A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices

Results From the MultiSENSE Study

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ABSTRACT

OBJECTIVES The aim of this study was to develop and validate a device-based diagnostic algorithm to predict heart failure (HF) events.

BACKGROUND HF involves costly hospitalizations with adverse impact on patient outcomes. The authors hypothesized that an algorithm combining a diverse set of implanted device-based sensors chosen to target HF pathophysiology could detect worsening HF.

METHODS The MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study enrolled patients with investigational chronic ambulatory data collection via implanted cardiac resynchronization therapy defibrillators. HF events (HFEs), defined as HF admissions or unscheduled visits with intravenous treatment, were independently adjudicated. The development cohort of patients was used to construct a composite index and alert algorithm (HeartLogic) combining heart sounds, respiration, thoracic impedance, heart rate, and activity; the test cohort was sequestered for independent validation. The 2 coprimary endpoints were sensitivity to detect HFE >40% and unexplained alert rate <2 alerts per patient-year.

RESULTS Overall, 900 patients (development cohort, n = 500; test cohort, n = 400) were followed for up to 1 year. Coprimary endpoints were evaluated using 320 patient-years of follow-up data and 50 HFEs in the test cohort (72% men; mean age 66.8 ± 10.3 years; New York Heart Association functional class at enrollment: 69% in class II, 25% in class III; mean left ventricular ejection fraction 30.0 ± 11.4%). Both endpoints were significantly exceeded, with sensitivity of 70% (95% confidence interval [CI]: 55.4% to 82.1%) and an unexplained alert rate of 1.47 per patient-year (95% CI: 1.32 to 1.65). The median lead time before HFE was 34.0 days (interquartile range: 19.0 to 66.3 days).

CONCLUSIONS The HeartLogic multisensor index and alert algorithm provides a sensitive and timely predictor of impending HF decompensation. (Evaluation of Multisensor Data in Heart Failure Patients With Implanted Devices [MultiSENSE]; NCT01128166) (J Am Coll Cardiol HF 2017;5:216–25) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

H ospitalizations are common in patients with heart failure (HF) (1) and are associated with high mortality, readmission, and economic burden. In the United States alone, there are more than 1 million hospitalizations for HF, with a direct cost of more than $20 billion attributed primarily to inpatient costs (1). Although monitoring weights and symptoms is recommended for managing HF (2), this has not proved to reduce hospitalizations (3). Given the economic and clinical impact of HF hospitalizations, there is a need for an effective method to detect worsening HF early enough to provide an opportunity for timely intervention.

A variety of sensors in implantable devices (implantable cardioverter-defibrillators, cardiac resynchronization therapy devices, and pacemakers) may indicate early changes before hospitalizations (4,5). Yet clinical trials using implanted devices have not consistently shown reductions in HF hospitalizations (6-8). Although the underlying causes are likely multifactorial, 1 reason could be the use of single sensors to try to predict outcomes in a complex clinical syndrome (9-11). We sought to develop an algorithm for the early detection of worsening HF by combining a diverse set of implanted sensors. These sensors target the different aspects of HF pathophysiology associated with common signs and symptoms of HF. We then sought to prospectively test the resultant algorithm against pre-defined and clinically relevant performance goals (PGs) in an independent test set.

METHODS

The MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study design was previously published and is summarized in Online Table 1 (12). In brief, MultiSENSE was an international, multicenter, nonrandomized study designed to determine how ambulatory sensor measurements change with worsening HF. The intent was to develop and prospectively evaluate a multisensor-based algorithm for the early detection of worsening HF. Patients were required to have an implanted COGNIS cardiac resynchronization therapy defibrillator (CRT-D, Boston Scientific, St. Paul, Minnesota) and bipolar right atrial, right ventricular, and left ventricular leads. Because of slow enrollment, after the first 62 patients, the inclusion criterion of recent HF therapy (at least 1 documented HF hospitalization or outpatient visit requiring administration of

intravenous [IV] diuretic agents within the past 6 months or 2 within the past 12 months) was replaced with an inclusion criterion of New York Heart Association functional class II, III, or IV within the past 6 months. A corresponding adjustment was made to the trial sample size to account for the lower expected rate of heart failure events (HFEs). A full list of inclusion criteria can be found in Online Table 1. All patients provided written informed consent.

SENSOR DATA COLLECTION. Upon enrollment, new software was downloaded into the implanted CRT-D, converting it to an investigational sensor research device (SRD). SRD conversion enabled data collection from sensors, including heart rate, accelerometer-based heart sounds, respiration rate, relative tidal volume, activity, and intrathoracic impedance. Sensor data were downloaded either during follow-up visits or using remote LATITUDE transmissions. Treating clinicians and investigators were blinded to the investigational sensor data. The study data were divided into 2 sets by order of enrollment. The development set was used to develop the composite index and alert algorithm. The test set was sequestered and used for independent validation of alert algorithm performance. The inclusion criteria change occurred during development set enrollment. Devices were restored to market-approved CRT-Ds following a 12-month visit.

HEART FAILURE EVENTS. An independent clinical events committee reviewed all hospitalizations and outpatient visits with any IV treatments or augmented oral HF therapies (12). The committee members were blinded to all sensor and algorithm data. An event was classified as an HFE if the primary cause was worsening HF and either of the following conditions was met: 1) the patient was admitted and incurred a calendar date change; or 2) the patient received 1 or more IV medications (including diuretic agents, inotropes, and vasodilators), aquapheresis, or other parenteral therapy. HFEs were considered "usable," for algorithm development and validation, if they occurred at least 45 days after the initiation of sensor data collection and before device reconversion. The 45-day period was required to establish a sensor baseline. Missed study visits resulted in SRD memory overflow, hence data availability criteria were established (Online Appendix).

MULTISENSOR ALERT ALGORITHM. The algorithm was developed using sensor data and HFE information from the development set. During the first phase of algorithm development, features that demonstrated

meaningful association with HFEs were extracted from individual sensor data into feature trends. Each feature trend was independently assessed on the basis of signal changes during pre-HFE and nonevent time periods. The next phase of development included combining the key feature trends into a composite index and an associated alert (HeartLogic). In brief, multiple feature changes from the patient's own baseline were aggregated and weighted on the basis of an individual daily risk for worsening HF assessment. The algorithm uses the first and third heart sounds, thoracic impedance, respiration rate, the ratio of respiration rate to tidal volume, heart rate, and patient activity. The clinical relevance of these metrics to HF is summarized in Table 1.

The HeartLogic index value is updated daily, and an alert is issued when the index crosses an alert threshold. The nominal alert threshold of 16 and the coprimary endpoints described later were pre-specified on the basis of the development set. The algorithm development team was blinded to the test set data until algorithm validation.

STATISTICAL ANALYSIS: PRE-SPECIFIED ENDPOINT DEFINITIONS. The coprimary endpoints used to validate the algorithm were pre-specified as follows before assessing the sequestered data from the test set using SAS version 9.2 (SAS Institute, Cary, North Carolina):

- Endpoint 1: Sensitivity for detecting usable HFE >40%. An exact 2-sided 95% (i.e., $\alpha = 0.025$) confidence interval (CI) for sensitivity was calculated on the basis of the binomial distribution, and the lower bound was tested against a PG of 40%.
- Endpoint 2: Unexplained alert rate (UAR) per patient-year <2.0. A 2-sided 95% CI for the UAR was calculated on the basis of the negative binomial distribution, and the upper bound was tested against the PG of 2.0.

Alerts were classified as true-positive if the alert onset occurred before a usable HFE that met the data availability criteria (and did not reset earlier than 30 days before the event). Similarly, HF-related alerts followed the same timing criteria but preceded HFEs meeting a broader definition (excluding the HFE definition). These included events such as HF admissions with a secondary cause of HF or oral HF therapy in an outpatient setting, as well as events that did not meet data availability criteria or that occurred within 45 days of device conversion. All remaining alerts were classified as unexplained alerts. Sensitivity was defined as the ratio of total number of detected usable HFEs to the total number of usable HFEs. UAR was

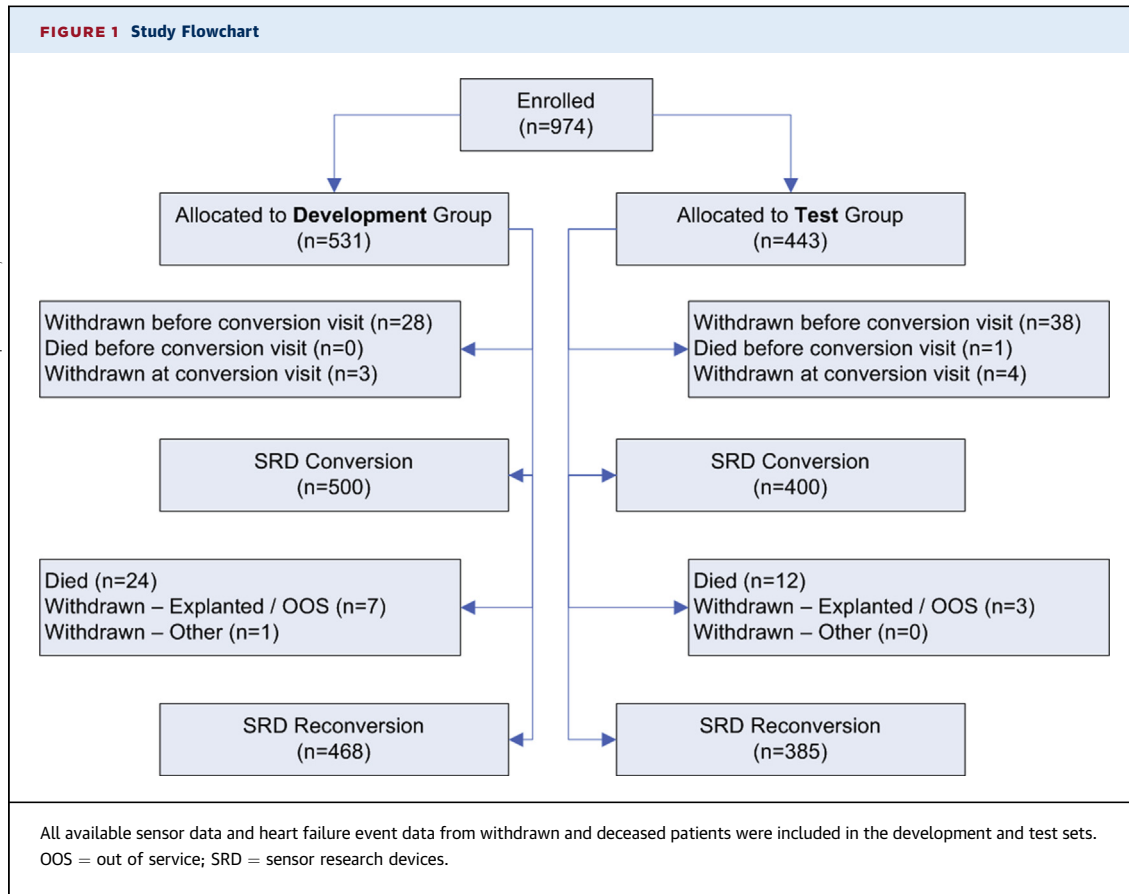| TABLE 1 Physiological Variables and Their Clinical Relevance	
Physiological Variable	**Clinical Relevance**
Heart sounds	
First heart sound	Associated with ventricular contraction status
Third heart sound	Associated with early diastolic filling
Thoracic impedance	Associated with fluid accumulation and pulmonary edema
Respiration	
Respiration rate	Rapid shallow breathing patterns associated with shortness of breath
Ratio of respiration rate to tidal volume	
Heart rate	Indicator of cardiac status
Activity	Global patient status and fatigue

defined as the ratio of the total number of unexplained alerts over the total usable follow-up duration (i.e., the total duration of patient-years when the index had valid values).

A study of 400 patients with an estimated 329 patient-years of total usable follow-up was projected to provide 40 HFEs meeting the usability criteria. With an expected sensitivity of 65%, it would provide 88% power for the sensitivity PG. With an expected UAR of 1.63 per patient-year, it would provide 80% power for the UAR PG. Assuming independence, the combined power was 71%. The targeted performance would represent real clinical benefit, with a low alert management burden, even if only a fraction of alerts prevented a hospitalization.

POST HOC ANALYSIS. Additionally, false-positive rate (FPR), positive predictive value (PPV), specificity, and negative predictive value were also computed. FPR was defined as the ratio of the total number of alerts that were not true-positive alerts over the total usable follow-up duration. PPV, defined as the proportion of alerts that were positively associated with HFEs, was separately calculated using both the ratio of HF-related alerts to total alert count, as well as the more restrictive definition of the ratio of true-positive alerts to total alert count. Specificity was calculated as true negative/(true negative + false positive) during non-HFE time periods (i.e., excluding periods from 30 days before to 15 days after an HFE). Individual days were classified as true negative if HeartLogic was not in alert state and false positive if HeartLogic was in alert state.

RESULTS

PATIENT DEMOGRAPHICS. There were 974 patients enrolled at 81 centers (64 U.S., 17 international) between July 2010 and October 2013, with last study

FIGURE 1 Study Flowchart

All available sensor data and heart failure event data from withdrawn and deceased patients were included in the development and test sets. OOS = out of service; SRD = sensor research devices.

follow-up in December 2014 and event adjudication completed in May 2015. The first 491 patients enrolled in the U.S. and the first 40 international patients were assigned to the development set, and the remainder of the U.S. (n = 362) and international (n = 81) patients were assigned to the test set (**Figure 1**). Baseline characteristics of each group are summarized in **Table 2**. There were significant differences between groups in the percentage of international patients, blood pressures, blood chemistry (sodium, hematocrit, and blood urea nitrogen), and medications (anticoagulant agents and aldosterone antagonists).

DEVELOPMENT SET CHARACTERIZATION AND OPERATING POINT SELECTION. Five hundred patients assigned to the development set completed SRD conversion (Online Table 2), of whom 468 (93.6%) completed the 12-month data collection (median SRD follow-up time 324 days; range 7 to 395 days) (**Figure 1**). Twenty-four patients (4.8%) in the development set died during follow-up. A total of 64 patients (12.8%) in the development set had 127 HFEs during follow-up (96 usable HFEs) (Online Figure 1).

The detection performance in the development set is presented in **Figure 2A**. At the nominal threshold of 16, the observed sensitivity was 82%, and the UAR was 1.33 per patient-year. Exclusion of the 62 patients enrolled before inclusion criteria change did not substantially change the observed sensitivity (82%) or UAR (1.29).

INDEPENDENT TEST SET CHARACTERIZATION. Four hundred patients in the test set completed SRD conversion, and 385 (96.2%) completed the 12-month data collection (median SRD follow-up time 322 days; range 18 to 357 days) (**Figure 1**). Thirteen patients (3.3%) in the test set died during follow-up (p = 0.31 vs. development set). One patient in the test set died before SRD conversion. A total of 42 patients (10.5%) in the test set had 65 HFEs during follow-up (p = 0.30 vs. development set). Fifty of these events met the usability criteria (**Figure 3**). Ninety-two additional events were classified as HF-related. These included 51 outpatient visits associated with significant oral HF medication changes, 26 events with HF as secondary cause, 8

TABLE 2   Patient Characteristics

	Measurement	Development Set (n = 531)	Test Set (n = 443)	p Value
Age at implantation (yrs)	Mean ± SD	66.3 ± 10.9	66.8 ± 10.3	0.51
Sex	Male	387 (73)	314 (71)	0.50
Race	White, not of Hispanic origin	367 (75)	285 (79)	0.31
United States	Yes	491 (92)	362 (82%)	<0.0001
History of cardiac ischemia	Yes	277 (52)	217 (49)	0.31
History of dilated cardiomyopathy	Yes	301 (57)	271 (61)	0.16
History of valvular disease	Yes	162 (31)	130 (29)	0.68
History of valve surgery	Yes	50 (9)	40 (9)	0.83
Previous MI	Yes	211 (40)	171 (39)	0.69
Previous CABG	Yes	156 (29)	128 (29)	0.87
Primary atrial arrhythmia	Atrial fibrillation	136 (26)	118 (27)	0.88
Renal disease	Yes	143 (27)	101 (23)	0.13
NYHA functional class	I/II/III/IV	5%/64%/27%/0%	4%/64%/25%/1%	0.30
LVEF (%)	Mean ± SD	29.3 ± 11.5	29.7 ± 11.4	0.63
Body mass index (kg/m²)	Mean ± SD	30.2 ± 6.7	30.5 ± 6.9	0.48
Systolic blood pressure (mm Hg)	Mean ± SD	121 ± 19	125 ± 19	0.009
Diastolic blood pressure (mm Hg)	Mean ± SD	71 ± 11	73 ± 11	0.02
Resting heart rate (beats/min)	Mean ± SD	71 ± 10	71 ± 10	0.72
Resting respiratory rate (breaths/min)	Mean ± SD	18 ± 6	18 ± 7	0.45
Sodium (mEq/l)	Mean ± SD	139 ± 3	140 ± 3	0.03
Potassium (mEq/l)	Mean ± SD	4.4 ± 0.6	4.4 ± 0.5	1.00
Hematocrit (%)	Mean ± SD	39.3 ± 4.8	40.3 ± 5.0	0.004
Total hemoglobin (g/dl)	Mean ± SD	13.1 ± 1.7	13.3 ± 1.8	0.05
Total plasma protein (g/dl)	Mean ± SD	7.1 ± 0.7	7.1 ± 0.6	0.58
BUN (mg/dl)	Mean ± SD	25.0 ± 13.7	23.1 ± 11.3	0.04
Urea (mmol/l)	Mean ± SD	5.6 ± 2.7	6.5 ± 1.8	0.09
Serum creatinine (mg/dl)	Mean ± SD	1.4 ± 0.9	1.3 ± 0.7	0.08
NT-proBNP (pg/ml)	Mean ± SD	2,142 ± 5,290	1,576 ± 3,023	0.07
Concomitant medications	Anticoagulant agents	462 (88)	356 (82)	0.005
	Beta-blockers	490 (94)	405 (93)	0.70
	Diuretic agents	399 (76)	340 (78)	0.50
	ACE inhibitors + ARBs	436 (83)	354 (81)	0.42
	Aldosterone antagonist	196 (37)	193 (44)	0.03
	Vasoactive drugs	123 (23)	102 (23)	0.98
	Cardiac glycosides	139 (27)	107 (25)	0.48
	Antiarrhythmic medications	113 (22)	97 (22)	0.80
	Calcium-channel blockers	42 (8)	31 (7)	0.60

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

availability criteria were due to missed study visits or data uploads.

ALGORITHM VALIDATION PERFORMANCE TESTING. At the nominal alert threshold of 16, the observed sensitivity was 70%. The exact 2-sided 95% CI was 55.4% to 82.1%, which exceeded the pre-specified PG of 40%. The median time from alert onset to HFEs was 34.0 days (interquartile range: 19.0 to 66.3 days). Sixty-three percent (22 of 35) had alert onsets at least 4 weeks, 74% (26 of 35) at least 3 weeks, and 89% (31 of 35) at least 2 weeks before the corresponding HFEs. Observed UAR associated with the nominal threshold was 1.47 alerts per patient-year. A negative binomial model estimated a 2-sided 95% CI of 1.32 to 1.65, lower than the pre-specified PG of 2.0. Thus, both primary endpoints were met. At the nominal threshold, the FPR was 1.56, with a 95% CI of 1.41 to 1.77, specificity was 85.7%, and negative predictive value was 99.98%. The PPV for HF-related alerts was 11.3%. Limiting the definition to only true positive alerts resulted in a PPV of 5.6%.

The algorithm performance across a range of thresholds is plotted in **Figure 2B**. Five thresholds (14, 16, 18, 20, and 22) met the PG (sensitivity >40% and UAR <2.0). For example, at a threshold of 18, sensitivity was maintained at 70%, with a reduction in UAR to 1.22, and further increasing the threshold to 22 reduced the UAR to 0.93 while still achieving sensitivity of 60%.

Figure 4 compares the temporal profiles of the HeartLogic index in patients with usable HFEs (blue), aligned with respect to the date of HFEs (day 0), with those without HFEs (black), aligned with respect to the date of the last available HeartLogic index (day 30). Patients who had HFEs had a median HeartLogic index of 8.6 (interquartile range: 2.5 to 16.4) over a 3-month baseline period ending 90 days before the HFEs. The index increased from this baseline value, becoming statistically significant 29 days before the HFE (p < 0.05, rank sum test), and decreased toward baseline following the event. In contrast, the Heart-Logic index for those patients without HFEs was significantly lower (median 2.9; interquartile range: 0.1 to 7.7) than the baseline for patients with HFEs (p < 0.001; rank sum test) and remained stable over the entire duration.

DISCUSSION

In the MultiSENSE trial, the HeartLogic algorithm demonstrated the capability to alert clinicians before the majority of HFEs (defined as hospitalizations or outpatient visits with IV therapies with HF as the

events that happened within 45 days of device conversion, and 7 events that did not meet the data availability criteria. All events not meeting the data

FIGURE 2 Modified Receiver Operating Characteristic Curves Showing the Sensitivity Versus Unexplained Alert Rate for the HeartLogic Index
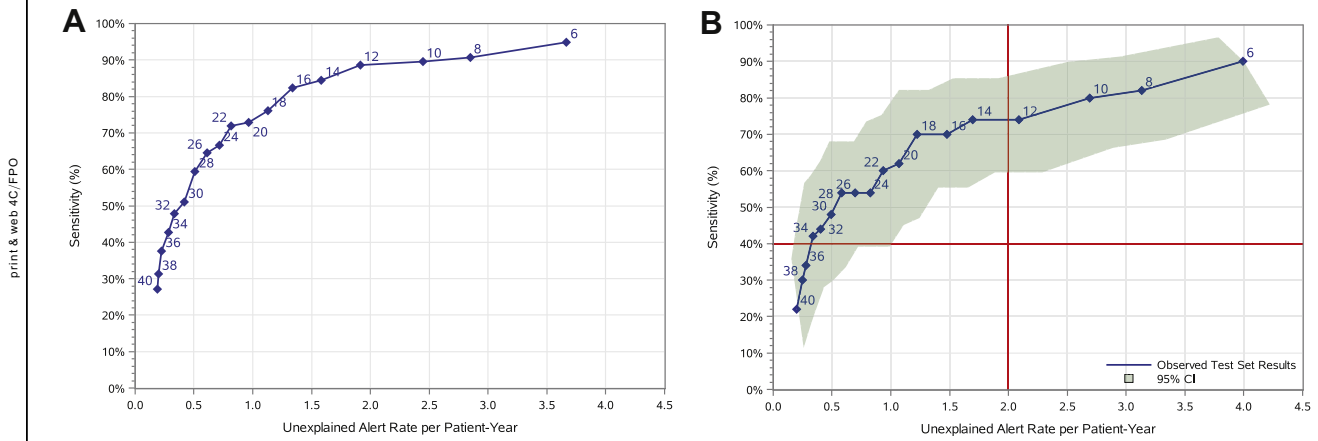
(A) Development Set. (B) Test Set. Each **point** corresponds to an alert threshold. The shaded regions represent the 95% confidence interval (CI) of the mean. The **red lines** indicate the pre-specified performance goals.

primary diagnosis). The algorithm was designed to detect gradual worsening of HF over days or weeks and had sensitivity of 70% with a median alert window of 34 days before the HFEs and a UAR of 1.47 per patient-year at the nominal threshold in the independent validation.

The prompting of clinical evaluation of patients with the HeartLogic alert is intended to identify worsening HF that otherwise would be undetected until signs or symptoms are prominent enough to warrant hospitalization or invasive treatment. Indeed, all of the HFEs that occurred in the trial were not mitigated by standard-of-care practice. This underscores the existing clinical need and opportunity for improvement. In this context, the ability to detect any event has the potential to benefit patient care.

Because a substantial number of patients with HF have implantable devices that can monitor physiological parameters, a number of studies have evaluated the merit of this type of monitoring (5). The most widely studied single parameter to date is intrathoracic impedance (4,6,8,9). In MIDHeFT (Medtronic Impedance Diagnostics in Heart Failure Trial) (4) and FAST (Fluid Accumulation Status Trial) (13), the OptiVol fluid index had sensitivity of 76% at an FPR of 1.5 to 1.9 per patient-year in small cohorts (33 and 156, respectively); however, a subsequent study (SENSE-HF [Sensitivity of the InSync Sentry OptiVol Feature for the Prediction of Heart Failure]) of 501 subjects reported sensitivity of only 20.7%,

with a PPV of 4.7% in the blinded validation phase (9). A post hoc analysis using the same sensitivity definition as this study resulted in sensitivity of 29.3% in the blinded phase (9). Similarly, the CorVue algorithm evaluated in the DEFEAT-PE (Detect Fluid Early From Intrathoracic Impedance Monitoring) study reported low sensitivity of 21.6% at an FPR of 0.9 per patient-year (10).

There have been other attempts to use implanted devices to detect worsening HF by using multiple parameters. The CLEPSYDRA (Clinical Evaluation of the Physiological Diagnosis Function in the PARA-DYM CRT Device) study evaluated the physiological diagnosis feature based on minute ventilation and activity but showed sensitivity of only 34% at an FPR of 2.4 per patient-year (11).

On the basis of these studies, we hypothesized that an algorithm combining multiple physiological sensors that evaluate different aspects of HF physiology would be superior to monitoring a single sensor. In MultiSENSE, HeartLogic had superior sensitivity of 70% at the nominal threshold. The parameters used to create the multisensor algorithm are well established, including vital signs such as heart rate and respiratory rate, indexing relative tidal volume to respiratory rate (i.e., rapid shallow breathing index or dyspnea index), a measurement of the third and first heart sounds, and activity. The fact that these parameters are objective measures of the underlying pathophysiology associated with signs and symptoms of worsening HF may have contributed to the

FIGURE 3 Event Classification in the Test Set

HFE = heart failure event; IV = intravenous.
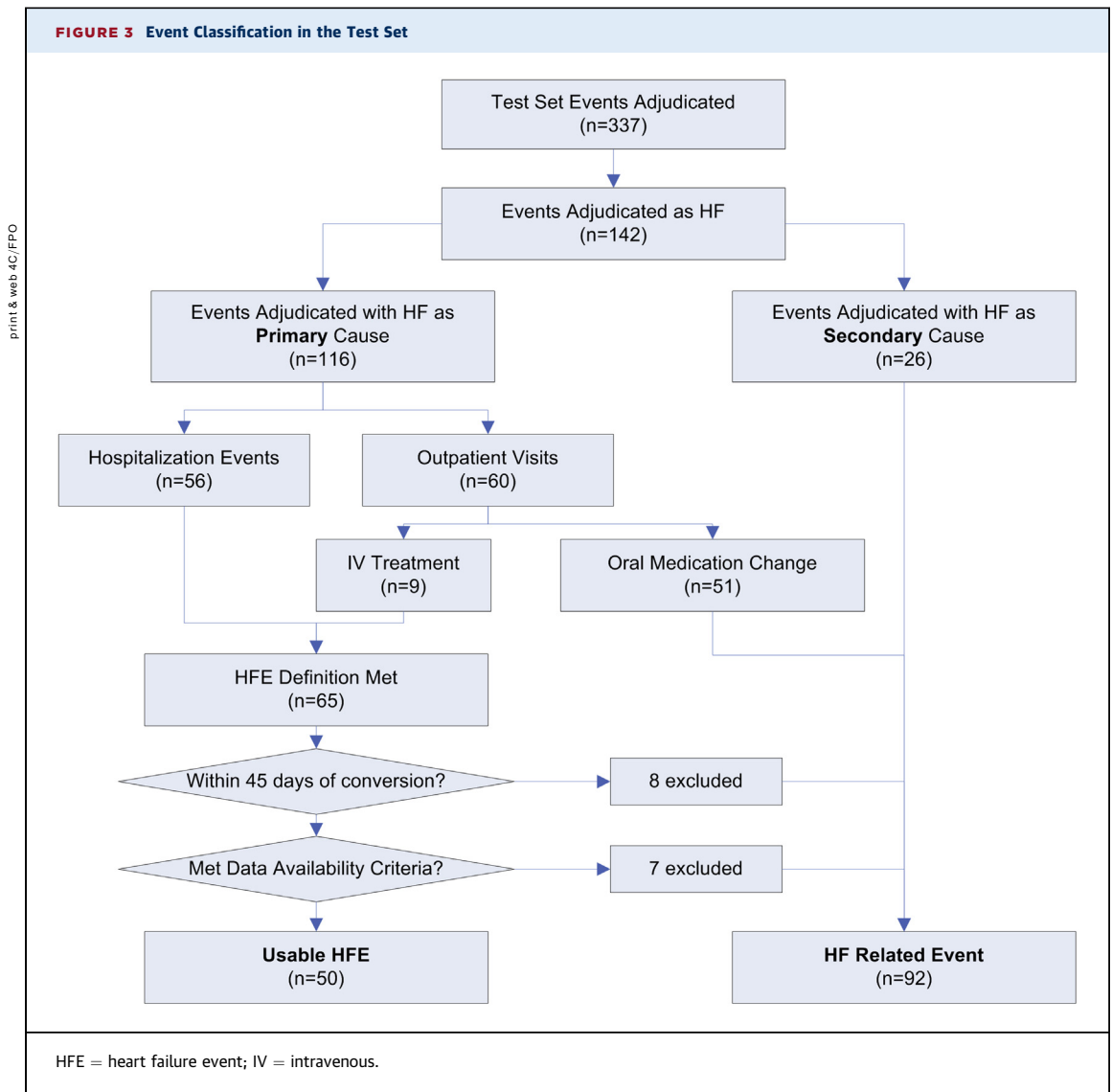
higher sensitivity observed in the independent validation.

The algorithm had a UAR of 1.47 per patient-year at the nominal threshold. We used the definition of UAR instead of the traditional FPR in assessing the alert performance because of the complex and heterogeneous nature of HF. Although HFEs were defined as hospitalization or outpatient visits with IV therapies with HF as the primary cause, patients may experience varying degrees of worsening HF that include treatment with different levels of intervention. Although clinicians in MultiSENSE were blinded to sensor and algorithm data, the patients in the study were being managed for HF following standard of care. This means that some occurrences of worsening

HF were caught by clinicians and corrective therapies were delivered (e.g., oral medication changes) that may have mitigated more severe events. Alerts that were associated with corrective HF therapy but did not meet the HFE usability criteria were considered HF-related alerts. These HF-related alerts appropriately detected the patients' HF decline and are consistent with intended algorithm behavior and use.
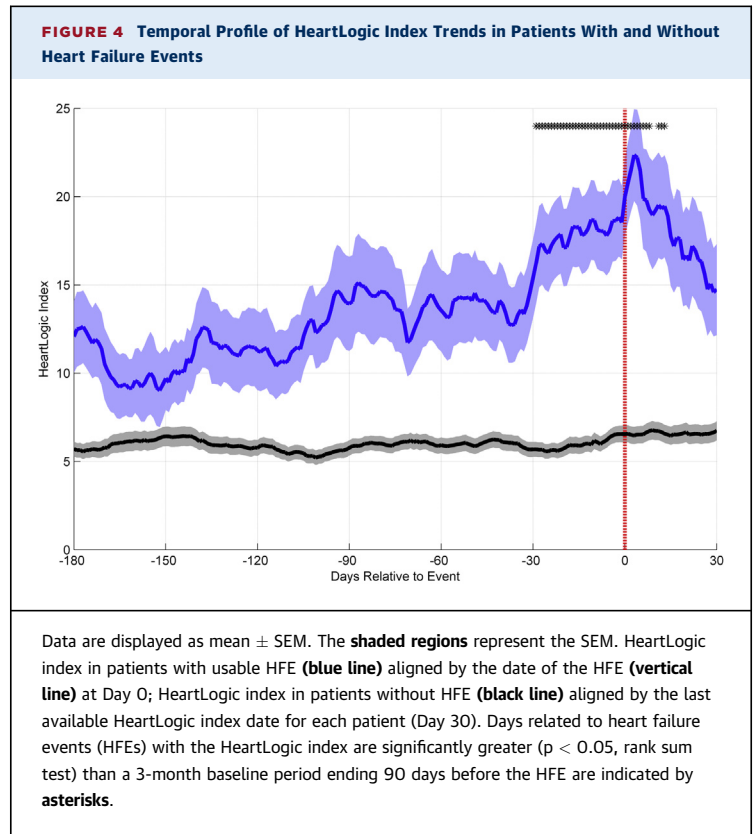
The HeartLogic algorithm alerted a median of 34 days before HFEs, providing enough time for corrective action to be taken. This is critically important, as the goal is to identify patients in order to enact treatment to prevent the event. Because of the high impact of HF on health care

expenditures and significant impact on quality of life (1), even relatively modest reductions in hospitalizations could have a significant benefit on overall disease burden. Furthermore, this benefit comes in the context of regularly used devices and does not introduce any added incremental implant or procedure risks.

The nominal threshold specified for algorithm validation represents 1 operating point intended to optimize sensitivity at a relatively low UAR, but there is wide variability in clinical perspective on what constitutes an optimal balance between sensitivity and UAR. The sensitivity and UAR performance across a range of thresholds demonstrates the potential to customize algorithm use to individual patient or clinic preferences by adjusting the alert threshold.

The PARTNERS-HF (Prospective Multicenter Observational Study in Patients Receiving Cardiac Resynchronization Therapy) study developed a combined score on the basis of available device diagnostics, including impedance-based OptiVol fluid index, duration in atrial fibrillation, patient activity, device therapy (biventricular pacing or device shocks), and abnormal autonomics (either increased heart rate or reduced heart rate variability) (14). Unlike algorithms that conduct daily evaluation for the detection of worsening HF episodes, this analysis instead risk-stratified patients into high-, medium-, and low-risk groups on the basis of monthly evaluations, demonstrating that the high-risk group had a >5-fold risk for HF hospitalization compared with the low-risk group. A Bayesian model, again developed for monthly evaluation, identified patients with a 10-fold higher risk for hospitalization when comparing the high-risk group with the low-risk group (15) but left nearly 40% monthly evaluations in the middle group.

Recent work that used pulmonary artery pressure monitoring closely coupled with medication changes to control pressures showed sustained improvement in HF hospitalizations (16-18). However, unlike implantable device diagnostics, pressure-based management requires a dedicated implant procedure and relies on patient compliance for daily measurement, as well as a support team to respond to frequent alerts. The HeartLogic index, incorporated into implanted cardiac devices, allows automated daily evaluation of a patient's HF status and early awareness of impending decompensation with high sensitivity. This, combined with the device's daily automatic remote monitoring, has the potential to provide actionable care to a patient early in the decompensation spectrum.

FIGURE 4 Temporal Profile of HeartLogic Index Trends in Patients With and Without Heart Failure Events

Data are displayed as mean ± SEM. The **shaded regions** represent the SEM. HeartLogic index in patients with usable HFE **(blue line)** aligned by the date of the HFE **(vertical line)** at Day 0; HeartLogic index in patients without HFE **(black line)** aligned by the last available HeartLogic index date for each patient (Day 30). Days related to heart failure events (HFEs) with the HeartLogic index are significantly greater (p < 0.05, rank sum test) than a 3-month baseline period ending 90 days before the HFE are indicated by **asterisks**.

STUDY LIMITATIONS. The HeartLogic alert was studied only in patients with CRT-Ds. However, the sensors used in the algorithm are independent of a left ventricular lead and could be incorporated into an implantable cardioverter-defibrillator or pacemaker.

To establish the algorithm in a timely fashion, patients were separated in the development and test set cohorts chronologically rather than in a randomized fashion. Because enrollment was not uniform at all sites and there was a protocol modification early in the study to increase enrollment, there were some modest differences in the patient populations for the development and test set cohorts. Although such a process could generate a patient selection bias, it would be more likely that such differences would diminish the test set algorithm performance (because it was generated from a dissimilar development set), so in that sense, it strengthens the validation results.

The ability of this study to both establish and test a multisensor algorithm is based on the number of events that could be evaluated. This study was limited by a 1-year follow-up. Additionally, some events were excluded because of inadequate data due

to noncompliance with the study follow-up schedule. Despite these limitations, a total of 96 events in the development set and 50 events in the test set were available, which met our established study goals.

The ultimate goal of any HF alert is to provide an opportunity to apply therapy to avoid morbid events such as HF hospitalizations. This multisensor algorithm has not been studied as a specific therapeutic approach. Further investigation is intended to determine whether managing patients to the Heart-Logic index will lead to improved outcomes. However, the performance of the alert, in terms of sensitivity to detect impending HFEs and UAR related to HFEs, is encouraging.

CONCLUSIONS

In this study, a multisensor algorithm was established using device-based sensors monitoring heart rate, heart sounds, thoracic impedance, respiration, and activity. The predictive sensitivity to HFEs was 70%, with a median early warning of 34 days before the event, balanced against an UAR of 1.47 per patient-year. Additional alert thresholds provide options for increased sensitivity or decreased UARs. Further studies will be needed to establish whether this type of HF alert can improve patient outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An algorithm for the detection of impending heart failure events was designed to mimic the analysis of a clinician by combining multiple sensors for the evaluation of different aspects of cardiac physiology. The resulting composite index and alert (HeartLogic) effectively detected 70% of worsening heart failure events a median of 34 days before the event, with a low rate of unexplained detections of <1.5 per patient-year in an independent test set.

TRANSLATIONAL OUTLOOK: When the algorithm is incorporated into implantable cardioverter-defibrillators and CRT-Ds, and linked with automatic remote monitoring, it will seamlessly evaluate a patient's heart failure status with no additional patient effort. The prolonged warning time may then allow proactive interventions and a decrease in heart failure hospitalizations. The next step is to evaluate clinical integration strategies and demonstrate whether patient management with the HeartLogic index and alert will lead to improved outcomes for patients with heart failure.

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APPENDIX For supplemental tables and a figure, please see the online version of this article.