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ORIGINAL ARTICLE

Prediction of heart failure events based on physiologic sensor data in HINODE defibrillator patients

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Abstract

Aims Hospitalizations are common in patients with heart failure and are associated with high mortality, readmission and economic burden. Detecting early signs of worsening heart failure may enable earlier intervention and reduce hospitalizations. The HeartLogic algorithm is designed to predict worsening heart failure using diagnostic data from multiple device sensors. The main objective of this analysis was to evaluate the sensitivity of the HeartLogic alert calculation in predicting worsening heart failure events (HFEs). We also evaluated the false positive alert rate (FPR) and compared the incidence of HFEs occurring in a HeartLogic alert state to those occurring out of an alert state.

Methods The HINODE study enrolled 144 patients (81 ICD and 63 CRT-D) with device sensor data transmitted via a remote monitoring system. HeartLogic alerts were then retrospectively simulated using relevant sensor data. Clinicians and patients were blinded to calculated alerts. Reported adverse events with HF symptoms were adjudicated and classified by an independent HFE committee. Sensitivity was defined as the ratio of the number of detected usable HFEs (true positives) to the total number of usable HFEs. A false positive alert was defined as an alert with no usable HFE between the alert onset date and the alert recovery date plus 30 days. The patient follow-up period was categorized as in alert state or out of alert state. The event rate ratio was the HFE rate calculated in alert to out of alert.

Results The patient cohort was 79% male and had an average age of 68 ± 12 years. This analysis yielded 244 years of follow-up data with 73 HFEs from 37 patients. A total of 311 HeartLogic alerts at the nominal threshold (16) occurred across 106 patients providing an alert rate of 1.27 alerts per patient-year. The HFE rate was 8.4 times greater while in alert compared with out of alert (1.09 vs. 0.13 events per patient-year; $P < 0.001$). At the nominal alert threshold, 80.8% of HFEs were detected by a HeartLogic alert [95% confidence interval (CI): 69.9%–89.1%]. The median time from first true positive alert to an adjudicated clinical HFE was 53 days. The FPR was 1.16 (95% CI: 0.98–1.38) alerts per patient-year.

Conclusions Results suggest that signs of worsening HF can be detected successfully with remote patient follow-up. The use of HeartLogic may predict periods of increased risk for HF or clinically significant events, allowing for early intervention and reduction of hospitalization in a vulnerable patient population.

Keywords HeartLogic; heart failure; remote monitoring; ICD; CRT; hospitalization

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Introduction

Hospitalizations are common in patients with heart failure (HF) and are associated with high mortality and morbidity, impaired quality of life, readmission and economic burden.[1–5] The number of hospital admissions for HF is expected to increase considerably due to population growth and ageing and increasing prevalence of comorbidities.[5] In addition, prevalence of HF has been reported to be higher in some Asian geographies compared with Western countries.[3] Detecting early signs of worsening HF may enable more timely intervention and reduce hospitalizations.[6,7]

Cardiac implantable electronic devices (CIED) reduce morbidity, mortality and improve cardiac function and quality of life.[5] The remote monitoring of physiological parameters with CIED has become standard of care. Many studies have investigated the ability of CIED diagnostics to identify patients at risk of HF events (HFEs).[8–11] CIED sensors have been used to develop HF diagnostics to detect early signals leading up to hospitalizations, with most using single physiological measures.[12–14] In the past decade, researchers have combined CIED diagnostics in order to better stratify and manage patients at risk of HFEs.[15–17] However, if the resultant algorithm lacks sufficient sensitivity and positive predictive value (PPV), it is difficult to use clinically.[9,18–20]

The HeartLogic™ algorithm is designed to sense deterioration of HF conditions which may lead to serious clinical events and worsening HF. It was previously validated in a multicentre, prospective, randomized blinded IDE study (MultiSENSE).[12]

The objective of this analysis was to assess HeartLogic performance in the Japanese population by evaluating the sensitivity of the algorithm to predict worsening HF, the false positive alert rate (FPR) and the PPV of alerts. We also compared the rate of HFEs and all-cause hospitalizations that occurred during an alert window to those that occurred outside of an alert window.

Methods

Study population

Details of the HINODE study (NCT03185832) design, including eligibility criteria, device programming, event adjudication and primary results have been published previously.[21,22] The study followed patients in four therapy cohorts: (1) implantable cardioverter-defibrillator (ICD) cohort; (2) cardiac resynchronization therapy defibrillator (CRT-D) cohort; (3) pacing cohort with standard right ventricular pacemaker or CRT-pacing; (4) non-device cohort. The study limited enrolment to patients with a minimum of two to a maximum of five specified risks: (1) left ventricular ejection fraction $\leq$ 35%; (2) New York Heart Association (NYHA) functional Class III or IV; (3) left bundle branch block (LBBB) with QRS $\geq$ 130 ms or any QRS morphology $\geq$150 ms; (4) renal dysfunction, defined as chronic blood urea nitrogen (BUN) $>$ 26 mg/dL or $\geq$9.28 mmol/L; (5) diabetes mellitus Types I and II; (6) chronic atrial fibrillation; (7) prior myocardial infarction (MI); (8) age $>$70 years; or (9) smoking currently or during the last 5 years. Risks were derived from those as shown by Goldenberg for the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) long-term follow-up.[23] Device implant and chosen therapy occurred prior to study enrolment. Patients were required to follow optimal medical therapy as per standard JCS medical guidelines for at least 3 months prior to enrolment and during study follow-up, including recommended HF medication and antiarrhythmic drugs. All device patients were intended per protocol to be connected to the LATITUDE™ remote monitoring system, with sensor data downloaded either during study follow-up visits or using remote transmissions.

Data collection and adjudication

Reported adverse events with HF symptoms were adjudicated and classified by an independent HFE committee. This included the review of all hospitalizations and outpatient visits with any IV treatment or augmented oral HF therapy. An event was classified as an HFE if the primary cause of the event was linked to cardiac dysfunction with signs and symptoms consistent with congestive HF and either of the following conditions was met: (1) the patient was hospitalized and received a new or increased decongestive HF regimen, with oral or parenteral medications; or (2) the patient was not hospitalized but received IV decongestive HF therapy. A consecutive HFE was only considered novel if a minimum of 30 days had passed since the original event. HFEs classified by the independent committee were defined as 'usable' if they occurred at least 45 days after implant and had HeartLogic data available within the 7 days preceding the event. The 45 day period was required to establish an index baseline.

HeartLogic algorithm

The HeartLogic algorithm (Boston Scientific, St. Paul, MN, USA) is implemented in some models of CEID. The inputs of the algorithm have been published previously.[12] Briefly, it functions by calculating an index with diagnostic data from five sensors (heart sounds, thoracic impedance, respiration rate, activity level and night heart rate) to automatically track patient physiology. When the HeartLogic index crosses over a programmed threshold (nominal 16), an alert is generated.

Calculation of HeartLogic alerts

HeartLogic sensor data were collected by CIED and transmitted to the LATITUDE remote monitoring system either during study follow-up visits or using remote transmissions. The sensor data were used for retrospective alert calculation with the HeartLogic algorithm. HINODE patients, clinicians and adjudication committee members were blinded to the HeartLogic index and calculated alerts. The analysis used the same definition of an 'in alert' state that is recommended for clinical practice using nominal settings. An alert was considered triggered when the index crossed over the nominal numerical threshold of 16. An alert was considered resolved when the HeartLogic index dropped below the nominal recovery threshold of 6.

A true positive alert was an alert that correctly predicted a usable HFE. MidHEFT rules[24] were used to classify true positive alert timing. To be a true positive, an HFE had to occur after an alert onset, and the alert recovery date could be no earlier than 30 days prior to the usable HFE. When a usable HFE occurred without a preceding alert, it was classified as a false negative alert. A false positive alert occurred when there was no usable HFE between the alert onset date and the alert recovery date plus 30 days.

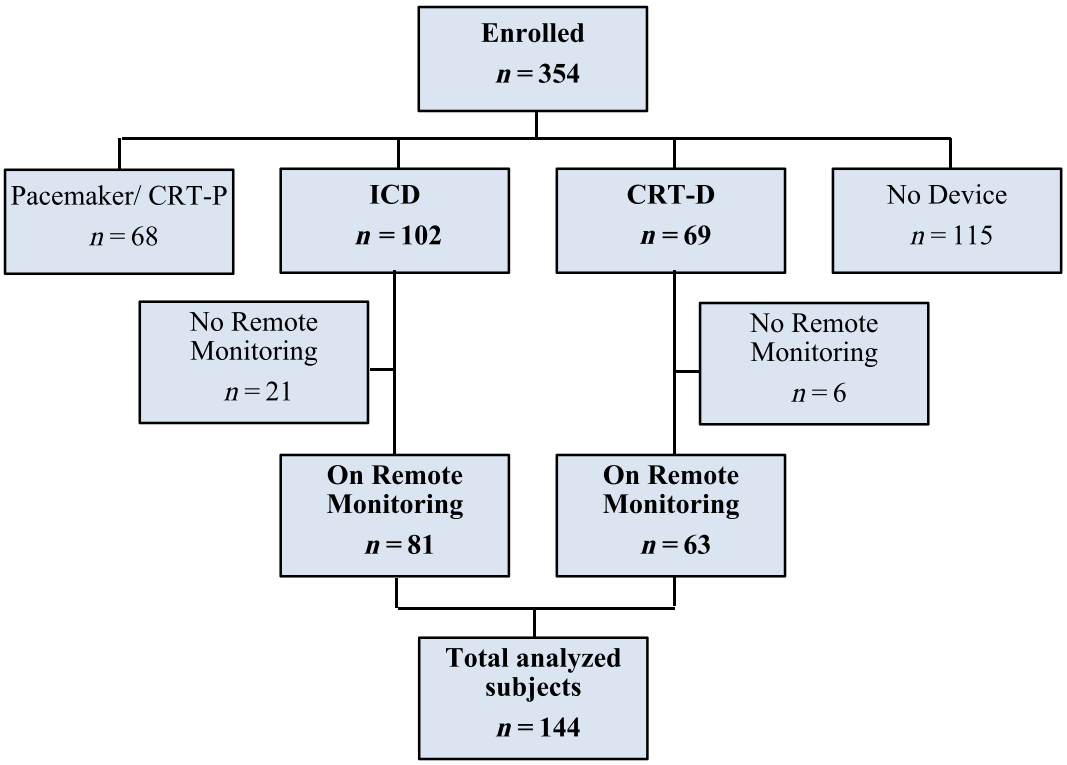
Statistical analysis

Sensitivity, FPR, PPV and alert duration were calculated. Sensitivity was defined as the ratio of the number of usable HFEs detected by a true positive alert to the total number of usable HFEs. The sensitivity value is presented with a two-sided 95% confidence interval (CI) calculated based on binomial distribution.

The FPR was the ratio of the total number of false positive alerts over the total usable follow-up duration. Usable follow-up duration started on the first day that the HeartLogic index had a valid value after implant or on the day of study enrolment, whichever occurred later, and continued to the last day of study follow-up. The FPR is presented with a two-sided 95% CI calculated based on negative binomial distribution.

The PPV was the proportion of all alerts that could be positively associated with a usable HFE. Expanded definitions of PPV assessed the proportion of all alerts that could be positively associated with all-cause hospitalization or a clinically significant event including all-cause hospitalization, HFE, serious adverse event, or ventricular arrhythmia (adjudicated by an independent committee as appropriately treated by anti-tachycardia pacing or shock or with hemodynamic insta-

Figure 1 Enrolment and LATITUDE™ remote monitoring system connection. Remote monitoring refers to device connection to the LATITUDE remote monitoring system. CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator.



bility which required treatment). Alerts were considered associated with all-cause hospitalization or clinically significant event if onset of the alert occurred before the event and the alert recovered no earlier than 30 days prior to event onset. This matched the timing requirement used for true positive alerts.

Alert duration was the days between alert onset and either alert recovery or event onset, whichever occurred first. Early warning time was the period between a true positive alert onset and a usable HFE. The percentage of follow-up time spent in an alert state was the total days spent in alert divided by the total days of usable follow-up.

Usable HFE rates and all-cause hospitalization rates in and out of a HeartLogic alert state were also assessed. Patient follow-up was categorized as in alert versus out of alert. Event rates were calculated for each state of follow-up by the ratio of total events to total patient follow-up duration in each state and presented as events per patient-year. The event rate ratio was the ratio of the event rate in alert state versus out of alert state. It was calculated and graphically displayed using arithmetic values, and further evaluated by deriving 95% CIs and *P* values from a generalized estimating equation (GEE) based on a negative binomial distribution using an exchangeable correlation structure. The GEE modelled events per patient-year while accounting for repeated assessment of the event rates per patient (patient could contribute to both the in and out of alert states).

Ethics statement

The protocol was approved by the responsible ethics committee for all participating centres and required a written informed consent from all enrolled patients. The study conforms to the principles outlined in the Declaration of Helsinki.

Results

Of the 171 enrolled patients with an ICD or CRT-D, 144 patients transmitted sensor data via the remote monitoring system LATITUDE (ICD: 81, CRT-D: 63) (*Figure* 1). Patients were followed for a median of 20 months, with none lost during follow-up. ICD and CRT-D patients were 79% male, average age of 68 ± 12 years and had a median of four predefined risk factors (*Table* 1). The ICD and CRT-D cohorts differed in patient and disease history. Patients with typical HF and CRT-D indications like QRS > 150 ms or LBBB are also present in the ICD cohort. Ten CRT-D indicated patients received ICD therapy. Additionally, 62% of ICD cohort and 70% of CRT-D cohort patients had a prior hospitalization for HF before inclusion in the study.

Table 1 Baseline characteristics in ICD and CRT-D cohorts on remote monitoring system.

Baseline characteristic	ICD on remote monitoring system (*N* = 81)	CRT-D on remote monitoring system (*N* = 63)
Predefined risk factors		
LVEF ≤ 35%	81 (100.0%)	63 (100.0%)
NYHA Class III or IV	16 (19.8%)	33 (52.4%)
LBBB with QRS > 130 ms or QRS > 150 ms	10 (12.3%)	58 (92.1%)
Renal dysfunction	22 (27.2%)	9 (14.3%)
Diabetes Types I and II	37 (45.7%)	23 (36.5%)
Chronic AF (permanent or persistent)	20 (24.7%)	6 (9.5%)
Prior myocardial infarction	41 (50.6%)	11 (17.5%)
Age > 70 years	41 (50.6%)	29 (46.0%)
Smoking history	24 (29.6%)	13 (20.6%)
Median number of risk factors	4.0	4.0
Baseline characteristics		
Age at time of consent (years) (mean ± *SD*)	69.2 ± 9.9	66.3 ± 13.6
Male	69 (85.2%)	45 (71.4%)
BMI (kg/m^2) (mean ± *SD*)	22.8 ± 3.2	22.3 ± 3.9
NYHA class		
I	0 (0.0%)	3 (4.8%)
II	65 (80.2%)	27 (43.5%)
III	16 (19.8%)	29 (46.8%)
IV	0 (0.0%)	3 (4.8%)
LVEF (%) (mean ± *SD*)	26.9 ± 6.1	24.7 ± 6.1
Systolic blood pressure (mmHg) (mean ± *SD*)	107.2 ± 14.2	105.9 ± 16.9
Diastolic blood pressure (mmHg) (mean ± *SD*)	63.2 ± 9.8	64.4 ± 13.6
Resting heart rate (beats/min) (mean ± *SD*)	68.3 ± 14.4	70.8 ± 16.1
QRS width (ms) (mean ± *SD*)	121.2 ± 24.4	153.3 ± 24.9
QRS morphology		
Normal	37 (46.3%)	5 (8.2%)
RBBB	11 (13.8%)	6 (9.8%)
LBBB	9 (11.3%)	39 (63.9%)
Other and IVCD	23 (28.8%)	11 (18.0%)
Ischaemic cardiomyopathy	46 (56.8%)	17 (27.0%)
Previous hospitalization for HF	50 (61.7%)	44 (69.8%)
Hypertension	41 (50.6%)	25 (39.7%)
Atrial fibrillation	29 (35.8%)	12 (19.0%)
Concomitant medications		
ACE or ARB	63 (77.8%)	43 (68.3%)
Antiarrhythmic	30 (37.0%)	22 (34.9%)
Anticoagulant	43 (53.1%)	24 (38.1%)
Antiplatelet	44 (54.3%)	24 (38.1%)
Aldosterone antagonist	31 (38.3%)	34 (54.0%)
Beta-blocker	75 (92.6%)	52 (82.5%)
Digitalis	2 (2.5%)	7 (11.1%)
Diuretics	64 (79.0%)	46/ (73.0%)
Statins	49 (60.5%)	24 (38.1%)
Calcium antagonists	11 (13.6%)	6 (9.5%)

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle branch block.

Of the 144 patients with data from the remote monitoring system, there were 93 events classified as HFEs by the independent adjudication committee (*Figure* 2). Twenty events did not meet the definition of usable HFE and were removed from analysis, leaving 73 usable HFEs. Reasons for event exclusion were being within 45 days of implant and prior to HeartLogic Index calculation (n = 9), missing sensor data in the 7 days prior to the event (n = 8), unknown onset date (n = 1), or onset dates that overlapped another HFE for the same subject (n = 2). In total, 37 patients had at least one usable HFE. The rate of usable HFEs was 0.30 events per patient-year, with 0.35 events per patient-year for the ICD cohort and 0.23 events per patient-year for the CRT-D cohort. Approximately, 74% of usable HFEs led to a hospitalization. Among those hospitalizations, the median length of stay was 24 days (interquartile range: 13–38).

A total of 311 HeartLogic alerts, at the nominal threshold (16), occurred across 106 patients providing an alert rate of 1.27 alerts per patient-year (*Table* 2). The median alert duration for all alerts was 44 days (ICD: 46 days, CRT-D: 42 days). The median early warning time was 53 days (ICD: 61 days, CRT-D: 52 days). The gross percentage of follow-up time in an alert state was 20.6%. At the nominal alert threshold, 81% (59/73, 95% CI: 70–89%) of usable HFEs were detected by an

Figure 2 HFE classification. The figure presents the HFE classification pathway and reasons for exclusion from analysis. The events for ICD and CRT-D patients connected to LATITUDE remote monitoring system are included. CRT-D, cardiac resynchronization therapy defibrillator; HFE, heart failure event; ICD, implantable cardioverter defibrillator.

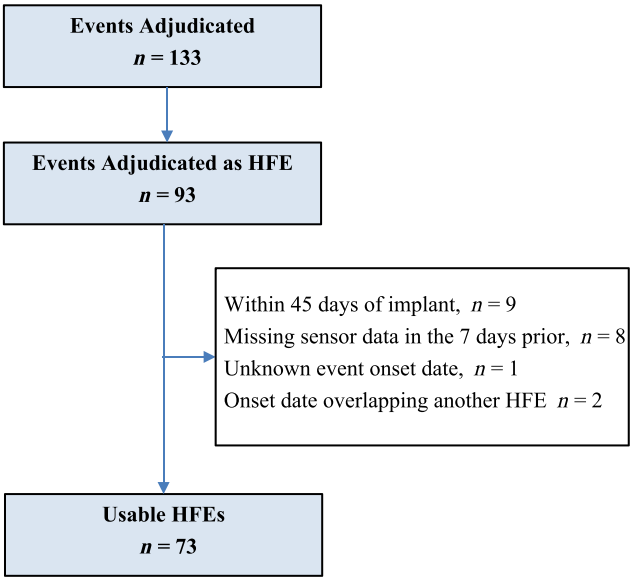


Figure 3 MultiSENSE and HINODE usable HFE detection. The figure shows the receiver operating characteristic curves for the performance of HeartLogic in HINODE study compared with MultiSENSE study patient population. Performance is measured by the false positive alert rate per patient-year (x-axis) and the sensitivity to detect usable HFEs (y-axis). Each point on the curve represents a programmable alert onset threshold. From left to right, the thresholds range from 40 to 10 by 2. The nominal threshold is indicated by a solid circle or solid diamond. CI, confidence interval; HFE, heart failure event.

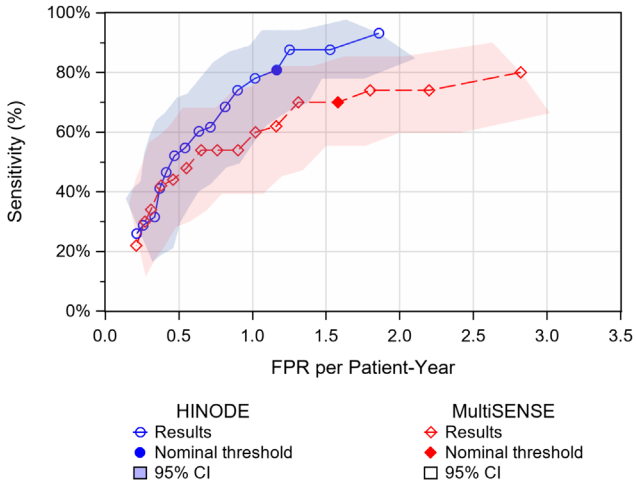


Table 2 HeartLogic alert performance.

Metric	All	ICD	CRT-D
Alerts	311	186	125
Alerts per patient year	1.27	1.37	1.16
Percent of follow-up time in alert state	20.6%	23.0%	17.7%
Median alert duration in days (25^{th}–75^{th} percentile)	44 (26–67)	47 (28–67)	42 (25–67)
Median early warning time in days (25^{th}–75^{th} percentile)	53 (23–96)	61 (30–99)	52 (12–75)
Sensitivity (95% CI)	80.8% (69.9%, 89.1%)	83.3% (69.8%, 92.5%)	76.0% (54.9%, 90.6%)
FPR (95% CI)	1.16 (0.98, 1.38)	1.24 (0.98, 1.56)	1.08 (0.84, 1.38)
PPV for HFE	17.7%	19.9%	14.4%
PPV for all-cause hospitalization	23.5%	27.4%	17.6%
PPV for clinically significant events	26.4%	31.2%	19.2%

Note: The table summarizes HeartLogic alerts and algorithm performance at the nominal threshold of 16.
Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; FPR, false positive rate; HFE, heart failure event; ICD, implantable cardioverter-defibrillator; PPV, positive predictive value;.

alert. There were 14 usable HFEs that went undetected by the algorithm, belonging to 12 distinct subjects (6 ICD and 6 CRT-D). The sensitivity within each cohort was 83.3% (40/48) for ICD and 76.0% (19/25) for CRT-D. The FPR was 1.16 (95% CI: 0.98–1.38) alerts per patient-year, and the FPR within each cohort was 1.24 for ICD and 1.08 for CRT-D. *Figure* 3 displays the receiver operating characteristic (ROC) curve characterizing sensitivity and FPR at numerous programmable HeartLogic alert thresholds. The PPV of 311 HeartLogic alerts for detection of usable HFEs was 17.7%. Similarly, the PPV for detection of all-cause hospitalizations and detection of clinically significant events were 23.5% and 26.4%, respectively. Results by cohort are displayed in *Table* 2.

Assessment of the usable HFE rate by alert state (*Figure* 4) yielded 1.09 events per patient-year in alert and 0.13 events per patient-year in out of alert. The HFE rate was 8.4 times greater while in alert ($P < 0.001$). Similar results were seen in ICD and CRT-D cohorts individually. The ICD HFE rate per patient-year was 1.16 in alert and 0.16 out of alert, with 7.4 times more HFEs in alert ($P < 0.001$). The CRT-D HFE rate per patient-year was 0.96 in alert and 0.10 out of alert, with 9.9 times more HFEs in alert ($P < 0.001$). Assessment of all-cause hospitalizations by alert state yielded 1.35 events per patient-year in alert and 0.50 events per patient-year in out of alert for the ICD and CRT-D cohorts combined. The all-cause hospitalization rate was 2.7 times greater while in alert ($P < 0.001$).

To obtain a profile of the HeartLogic index over time, data from patients with usable HFEs were plotted, as performed in MultiSENSE.[12] *Figure* 5 compares the respective HeartLogic index for patients with a usable event (blue) with patients without an HFE (black). Data are aligned with respect to either the date of the usable HFE (Day 0) or to the date of the last available index value (Day 30) for patients with a usable HFE or without an HFE event, respectively. A baseline index was calculated for patients with usable HFEs over a 3 month period ending 90 days before the HFEs. These patients had a median HeartLogic index of 11.9 (interquartile range: 3.6 to 23.0). The index increased from the median baseline, becoming statistically significant 51 days before the HFE ($P < 0.05$, rank sum test), and decreased following the event. For patients without HFEs, the HeartLogic index was significantly lower (median 2.5; interquartile range: 0.3 to 6.8) than the baseline for patients with HFEs ($P < 0.001$; rank sum test).

Discussion

Monitoring of patient condition with HeartLogic shifts HF patient management from reactive treatment to proactive individualized care, which may help to increase patient welfare and focus available healthcare resources. The results of the

Figure 4 Event rates in and out of alert state. The figure displays the usable HFE rate (left) and the all-cause hospitalization rate (right) per patient-year of follow-up in and out of HeartLogic alert state. Cohorts are listed along the *x*-axis. 'All' refers to ICD and CRT-D cohorts combined. Listed above each set of bars is the event rate ratio (ratio of event rate in alert vs. out of alert) and the *P* value evaluating if the event rate ratio is significantly different from 1. Additional data are available in Data S1. CRT-D, cardiac resynchronization therapy defibrillator; HFE, heart failure event; ICD, implantable cardioverter defibrillator.

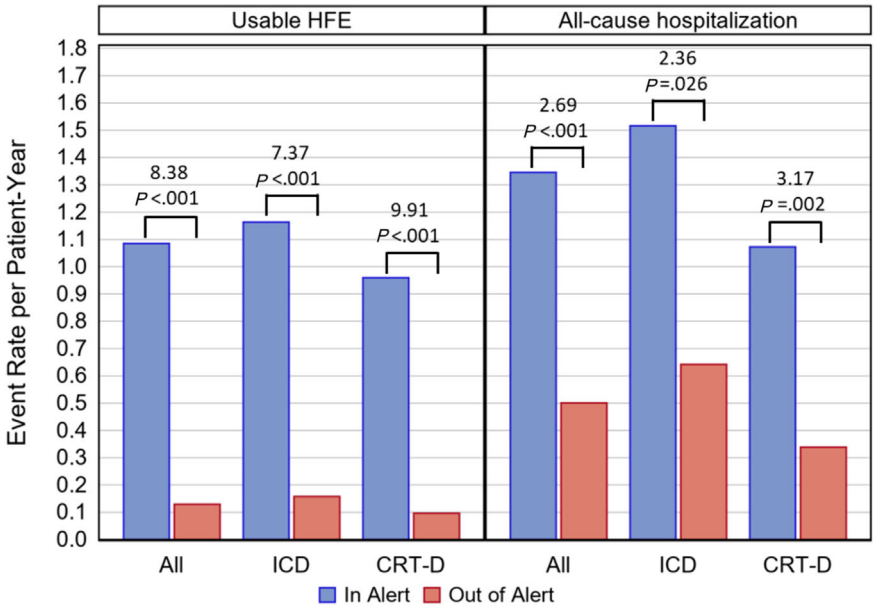
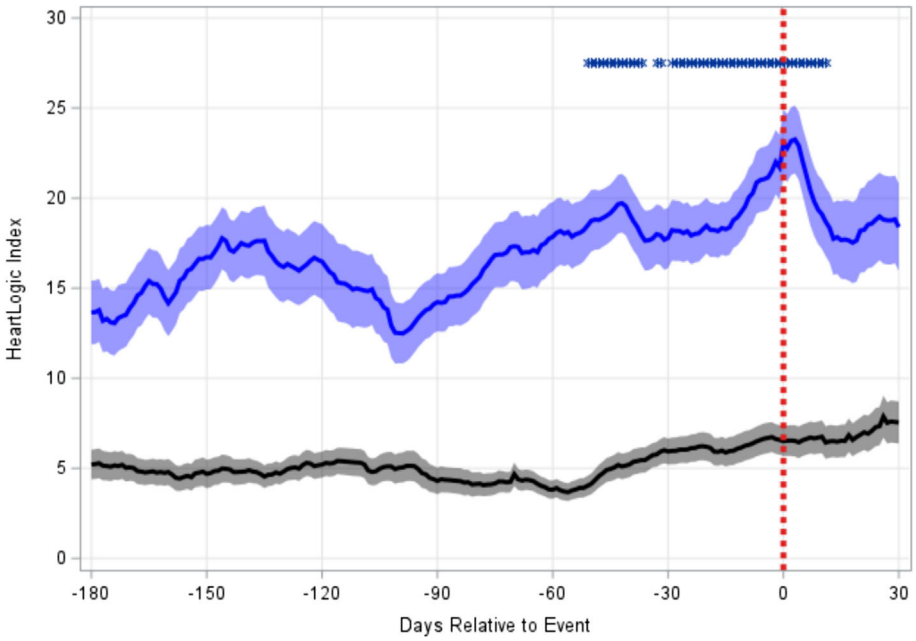


Figure 5 HeartLogic index trends in patients with and without heart failure events (HFEs). The figure displays the mean HeartLogic index for patients with HFEs (blue line) aligned by the day of the HFE (vertical line at Day 0) and displays the mean HeartLogic index for patients without an HFE (black line) aligned by the last available HeartLogic index (Day 30). The shaded regions represent the standard error of the mean. Asterisks mark days where the HL index for patients with HFEs is significantly different ($P < 0.05$, rank sum test) from the 3 month baseline period ending 90 days before the HFE.



present analysis suggest that signs of worsening HF can be sensed successfully with remote patient follow-up. The sensitivity of HeartLogic for HF was 81% and the FPR was just 1.16 alerts per patient-year.

The necessity for reliable biomarker to detect deteriorated HF

The number of HF patients continues to increase, and action is urgently needed to adequately respond to this growing patient population. Patients with HF are known to have repeated HF hospitalizations, with associated poor prognosis.[25] Data from the MADIT-CRT trial indicate that patients who are hospitalized for HF are eight times more likely to die and nine times more likely to be re-hospitalized for HF than those who are not hospitalized for HF. The costs associated with HF patients are also enormous, especially the costs associated with HF hospitalizations, which account for approximately 60% of all HF costs. Prevention of HF hospitalizations is thus a critical issue.

For some time, telemonitoring has been used to assess patients remotely, based on symptoms and weight. While there have been communications that this has reduced HF hospitalizations, Chaudrhry et al.[26] reported that monitoring weight and HF symptoms does not reduce HF hospitalizations. The HINODE patients examined in this study experienced 54 HF hospitalizations with a median stay of 24 days, meaning remote monitoring of patient condition through alerts may finally represent reduced hospitalization and a large potential cost savings.

In comparison with single- or dual-sensor monitoring,[26,27] the HeartLogic algorithm uses data from additional sensors to target variations of HF pathophysiology. The algorithm combines data from the following physiological variables: thoracic impedance,[27] which is indicative of fluid accumulation and pulmonary oedema; first and third heart sounds, especially S3 as a sign of elevated filling pressure (detected by the accelerometer); respiration sensor to detect breathing patterns associated with dyspnoea; heart rate as an indicator of general cardiac status; and activity for global patient status and fatigue. Combined sensor data are used to assess multiple signs and symptoms of HF to follow a continuously changing patient condition. Previous studies monitoring a single physiological parameter failed to reduce HF hospitalization.[9,11,18] A high FPR alert may lead to less effective follow-up when compared with follow-up of alerts with higher sensitivity and specificity. Algorithms that summarize several HF-related factors and not a single parameter,[10,17] have been reported to be useful in increasing sensitivity and PPV.[28] A high intervention rate is important to reduce HF hospitalization[17,18] and requires a credible detection

algorithm.

Comparison to performance in Western countries

In the MultiSENSE trial, alert performance and prediction of HFEs were validated with a high sensitivity of 70% for detecting usable HFEs, weeks of advance notice of a potential HFE and low alert burden of less than 2 per patient per year.[29–32] MultiSENSE also reported a PPV of 5.6% when using only true positive alerts.[12] The HeartLogic alert rate at the nominal threshold (16) was 1.47 alerts per patient-year and the median time from first true positive alert to usable HFE was 34 days. The median HeartLogic index over a 3 month baseline period ending 90 days before an HFE was 8.6, and HeartLogic index was significantly increased compared with the baseline period starting 29 days before the HFE. The FPR was 1.56 alerts per patient-year. *Figure* 3 compares HeartLogic performance between HINODE and MultiSENSE studies with ROC curves measuring sensitivity and FPR. The overlapping CIs of the ROC curves demonstrate similarity in HeartLogic performance between both studies, although point estimates suggest a higher sensitivity and lower FPR at the nominal threshold in HINODE. Importantly, usable HFEs in MultiSENSE were required to have at least 60% of relevant sensor data within a 60 day pre-event window and at least 70% within a 15 day pre-event window whereas usable HFEs in HINODE were required to have HeartLogic data within the 7 days prior to the event. In addition, although both studies were multicentre prospective trials, they were not randomized and were observational only. Nevertheless, the ability of HeartLogic to pre-emptively detect HFE in the MultiSENSE and the HINODE cohorts supports its utility as a diagnostic.

How to use HeartLogic clinically

In a previous study with remote monitoring of fluid status,[18] it was suggested the composite of all-cause death and cardiovascular hospitalization was not improved because of a low intervention rate; only 67.5% of symptomatic HF patients who were detected by remote monitoring received intervention. On the other hand, in IN-TIME,[17] patients in the telemonitoring group had a higher intervention rate and better outcomes (i.e., fewer patients had a worsened clinical composite score relative to the controls). Clinician use of HeartLogic alerts may allow early intervention, more than 50 days before the occurrence of severe HFEs. During the early warning time, therapy adjustments can be made, which may include better medication adherence by the patients, additional device follow-up, as well as diagnostics and drug changes. The proactive individualized follow-up may reduce hospitalization in these vulnerable patients. In a non-randomized study,[33] HeartLogic alert management was safely implemented into HF care and N-terminal pro-B-type natriuretic peptide (NTproBNP) values decreased from baseline to 12 months. In this study, diuretics were used more than other medications to manage HF in response to alerts. Similarly, in our previous study, diuretics, nitrate and lifestyle modification were effective to manage early stages of HF.[34]

Adjustments and patient care could be performed with remote or telephone follow-up. The HINODE results suggest that during remote follow-up, nearly one out of five alerts is related to a severe HF worsening (PPV of 17.7%). Improved medication adherence is expected with remote follow-up, but the impact of remote follow-up on HFE rate and hospitalization duration must be studied.

Limitations

The HINODE study sample size was smaller than initially planned; however, the longer enrolment period increased the mean follow-up duration per patient, compensating for missing observational time. In addition, no patients were lost to follow-up as vital status was collected for all study subjects at the time of withdrawal or study completion.

HeartLogic performance analyses required available sensor data and adverse event data. Of the 171 ICD and CRT-D cohort patients, 27 were excluded from analysis for having no sensor data collected in LATITUDE. Out of 93 Clinical Endpoint Committee adjudicated HFEs, 20 were excluded from analysis for (1) occurring within 45 days of implant, before an established sensor baseline (n = 9), (2) missing sensor data in the 7 days prior to the event (n = 8), (3) missing adverse event onset date (n = 1), or (4) overlapping another HFE for the same subject (n = 2). Despite these limitations, 144 subjects and 73 HFEs were available. Analysis of biomarkers for HF, such as NTproBNP, was not possible due to the limited amount of biomarker data collected during the study. Assessment of biomarkers in conjunction with HeartLogic may aid in identification of patients at risk for HF.[29] Because physicians were blinded to HeartLogic alerts, the true impact of a given alert on patient care remains unknown and requires further evaluation.

Conclusions

The study data show that HeartLogic alerts predict 80.8% of HFEs at the nominal alert threshold, with a median of 53 days from alert to event in Japanese ICD and CRT-D cohorts. The majority of HFE and all-cause hospitalizations occurred after calculated alert onset and during the alert window for ICD and CRT-D patients, suggesting HeartLogic alerts may predict periods of increased risk for an HFE or hospitalization.

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Conflict of interest statement

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Supporting information

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

Data S1. Supporting Information.

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