Multiparametric Implantable Cardioverter-Defibrillator Algorithm for Heart Failure Risk Stratification and Management

An Analysis in Clinical Practice

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BACKGROUND: The HeartLogic algorithm combines multiple implantable cardioverter-defibrillator sensors to identify patients at risk of heart failure (HF) events. We sought to evaluate the risk stratification ability of this algorithm in clinical practice. We also analyzed the alert management strategies adopted in the study group and their association with the occurrence of HF events.

METHODS: The HeartLogic feature was activated in 366 implantable cardioverter-defibrillator and cardiac resynchronization therapy implantable cardioverter-defibrillator patients at 22 centers. The median follow-up was 11 months [25th–75th percentile: 6–16]. The HeartLogic algorithm calculates a daily HF index and identifies periods IN alert state on the basis of a configurable threshold.

RESULTS: The HeartLogic index crossed the threshold value 273 times (0.76 alerts/patient-year) in 150 patients. The time IN alert state was 11% of the total observation period. Patients experienced 36 HF hospitalizations, and 8 patients died of HF during the observation period. Thirty-five events were associated with the IN alert state (0.92 events/patient-year versus 0.03 events/patient-year in the OUT of alert state). The hazard ratio in the IN/OUT of alert state comparison was (hazard ratio, 24.53 [95% CI, 8.55–70.38], $P<0.001$), after adjustment for baseline clinical confounders. Alerts followed by clinical actions were associated with less HF events (hazard ratio, 0.37 [95% CI, 0.14–0.99], $P=0.047$). No differences in event rates were observed between in-office and remote alert management.

CONCLUSIONS: This multiparametric algorithm identifies patients during periods of significantly increased risk of HF events. The rate of HF events seemed lower when clinical actions were undertaken in response to alerts. Extra in-office visits did not seem to be required to effectively manage HeartLogic alerts.

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Key Words: algorithm ■ defibrillator, implantable ■ heart failure ■ hospitalization ■ risk

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WHAT IS NEW?

- The HeartLogic algorithm is able to identify patients during periods of significantly increased risk of heart failure events.
- When clinical actions are undertaken in response to alerts, the rate of heart failure events seems lower.
- The rate of alerts is low, and this would not generate a high workload at the centers in case an alert-based management strategy is adopted.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Because the time in alert state is much shorter than that of out of alert state periods, the adoption of the HeartLogic algorithm may enable an efficient use of healthcare resources for the management of patients with heart failure.
- Moreover, heart failure events seem less frequent when clinical actions are undertaken in response to alerts. Thus, we may hypothesize a positive clinical impact of a more proactive strategy in which Heart-Logic alerts are systematically followed by actions.

Nonstandard Abbreviations and Acronyms

CRT-D	cardiac resynchronization therapy defibrillator
DOT-HF	Diagnostic Outcome Trial in Heart Failure study
HF	heart failure
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
MultiSENSE	Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients

Heart failure (HF) causes a significant economic burden, morbidity, and mortality.[1] The use of implantable defibrillators (ICD) and defibrillators for resynchronization therapy (cardiac resynchronization therapy defibrillator [CRT-D)] has been demonstrated to improve the outcome of selected patients with HF and has been included in the current guidelines for the management of chronic HF.[1] Modern cardiac devices can continuously measure clinical variables, thus potentially providing early warning of changes in clinical status. Many studies have investigated the ability of ICD diagnostics to identify patients at risk of HF events, with contradictory results.[2–6] In the past decade, many studies have reported combining ICD diagnostics to better stratify and manage patients at risk of HF events,[7–9] and current guidelines suggest that ICD-based multiparameter monitoring may be considered in symptomatic patients with reduced ejection fraction, to improve clinical outcomes.[1] In the MultiSENSE study (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients),[10] a novel algorithm for HF monitoring was implemented: the HeartLogic (Boston Scientific, St. Paul, MN) index, which combines data from multiple ICD and CRT-D–based sensors. This proved to be a sensitive and timely predictor of impending HF decompensation. A subanalysis of the MultiSENSE study[11] also demonstrated the ability of the index to identify patients during periods of significantly increased risk of HF events and thus potentially better triage resources to this vulnerable patient population.

In the present study, we sought to evaluate the risk stratification ability of the algorithm in a group of patients who received HeartLogic-enabled ICDs and CRT-Ds in clinical practice. Moreover, we analyzed the management strategies adopted in the study group and their association with the occurrence of HF events.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. At 22 study centers (full list of participant centers is in the Appendix) HeartLogic was activated in all patients with HF with reduced left ventricular ejection fraction (≤35% at the time of implantation) who had received a HeartLogic-enabled ICD or CRT-D device (RESONATE family, Boston Scientific) in accordance with standard indications[1] and were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform. Patients were followed up in accordance with the standard practice of the participating centers, based on current international recommendations.[12] Clinics periodically checked the remote monitoring website for transmissions. Moreover, remote data reviews and patient phone contacts were undertaken at the time of HeartLogic alerts (when the index crossed the nominal threshold value of 16), to assess the patient's decompensation status and, if possible, to prevent further worsening. However, the study protocol did not mandate any specific intervention algorithm and physicians were free to remotely implement clinical actions (eg, drug adjustments, educational interventions), to schedule extra in-office visits when deemed necessary for additional investigations or for interventions, or to adopt an active monitoring approach. Data on the clinical events that occurred during follow-up were collected at the study centers in the framework of a prospective registry. The Institutional Review Boards approved the study, and all patients provided written informed consent for data storage and analysis.

HeartLogic Index and Heart Failure Risk Stratification

The primary objective of the study was to assess the risk of HF events in patients who received the system in clinical practice and to evaluate the performance of the HeartLogic Index for detecting follow-up periods of significantly increased HF risk. The details of the HeartLogic algorithm have been reported previously.[10] Briefly, the algorithm combines data from multiple sensors: accelerometer-based first and third heart sounds,

intrathoracic impedance, respiration rate, the 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. When the index enters into an alert state, the threshold to exit alert is automatically dropped to a recovery value (nominal value 6). The study end point consisted of all hospitalizations with a primary or secondary diagnosis of HF and requiring at least 1 overnight stay and all HF deaths. Physicians were not blinded to the HeartLogic index. In our analysis, we classified the alerts according to the management strategy adopted at the centers. We, therefore, distinguished between alerts followed or not by clinical actions, alerts that required extra in-office visits or that were managed remotely, and alerts associated or not with symptoms of HF reported by the patient during remote examination at the time of HeartLogic threshold crossing.

Statistical Analysis

Descriptive statistics are reported as means±SD for normally distributed continuous variables, or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov-Smirnov test. HeartLogic index values >16 identified periods as IN an alert state versus OUT of an alert state. HF event rates were calculated separately during IN and OUT alert states in terms of the ratio between the total count of HF hospitalizations occurring in each state and the respective patient follow-up durations and were expressed as events per patient-year. The IN and OUT of alert evaluation periods were compared in terms of time to the first HF event by means of the Andersen-Gill model, an extension of the Cox proportional hazards model that takes into account multiple evaluations in patients. To account for the correlation among evaluation periods within a patient, the robust sandwich variance estimate for the hazard ratio was applied. The model was adjusted for those baseline variables that proved to be associated with the occurrence of events on univariate analysis, that is, those displaying statistical significance ($P<0.05$). IN alert evaluation periods started when the HeartLogic index crossed the threshold, ended at the time of the first HF event, or were censored when the index decreased to below the recovery threshold (or at the end of follow-up). OUT of alert evaluation 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, ended at the time of the first HF event, or were censored when the index rose above the threshold (or at the end of follow-up). The Kaplan-Meier method was used to compute the curves of time to the first HF event. A $P<0.05$ was considered significant in all tests. All statistical analyses were performed by means of R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From December 2017 to December 2019, HeartLogic was activated in 366 patients who had received an ICD or CRT-D. Table 1 shows the baseline clinical variables

Table 1. Demographics and Baseline Clinical Parameters of the Study Population

Parameter	Total N=366
Male sex, n (%)	286 (78)
Age, y	69±11
Ischemic cause, n (%)	174 (47)
NYHA class	
Class I, n (%)	25 (7)
Class II, n (%)	197 (54)
Class III, n (%)	135 (37)
Class IV, n (%)	9 (2)
LV ejection fraction, %	31±9
AF history, n (%)	144 (39)
AF on implantation, n (%)	77 (21)
Valvular disease, n (%)	77 (21)
Coronary artery disease, n (%)	165 (45)
Diabetes, n (%)	112 (31)
COPD, n (%)	73 (20)
Chronic kidney disease, n (%)	121 (33)
Hypertension, n (%)	240 (66)
β-blocker use, n (%)	333 (91)
ACE-inhibitor/ARB/ARNI use, n (%)	288 (79)
Aldosterone antagonist use, n (%)	110 (31)
Diuretic use, n (%)	326 (89)
Antiarrhythmic use, n (%)	106 (29)
Ivabradine use, n (%)	37 (10)
CRT device, n (%)	281 (77)
Primary prevention, n (%)	337 (92)

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

of all patients in analysis. The median follow-up was 11 months [25th–75th percentile: 6–16] (a total of 361 patient-years).

HeartLogic Alerts and Heart Failure Events

The HeartLogic index crossed the threshold value 273 times (0.76 alerts/patient-year) in 150 patients (up to 6 times per patient). The IN alert state lasted a median of 42 days [25th–75th percentile: 24–61]. Overall, the time IN the alert state was 38 years (11% of the total observation period).

During the observation period, 21 patients experienced 36 HF hospitalizations requiring at least 1 overnight stay; 8 patients died of HF and 13 of other causes. The rate of hospitalizations or death due to HF was 0.12/patient-year (44 events in 27 patients). Thirty-five events were associated with the HeartLogic IN alert state (an event rate of 0.92/patient-year), whereas the remaining 9 events occurred in the OUT of alert state (a rate of 0.03/

patient-year). The median time from alert onset to HF event was 29 days [25th–75th percentile: 4–83]. Comparison of the event rates in the IN alert state with those in the OUT of alert state yielded a hazard ratio (HR) of 30.63 (95% CI, 13.04–71.95), *P*<0.001. Figure 1 shows the Kaplan-Meier plot of the time to the first HF event in the IN and OUT alert states. The results were similar (HR, 24.53 [95% CI, 8.55–70.38], *P*<0.001) when the model was adjusted for those baseline clinical variables (chronic kidney disease and history of atrial fibrillation) that had proved to be associated with the occurrence of events on univariate analysis (Table 2 and Figure 2). The Kaplan-Meier plot of the time to HF death is reported in Figure I in the Data Supplement (HR, 11.45 [95% CI, 5.55–23.60], *P*<0.001). Figure II in the Data Supplement shows the alert recovery probability curve.

Alert Management and Association With Heart Failure Events

Of the 273 reported HeartLogic alerts, 204 (75%) did not require extra in-office visits and were managed remotely. Of the 69 in-office visits, 42 (61%) were scheduled examinations previously planned within 7 days from the alert. The median number of phone contacts per alert period was 1 [25th–75th percentile: 1–2]. Symptoms of clinical deterioration of HF were reported by the patient during the first remote examination in 107 (39%) cases of alerts. The most frequent symptoms reported were worsening of dyspnea on effort or at rest in 93 (87%), fatigue in 65 (61%), and orthopnea in 22 (21%). Alert-triggered actions were reported in 117 (43%) cases. The most frequent actions taken to manage the HF condition detected by the alert were (multiple actions per alert): diuretic dosage increase in 77 (66%), other drug adjustment in 40 (34%), patient

education on therapy adherence in 7 (6%), device reprogramming in 3 (3%). On comparing the event rate measured after HeartLogic alerts that were followed by clinical actions with the rate of events that were not followed by clinical actions, the hazard ratio was HR, 0.37 (95% CI, 0.14–0.99), *P*=0.047. A possible bias in this analysis could derive from the HF events occurred early after the alert, which may not have allowed any action to be taken. To account for this bias, a time window of 7 days was considered (data are transmitted weekly IN alert state), and a landmark analysis was performed starting at day 7. The result was confirmed, with a lower rate of events associated with alerts followed by clinical actions: HR, 0.34 (95% CI, 0.12–0.96), *P*=0.047 (Figure III in the Data Supplement). No differences in event rates were noted between in-office and remote alert management. By contrast, the presence of HF symptoms at the time of HeartLogic threshold crossing was associated with a higher risk of HF events (HR, 5.23 [95% CI, 1.98–13.83], *P*<0.001). Figure 3 shows the Kaplan-Meier plots of time to the first HF event.

DISCUSSION

Main Findings

This multiparametric ICD algorithm identifies patients during periods of significantly increased risk of HF events. Its adoption may enable an efficient use of healthcare resources for the management of patients with HF because the time IN alert state (when more focus is required to mitigate any potential HF deterioration) is much shorter than that of OUT of alert state periods. Moreover, the rate of alerts is low, and this would not generate a high workload at the centers in case an alert-based management strategy was adopted. In addition,
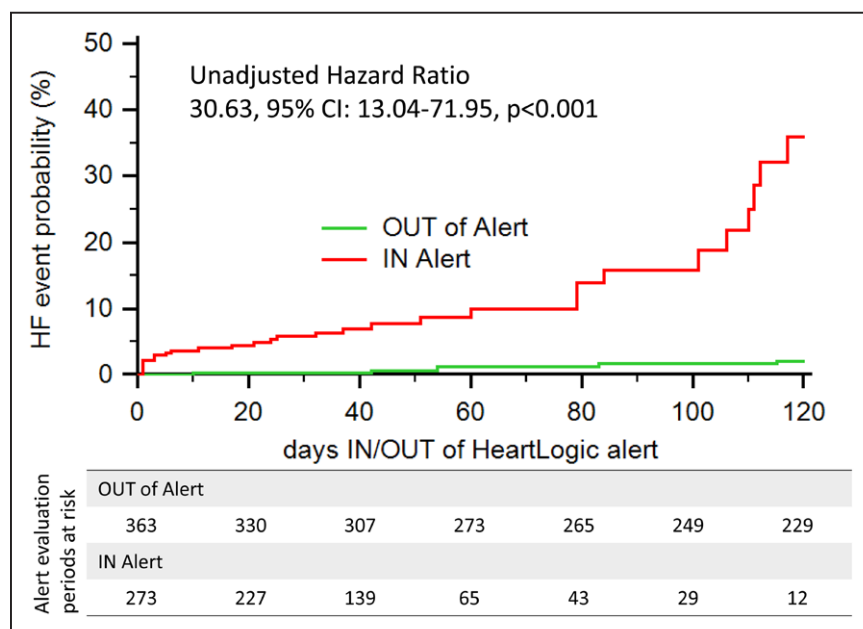

Figure 1. Kaplan-Meier curves for time to first heart failure (HF) event IN/OUT of HeartLogic alert.

Table 2.   Univariate Analysis of Variables Associated With a HF Event

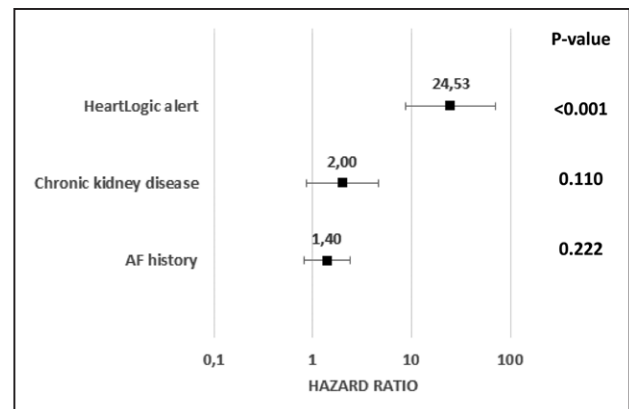|	Univariate analysis		
	Hazard ratio	95% CI	P value
Male sex	0.45	0.17–1.18	0.106
Age	1.01	0.95–1.08	0.716
NYHA class	2.80	0.96–3.38	0.067
LV ejection fraction	0.99	0.94–1.04	0.613
AF history	1.75	1.20–2.57	0.004
Coronary artery disease	1.17	0.42–3.21	0.768
Diabetes	2.12	0.72–6.26	0.172
COPD	3.07	0.94–8.56	0.066
Chronic kidney disease	3.55	1.29–9.76	0.014
Hypertension	0.81	0.30–2.21	0.685
CRT device	1.42	0.46–4.35	0.544
HeartLogic Alert	30.63	13.04–71.95	<0.001

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; LV, left ventricle; and NYHA, New York Heart Association.

when clinical actions are undertaken in response to alerts, the rate of HF events seems lower.

Comparison With Previous Studies

In this study, the rate of HF events was 24× higher when the patient was in the IN alert state than in the OUT of alert state, after correction for clinical confounders. This finding confirms the results of the subanalysis of the MultiSENSE study by Gardner et al.[11] Indeed, these authors demonstrated that dynamic assessment using HeartLogic could identify time-intervals when CRT-indicated patients were at significantly increased risk of worsening HF and that HeartLogic alerts significantly augmented the ability of baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) to stratify this risk. We extended their results to a population of patients who received either ICDs or CRT-Ds in clinical practice. In agreement with the MultiSENSE analysis, the majority of patient-days of follow-up were spent in the OUT of alert state (89%), in which the risk of an HF event was very low (0.03 events/patient-year). This potentially allows resources to be redirected from patients in their low-risk periods to more vulnerable patients in their high-risk periods.

Previous studies investigated the risk stratification ability of an alternative multiparametric HF risk score obtained by combining ICD-measured variables (intrathoracic impedance, atrial fibrillation burden, percentage of CRT, ventricular arrhythmias, night heart rate, heart rate variability, and patient activity).[7,8] The authors showed that diagnostic evaluations that yielded a risk score classified as high were 10 times more likely to be followed by HF hospitalization than evaluations with a low-risk score. More recently, Burri et al[13] found a lower value (6.3) of the relative risk of HF hospitalization.

Figure 2. Multivariate analysis.
Patients had a 24.53-fold increased risk of an heart failure event after HeartLogic alert, after adjusting for clinical variables. AF indicates atrial fibrillation.

Regarding the ability to risk-stratify patients for HF hospitalization, Gardner et al[11] demonstrated that, in the same conditions adopted in the PARTNERS HF study (Program to Assess and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure)[7] and by Cowie et al,[8] HeartLogic performed better, displaying an event rate ratio of 22 between the high- and low-risk groups; this ratio is comparable to the 24× value found in our analysis after multivariate correction.

The HeartLogic algorithm was designed to allow an alert-based follow-up strategy and to promptly detect high-risk conditions. Therefore, we measured the time to the first HF event starting from the day of the HeartLogic alert. By contrast, the algorithm tested by Cowie et al[8] is not equipped with an alert feature, and periodic evaluations are needed to assess the risk status. For this reason, their comparison of risk score groups in terms of time to the first HF event was performed after monthly diagnostic evaluations over periods of 30 days, which was identified as the period associated with the greatest ability of the algorithm to identify patients at higher risk.[7] In our analysis, the higher hazard ratio associated with the IN alert state may be ascribed to the ability of the HeartLogic algorithm to detect impending HF events beyond the 30-day window. Indeed, the median time between HeartLogic alert and HF event was 29 days in the present analysis and 34 days in the MultiSENSE study.[10] The long warning times and the high sensitivity of the algorithm observed in the validation study[10] and in subsequent clinical experience[14] are probably due to the fact that the parameters used to create the multisensor algorithm (heart rate and respiratory rate, rapid shallow breathing index, a measurement of the third and first heart sounds, and activity) are objective measures of the underlying pathophysiology associated with signs and symptoms of worsening HF.[15,16] Long warning times are also directly associated with the availability of alert-based remote transmissions, which allow events to be
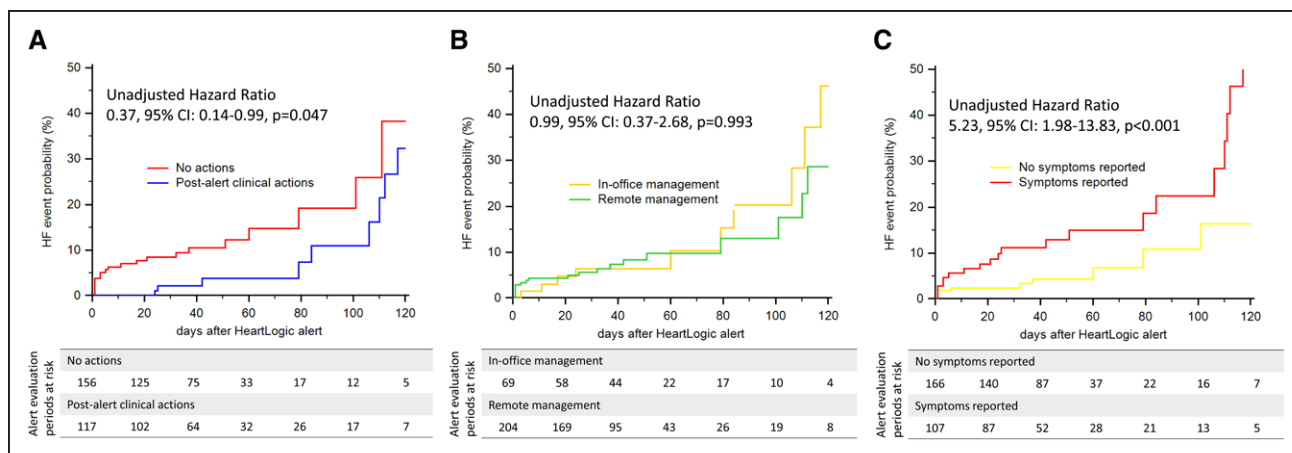
Figure 3. Kaplan-Meier curves for time to first heart failure (HF) event.
Periods are stratified by: (**A**) the implementation of clinical actions after HeartLogic alert, (**B**) the in-office or remote management strategy, (**C**) presence of symptoms reported by the patient on postalert contact.

detected about 2 weeks earlier than with scheduled remote transmissions.[17]

Unlike the MultiSENSE study, the physicians involved in our study were not blinded to the HeartLogic index, and this may have introduced a bias into the present analysis. Indeed, we cannot exclude that a proportion of hospitalizations in the IN alert state may well have been driven mainly by the alert, even in the absence of a real clinical need. This may have increased the IN/OUT event rate ratio, as in the case of the increase in HF hospitalizations seen in the DOT-HF (Diagnostic Outcome Trial in Heart Failure),[3] in which the management of patients with HF with ICD was based on intrathoracic impedance monitoring. However, our additional results do not seem to confirm this hypothesis. Indeed, we also observed a significantly different rate of the HF death component of our primary combined end point, ie, a harder end point plausibly not affected by the lack of blinding. Moreover, the rate of HF events was lower when the HeartLogic alerts prompted clinical actions. Most HF events occurred a long time after the first HeartLogic alert notification, and when no action was taken. In our opinion, it is implausible that the first action taken in the absence of a real clinical need was hospital admission for more than 1 day (the study end point). Indeed, this lower rate of HF events is more consistent with the hypothesis that events were more frequent in patients classified at higher risk of HF by the algorithm and in whom a strategy of mere active monitoring was adopted. Moreover, the lower rate of events associated with the clinical actions was also confirmed by our additional landmark analysis starting at day 7 after the alert onset. The analysis allowed to exclude those HF events (assigned to the no-action group) that were plausibly detected in a more advanced stage and that could only be managed by admitting the patient to the hospital. Overall, actions (mainly drug adjustments) were taken in less than half of the alerts. This result is similar to that reported in the first experience of the use of HeartLogic in clinical practice.[17] A previous study showed that adjusting

medications in response to elevated filling pressure values transmitted by an implanted device reduced hospitalizations more effectively than therapy guided only by clinical signs and symptoms of congestion[18] and that a greater frequency of therapeutic interventions was linked to a greater reduction in HF events.[19] Checking symptoms before any clinical action probably reduces the risk of inappropriate interventions, but it makes actions less timely. Investigations are therefore needed to evaluate the possible clinical impact of a more proactive strategy in which HeartLogic alerts are systematically followed by actions. Of course, this would require a structured protocol and a prospective controlled design, such as in the ongoing MANAGE-HF trial (Multiple Cardiac Sensors for the Management of Heart Failure; https://www.clinicaltrials.gov; Unique identifier: NCT03237858).

Other interesting results concern the method of alert management. Previous studies reported that, despite a better management of emergencies and urgent hospital accesses, remote ICD management may result in more unscheduled in-office visits.[20,21] In the present analysis, we found that the absence of an in-office visit after a HeartLogic alert did not impair the patient's outcome. Therefore, alerts may be safely managed remotely, without increasing the workload of the clinic. This, together with the possibility of relying on an alert-based remote review strategy, instead of a more burdensome scheduled remote review strategy,[17] enables a very efficient protocol of patient follow-up management to be designed.

The last finding concerns the verification of symptoms at the time of HeartLogic threshold crossing. As already observed by Santini et al,[17] the HeartLogic IN alert state is associated with HF symptoms reported by the patient. In the present analysis, we observed that the verification of symptoms at the time of HeartLogic threshold crossing was associated with a higher risk of HF events. This supports the usefulness of telephone contacts with the patient to assess the patient's status; this could be done by a triage

nurse, as suggested by current guidelines.[12,22] In this era of rapidly growing mobile health applications,[23] this result might also support the development and use of such applications for self-monitoring, disease management, and care coordination for patients with HF, to complement and possibly empower automatic multiparametric ICD algorithms.

Limitations

The main limitation of this study is its observational non-randomized design. Moreover, as mentioned above, physicians were not blinded to the HeartLogic index, and this may have introduced a bias into our analysis of the risk stratification ability of the algorithm. In addition, no predetermined actions were prescribed in response to HeartLogic alerts or to the individual subject's reported signs or symptoms. Furthermore, the relatively small number of patients enrolled in each center, together with the limited experience with the algorithm, may have influenced the patient management (eg, the propensity to carry out actions in response to alerts), affecting the results.

Conclusions

This study demonstrated the ability of the HeartLogic algorithm to identify patients during periods of significantly increased risk of HF events in a population of patients who had received ICDs or CRT-Ds in clinical practice. The rate of HF events seemed to be lower when clinical actions were undertaken in response to HeartLogic alerts than when a wait-and-see strategy was adopted. Extra in-office visits did not seem to be required to effectively manage HeartLogic alerts, whereas verification of symptoms seemed useful to better stratify patients at risk of HF events.

Affiliations

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Disclosures

M. Campari and Dr Valsecchi are employees of Boston Scientific. The other authors report no conflicts.

Supplemental Materials

Figures I–III

APPENDIX

Full list of participant centers and investigators

Policlinico Casilino, Rome, Italy: Calò L, De Ruvo E, Minati M, Tota C, Martino A. Monaldi Hospital, Naples, Italy: D'Onofrio A, Bianchi V, Tavoletta V. OO.RR. San Giovanni di Dio Ruggi d'Aragona, Salerno, Italy: Ferraioli G, Manzo M. "Giovan Battista Grassi" Hospital, Rome, Italy: Santini L, Ammirati F, Mahfouz K, Colaiaco C. Università Politecnica delle Marche, "Ospedali Riuniti," Ancona, Italy: Dello Russo A, Guerra F. Azienda Ospedaliera Universitaria Ospedali Riuniti di Trieste − Cattinara, Trieste, Italy: Carriere C, Zorzin Fantasia A. University of Bari, Policlinico di Bari, Bari, Italy: Santobuono V.E, Amato V. S. Giovanni Battista Hospital, Foligno, Italy: Andreoli C, Savarese G, Pellegrini D, Pimpinicchio L. Fondazione Poliambulanza, Brescia, Italy: La Greca C, Pecora D. Ospedale Civile Apuane, Massa, Italy: Arena G, Bartoli C, Borrello V.M, Ratti M. SS. Annunziata Hospital, Cosenza, Italy: Talarico A, De Rosa F, Quirino F, Tomaselli C. Vito Fazzi Hospital, Lecce, Italy: Pisanò E, Marino E. Azienda Ospedaliera Universitaria Senese, Policlinico Santa Maria alle Scotte, Siena, Italy: Santoro A, Baiocchi C, De Vivo O, Baccani B. Maria Vittoria Hospital, Turin, Italy: Giammaria M, Amellone C, Lucciola M.T. University of Bologna, S.Orsola-Malpighi University Hospital, Bologna, Italy: Ziacchi M, Angeletti A, Frisoni J. S. Anna e S. Sebastiano Hospital, Caserta; Italy: Viscusi M, Brignoli M. Sacro Cuore Don Calabria Hospital, Negrar (VR), Italy: Costa A. "Bianchi-Melacrino-Morelli" Hospital, Reggio Calabria, Italy: Pangallo A, Benedetto F. "Carlo Poma" Hospital, Mantova, Italy: Pepi P, Nicolis D. IRCCS Policlinico San Matteo, Pavia, Italy: Petracci B. "Spaziani" Hospital, Frosinone, Italy: Giubilato G, Carbonardi L. S. Pietro Fatebenefratelli Hospital, Rome, Italy: Porcelli D, Romani B, Zuccaro L.M.

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