

Predicting all-cause mortality by means of a multisensor implantable defibrillator algorithm for heart failure monitoring

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BACKGROUND The HeartLogic algorithm (Boston Scientific) has proved to be a sensitive and timely predictor of impending heart failure (HF) decompensation.

OBJECTIVE The purpose of this study was to determine whether remotely monitored data from this algorithm could be used to identify patients at high risk for mortality.

METHODS The algorithm combines implantable cardioverter-defibrillator (ICD)-measured accelerometer-based heart sounds, intrathoracic impedance, respiration rate, ratio of respiration rate to tidal volume, night heart rate, and patient activity into a single index. An alert is issued when the index crosses a programmable threshold. The feature was activated in 568 ICD patients from 26 centers.

RESULTS During median follow-up of 26 months [25th–75th percentile 16–37], 1200 alerts were recorded in 370 patients (65%). Overall, the time IN-alert state was 13% of the total observation period (151/1159 years) and 20% of the follow-up period of the 370 patients with alerts. During follow-up, 55 patients died

(46 in the group with alerts). The rate of death was 0.25 per patient-year (95% confidence interval [CI] 0.17–0.34) IN-alert state and 0.02 per patient-year (95% CI 0.01–0.03) OUT of the alert state, with an incidence rate ratio of 13.72 (95% CI 7.62–25.60; $P < .001$). After multivariate correction for baseline confounders (age, ischemic cardiomyopathy, kidney disease, atrial fibrillation), the IN-alert state remained significantly associated with the occurrence of death (hazard ratio 9.18; 95% CI 5.27–15.99; $P < .001$).

CONCLUSION The HeartLogic algorithm provides an index that can be used to identify patients at higher risk for all-cause mortality. The index state identifies periods of significantly increased risk of death.

KEYWORDS Cardiac resynchronization therapy; Death; Heart Failure; Implantable cardioverter-defibrillator; Remote monitoring; Risk stratification

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Introduction

Implantable cardioverter-defibrillators (ICDs) and defibrillators for resynchronization therapy (cardiac resynchronization therapy defibrillator [CRT-D]) are widely adopted for the treatment of chronic heart failure (HF).¹ Some modern ICDs are equipped with automated algorithms that provide detailed information on the patient's HF condition on a daily basis. Many studies have reported combining ICD diagnostics in order to better stratify and manage patients at risk for HF events.²⁻⁴ In the MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study,⁵ a novel algorithm for HF monitoring was implemented: the HeartLogic™ (Boston Scientific, St. Paul, MN) index, which combines physiological data from multiple ICD-based sensors. The index enabled dynamic assessment of HF, identifying periods when patients were at significantly increased risk for worsening HF.⁶ However, no study has explored whether the index predicts all-cause death. In the present study, we sought to determine whether remotely monitored data from this algorithm could be used to identify patients at high risk for mortality, and whether its predictive ability was independent of the patient's demographic and clinical variables.

Methods

Patient selection

The study was a prospective, nonrandomized, multicenter evaluation of patients who had received an ICD or CRT-D having the HeartLogic diagnostic algorithm. Consecutive HF patients with reduced left ventricular ejection fraction ($\leq 35\%$ at the time of implantation) who had received a device in accordance with standard indications¹ and were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform were included at 26 study centers (full list of participating centers is given in the [Supplemental Appendix](#)) and underwent follow-up in accordance with the standard practice of the participating centers. The study protocol did not mandate any specific intervention algorithm, and physicians were free to remotely implement clinical actions or to schedule extra in-office visits when deemed necessary. Data on the clinical events that occurred during follow-up were collected at the study centers within the framework of a prospective registry ([ClinicalTrials.gov](#) Identifier: NCT02275637). The Institutional Review Boards approved the study, and all patients provided written informed consent for data storage and analysis. The research reported in this paper adhered to the Helsinki Declaration. (The experimental data used to support the findings of this study are available from the corresponding author upon request.)

Device characteristics

Commercially available ICD/CRT-Ds equipped with the HeartLogic diagnostic feature and standard transvenous leads were used in this study. The details of the HeartLogic algorithm have been reported previously.⁵ In brief, the algorithm combines data from multiple sensors: accelerometer-based

first and third heart sounds, intrathoracic impedance, respiration rate, ratio of respiration rate to tidal volume, night heart rate, and patient activity. Each day, the device calculates the degree of worsening in sensors from their moving baseline and computes a composite index. An alert is issued when the index crosses a programmable threshold (nominal value = 16). When the index enters an alert state, the "exit-alert" threshold is automatically dropped to a recovery value (nominal value = 6).

Association between HeartLogic alert state and death

The objective of the present analysis was to assess the risk of death in patients who received the system in clinical practice and to evaluate the performance of the HeartLogic index in detecting follow-up periods of significantly increased risk of death. The study endpoint was death due to any cause. Moreover, we also evaluated the occurrence of death from cardiovascular causes and the occurrence of appropriate ICD shock therapies, according to local site adjudication. HeartLogic index values >16 identified periods as IN an alert state vs OUT of an alert state.

Statistical analysis

Descriptive statistics are given as mean \pm SD for normally distributed continuous variables or median [25th-75th percentiles] in the case of skewed distribution. Normality of distribution was tested by the nonparametric Kolmogorov-Smirnov test. Categorical data are given as percentages. Analysis of the time to the first episode was made by the Kaplan-Meier method. Cox proportional hazards models were used to determine the association between the occurrence of death, baseline characteristics, and the average values of contributing sensors, and to estimate hazard ratio (HR) and 95% confidence interval (CI). All variables displaying statistical significance ($P < .05$) were entered into a multivariate regression analysis. Death rates were calculated separately during IN and OUT alert states in terms of the ratio between the total count of deaths occurring in each state and the respective patient follow-up durations, and were expressed as events per patient-year. To evaluate the performance of the index in detecting follow-up periods of significantly increased risk of death, we compared the IN- and OUT-of-alert periods in terms of time to death by means of the Anderson-Gill model, an extension of the Cox proportional hazards model that takes into account multiple evaluations in patients. The model was adjusted for those baseline variables that proved to be associated with the occurrence of death on univariate analysis. IN-alert periods started when the HeartLogic index crossed the threshold and ended at the time of death, or were censored when the index decreased to below the recovery threshold (or at the end of follow-up). OUT-of-alert periods started on the day of HeartLogic activation (at the end of the initialization period) or at the end of a previous IN-alert period and ended at the time of death, or were censored when the index

Table 1 Demographics and baseline clinical parameters of the study population (N = 568)

Male	453 (80)
Age (y)	69 ± 10
Ischemic etiology	285 (50)
NYHA functional class	
I	36 (6)
II	351 (62)
III	171 (30)
IV	10 (2)
LV ejection fraction (%)	32 ± 9
AF history	196 (35)
AF on implantation	100 (18)
Diabetes	167 (29)
COPD	89 (16)
Chronic kidney disease	153 (27)
Hypertension	334 (59)
β-Blocker use	520 (92)
ACE-I, ARB, or ARNI use	536 (94)
Diuretic use	506 (89)
Antiarrhythmic drug use	116 (20)
CRT device	410 (72)
Primary prevention	500 (88)

Values are given as n (%) or mean ± SD.

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; LV = left ventricle; NYHA = New York Heart Association.

rose above the threshold (or at the end of follow-up). All statistical analyses were performed using R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

From December 2017 to June 2021, HeartLogic was activated in 568 patients who had received an ICD (n = 158) or CRT-D (n = 410). Baseline clinical variables of all patients in the present analysis are listed in [Table 1](#).

Follow-up

During median follow-up of 26 months [16–37], 55 patients (10%) died. According to local site adjudication, 33 deaths were from cardiovascular causes. One or more appropriate ICD shocks were documented in 74 patients (13%). The HeartLogic index crossed the threshold value 1200 times (0.71 alerts per patient-year) in 370 patients. The time in the IN-alert state was 13% of the total observation period in the overall population and 20% of the follow-up period in the 370 patients with alerts. The centers did not adjust the threshold, which was set to the nominal value in all patients. Atrial fibrillation history was more frequent in patients with alerts (158 [43%] vs 38 [19%]; $P < .001$), as well as chronic kidney disease (120 [32%] vs 33 [17%]; $P < .001$). However, the use of CRT was similar between patients with and those without alerts during follow-up (273 [74%] vs 137 [69%]; $P = .245$). In the CRT group, median percent-

age of biventricular pacing was similar between patients with and those without alerts (98% [95%–100%] vs 99% [96%–100%]; $P = .397$).

Association between HeartLogic alerts and death

Of the 55 patients who died, 46 (84%) had experienced ≥ 1 alert episodes during follow-up. Sensitivity of a time IN alert $\geq 20\%$ for detecting death was 56% (31/55), and specificity was 77% (394/513). Rate of death was 0.25 per patient-year (95% CI 0.17–0.34) with the HeartLogic IN the alert state and 0.02 per patient-year (95% CI 0.01–0.03) OUT of the alert state, with an incidence rate ratio of 13.72 (95% CI 7.62–25.60; $P < .001$). [Figure 1](#) shows the Kaplan-Meier analysis of time to death for any cause from device implantation. Patients are stratified according to the occurrence of at least 1 HeartLogic alert (HR 2.08; 95% CI 1.16–3.73; $P = .039$) and to a time IN alert $\geq 20\%$ (HR 4.07; 95% CI 2.19–7.54; $P < .001$). Kaplan-Meier analysis of patients stratified according to the occurrence of ≥ 1 HeartLogic alerts and according to different levels of time IN alert is shown in [Supplemental Figure 1](#). The occurrence of death from cardiovascular causes was significantly associated with at least 1 HeartLogic alert during follow-up (HR 6.07; 95% CI 2.84–12.97; $P = .004$) and with a time IN alert $\geq 20\%$ (HR 5.59; 95% CI 2.51–12.44; $P < .001$) ([Supplemental Figure 2](#)). Moreover, the occurrence of appropriate ICD shock therapies was associated with ≥ 1 HeartLogic alert (HR 2.44; 95% CI 1.49–3.97; $P = .003$) and with a time IN alert $\geq 20\%$ (HR 2.01; 95% CI 1.18–3.43; $P = .003$). The results of the regression analysis of variables associated with death are listed in [Table 2](#). The occurrence of at least 1 HeartLogic alert and a time IN alert $\geq 20\%$ were significantly associated with death. Among the contributing sensors, higher average values of

Table 2 Univariate analysis of baseline variables and average sensors associated with death from any cause

	HR	95% CI	P value
Age	1.07	1.03–1.10	<.001
Male gender	0.81	0.42–1.56	.526
NYHA functional class	1.38	0.91–2.11	.136
Ischemic heart disease	1.78	1.03–3.06	.039
LV ejection fraction	0.99	0.96–1.02	.605
AF on implantation	1.90	1.07–3.37	.029
Hypertension	0.73	0.43–1.24	.249
Pulmonary disease	1.60	0.84–3.02	.153
Diabetes	1.02	0.58–1.80	.955
Chronic kidney disease	2.46	1.44–4.19	.001
CRT device	0.99	0.54–1.81	.965
≥ 1 HeartLogic alert	2.09	1.03–4.27	.043
Time in alert $\geq 20\%$	4.15	2.42–7.10	<.001
S3 amplitude	3.65	1.94–6.86	<.001
S1 amplitude	0.88	0.65–1.19	.882
Thoracic impedance	0.95	0.92–0.98	.001
Respiratory rate	1.22	1.09–1.36	<.001
Night heart rate	1.07	1.03–1.11	<.001
Patient activity	0.97	0.96–0.98	<.001

CI = confidence interval; HR = hazard ratio; other abbreviations as in [Table 1](#).

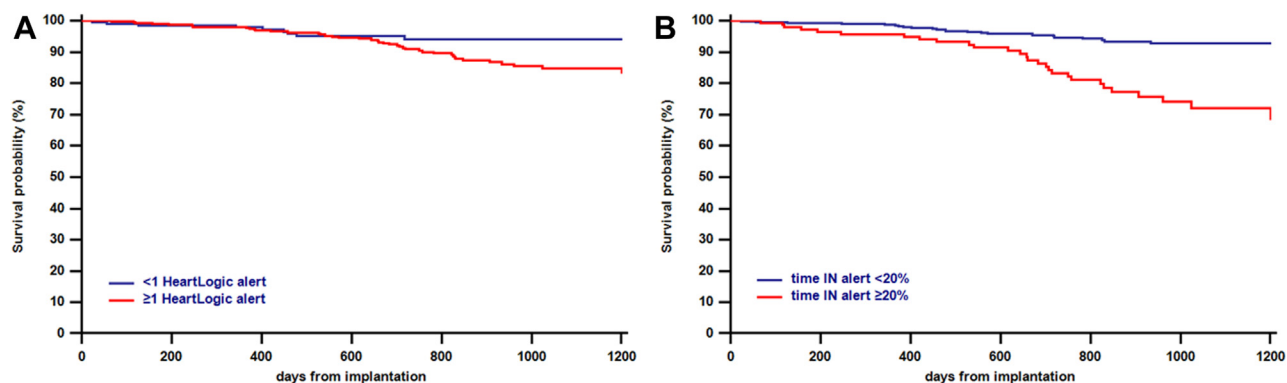


Figure 1 Kaplan-Meier analysis of time to death due to any cause. Patients are stratified according to the occurrence of at least one HeartLogic alert (A) and a time IN alert $\geq 20\%$ (B).

third heart sound amplitude, respiratory rate, and night heart rate were associated with death, as well as lower thoracic impedance and patient activity. Other baseline variables associated with death were age, ischemic cardiomyopathy, chronic kidney disease, and atrial fibrillation on implantation. Figure 2 shows a Kaplan-Meier plot of time to death after the start of IN- and OUT-of-alert states (HR 11.00; 95% CI 6.19–19.48; $P < .001$). After multivariate correction for age, ischemic cardiomyopathy, chronic kidney disease, and atrial fibrillation on implantation, the IN-alert state remained significantly associated with the occurrence of death due to any cause (HR 9.18; 95% CI 5.27–15.99; $P < .001$) (Figure 3).

Discussion

In the present study, we demonstrated the ability of the HeartLogic algorithm to identify subjects at high risk for death among HF patients who had received ICD and CRT-D. The occurrence of at least 1 HeartLogic alert and a time IN

alert $\geq 20\%$ were significantly associated with mortality due to any cause. Moreover, the rate of fatal events was substantially higher with the HeartLogic IN the alert state, and the association between the alert state and mortality was confirmed even after correction for baseline confounders.

In the management of HF patients, prognostic stratification is important in order to identify the ideal time for referral to specialists, to plan treatment and follow-up strategies, and to properly convey expectations to patients and families.¹ However, predicting mortality in an HF population is challenging. HF has multiple etiologies with different risk profiles and has an uneven clinical course. Numerous clinical variables and investigations are needed in order to obtain prognostic information and to guide potential therapy.¹ Moreover, although prognostic scores have been proposed for HF patients and more specifically for patients with ICD,^{7,8} they are of limited use in everyday practice. Their calculation can be onerous, and the information provided is static and does not reflect the clinical course of the disease. Modern ICD diagnostic algorithms continuously measure

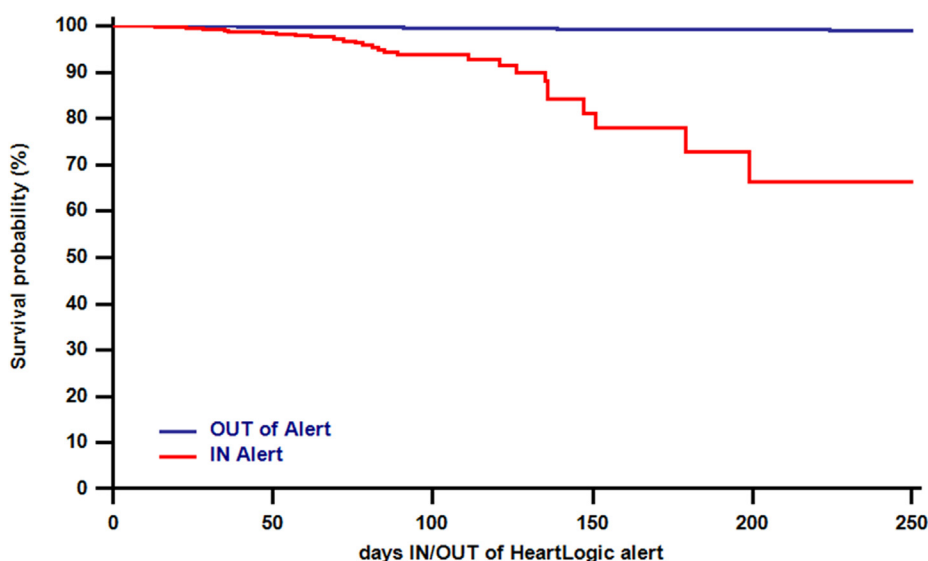


Figure 2 Kaplan-Meier plot of time to death due to any cause in the IN- and OUT-of-alert states.

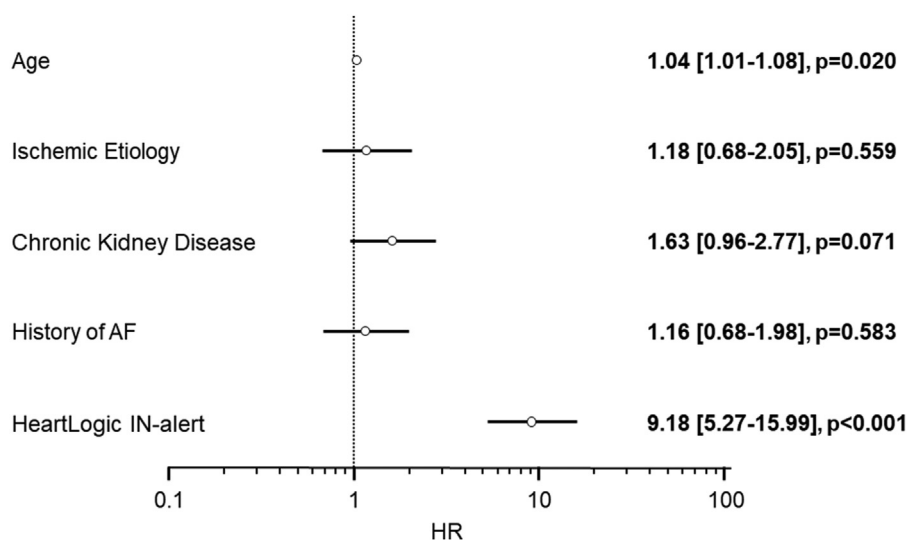


Figure 3 Results of the time-dependent Cox model. Association between IN-alert state and death due to any cause, after adjustment for clinical variables. AF = atrial fibrillation; HR = hazard ratio.

clinical variables²⁻⁵ and have been designed to provide early warning of changes in HF status and to allow prompt intervention to prevent disease progression. Previous retrospective analyses have reported an association between all-cause mortality risk and the high-risk status defined by a remote monitoring system from another manufacturer, based on monthly data downloads instead of an alert-based approach.^{9,10} The multiparameter algorithm used in the present analysis combines data from multiple sensors, which record parameters (heart rate and respiratory rate, rapid shallow breathing index, third and first heart sounds, thoracic impedance and activity) that are objective measurements of the underlying pathophysiology associated with signs and symptoms of worsening HF.¹¹⁻¹⁵ This system displayed high sensitivity and long warning times both in the validation study⁵ and in subsequent clinical experiences.¹⁶⁻¹⁸ The IN- or OUT-of-alert state defined by the algorithm has also proved able to identify periods when patients are at significantly increased risk for worsening HF,^{6,19} potentially allowing resources to be better targeted to this vulnerable patient population. Although the ICD index was designed for the early detection of individuals at increased risk for HF events, we demonstrated that its use may help to identify patients at high risk for death due to any cause. During HeartLogic alerts, a previous study measured higher levels of N-terminal pro-B-type natriuretic peptide¹⁸ (ie, a sign of poor prognosis).²⁰⁻²² In our study, we observed a 2-fold higher risk of death among patients who had experienced at least 1 HeartLogic alert and a 4-fold higher risk among patients who had spent >20% of their follow-up period IN the alert state. Moreover, the risk of death was also associated with the average values of components of the combined index. In our study, the most frequent cause of death was cardiovascular. The algorithm demonstrated its ability to identify cardiovascular death, in addition to the higher risk of ICD shock therapies. These results further confirm the sensitivity of the algorithm, specifically for HF disease progression. Most fatal

events were plausibly the outcome of refractory HF events, which may also have fostered ventricular arrhythmias.

Utilizing ICD-measured data for prognostic stratification is ideal. They are collected automatically by the devices and are continuously available through remote monitoring. Current guidelines recommend that multidisciplinary management programs should take a holistic approach to the patient rather than focusing solely on HF to reduce the risk of mortality.¹ However, the prevalence of death from cardiovascular causes and the ability to identify such events seem to suggest the use of ICD-measured data mainly for the management of cardiovascular therapies. They may help clinicians make decisions on the frequency of monitoring and focus their attention on ensuring that the patient receives guideline-directed therapies designed to improve prognosis rather than prevent an immediate decompensation. Although the principal treatment pattern in response to HF alerts typically is augmentation of decongestive treatment,²³ an effort should be made to enhance medical therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors, reaching target doses with physiological monitoring. Moreover, personalized prognostic data may help the clinician to formulate an indication for a coronary revascularization attempt or aortic or mitral valve intervention.¹ Moreover, the patient's life expectancy may be considered, in order to discuss with the patient whether the ICD generator should be replaced.²⁴ However, additional work is required in order to test the efficacy of specific interventions to delay or manage the patient's end of life.

Study limitations

The main limitation of this study is its observational design. We investigated the performance of a specific ICD algorithm, so the generalizability of the results to other systems remains to be demonstrated. Although only HeartLogic-enabled

devices were included, no selection bias was introduced because patients were enrolled consecutively, and device choice and activation of the algorithm were not driven by clinical characteristics. Moreover, physicians were not blinded to the HeartLogic index, and no predetermined actions were prescribed in response to alerts; this may have introduced a bias into our analysis of the risk stratification ability of the algorithm. In addition, the analysis of the predictive performance of the algorithm with regard to cardiovascular-related mortality presents limitations. The smaller number of events could make the sample size inadequate, and identifying the leading cause of death is uncertain within the framework of a multicenter registry in clinical practice. Finally, some patients died in the hospital without transmitting data during the period of hospitalization, and some of these hospitalized patients might have entered the IN-alert state only after admission. Our analysis considered the alert state before admission. We believe that, when evaluating the predictive ability of remotely monitored data, the relevance of data collected when the patient already is in the hospital is limited.

Conclusion

This study demonstrated the ability of the HeartLogic algorithm to provide an index that can be used to identify patients at higher risk for all-cause death. The index state identifies periods of significantly increased risk of death in patients who have received an ICD or CRT-D in clinical practice.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2023.03.026>.

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