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DEVICES

Baseline and decline in device-derived activity level predict risk of death and heart failure in patients with an ICD for primary prevention

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Abstract

Background: Implanted defibrillators are capable of recording activity data based on company-specific proprietary algorithms. This study aimed to determine the prognostic significance of baseline and decline in device-derived activity level across different device companies in the real world.

Methods: We performed a retrospective cohort study of patients (n = 280) who underwent a defibrillator implantation (Boston, Medtronic, St. Jude, and Biotronik) for primary prevention at the University of Michigan from 2014 to 2016. Graphical data obtained from device interrogations were retrospectively converted to numerical data. The activity level averaged over a month from a week postimplantation was used as baseline. Subsequent weekly average activity levels (SALs) were standardized to this baseline. SAL below 59.4% was used as a threshold to group patients. All-cause mortality and death/heart failure were the primary end-points of this study.

Results: Fifty-six patients died in this study. On average, they experienced a 50% decline in SAL prior to death. Patients (n = 129) who dropped their SAL below threshold were more likely to be older, male, diabetic, and have more symptomatic heart failure. They also had a significantly increased risk of heart failure/death (hazard ratio [HR] 3.6, 95% confidence interval [95% CI] 2.3-5.8, $P < .0001$) or death (HR 4.2, 95% CI 2.2-7.7, $P < .0001$) compared to those who had sustained activity levels. Lower baseline activity level was also associated with significantly increased risk of heart failure/death and death.

Conclusion: Significant decline in device-derived activity level and low baseline activity level are associated with increased mortality and heart failure in patients with an ICD for primary prevention.

KEYWORDS
defibrillation-ICD, device-derived activity, outcomes

1 | INTRODUCTION

Implantable defibrillators and pacemakers continuously collect a variety of prognostically validated patient parameters, including activity level. Each device company uses their own unique proprietary algorithms to calculate and report these values.[1] The available graphical data are not easily interchangeable and comparable across different companies and different time points in a patient's care especially in clinical practice (Figure S1).

Previous studies demonstrating the prognostic importance of device-derived activity typically included patients enrolled in clinical studies with devices from one major company only.[2-7] Given the company-specific proprietary algorithms, limited real-world data, and limitations in cross-company comparisons, device-derived activity level has not been readily integrated in clinical practice.[1] Such data, in combination with other parameters, has the potential to identify clinical decompensation before the onset of symptoms but requires further validation in a real-world cohort using devices from several manufacturers.

The purpose of this study is to address this deficit by assessing the prognostic significance of device-derived activity level, across multiple companies, in a high volume outpatient clinical practice. We designed this descriptive retrospective study to assess the prognostic value of baseline activity level and change in activity in predicting heart failure and all-cause mortality.

2 | METHODS

2.1 | Study population

This was a single center, retrospective study that included all patients who underwent defibrillator implantation for primary prevention at the University of Michigan Hospital from May 2014 to December 2016. Patients were excluded if they died within 5 weeks of implantation or did not have postimplantation data available. The defibrillators implanted included those capable of biventricular pacing and were produced by Medtronic (Minneapolis, MN), Boston-Scientific (Marlborough, MA), Biotronik (Berlin, Germany), and St. Jude (Memphis, TN). The study protocol was approved by the Institutional Review Board at the University of Michigan prior to initiation of the study.

2.2 | Collection of patient activity level

All implanted devices in this study were capable of storing continuous patient activity level based on company proprietary algorithms. The data were presented graphically and stored for varying duration at the time of periodic device interrogations in-clinic and via home monitoring, if applicable. Postmortem device interrogations were not performed at our institution. Continuous graphical data for patient activity were retrospectively collected from stored device interrogations and processed anonymously. Graphical data were converted to numerical values using noncommercially available, open source software (Engauge Digitizer, version 10.8). These data were then used for further analysis.

2.3 | Baseline activity, standardization, and grouping

The average activity level over a month following a week postimplantation was used as the baseline value in our study. The duration and timing for this baseline value is based on our clinical experience managing patients postimplantation and to maximize the observational window. Subsequent weekly average activity levels (SALs) up to 2 years postimplantation were then standardized to this baseline to allow comparison among devices over time (Figure S2). Further activity level was not collected in those with device explantation, upgrade or change. Baseline activity level was also used to stratify and group patients based on median activity level by device company (Table S2). Those in each median of activity were then combined across all companies for further stratification.

2.4 | Optimal threshold of standardized activity level

The primary predictor variable was a weekly SAL below 59.4% within 2 years following device implantation. This threshold was used to define declining physical activity as it was previously reported[4] to be associated with increased risk of adverse cardiovascular outcomes including death.

2.5 | Outcomes of interest

The outcomes of interest for this study were the combination of heart failure hospitalization and death and all-cause mortality. The date and etiology of death were obtained from the individual review of the electronic medical record. Heart failure events were defined as a hospital admission requiring intravenous diuresis. These events identified for each patient in our cohort using DataDirect, an electronic medical search application offered through the University of Michigan Office Research. Patients admitted with a primary admission diagnosis of heart failure were first identified using standard International Classification of Diseases codes for acute and acute on chronic heart failure (ICD 9 and 10 codes: 428.* and I50.*). Charts were then reviewed to ensure accuracy of diagnostic coding. Over 75% of coded admissions were done so accurately and were included in the study.

2.6 | Statistical analysis

Baseline characteristics were compared using the chi-square test or *t*-test as indicated. Univariable and multivariable Cox proportional

TABLE 1 Baseline demographics of the total cohort and the subsequent two randomized subgroup populations

Clinical characteristics	SAL ≤59.4%	SAL >59.4%	*P* Value
Number of patients	129	151	
Boston	53	68	
Medtronic	55	55	
Biot/St. Jude	21	28	
Male (%)	90 (69.7)	91 (60.2)	.03
Age	64.3	59.9	.006
CRT (%)	67 (51.9)	65 (43.0)	.30
Nonischemic	69 (53.4)	73 (48.3)	.28
LVEF	28.2	30.8	.39
NYHA III-IV	75 (58.1)	58 (38.4)	.02
Diabetes	50 (38.8)	41 (27.2)	.04
Diagnosis of HF	118 (91.4)	127 (84.1)	.56
QRS	131.2	122.9	.30
BUN	27.1	22.8	.24

Abbreviations: CRT, cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction.

hazard modeling was used for survival analysis with SAL as a time-dependent variable. Cox models were adjusted for age, gender, left ventricular ejection fraction, biventricular pacing, and severity of heart failure (NYHA Class III-IV); these variables were selected a priori based on their clinical relevance to the outcome of interest.[8-10] The proportional hazards assumption was fulfilled for the model incorporating heart failure/death but not all-cause mortality itself. Kaplan-Meier and multivariable Cox proportional analysis (static variables) were also used to demonstrate cumulative incidence of our end-points based on baseline activity level. GraphPad Prism 8 (Prism, San Diego, CA) and Stata 15 (StataCorp, College Station, TX) were used for analyses.

3 | RESULTS

3.1 | Demographics

Two hundred eighty-nine patients underwent device placement over the study period. Three were excluded due to death shortly after implant, and six were lost to follow-up after 5 weeks for a final population of 280 patients. Implanted devices included models from Boston Scientific (n = 122), Medtronic (n = 109), and St. Jude/Biotronik (n = 49). There were no major adverse events directly attributable to device implantation.

Of the 280 patients enrolled in this study, 129 had at least 1 week of significantly reduced SAL following standardization within 2 years of implantation. Patients who met threshold reduction in weekly SAL were more likely to be older, male, diabetic with NYHA class III-IV symptoms (Table 1). Patients after meeting SAL threshold had a median follow-up period of 1.8 years. Those with stable activity level had a median follow-up of 2.4 years after standardization.

3.2 | Cause of death and standardized activity level prior to death

Fifty-six patients died in the follow-up period. The majority of patients who died of an identifiable cause (n = 42) died of a cardiac process (end stage heart failure n = 15, cardiogenic shock n = 6, sudden cardiac death n = 6, Table S1). Patients who died had on average lower SAL compared to those who did not and experienced a significant progressive reduction in their SAL weeks prior to death (Figure S3).

3.3 | Prognostic significance of threshold SAL as a time-dependent variable

Using Cox proportional hazards regression with SAL as a time-dependent variable, patients whose weekly SAL declined below threshold of 59.4% had a higher incidence of death and heart failure/death compared to those who did not (Figure 1A, B). Adjusted Cox proportional hazard modeling with SAL as a time-dependent variable demonstrated that meeting SAL threshold was associated with a significantly increased risk of heart failure/death (hazard ratio [HR] 3.6, 95% confidence interval [95% CI] 2.3-5.8, $P < .0001$) and death (HR 4.2, 95% CI 2.2-7.7, $P < .0001$).

3.4 | Prognostic significance of baseline activity level

To assess the prognostic significance of baseline activity, patients were stratified by median baseline activity level in each company and combined. Using Kaplan-Meier survival analysis, those in the lower half of baseline activity had a significantly increased 3-year cumulative incidence of heart failure/death (38.3% vs 17.4%, log rank $P < .0001$) and death (25.8% vs 9.4%, log rank $P < .0001$) compared to those with the higher baseline activity (Figure 2).

After adjusting for relevant clinical covariates, patients with higher baseline activity were at a reduced risk of death and heart failure/death compared to those with lower baseline activity. Those in the upper half had a 51% (95% CI 0.22-0.70, $P < .0001$) reduced risk of heart failure/death and 58% (95% CI 0.19-0.78, $P < 0.0001$) reduced risk of death compared to those with lower baseline activity (Table 2).

3.5 | Prognostic significance of baseline activity level and threshold SAL

Among patients who dropped their weekly activity level past identified threshold (SAL <59.4%), baseline activity provided significant risk differentiation per Kaplan-Meier survival analysis. In this patient

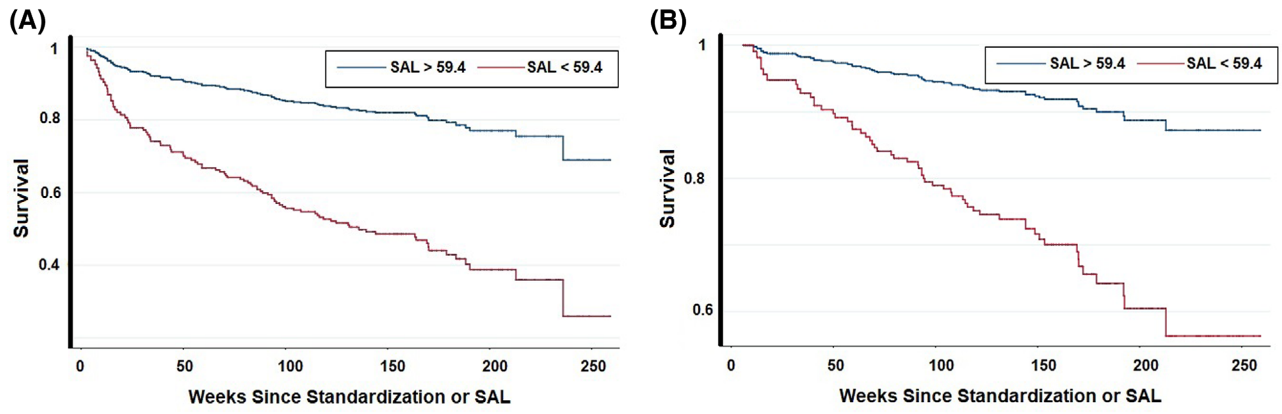

FIGURE 1 A and B, Graphical survival curve estimates for heart failure/death (1A) and death (1B) from SAL threshold as time-dependent covariate in a Cox proportion hazard regression model [Color figure can be viewed at wileyonlinelibrary.com]

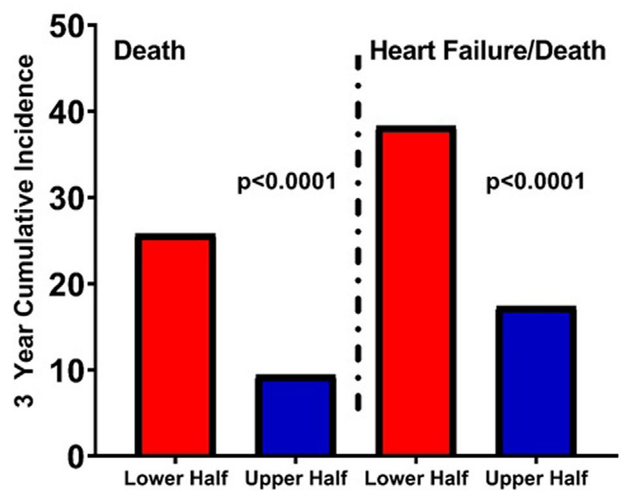

FIGURE 2 Three-year cumulative incidence of the death and heart failure/death from standardization comparing those in the lower to the upper half of baseline activity level [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariate analysis of death and heart failure/death comparing upper to lower half baseline activity level

	Upper vs lower half baseline activity level		
	HR	95% CI	*P*-value
Death	0.42	0.22-0.81	<.0001
Heart failure/death	0.49	0.31-0.79	<.0001

Model was adjusted for the following covariates: age, gender, systolic function (LVEF), severity of heart failure (NYHA class III-IV), biventricular pacing.
Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

population, those in the lower half of baseline activity level had a significantly increased 3-year cumulative incidence of heart failure/death (67.3% vs 33.7%, log rank $P < .0001$) and death (49.3% vs 15.3%, log rank $P < .0001$) compared to those with higher baseline activity level (Figure 3A).

In patients who did not drop their activity level, baseline activity was not a significant differentiator. Although patients in the lower half of baseline activity with consistent SAL had higher 3-year cumulative incidence of heart failure/death (21.8%, 11.4%, $P = .08$) and death (12.1% vs 5.4%, $P = .11$), the comparison was not significant (Figure 3B).

4 | DISCUSSION

We have demonstrated in this study that baseline and change in device-derived activity level are prognostic predictors of death/heart failure and death in patients with a defibrillator for primary prevention across multiple device companies. Patients who experience a near 41% reduction in their activity level for at least 1 week fare poorly compared to those who do not. Likewise, those with reduced baseline activity level postimplantation are at an increased risk of dying and experiencing a heart failure event compared to those with higher baseline activity level. The majority of events occur shortly after the decline. As per our data, the highest risk patients are those with reduced baseline activity who subsequently experience a drop in their activity level. These patients have significantly elevated 3-year cumulative incidence of death (49%) and heart failure/death (67%). Taken together, this suggests that device-derived activity level can help risk stratify patients soon after device implantation.

Activity data are continuously collected by a range of different implantable devices —from pacemakers, defibrillators, and even loop recorders —in a variety of different patients. These device-derived activity levels have been previously shown to correlate with validated hemodynamic testing including 6-minute walk test and external accelerometers.[11-17] Others, using single-device registries or studies (Medtronic and Boston Scientific), have also shown the prognostic significance of device-derived activity.

A retrospective study by Conraads et al enrolled 836 patients with a Medtronic ICD or CRT-D device. The authors demonstrated that the initial 30-day average device-derived activity corresponded with death or heart failure hospitalization.[3] Subsequently Kramer et al, in a retrospective study of Boston Scientific LATITUDE database, showcased the

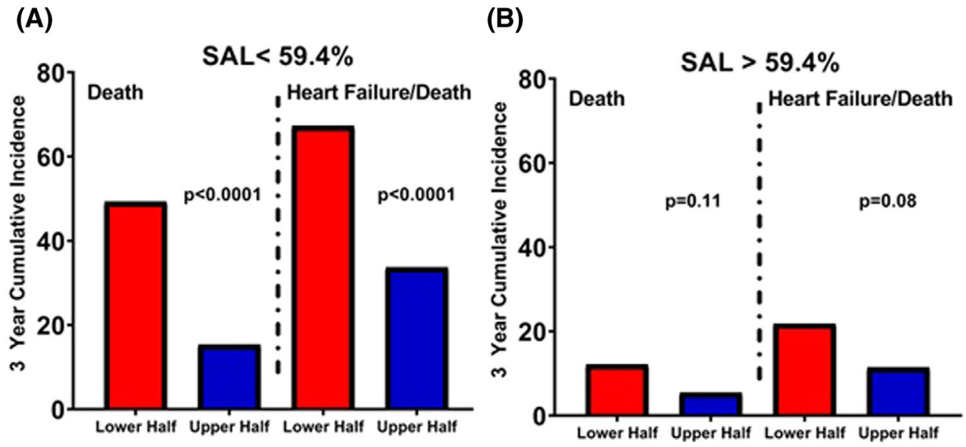

FIGURE 3 A and B, Three-year cumulative incidence of death and heart failure/death based on SAL (reduced: A; sustained: B) and baseline activity level half (lower half or upper half) [Color figure can be viewed at wileyonlinelibrary.com] [Color figure can be viewed at wileyonlinelibrary.com]

significance of initial activity level with long-term mortality. Patients with a decline in their activity level also fared poorly in their analysis.[5] Finally, Jamé et al in a retrospective study of MADIT-CRT data demonstrated the prognostic value of a decline in device-derived activity level in patients with Boston-Scientific devices. Patients whose activity level declined by 40%, which was a threshold used in this study as well, had increased adverse cardiovascular events.[4] This study further advances the above findings. We have shown that a significant decline from baseline activity level in patients with devices from multiple companies is of a strong clinical value and is applicable to a large outpatient clinical practice.

Although ubiquitous and, as shown, objectively relevant, the clinical integration of device-derived activity is difficult. There are significant obstacles arising from data representation at the time of interrogation and the absence of an available baseline for any comparison. Depending on the device company, the graphically reported data are shown for varying durations with no comparison to a baseline or prior interrogation. Due to the proprietary nature of the algorithms used to calculate and process activity level and the absence of publicly available data, the absolute reported values are not comparable across different companies or to other patients.[1] As a result, current utility of device-derived activity level is limited. We hope to raise awareness of the clinical utility of this often clinically neglected value and highlight the need for better reporting and clinical integration.

Additionally, the median absolute baseline activity-level value for each company can be found in Supporting Information (Table S2). We hope that by reporting these values, other researchers can validate our findings in their respective patient cohorts and, more importantly, providers can begin to incorporate activity level in stratifying their patients immediately postimplantation across multiple companies. We have shown in this study that patients with lower activity level perform poorly independently of age, heart failure severity, and systolic function.

Likewise, we are hopeful that the nearly 40% decline threshold used in this study can serve as an easily identifiable cut-off for other providers in risk stratifying patients. The underlying etiology of activity decline in our patients appears to be nonspecific and ranges from both cardiovascular (heart failure progression, worsening valvular function, or arrhythmias) to non-cardiovascular events (falls, strokes, surgeries, or infections). In our cohort, patients whose activity level remained stable fared well compared to those whose activity level met this threshold. Regardless of the underlying etiology, it appears that a significant decline in objective activity level requires further evaluation and serves as a useful clinical vital sign.

Further validation of our findings is necessary. It also remains to be seen if clinical intervention in those with declining activity level has any impact on outcomes. At the very least, device-derived activity level can help serve as an additional objective parameter in the overall clinical assessment of patients and potentially help patients and providers in their preparation for end of life care.

4.1 | Limitations

There are specific limitations associated with this study given its retrospective nature. Continuous activity levels could not be ascertained postimplantation for all patients due to deficiencies in patient follow-up. Likewise, St. Jude and Biotronik devices do not record activity level during episodes of atrial arrhythmias by the nature of their proprietary algorithms. Furthermore, our SAL cut-off threshold of 59.4% (sensitivity 70.1%; specificity 79.5%) was validated in a similar patient population but only included patients undergoing biventricular pacing.

Additionally, the outcomes assessed in this study were obtained through chart review. Heart failure episodes diagnosed and managed outside of our institution were inherently not included in this study. Although the electronic medical system allowed for across-institutional identification of mortality, the underlying etiology was not readily available. Finally, postmortem interrogations were not performed at our institution.

5 | CONCLUSION

In patients with a defibrillator for primary prevention, low baseline and a decline in device-derived activity level help identify patients at increased risk of dying.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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