Utility of cardiovascular implantable electronic device–derived patient activity to predict clinical outcomes

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BACKGROUND The role of cardiovascular implantable electronic device (CIED)–derived activity to predict implantable cardioverter-defibrillator (ICD) therapy or death is not known.

OBJECTIVE We aimed to assess CIED-derived activity to predict clinical outcomes.

METHODS In 1500 patients enrolled in MADIT-RIT, CIED-derived patient activity was acquired daily, then averaged for the first 30 days following randomization to predict inappropriate/appropriate therapy or death. Kaplan-Meier analysis and Cox proportional regression models were used to evaluate inappropriate/appropriate therapy, heart failure, or death by 30-day CIED-derived patient activity quintiles.

RESULTS There were 1463 patients with CIED activity data (98%). Patients in the highest quintile (Q5) of activity (more active) had the highest rate of inappropriate therapy, 21% at 2 years, as compared to 7%–11% in the other 4 quintiles (P < .001), a 1.75 times higher risk (95% confidence interval [CI]: 1.23–2.50, P = .002). However, patients in the lowest quintile of activity (Q1, 1 hour/day) had the highest risk of mortality, 15% in 2 years, as compared to Q2–3 (1–2 hours/day, 8%–7% mortality), and Q4–5 (>2 hours/day, 2%–3% mortality) (P < .001). Patients with the lowest level of activity (Q1) had a 2.02 times higher risk of mortality (95% CI: 1.21–3.38, P = .007), and they had an 82% higher risk of heart failure hospitalization (95% CI: 1.28–2.57, P = .001).

CONCLUSIONS High CIED-derived 30-day median patient activity predicted inappropriate therapy, while low patient activity predicted mortality and heart failure in ICD and cardiac resynchronization therapy with defibrillator patients enrolled in MADIT-RIT. Device-derived activity assessment could serve as a useful predictor of outcomes.

KEYWORDS Death; Inappropriate ICD therapy; ICD programming; MADIT-RIT; Outcome

Introduction

Implantable cardioverter-defibrillator (ICD) technologies have consistently been shown to reduce mortality.1,2 Despite the advances in technological and medical management of ICD patients, they are still at higher risk of inappropriate ICD firing, an adverse event associated with impaired quality of life and adverse clinical outcome.1,3,4

The Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (MADIT-RIT) was a randomized multicenter clinical trial evaluating ICD programming strategies to reduce inappropriate ICD therapy in patients receiving an ICD for primary prevention,1,5 providing us with continuous activity data derived from follow-up interrogations. The study has shown that high-rate cut-off ventricular tachycardia (VT) therapy with a VT zone ≥ 200 beats per minute (bpm), or 60 seconds delayed therapy during VT zone 170–199 bpm was associated with a significant reduction in inappropriate ICD therapy and mortality, as compared to conventional ICD programming with a VT zone 170–199 bpm.1

Cardiac implantable electronic devices (CIEDs) such as the ICD utilized in the MADIT-RIT trial are capable of routinely collecting daily physical activity data via an
accelerometer integrated within the device. A few recent studies suggested an association between activity and outcomes in ICD and cardiac resynchronization therapy with defibrillator (CRT-D) patients using large remote monitoring registry data to ascertain outcomes. However, the role of activity to predict inappropriate therapy has not been previously studied. Furthermore, the association between CIED-derived activity and inappropriate ICD therapy or death has not been evaluated in large clinical trials with centrally adjudicated outcomes data.

The aim of this study was (1) to evaluate the impact of CIED-derived activity on the risk of subsequent inappropriate ICD therapy; and (2) to determine whether activity, as a digital biomarker, predicts subsequent risk of heart failure hospitalization (HFH) or death among patients with ICDs.

Methods

Study population

The design and the primary results of the MADIT-RIT trial have been published previously. Briefly, the study enrolled 1500 patients in 98 centers from the United States, Canada, Europe, Israel, and Japan. All patients met the guideline criteria to receive an ICD or CRT-D for the primary prevention of sudden cardiac death. Patients were excluded if they were younger than 21 years, if they had a recent myocardial infarction or revascularization procedure (within 3 months), if they had permanent atrial fibrillation (AF), or if they had previously been implanted with a pacemaker or an ICD. Patients were randomized to 1 of 3 ICD programming schemes: conventional therapy, high-rate therapy, or duration delay for the detection and initiation of therapy for VT or ventricular fibrillation (VF). This current study included 1463 of 1500 patients (90%) with activity data available. The study was approved by the Institutional Committee on Human Research at participating institutions.

Device programming

Conventional programming, arm A, involved a VT zone $\geq 170$ bpm (detection delay 2.5 seconds, treatment with antitachycardia pacing [ATP] and shocks) and a VF zone $\geq 200$ bpm (detection delay 1 second, treatment with Quick Convert ATP and shocks). High-rate cut-off VT therapy programming, arm B, consisting of a monitor-only VT zone $\geq 170$ bpm, and VT $\geq 200$ bpm (VF zone, delay 2.5 seconds), were treated with antitachycardia treatment (Quick Convert ATP) and shocks. Long-delay VT therapy programming, arm C, comprised a VT zone $\geq 170$ bpm (detection delay 60 seconds, treatment with ATP and shocks), a second VT zone 200–249 bpm (detection 12 seconds, treatment with ATP and shocks), and a VF zone $\geq 250$ bpm (detection delay 2.5 seconds, Quick Convert ATP and shocks).

Interrogation and follow-up

Patients were followed every 3 months within the first year and every 6 months thereafter until trial termination on July 10, 2012. During each visit, a physical examination and device interrogation was carried out. Device reprogramming was left to the physicians’ discretion after the first inappropriate ICD therapy. Clinical data and interrogation data from the ICD were sent to the study Coordination and Data Center at the University of Rochester, Rochester, NY. Episodes from device interrogations were independently reviewed by the interrogation adjudication committee blinded to the programming arm or clinical characteristics of the patients.

Endpoints and definitions

In MADIT-RIT, inclusion criteria included sinus rhythm at enrollment. Patients with permanent AF or cardioversion for AF within 3 months prior to enrollment were excluded from the trial, as prespecified in the study protocol.

Inappropriate ICD therapy was defined as therapy delivered (ATP or shock) for arrhythmias other than ventricular; thus the endpoint included sinus tachycardia, AF, atrial flutter, or regular supraventricular tachycardia (SVT); or for nonarrhythmic events included detected noise, myopotentials, electromechanical interference, and T-wave oversensing. Death or HFH events were reported by study sites, and were independently adjudicated by the event committee blinded to programming arm or treatment assignments.

CIED-derived patient activity was obtained from the ICD device interrogation. Patient activity data were measured via a 2-D accelerometer integrated within the Boston Scientific ICD pulse generator. The accelerometer can detect motion and frequency in 2 directions, converting the information into an electrical voltage using validated manufacturer-specific algorithms. Patient activity is further classified into 1 of 2 states, active or nonactive, as a percentage of time during a 24-hour period, providing percent time active per day. In this study, CIED-derived patient activity was averaged for the first 30 days following randomization to evaluate inappropriate therapy after the 30-day period.

Patients were divided into quintiles based on their average 30-day activity recorded by their CIEDs using statistical methods to arbitrarily group them in 5 equal groups.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared in patients by activity quintiles, using Wilcoxon rank sum test for continuous variables and $\chi^2$ test for dichotomous variables, as appropriate.

Cumulative probability of appropriate therapy, inappropriate therapy, or death by patient activity quintiles was displayed according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was carried out to identify and evaluate the impact of activity during the initial 30 days after enrollment on subsequent inappropriate and appropriate therapy, or death. The Cox
models were adjusted for relevant clinical covariates using best subset regression, as shown in the tables.

Analyses were carried out with SAS software (version 9.4; SAS Institute, Cary, NC). All statistical tests were 2-sided; a P value of <.05 was considered as statistically significant.

Results
Baseline clinical characteristics
The present study included 1463 patients (98%) with daily activity data available during the initial 30 days after randomization in MADIT-RIT. Baseline characteristics were distributed by median activity quintile, with Q5 (13%, approximating 3 hours of daily activity) representing the group of patients with the greatest activity and Q1 representing the lowest activity group (2.3%, approximating 0.5 hours of daily activity) (Supplemental Table). Patients with lower activity were significantly older (P < .001), were more often female (P < .001), had significantly higher resting heart rates (P < .001), and were more frequently implanted with CRT-D vs an ICD. In MADIT-RIT, the median 30-day patient activity was not significantly different by assigned programming arms A, B, or C. There were no significant differences in beta-blocker or antiarrhythmic therapies or etiology of cardiomyopathy in patients by activity level quintiles.

Activity predicting inappropriate ICD therapy
During the mean follow-up period of 1.3 ± 0.6 years, 139 patients (10%) had at least 1 episode of inappropriate ICD therapy (mainly owing to supraventricular tachycardia, 74%). At 2 years, the cumulative probability of inappropriate defibrillator therapy was 21% among patients in the most active group (Q5), and was significantly higher than in other groups, P < .001 for comparison between all 5 different groups (Figure 1). Multivariate hazards Cox regression modeling assessing the effect of higher activity level (Q5) vs other activity levels showed an increased risk for inappropriate therapy, with a hazard ratio (HR) of 1.75; 95% confidence interval

Figure 1  Cumulative probability of inappropriate implantable cardioverter-defibrillator (ICD) therapy by activity quintiles (act Q).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All inappropriate therapy</td>
<td>1.75</td>
<td>1.23–2.50</td>
<td>.002</td>
</tr>
<tr>
<td>All inappropriate therapy activity (per 10% increase)</td>
<td>1.73</td>
<td>1.17–2.54</td>
<td>.005</td>
</tr>
<tr>
<td>Inappropriate therapy by type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate ATP</td>
<td>1.69</td>
<td>1.14–2.49</td>
<td>.009</td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>1.73</td>
<td>1.21–2.47</td>
<td>.002</td>
</tr>
<tr>
<td>Inappropriate &lt;200 bpm</td>
<td>1.78</td>
<td>1.20–2.64</td>
<td>.004</td>
</tr>
<tr>
<td>Inappropriate ≥200 bpm</td>
<td>1.43</td>
<td>0.67–3.04</td>
<td>.35</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>0.71</td>
<td>0.08–6.62</td>
<td>.76</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>3.23</td>
<td>1.60–6.52</td>
<td>.001</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1.89</td>
<td>1.25–2.85</td>
<td>.003</td>
</tr>
<tr>
<td>Malfunction, noise, sensing problems, other</td>
<td>0.55</td>
<td>0.06–4.73</td>
<td>.59</td>
</tr>
</tbody>
</table>

P < .05 are in italics.

ATP = antitachycardia pacing; bpm = beats per minute; CI = confidence interval; HR = hazard ratio.

Each endpoint was tested separately; each model was adjusted for treatment arm, age, atrial arrhythmias, diabetes mellitus, hypertension, and ejection fraction <25%.
This effect was similar in all programming arms, and it was similar for both inappropriate therapy for AF and inappropriate therapy for supraventricular tachyarrhythmias (data not shown). Higher activity level was also associated with increased risk for inappropriate shock alone (HR 1.73; 95% CI 1.21–2.47; P = .002). When the effect of high activity was assessed as a continuous parameter, each 10% increase in activity was associated with 73% increased risk for inappropriate therapy (Table 1).

Further analysis demonstrated that higher activity was associated with increased risk for inappropriate therapies owing to AF (HR = 3.23; 95% CI 1.60–6.52; P = .001) or SVT (HR = 1.89; 95% CI 1.25–2.85; P = .003), but not for sinus tachycardia (HR = 0.71; 95% CI 0.08–6.62; P = .76) or device-related issues (malfunction, lead fractures, sensing problems, or other device/programming-related issues) (HR = 0.55; 95% CI 0.06–4.73; P = .59) (Table 1).

### Activity predicting appropriate ICD therapy

During the study follow-up period, 175 patients (12%) had at least 1 episode of appropriate defibrillator therapy. At 2 years, the cumulative probability of appropriate therapy was similar in all groups and was 15% in the high-activity group and 17% in the low-activity group, P = .92 for comparison between all 5 groups (Figure 2). Multivariate Cox regression models assessing the effect of higher activity level (Q5) vs lower activity levels confirmed that there is no significant association between activity and appropriate therapy (Table 2).

### Activity predicting heart failure hospitalization

In contrast to the effects of activity on inappropriate therapy, high activity was associated with decreased risk for HFH, whereas low activity was an independent factor for increased risk of subsequent HFH. At 2 years, the cumulative probability of death was 22% in the low-activity group (Q1) compared to 11% in the high-activity group (Q5) (P < .001) (Figure 3).

Consistently, multivariate Cox regression models assessing the effect of activity level on HFH showed that patients with the lowest level of 30-day median patient activity (Q1) had 1.82 times higher risk of HFH as compared to other levels of activity (Q2–5) (95% CI 1.28–2.57, P = .001) (Table 3).

### Table 2  Multivariate Cox regression assessing the effects of higher activity (quartile 5) vs other activity levels on appropriate therapy and/or shock

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All appropriate therapy</td>
<td>1.01</td>
<td>0.49–2.04</td>
<td>.99</td>
</tr>
<tr>
<td>Appropriate ATP</td>
<td>1.06</td>
<td>0.71–1.6</td>
<td>.09</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>0.92</td>
<td>0.64–1.34</td>
<td>.67</td>
</tr>
<tr>
<td>Appropriate &lt;200 bpm</td>
<td>1.01</td>
<td>0.62–1.65</td>
<td>.98</td>
</tr>
<tr>
<td>Appropriate ≥200 bpm</td>
<td>1.02</td>
<td>0.65–1.6</td>
<td>.93</td>
</tr>
<tr>
<td>All appropriate therapy</td>
<td>0.69</td>
<td>0.32–1.55</td>
<td>.37</td>
</tr>
</tbody>
</table>

ATP = antitachycardia pacing; bpm = beats per minute; CI = confidence interval; HR = hazard ratio.

Each endpoint was tested separately; each model was adjusted for treatment arm, female, atrial arrhythmias, diabetes, ejection fraction, systolic blood pressure.
Activity predicting death

There were 66 patients (5%) who died during the study. In contrast to the effects of activity on inappropriate therapy, high activity was associated with decreased risk for death. At 2 years, the cumulative probability of death was 15% in the low-activity group (Q1) and 3% in the high-activity group (Q5) ($P < .001$) (Figure 4). Consistently, multivariate Cox regression models assessing the effect of activity level on mortality showed that for each quintile decrease in activity, there was a 40% increase in the risk of death ($P = .001$). Patients with the lowest level of 30-day median patient activity (Q1) had 2 times higher risk of mortality as compared to patients with higher levels of activity (Q2–5) (95% CI 1.21–3.38, $P = .007$) (Table 3).

Discussion

The present study provides important findings on the utility of CIED-derived activity, a novel digital biomarker, in predicting the risk of inappropriate ICD therapy and all-cause mortality in a heart failure population. We have shown that (1) 30-day median patient activity predicted subsequent inappropriate therapy in ICD and CRT-D patients, and (2) patients with moderate and low levels of 30-day activity were at a significantly higher risk of death as compared to those with higher levels of activity. We found no correlation between CIED-derived activity levels and appropriate ICD therapy.

Despite recent advances in the medical and device-based management of heart failure, patients remain at high risk of inappropriate ICD therapy, associated with impaired quality of life and increased cardiovascular morbidity and mortality.\textsuperscript{1,8,9} Atrial high rate episodes (AHREs), mainly due to fibrillation/flutter (AF), or rapid SVT episodes comprise the majority of the underlying reasons for inappropriate ICD firing.\textsuperscript{8,10}

Several studies reported a U-shaped correlation between physical activity and AF. In the general population, low fitness levels have been shown to be an independent risk factor for AF, while increased exercise is associated with increased risk of developing AF among non-athletes.\textsuperscript{11–13} Furthermore, prior studies and case reports also reported on exercise-induced SVT.\textsuperscript{14,15} In ICD patients, the onset of AHREs affects activity levels remarkably, which makes the understanding of the correlation between AHREs and exercise/activity in this population more complicated to interpret.

Table 3  Multivariate Cox regression assessing the effects of activity level on heart failure hospitalizations and death

<table>
<thead>
<tr>
<th>Endpoint: heart failure</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 1 decrease in activity quintiles\textsuperscript{†}</td>
<td>1.20</td>
<td>1.07–1.35</td>
<td>.003</td>
</tr>
<tr>
<td>Lowest activity (Q1) vs others</td>
<td>1.82</td>
<td>1.28–2.57</td>
<td>.001</td>
</tr>
<tr>
<td>Activity as a continuous parameter</td>
<td>0.62</td>
<td>0.40–0.98</td>
<td>.042</td>
</tr>
<tr>
<td>Endpoint: death</td>
<td>Per 1 decrease in activity quintiles\textsuperscript{†}</td>
<td>1.40</td>
<td>1.15–1.71</td>
</tr>
<tr>
<td>Lowest activity (Q1) vs others</td>
<td>2.02</td>
<td>1.21–3.38</td>
<td>.007</td>
</tr>
<tr>
<td>Activity as a continuous parameter</td>
<td>0.29</td>
<td>0.13–0.66</td>
<td>.003</td>
</tr>
</tbody>
</table>

\textsuperscript{CI} = confidence interval; \textsuperscript{HR} = hazard ratio; \textsuperscript{Q} = quintile.

Models are adjusted for treatment arm, ischemic etiology, diastolic blood pressure, diabetes, hypertension, ejection fraction, age, and sex.

\textsuperscript{†}From highest activity towards lower activity level.
The profound decline of patients’ activity after the onset of AHREs reflects the limited cardiovascular reserve present in ICD patients.\textsuperscript{16,17}

Daily physical activity is measured by accelerometers integrated within modern ICDs. CIED-derived activity provides a quantitative and accessible measure that may reflect individual functional status and exercise capacity.\textsuperscript{18,19} Previous studies have demonstrated a strong correlation between device-derived activity and adverse cardiovascular events, including death.\textsuperscript{7,20} The effect of activity on inappropriate ICD therapy has not been previously studied.

In the present study, the highest quintile of activity was associated with a 75\% increase in the risk for inappropriate ICD therapy after adjustment for ICD programming arm, age, prior atrial arrhythmias, and comorbidities. Andersen and colleagues\textsuperscript{21} studied 1.1 million healthy Swedish men and found that higher exercise capacity was associated with increased risk of arrhythmia, driven by a direct association with risk of AF. Patients with an implanted ICD and heart failure are at increased risk for AHREs, predominantly due to AF. However, in MADIT-RIT, most of the inappropriate therapies were attributable to SVT,\textsuperscript{22} and SVT could be linked to higher levels of activity. This is further supported by the fact that inappropriate therapies were predicted by age,\textsuperscript{22} and age is an indicator for more active patients. Moreover, our results showed that the risk for inappropriate therapy in this high-activity group was observed only for patients who developed AF or SVT, and was not significant for other related inappropriate therapies. This supports our explanation that the link between activity level and inappropriate therapy lies in the underlying arrhythmia triggering the inappropriate treatment.

Another possible explanation of a higher risk of inappropriate therapy in more active patients could be the increased risk of death as a competing risk in the lowest activity group, as described in our study. However, the rate of death in MADIT-RIT was quite low, and only 66 patients died during the follow-up, limiting the statistical power of our analysis.\textsuperscript{23}

In a retrospective study by Palmisano and colleagues,\textsuperscript{24} low activity was associated with an increased risk for AHREs, while high activity had no significant effect during the 25 months of follow-up. Our results have different findings, although this is likely due to differences between our cohort and the cohort studied in the IMPLANTED registry. In MADIT-RIT, in the highest-activity quartile, the median activity level was 3 hours per day, while in the IMPLANTED registry, all patients in the high-activity group had a mean activity level of $\geq 3.5$ hours per day. Furthermore, the rate of patients with AF at baseline was significantly higher than in our study (15\% vs 10\%, $P < .001$). The sample size and the mortality rates were also very different between the 2 studies. In addition, according to the results of the IMPLANTED registry, low activity was not associated with an increased risk for death, whereas many registry studies comprising more than 100,000 ICD patients have demonstrated a clear link between death and activity level.\textsuperscript{7,19} In our study, activity was associated with a 41\% increase in the risk for death for each reduction in activity quintile, showing a linear effect. One major challenge when assessing device-derived activity is the interpretation of the time effect. In our analysis, activity was defined based on the first 30 days post implantation, and was used thereafter as a baseline variable in the statistical models. Therefore, this study identifies baseline activity level
as a marker of subsequent inappropriate therapy or death, and not as a causal relationship.

Nevertheless, continuous assessment of activity such as using a moving window analysis could shed further light on the intricate associations and a potential causal relationship between activity levels and inappropriate therapy or death. In fact, the Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients (MultiSENSE) study collecting continuous data on heart sounds, respiration, thoracic impedance, heart rate, and activity data sought to properly identify patients at risk for heart failure events. Device-derived patient activity measurements could be relevant not only to predict heart failure events, but also to predict inappropriate ICD therapy, as first shown by our study. Further research is warranted to understand the time-varying association between changes in activity levels and inappropriate therapy and the implications of this finding.

Our results have significant clinical implications. First, device-derived activity, a digital biomarker readily acquired in today’s devices, may have utility in predicting and managing clinical outcomes, including the risk of inappropriate therapy, which may assist physicians when programming patients with defibrillators. A patient with high activity has a high risk for inappropriate therapy owing to AF or SVT, but no additional risk for VT/VF; therefore these patients may benefit from higher rates programming. Second, patients with low and moderate activity are high-risk cohorts that could benefit from further device and medical therapy optimization to improve outcomes. Third, if a more causal relationship between changes in activity and outcomes can be proven, specific interventions could target activity to improve outcomes.

Our study has potential limitations. First, this is a post hoc analysis of a randomized clinical trial, and evaluating device-derived activity was not part of the prespecified primary and secondary endpoints of MADIT-RIT. Second, MADIT-RIT excluded patients with permanent AF or cardioversion for AF within 3 months prior to enrollment. The exclusion of these patients may introduce a significant bias into the current analyses and may result in an underestimation of patients who would have received inappropriate therapies for AF. Third, we only assessed device-derived activity in the first 30 days and its relation to outcomes, and therefore our results could be affected by subsequent changes in activity. The rate of missing data was, however, very low in the study (2%).

Conclusion
In conclusion, we have shown that high CIED-derived 30-day patient activity predicted inappropriate therapy, while low patient activity predicted mortality in ICD and CRT-D patients enrolled in MADIT-RIT. These data suggest that device-derived patient activity assessment in the first 30 days following ICD or CRT-D implantation could serve as a useful predictor of subsequent outcomes of inappropriate ICD therapy or death in ICD and CRT-D patients.

Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.04.013.

References


