Circulation: Heart Failure

EDITORIAL

The Luck of Having a Cardiac Implantable Electronic Device

See Article by Gardner et al

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Shallow men believe in luck or in circumstance.
Strong men believe in cause and effect.

—Ralph Waldo Emerson

The principle aims of the post hoc analysis by Gardner et al[1] were to use data from the MultiSENSE study (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) to further stratify the 1-year risk of heart failure events (HFE) based on different thresholds of the HeartLogic alert algorithm, compare their prognostic power to that of different NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, and assess whether the combination of algorithm and biomarker values stratified the risk of an HFE better than each measure alone.[2] To develop the HeartLogic alert algorithm, data collected from multiple device sensors were used in combination with clinical baseline and HFE data. Initial analyses evaluated the performance of each sensor parameter to predict an HFE. Heart sounds (S1 and S3), thoracic impedance, respiration, heart rate, and activity emerged as variables detectable by device sensors that are predictive of an HFE. Changes in these features from each patient's baseline were aggregated and weighted based on an individual's daily risk for worsening HF. The HeartLogic index value is updated daily, and an alert is issued when the index crosses the nominal threshold of 16. In the MultiSENSE study, this alert index predicted the occurrence of HFE with a 70% sensitivity and a median of 34-day warning.[2] The findings of the analysis by Gardner et al[1] are undoubtedly impressive. Among 900 patients (average event rate: 0.20/patient-year), 145 HFE occurred over 1 year in 88 patients with evaluable HeartLogic alert algorithm. The risk of a HFE during periods in alert status was 10-fold that occurring during periods out of alert status (0.80 versus 0.08/patient-year).[2] Substratification showed that, compared with the lowest risk group, defined as having low NT-proBNP and not in alert status, the highest risk group, identified by high NT-proBNP levels and being *in* alert status, had a 50-fold increased risk of an HFE (1.00/patient-year versus 0.02/patient-year).[2] Importantly, atrial fibrillation and ischemic HF cause decreased, but did not eliminate the predictive power of the HeartLogic alert algorithm, underscoring its value across diverse subgroups of HF patients with LVEF ≤35% and implanted with a COGNIS (Boston Scientific, St. Paul, MN) cardiac resynchronization therapy-defibrillator device.[2] In addition, although NT-proBNP levels had independent predictive power for HFE, it was significantly lower than that of the HeartLogic alert algorithm alone (event rates: 0.42 versus 0.80/patient-year). Furthermore, the risk for an HFE was greater in patients with low NT-proBNP levels but in HeartLogic alert status than in subjects with high NT-proBNP levels but out of device alert status (event rates: 0.47 versus

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0.16/patient-year).[2] These findings are reassuring, as it is neither practical nor recommended by US and European HF guidelines to serially assess biomarker levels and use them to guide therapy.[3,4]

In addition to MultiSENSE, other studies have been conducted for risk stratification of HF patients based on combinations of data obtainable from cardiac implantable electronic devices (CIEDs); see Table. It is exceedingly difficult, if not altogether impossible, to meaningfully compare the performance of the various proposed indices as predictors of impending worsening HF: device, manufacturer, analytic methods, assessed parameters, end points, frequency of evaluation, type of risk stratification, length of follow-up, and results vary significantly between studies. However, all analyses have some aspects in common: (1) the relative weight of each measure in contributing to the final risk index cannot be determined. This is important because elevated values of a given index may lead to wrong therapeutic interventions without the knowledge of which variable(s) predominantly contributed to its elevation. Let us take for example a HeartLogic index rising above the nominal value of 16 primarily because of increased respiratory rate and rapid shallow breathing. In the absence of a position sensor, it is impossible to know whether the respiratory abnormality is because of paroxysmal nocturnal dyspnea from pulmonary edema or to sleep disorder breathing, conditions which require different interventions (diuretics versus polysomnogram-guided treatment of sleep apnea); (2) the extent to which changes in therapy occurring during both development and validation phases influenced the threshold of risk is unknown because the studies neither tracked nor standardized treatment approaches in their populations; (3) all indices were developed in HF patients with reduced LVEF who met criteria for CIEDs; and (4) none of the studies have yet demonstrated whether consistent treatment protocols targeting each specific risk index result in improvement of HF outcomes.[2,5–7]

According to the 2017 American Heart Association Heart Disease and Stroke Statistics of an estimated 6.5 million Americans with symptomatic HF, 55% have HF with preserved LVEF. These patients account for 47% of >1 million annual hospital discharges for HF. The proportion of HF with preserved LVEF and their HFE rates are similar in Europe.[4,8]

According to the IMPROVE HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) among 167 cardiology practices in the United States, of patients eligible for cardiac resynchronization therapy or implantable cardioverter-defibrillator, only 38% and 49%, respectively, received the therapy.[9]

The obvious consequence of these facts is that stratification of risk for HFE based on device data cannot be accomplished in a substantial proportion of the HF population.

The advent of implantable hemodynamic sensors has greatly improved the understanding of hemodynamic congestion, the gradual transition to a decompensated HF state, identification of periods at risk for an HFE and opportunities for prevention of these events with the appropriate therapeutic interventions. The CHAMPION-HF trial (CardioMEMS [Cardio-Micro-ElectroMechanical Systems] Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure) showed that ambulatory monitoring of intracardiac pressures coupled with standardized pharmacological interventions resulted in a 39% decrease in HFE compared with standard of care over an average follow-up period of 15 months.[10] The pharmacological algorithm used in the CHAMPION-HF trial recommended use of sequential doses of diuretics and vasodilators to reduce and maintain the pulmonary artery diastolic pressure <20 mm Hg.[11] The therapeutic recommendations also pro-

Table. Studies of Heart Failure Risk Stratification Using Variables From Cardiac Implantable Electronic Devices With 1-Year Follow-Up

Study (Sample Size)	Study Type	Blinding	Variables Evaluated in Score	Frequency of Evaluation	Selected Outcomes
MultiSENSE; Boehmer et al[2] (N=500/400)	Multicenter, nonrandomized	Investigators, Events comm.	S1, S3, respiration, thoracic impedance, heart rate, activity	Daily	HFE detection; Sensitivity=70% [95% CI, 55.4–82.1]
IN-TIME; Hindricks et al[5] (N=333/331)	Multicenter, randomized	None	Arrhythmias, %CRT, PVCs, activity, abnormal ICE	Daily (working days)	CCS (Algorithm vs SOC): 61 (18.9%) vs 90 (27.2%); *P*=0.013; Deaths: 10 vs 27
7 studies Cowie et al[6] (N=921/1310)	Combined analysis	N/A	Thoracic impedance, AF burden, VRAF, VT, patient activity, heart rate, HRV, %CRT	Monthly	HFH ↓; Hazard ratio, 10.0; 95% CI, 6.4–15.7; *P*<0.001
PARTNERS HF; Whellan et al[7] (N=694)	Multicenter, observational	Events comm.	AF, ≥60 Ω Fluid Index, activity, night heart rate, HRV, device therapy	Monthly	HFH ↓; Hazard ratio, 4.8; 95% CI, 2.9–8.1; *P*<0.0001

AF indicates atrial fibrillation; CCS, clinical composite score; CI, confidence interval; comm., committee; CRT, cardiac resynchronization therapy; HF, heart failure; HFE, heart failure event; HFH, heart failure hospitalization; HRV, heart rate variability; ICE, intracardiac electrogram; IN-TIME, Implant-Based Multiparameter Telemonitoring of Patients With Heart Failure; MultiSENSE, Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients; N/A, not applicable; PARTNERS-HF, Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure; PVC, premature ventricular contractions; SOC, standard of care; VRAF, ventricular rate during atrial fibrillation; and VT, ventricular tachycardia.

vided guidance for reduction in diuretic and vasodilator doses if intracardiac filling pressures were low, to prevent hypovolemia and consequent hypotension-related increases in serum creatinine. With this approach, more than twice as many bidirectional medications changes occurred in the active monitoring group compared with controls without differences in estimated glomerular filtration rate between groups.[11] Therefore, the observed decrease in HFE because of appropriate hemodynamic management was not achieved at the expense of worsening renal function, as seen in studies lacking objective therapeutic targets that can be easily and continuously tracked.[11] The analysis of the stepped-up pharmacological algorithm and resulting changes in pulmonary artery pressures has completed the circle by linking reduction of elevated pulmonary artery pressures to reduced HFE through a more frequent adjustment of diuretics and vasodilators compared with changes triggered by clinical signs and symptoms alone. Moreover, the analysis demonstrates that specification of both the targets of therapeutic interventions and the algorithm which guides them is essential to validate any risk stratification method or novel management strategies.[11] A recent analysis from the CHAMPION-HF trial showed that pulmonary artery pressure-guided HF management also reduces mortality in patients with HF with reduced LVEF who receive guideline-directed medical therapy, further highlighting the important synergy of addressing hemodynamic and neurohormonal targets of HF therapy.[12] A separate analysis of the CHAMPION trial examined the impact of hemodynamically guided HF management in patients with LVEF ≥40%, the only prespecified subgroup of the study. After an average of 17-month randomized follow-up, patients in the active monitoring group had 50% less HFE than controls (hazard ratio, 0.50; 95% confidence interval, 0.35–0.70; $P<0.0001$). This analysis was one of the first to report a clinically successful medical management strategy in HF patients with LVEF ≥40%.[13] The favorable outcomes of the CHAMPION trial are now being replicated and expanded in the real world, as shown by recent analyses from the CardioMEMS postapproval study.[14,15]

The MultiSENSE study Investigators are correct in stating that the effective stratification of risk for HFE by the HeartLogic algorithm occurs in the context of commonly used CIEDs and does not introduce any additional risk from separate invasive procedures.[2] However, the limitations of the HeartLogic algorithm must also be recognized, including inability to stratify the risk of HF patients with LVEF ≥35% and lack of treatment protocols aimed at specific targets. The upcoming MANAGE-HF trial (Multiple Cardiac Sensors for Management of Heart Failure; URL: http://www.clinicaltrials.gov. Unique identifier: NCT03237858) may help to optimize the clinical integration of the HeartLogic algorithm, but it will not address stratification of risk for HFE in patients lacking an indication for CIEDs.

Ongoing research efforts are focused on the development of wearable devices that can detect CIED parameters such as those shown by MultiSENSE to accurately stratify the risk for HFE with enough warning to enable the timely implementation of therapies that can effectively prevent HF decompensation. Wearable devices do not require an invasive procedure and can be used in all HF patients, regardless of LVEF. As for CIED-derived risk indices, those arising from wearable devices must provide targets sufficiently specific to trigger the correct therapy.

ARTICLE INFORMATION

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