT response). The ability to quantify effective BIVP capture (ie, the quality of CRT) in addition to the BIVP% (ie, the quantity of CRT) remains an unmet need.

**AF Patients: Significant Opportunity to Improve CRT Efficacy**

The European Heart Rhythm Association and Heart Rhythm Society expert consensus on CRT repeatedly highlights the need to achieve high BIVP%, “as close as possible to 100%,” and that this “is particularly important in patients with AF.”\textsuperscript{16} AV node ablation has risen as an adjunctive therapy such that the expert consensus now recommends “that it should be considered earlier rather than later during follow-up.” The European Society of Cardiology guidelines note that patients with permanent AF are considered as class IIa level B only if an AV node ablation is performed so that nearly 100% BIVP can be reached.\textsuperscript{17} Gasparini et al\textsuperscript{18} showed that CRT-D patients with permanent AF who received AV node ablation had significantly lower mortality than the drug-treated AF patients despite these patients receiving >85% BIVP. Several other studies and meta-analyses have shown benefits including increased ejection fraction, exercise tolerance, clinical response, and survival.\textsuperscript{11,19} The BIVP% was high (>98%) in all 6 of the studies reporting on BIVP% that included patients with AF and an AV node ablation.\textsuperscript{19} In a more recent multivariable analysis, Gasparini et al\textsuperscript{20} found that patients with permanent AF who were treated with an AV nodal ablation (N=443)
had a 52% reduction in mortality compared with patients with permanent AF treated with rate-slowing drugs (N=895). The patients with permanent AF with AV nodal ablation also had similar mortality to sinus rhythm patients (N=6046).

Device BIVP% counters are the most optimistic report on pacing therapy, yet two thirds of patients with persistent or permanent AF are still not receiving high BIVP%. Our study cannot report on the use of medications or ablations, but it is obvious that the majority of patients with persistent and permanent AF are not receiving sufficient rate control to achieve the goal of high BIVP. There are thousands of patients with years of AF and reduced BIVP in widespread practice. Gasparini and Boriani21 pointed out that studies like the RAFT subanalysis of patients with permanent AF “may be misleading and create confusion” about the true benefit of CRT in patients with AF because the BIVP% was not high. Likewise, patients with persistent and permanent AF in widespread practice are likely not reaping the outcome benefits that CRT can provide.

Limitations
Our study is a retrospective analysis of prospectively collected data looking at mortality with respect to AF classification and BIVP. Lack of complete clinical data may limit interpretation of our mortality results. The absence of information regarding ejection fraction, heart failure status, medication use, or the use of procedures such as ablations or other clinical factors precludes analysis of these variables and their relationship to mortality. Nevertheless, given the size of our cohort and the fact that most CRT-D patients in the time frame of our study shared a set of similar characteristics based on their indication for a CRT-D device (ejection fraction ≤35%, wider QRS, class III–IV heart failure symptoms, and optimal medical therapy), these are important findings that reflect the real-world experience.

By excluding patients without an atrial lead, we may have excluded a portion of patients with persistent or permanent AF with CRT-Ds in whom atrial leads are not typically implanted; however, the atrial lead helps provide accurate continuous AF diagnostic information. Our results are not generalizable to patients without an atrial lead, but our study does include 8686 patients with persistent or permanent AF which are more than all prior studies and meta-analyses.

The devices in this study used an algorithm that does not distinguish between AF and other rapid >1:1 atrial tachyarrhythmias (eg, atrial flutter); therefore, the patients may have these rhythms included in their AF durations.

Finally, in this analysis, one has to keep in mind that the device-measured BIVP% may overestimate the actual effective BIVP%, especially in patients with AF.

Conclusions
Rate control and programming were inadequate to achieve high BIVP% in two thirds of patients with persistent or permanent AF. Patients with AF or reduced BIVP% were associated with an increased risk of death independent of each other and age, sex, or ICD shocks. Delivering high BIVP was associated with the greatest mortality benefit in patients with permanent AF. Our findings suggest that in widespread practice there is a lack of adherence to following the expert consensus statements and guidelines for BIVP in patients with persistent or permanent AF. A systematic shift toward more aggressive rate control and more pacing may be necessary in patients with AF to maximize the benefits of CRT.

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Disclosures
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