The Role of Atrial Fibrillation in CRT-D Patients: The ALTITUDE Study Group

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ABSTRACT. Atrial fibrillation and flutter (AF) are common and can have adverse effects in patients with left ventricular dysfunction. The present study assessed the long-term implications of AF on shock incidence and survival in patients with implantable cardiac resynchronization devices followed on a remote monitoring network. Patients implanted with cardiac resynchronization therapy defibrillators (CRT-D) manufactured by Boston Scientific, who regularly communicated information over a secure network, were eligible for enrollment in this study. Atrial fibrillation burden was calculated using atrial sense histograms. Shock episode electrograms were adjudicated by a panel of electrophysiologists. Both univariate and multivariate logistic regression models adjusting for age, gender, and device type were used to analyze the effects of AF on overall survival and the incidence of ICD therapies. A total of 63,866 patients were included in this analysis and 2,173 first shock episodes were adjudicated. Three hundred and eighty-eight first shock episodes (18%) were classed as due to AF with a rapid ventricular response. The overall incidence of AF was 47.1%. Regardless of shock occurrence, any AF burden was associated with decreased survival compared with no AF (AF burden >0.01%, p<0.001). Conclusions: In an unselected population of patients with implantable resynchronization cardiac devices, remotely followed via a secure network, atrial fibrillation is extremely prevalent, and even low burdens of AF are associated with worsened outcome.

KEYWORDS. atrial fibrillation, clinical studies, heart failure.

Background

Atrial fibrillation/flutter (AF) is the most commonly encountered clinical arrhythmia and currently affects more than 2.5 million people in the United States and 4.5 million in the European Union. Compromised left ventricular function and heart failure predispose to AF that may reciprocally lead to the development and/or worsening of heart failure in susceptible individuals. Symptomatic and asymptomatic atrial fibrillation is detected in 15–50% of patients with advanced symptom class heart failure. Additionally asymptomatic AF is found in 25% of pacemaker patients, with no history of AF. Atrial fibrillation is also independently associated with increased risk for morbid events and mortality in...
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patients with heart failure due to depressed systolic function. Multicenter randomized clinical trials have demonstrated that the use of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRT-D) devices improves survival in patients with reduced systolic function and heart failure. These results led to updated national treatment guidelines expanding the indications for the implantation of ICD and CRT-D devices to include primary prevention patients with reduced systolic function and heart failure. The expanded population of heart failure patients with implanted CRT-D devices and the ability to detect AF episodes offers the opportunity to explore the input of AF on device therapy and outcomes. In the setting of an implantable device and heart failure, AF can have a number of adverse consequences including increasing the risk for shock therapies, reducing the percent of CRT pacing and exacerbating heart failure due to loss of atrial transport and/or rapid ventricular rates.

Current estimates are that more than 700,000 patients are transmitting device data to a protected network. This influx of remote data has led to a greater potential to monitor for atrial arrhythmia burden and to intervene earlier in patients with networked implantable devices.

The goal of the present study is to assess the long-term complications of atrial tachyarrhythmias on shock incidence and survival in a large population of CRT-D device recipients implanted across the United States and followed on a remote monitoring network.

Methods

The ALTITUDE Study Group project is an independent clinical science initiative that launched in 2008 and was formed to prospectively analyze data from implanted devices manufactured by Boston Scientific Corp. (Natick, MA) that regularly communicate information over a network from patient homes. The LATITUDE™ patient monitoring system was market released in 2006.

Patients implanted with CRT-D devices from January 2006 to January 2011 were included. The first year of follow-up was used as a baseline period in which AF burden was calculated. Survival following this baseline period (i.e., survival beyond the first year post implant) was treated as outcome. Survival status was obtained by cross-referencing the database to the Social Security Death Index provided to Boston Scientific for implanted patients on a quarterly basis. Follow-up for vital status was continued for an additional 12 months after study data collection was closed to allow for lag time in death reporting. Patients without social security numbers were excluded from analysis.

Atrial fibrillation detection

Atrial fibrillation was detected using two device-based diagnostics: atrial high rate episodes and atrial high rate burden. A panel of electrophysiologists adjudicated shock episodes for validation that the shock was delivered for AF associated with a rapid ventricular rate. Conversion of AF to sinus rhythm was also evaluated. The methods for electrogram review and level of agreement have been previously published. Appropriate shocks for ventricular arrhythmias were further classified by morphology as sustained monomorphic ventricular tachycardia (SMVT) and polymorphic ventricular tachycardia (PMVT), or ventricular fibrillation (VF).

The nominal device setting to trigger atrial high rate episode detection is 170 bpm. Patients were classified according to the longest ATR episode by <1 min, 1 min to 1 day, 1–7 days, and >7 days. CRT-D patients programmed to a non-tracking mode (i.e., VVI) did not have the ability to store ATR episodes and were classified with patients having an ATR episode lasting longer than 7 days. Regardless of programmed pacing mode, atrial high rate burden was calculated using atrial sense histograms. Atrial paced and sensed beats were recorded in device memory counters and grouped by the device according to the rate, ranging from 35 to 255 bpm in 10 bpm groups. The percentage of atrial beats that were sensed at rates above 170 bpm was calculated. Atrial fibrillation burden was grouped by <0.01%, 0.01–1%, 1–10%, 10–90%, >90% of beats above 170 bpm.

Statistical methods

Kaplan–Meier curves and multivariate Cox proportional hazard models adjusting for baseline covariates of age, gender, and implantation year were used to calculate cumulative mortality and to assess the relationship between mortality risk and the following: burden of AF and occurrence of shock therapy. Appropriate and inappropriate shocks were assessed in the first year of follow-up and included as covariates for Cox model analysis.

Results

A total of 63,886 patients were included in our analyses. The mean age at implant was 69.9 ± 11 years, 71.5% were male, and mean follow-up duration was 3.2 ± 1.2 years (Table 1).

A total of 2,173 first shock episodes were adjudicated and 388 (18%) were classified as inappropriate due to rapidly conducted AF. Of all patients, 73% had <1% AF burden in the first year (53% <0.01%, 20% <1% and 27% had an AF burden of >1% (8% 1–10%, 14% 10–90%, 5% >90% AF burden). The cumulative incidence and burden of AF in the first year after the implant is shown in Figure 1.

Survival by AF burden and duration (<1 day, 1–7 days, >7 days) is shown in Figure 2a,b. Patients with an AF burden >0.01% with an AF episode lasting >1 min had decreased survival compared with patients with no AF burden or AF duration <1 min (p<0.001, Figure 2A). Subjects with AF lasting 1 day and an AF burden >10% had the lowest long-term survival rates (2B).

Figure 3 depicts the relationship between atrial fibrillation and flutter (AF) and survival according to patient
gender. Any AF burden >0.01% and AF duration more than 1 min were included. Across both genders, AF patients had worse survival. Females without AF had the highest rate of survival rates and males with AF had the lowest rate of survival.

Survival outcomes after shock are shown in Figure 4. While patients with AF had lower survival, there was no significant difference in survival between patients who received an inappropriate shock for AF compared with patients with AF duration >24 h who did not receive a shock (Figure 4a). This association was true after matching for age, gender, and implant date (Figure 4b). In patients experiencing a shock for AF, no difference in survival was observed whether or not the AF episode

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
<th>Value (n=37,643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration (years)</td>
<td>Mean ± SD (min, max)</td>
<td>3.2 ± 1.2 (1.0, 5.0)</td>
</tr>
<tr>
<td>Age at implant (years)</td>
<td>Mean ± SD (min, max)</td>
<td>69.9 ± 11.0 (6, 99)</td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>10,716 (28.5%)</td>
</tr>
<tr>
<td>Implant year</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td>6,991 (18.6%)</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td>9,781 (26.0%)</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td>8,531 (22.7%)</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td>9,854 (26.2%)</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td>1,966 (5.2%)</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>520 (1.4%)</td>
</tr>
<tr>
<td>Biv pacing %</td>
<td>Median (25th, 75th percentile)</td>
<td>98% (95%, 100%)</td>
</tr>
<tr>
<td>Shock</td>
<td>n (%)</td>
<td>2,931 (7.8%)</td>
</tr>
<tr>
<td>AF** burden</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.01%</td>
<td></td>
<td>19,917 (52.9%)</td>
</tr>
<tr>
<td>0.01–1%</td>
<td></td>
<td>7,655 (20.3%)</td>
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<tr>
<td>1–10%</td>
<td></td>
<td>2,922 (7.8%)</td>
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<tr>
<td>10–90%</td>
<td></td>
<td>5,328 (14.2%)</td>
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<tr>
<td>&gt;90%</td>
<td></td>
<td>1,821 (4.8%)</td>
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<tr>
<td>Longest AF episode</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 min</td>
<td></td>
<td>22,469 (59.7%)</td>
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<tr>
<td>1 min to 1 day</td>
<td></td>
<td>6,633 (17.6%)</td>
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<td>1–7 days</td>
<td></td>
<td>1,606 (4.3%)</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td></td>
<td>6,935 (18.4%)</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; Biv: biventricular pacing.

Figure 1: One-year atrial fibrillation/flutter incidence and burden after cardiac resynchronization therapy defibrillators implant.
was converted to sinus rhythm or atrial pacing by the shock (Figure 5).

**Discussion**

The key and novel findings of this analysis are that any AF is very common in CRT-D device recipients and that AF burden is associated with worsened survival for both female and male CRT-D patients. Shock therapies delivered in AF, whether or not sinus or atrial paced rhythm was restored, do not alter mortality risk. Our finding that even a small burden and duration of AF is associated with worsened survival, regardless of the presence or absence of device therapies, indicates that conversion to normal sinus rhythm (NSR) or atrial pacing does not reduce mortality risk in CRT-D device recipients.7,10 This may be attributable to the fact that AF is a marker of more advanced heart disease in device recipients or due to associated risks that accompany the presence and treatment of AF such as thromboembolic strokes, compromised hemodynamics, device therapy delivery, and antiarrhythmic drug use.25 Recent data suggest that even brief asymptomatic episodes of AF are associated with increased risk of adverse outcomes in certain patient populations.26 In our study, the highest risk groups for increased mortality were those with AF that represented a burden of (10–90%). Patients with duration of AF episodes of 1–7 days had similar survival to those with the longer duration of AF lasting >7 days. These data suggest that there is significant risk associated with a broad range of AF durations. There has been conflicting evidence as to whether the presence of atrial fibrillation is independently associated with increased mortality in ICD or CRT-D recipients. Zareba and colleagues17 performed a post hoc analysis of the MADIT II (Multicenter Automatic Defibrillator Implantation Trial) data, in which they compared patients with sinus rhythm, on a baseline ECG performed at the time of study enrollment, and those with atrial fibrillation. This study did not find a relationship between atrial fibrillation and mortality after adjustment for other variables.17 Conversely, Borleffs et al.6 analyzed 913 consecutive patients receiving an ICD at a single academic medical center and found that patients with permanent atrial fibrillation had more than double the

![Figure 2](image1.png)  
**Figure 2:** Survival according to atrial fibrillation and flutter (AF) burden and duration by AF burden (a) and by AF duration (b).

![Figure 3](image2.png)  
**Figure 3:** Atrial fibrillation and flutter (AF) survival according to gender; by survival according to gender and Burden of AF (a) and by survival according to gender and duration of AF (b).
Figure 4: Survival following a shock for atrial fibrillation and flutter (AF) compared with no shock and no AF.
mortality risk and had more ventricular arrhythmias resulting in device discharge, and more inappropriate device therapy. In that study, patients with paroxysmal or persistent atrial fibrillation did not have a significant increased risk of mortality or appropriate device therapy, but demonstrated an almost threefold increase in the risk of inappropriate device therapy.\textsuperscript{6} This apparent difference from our results may be explained by several differences in methodology. First, in the previous studies, atrial fibrillation was defined at the time of enrollment by history and baseline ECG. Our study evaluated AF in a continuous and dynamic manner that was verified by adjudication. In our study the presence of atrial tachyarrhythmias was defined using device algorithms. Additionally, since we used automated device algorithms to define arrhythmia burden in our patient population we may have included patients with supraventricular tachycardias (SVTs) other than atrial fibrillation and/or atrial flutter. This is unlikely however, given the high correlation between the device algorithms and our adjudicated subset. The recently published The ASSERT study provides additional data supporting the accuracy of device algorithms to detect AF, finding that false positive identification of AF is under 10% for AF durations greater than 30 minutes.\textsuperscript{27}

In the setting of reduced left ventricular function, symptomatic heart failure and QRS delay, a clinical feature of most CRT device recipients, AF may worsen outcome by adversely impacting cardiac performance due to loss of atrial mechanical function, and rate related impairment of cardiac timing cycles. These changes can result in further adverse increases in sympathetic tone and decreases in parasympathetic tone that have known associations with mortality risk in heart failure.\textsuperscript{28–30} In a CRT recipient, AF can also compromise device therapies such as biventricular (BiV) pacing or introduce ventricular arrhythmia risk.\textsuperscript{31,32} However, it is more likely that the worsened outcome seen in our study was related, at least in part, to the fact that AF is a sensitive marker of disease severity. The fact that shocks that terminate AF do not improve outcome supports this explanation. Inappropriate shocks for AF have been associated with worsened outcome.\textsuperscript{33} In the current study, the presence of AF was a greater risk factor for mortality than an AF associated shock. A recent publication from the ALTITUDE dataset found that inappropriate shocks attributed to non-AF rhythms were not associated with increased mortality. This adds further support to the concept that in device recipients, AF alone is the causative factor for increased mortality risk.\textsuperscript{34}

Our observation that gender did not influence AF outcome in device recipients is novel. Another recent study reported a higher relative mortality risk in females with AF.\textsuperscript{35} While the same increase in relative risk can be seen in our analysis, this is related to the fact that women without atrial tachyarrhythmias have lower mortality rates than men without atrial tachyarrhythmias in the ALTITUDE dataset. This explains the similar absolute increase in mortality risk in both men and women in our study population.

**Study limitations**

The ALTITUDE database has limited data on baseline characteristics and no information on concomitant medications or hospitalizations. Atrial arrhythmia burden was determined by the device. ATR episodes could
be overwritten in the device memory and therefore our estimates may under report the true incidence of atrial tachyarrhythmias that occurred in our patient population. Additionally, due to our device based algorithms for determining the presence of atrial tachyarrhythmias we could not determine the actual percentage of patients having true atrial fibrillation versus other atrial tachyarrhythmias such as atrial flutter, atrial tachycardias, or other types of supraventricular tachycardias. Furthermore, as we have mentioned previously, solely using device based cut-offs based on brief time intervals (<6 min) and rapid atrial rates has been associated with high false positive rates for atrial high rate episode detection, and physician review is important.35

Conclusions
In a large population of patients receiving implantable cardiac devices and remotely followed via a secure network, low burden and short duration AF is frequent and is associated with increased mortality risk, but risk is greatest with frequent AF. Mortality risk associated with AF is not impacted by device shocks that terminate AF, suggesting that AF is an important clinical event in CRT-D recipients. It is unclear if strategies to maintain regular rhythm in this population will positively impact risk.

References
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