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EDITORIAL COMMENT

Easy to Predict, Difficult to Prevent*

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In this issue of *JACC: Heart Failure*, Boehmer et al. (1) present the results of the MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study. The study was a prospective registry of patients with chronic heart failure (HF) and reduced left ventricular function with an existing, appropriately implanted cardiac resynchronization therapy defibrillator (COGNIS, Boston Scientific, Natick, Massachusetts). Eligible patients had study software downloaded into their devices to collect a number of physiological parameters. Some of these parameters had been examined in previous studies (heart rate, intrathoracic impedance, and activity), whereas others were quite novel (heart sounds, respiration rate, and relative tidal volume). Using these diagnostics, the investigators and sponsor created an algorithm that combined the sensor data after an unspecified calculation and produced a single composite index number to use in predicting HF events.

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Using the first 531 patients enrolled for the development set and the second 443 patients as a validation set, the investigators identified a nominal threshold of 16 as the optimal index number to provide a sensitivity of 70% (95% confidence interval: 55.4% to 82.1%) for predicting HF events. This sensitivity exceeded the 40% sensitivity pre-specified by the investigators. It is important to note that HF events were used in the analysis only if the device data were available. Data were not always available due to storage limitations in the experimental device memory—a problem that would likely not be present in a commercial device. The algorithm also met a second endpoint threshold of fewer than 2 unexplained alerts per patient year.

Due in part to the endpoints and analysis method selected, comparisons with other studies are difficult. The authors correctly note the 20.7% sensitivity and 4.7% positive predictive value of intrathoracic impedance, a single device diagnostic, that was identified in the SENSE-HF (Sensitivity of the InSync Sentry OptiVol Feature for the Prediction of Heart Failure) study (2). However, in the SENSE-HF study, sensitivities increased to 42.0% over time, due in large part to a high HF event rate early in the study. The positive predictive value increased to 38.1% when worsening HF symptoms were included as events. In a separate analysis that combined data from multiple studies enrolling stable HF patients, the sensitivity for low- and medium-risk patients was 82.8% and for high-risk patients was 46.0% (3). This analysis included multiple device parameters and included a large development (n = 921) and validation cohort (n = 1,310).

In contrast to previous diagnostic studies, the software used in the MultiSENSE study provides limited information about specific device parameters and focuses instead on providing the composite index score (1). In previous device studies, readers could see the relative weight of individual parameters in predicting future HF events (4). The "black box" approach taken in the MultiSENSE study leads to at least potential issues with the direction of change and the rate of change (1). First, it is possible that an elevated index value could lead providers to intervene inappropriately without details of the monitored parameters available, and second, the continuous value of some individual parameters may have diagnostic significance that could impact the action of the provider. For example, the combination of a falling impedance and a rising respiration rate

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might lead to a threshold crossing and result in an appropriate increase in diuretic dose. However, a decrease in activity and an increase in heart rate reflecting dehydration might also result in a threshold crossing, leading to the same increase in diuretic dose, which would be the wrong response. The clinical utility of monitoring the continuous value of an individual parameter values was demonstrated in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, which compared monitoring of pulmonary artery pressures using an implanted sensor monitor to no monitoring. In the CHAMPION study, active monitoring resulted in a significant reduction in HF hospitalizations (5). Medication changes, primarily of diuretics and vasodilators, occurred more than twice as often in the active monitoring group (6). Both increases and decreases in medications were much more common in the active monitoring group compared with the control group. However, about one-third of all medication changes in response to pulmonary pressure changes were decreases in diuretics and vasodilators. The decreases in medications would presumably not have occurred more often in the monitored group if only a threshold value and not the continuous value for pulmonary artery pressure had been reported.

Despite the drawbacks of the current study, a multisensor approach provides the possibility of improved sensitivity for predicting HF events and may be expanded to provide other potential advantages. Just over one-third of hospital readmissions following an index HF admission are for recurrent decompensated HF—the remaining two-thirds are due to pneumonia, kidney disease, and a number of other diagnoses (7). A multisensor technology might have predictive value for other causes of readmission. For example, an increase in respiration rate and heart rate with a stable thoracic impedance might warn of a chronic obstructive pulmonary disease exacerbation.

This study is just the first step in evaluating the use of this novel algorithm as a therapeutic target. The history of device diagnostics interventions is strewn with failures. The inability to turn diagnostic data into a therapeutic response that reduces clinical events is due to a number of issues. In some cases, investigators have been unwilling to act on device data without corroborating symptoms. The COMPASS HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study did not achieve a significant change in HF-related events due in part to the lack of response from investigators to diagnostic data (8). Alternatively, when providers do intervene, their responses may not achieve the desired outcomes. In the DOT HF (Diagnostic Outcome Trial in Heart Failure) study, participants in the alert arm of the study, which evaluated impedance and other device diagnostics, had 3 times more clinic visits (250 vs. 84; $p < 0.0001$) (9). The result of device monitoring with audible alert was an actual increase in HF hospitalizations (hazard ratio 1.52; 95% confidence interval: 0.97 to 2.37; log-rank $p = 0.063$) (9).

The MultiSENSE study describes software that can be downloaded into existing cardiac resynchronization therapy defibrillator devices to provide a multisensor-derived algorithm using some standard and some novel parameters (1). The algorithm provides an index number that will alert providers of an impending HF exacerbation. The value-added proposition of monitoring multiple parameters may be in enhanced sensitivity for HF events as well as a potential to predict other common causes for readmissions. Potential limitations include the inability to evaluate the individual components of the index number as well as the lack of continuous values for some parameters that guide both increases and decreases in medical therapy. The proof of this new technology will be in demonstrating its utility in the prevention of HF events.

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