A Multi-sensor Algorithm Predicts Heart Failure Events in Patients with Implanted Devices

Results from the MultiSENSE Study

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on behalf of the MultiSENSE investigators
Goal: Develop an alert algorithm for the early notification of worsening heart failure by combining information from a diverse set of implanted sensors chosen to target the different aspects of heart failure pathophysiology associated with common signs and symptoms of worsening heart failure.

Heart Failure Monitoring Solution

**Heart Sounds**
Signs of elevated filling pressure (S3)

**Thoracic Impedance**
Fluid accumulation and pulmonary edema

**Respiration**
Rapid breathing and reduced tidal volume – shortness of breath

**Heart Rate**
Indicator of cardiac status

**Activity**
Global patient status and fatigue
MultiSENSE Trial Design

- International, multi-center, non-randomized, clinical study designed to
  1) develop and
  2) prospectively evaluate
  a multi-sensor index and alert for the early detection of worsening heart failure

Key inclusion criteria
- Age 18 or above
- Currently implanted with a COGNIS CRT-D system
- NYHA Class II, III or IV within the last 6 months

Key exclusion criteria
- Documented as pacemaker dependent
- A history of appropriate tachycardia therapy within 1 week prior to enrollment
- Likely to undergo lead or PG revision
- Subjects that have received a heart or lung transplant
- Receiving mechanical circulatory transplant
- A life expectancy of less than 12 months
MultiSENSE Study Design

• *Investigational software* was downloaded into cardiac resynchronization defibrillator devices (CRT-D) to enable high resolution data collection.

• Treating clinicians, investigators and clinical event committee members were *blinded* to the investigational sensor data.

• The study data were chronologically allocated into a:
  
  **Development Set**
  
  Used to develop the composite index and alert algorithm
  
  **Test Set**
  
  *Sequestered* and used for independent validation of algorithm performance.
### Event and Alert Classification

**Independent clinical events committee (CEC) Adjudication:**

| Heart Failure Events (HFE) | **Primary** cause of event was worsening heart failure and  
|                           | • is *admitted* for HF and receives an augmented HF regimen with  
|                           | oral or intravenous medications, or  
|                           | • receives unscheduled *intravenous* decongestive therapy that  
|                           | does not involve formal in-patient hospital admission,  
|                           | regardless of the setting |
| True Positive Alerts      | • Onset before a usable HFEs  
|                           | • Recovery no earlier than *30 days* before usable HFEs |
| HF Related Alerts         | • Same onset and recovery window but *broader set of HF events*:  
|                           |   o hospitalizations with a *secondary* cause of HF,  
|                           |   o outpatient visits with a primary cause of HF and  
|                           |   augmented *oral* medication changes,  
|                           |   o HFEs that did not meet sensor *data availability* criteria or  
|                           |   occurred within 45 days of device conversion |
| Unexplained Alerts        | • All other alerts |
Predefined Endpoints

Endpoint 1: Sensitivity for detecting usable heart failure events >40%.
- An exact two-sided 95% confidence interval (CI) for the sensitivity calculated based on the binomial distribution and the lower bound tested against a performance goal of 40%.

Endpoint 2: Unexplained alert rate (UAR) per patient year <2.0
- A two-sided 95% CI for the unexplained alert rate calculated based on the negative binomial distribution and the upper bound tested against the performance goal of 2.0.
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Measurement</th>
<th>Develop. (N=531)</th>
<th>Test (N=443)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Implant (years)</td>
<td>Mean ± SD</td>
<td>66.3 ± 10.9</td>
<td>66.8 ± 10.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Gender [N (%)]</td>
<td>Male</td>
<td>387 (73)</td>
<td>314 (71)</td>
<td>0.50</td>
</tr>
<tr>
<td>Race [N (%)]</td>
<td>White, Not Of Hispanic Origin</td>
<td>367 (75)</td>
<td>285 (79)</td>
<td>0.31</td>
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<tr>
<td>United States [N (%)]</td>
<td>Yes</td>
<td>491 (92)</td>
<td>362 (82%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Body Mass Index (kg/m2)</td>
<td>Mean ± SD</td>
<td>30.2 ± 6.7</td>
<td>30.5 ± 6.9</td>
<td>0.48</td>
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<tr>
<td>Renal Disease [N (%)]</td>
<td>Yes</td>
<td>143 (27)</td>
<td>101 (23)</td>
<td>0.13</td>
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<tr>
<td>Ischemic Etiology [N (%)]</td>
<td>Yes</td>
<td>277 (52)</td>
<td>217 (49)</td>
<td>0.31</td>
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<tr>
<td>NYHA Class [%]</td>
<td>I / II / III / IV</td>
<td>5 / 64 / 27 / 0</td>
<td>4 / 64 / 25 / 1</td>
<td>0.30</td>
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<tr>
<td>LVEF (%)</td>
<td>Mean ± SD</td>
<td>29.3 ± 11.5</td>
<td>29.7 ± 11.4</td>
<td>0.63</td>
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<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>Mean ± SD</td>
<td>121 ± 19</td>
<td>125 ± 19</td>
<td>0.009</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>Mean ± SD</td>
<td>71 ± 11</td>
<td>73 ± 11</td>
<td>0.02</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>Mean ± SD</td>
<td>2142 ± 5290</td>
<td>1576 ± 3023</td>
<td>0.07</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>Mean ± SD</td>
<td>139 ± 3</td>
<td>140 ± 3</td>
<td>0.03</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Mean ± SD</td>
<td>39.3 ± 4.8</td>
<td>40.3 ± 5.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>Mean ± SD</td>
<td>1.4 ± 0.9</td>
<td>1.3 ± 0.7</td>
<td>0.08</td>
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<tr>
<td>Concomitant Medications [N (%)]</td>
<td>Ace-Inhibitors/ARBs</td>
<td>436 (83)</td>
<td>354 (81)</td>
<td>0.42</td>
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<td></td>
<td>Beta Blockers</td>
<td>490 (94)</td>
<td>405 (93)</td>
<td>0.70</td>
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<td></td>
<td>Diuretics</td>
<td>399 (76)</td>
<td>340 (78)</td>
<td>0.50</td>
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<tr>
<td></td>
<td>Anticoagulants</td>
<td>462 (88)</td>
<td>356 (82)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Alert Development

- Development data set:
  - 500 patients with SRD-1 Conversion
  - Median Follow-up time 324 days
  - 64 patients (12.8%) with heart failure events (HFE)
  - 127 total HFEs
- Sensor feature trends assessed for meaningful associations with HFE

**Composite index (HeartLogic™)**
- Accelerometer-based first and third heart sounds,
- thoracic impedance,
- respiration rate,
- a ratio of respiration rate to tidal volume,
- heart rate,
- patient activity

![Graph showing sensitivity and alert threshold](image)
Primary Endpoints

Sensitivity = 70% [55.4 - 82.1%]

Unexplained Alert Rate = 1.47 [1.32-1.65]

FPR = 1.56 [1.41-1.77]
HeartLogic Index Trends

Median Time from Alert Onset to HFEs was 34 days

![Graph showing trends in HeartLogic Index over days relative to event. The graph illustrates the median time from alert onset to heart failure events, with a peak around day 30.](image)

- **Index Leading to Heart Failure Event, Mean ± SEM**
- **Non-Event Patient Index, Mean ± SEM**
- **Event day or last available index date**

* p<0.05; rank sum test; days -180 to -90
Limitations

- Further studies will be needed to establish whether this type of heart failure alert can improve patient outcomes.

- The HeartLogic alert was studied only in patients who have a CRT-D indication and implant.

- Patients were enrolled in the Development and Test Set cohorts sequentially rather than in a randomized format.

- This study was limited by a 1 year duration of follow-up.

- Some events were excluded because of inadequate data (due to non-compliance with study related data collection).
Conclusion

- A multi-sensor index and alert algorithm was established

- Alert performance was validated in an independent patient data set.

- Pre-specified performance goals were exceeded:
  - Sensitivity = 70%
  - UAR = 1.47 alerts / patient-year

- The multi-sensor algorithm provides a timely alert predicting impending HF decompensation.
  - Median time to alert = 34 days
  - Additional alert thresholds provide options for increased sensitivity or decreased unexplained alert rates.
Thank you on behalf of MultiSENSE investigators

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