Multisensor system as guide for the management of patients with heart failure

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- Ancona

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Disclosure

• Speaker fee: Bayer, Biotronik, Boheringer,Boston Scientific,LivaNova,Mayland, Medtronic, Menarini, Pfizer

• Research grant: LivaNova,Susan Komen inst.
Heart Failure is a growing concern due to poor patient prognosis and economic burden

**Patient Quality of Life**
- Heart failure limits length of life and profoundly impacts function and quality of life\(^1\)
- In MADIT-CRT, an initial HF hospitalization was associated with
  - 8-fold increase in mortality
  - 9-fold increase in recurrent hospitalizations\(^2\)

**Healthcare Economics**
- HF is the #1 DRG in the US with >1.1M hospitalizations annually and total HF spend to reach nearly $100B by 2030\(^3\)
- US Hospitals lose $2K on average per admission\(^4\)
- **HF Consumes** ~2.5% of the total European healthcare budget\(^5\)

Nearly 60% of spend on hospitalization\(^3\)

Figure adapted from Goodlin\(^1\)

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4. MedPar 2013, MS-DRG 291, 292, 293
5. SHAPE Survey Results to the General Public, ESC in Vienna, Sept 2003
Among 1 year survivors after index EFFECT-HF discharge, the number of heart failure hospitalizations in the preceding year stratified the risk of death in crude analysis.¹

KP cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.²

Studies show each admission decreases a patient’s chance of survival.

CRT Device Therapy

Right Therapy at the Right Time

- Early intervention reduced death and heart failure (HF) events by 57% compared to ICD*. This was driven by:
  - 35% relative risk reduction of all-cause mortality &
  - 63% relative risk reduction of HF event
- Heart failure events could have been inpatient or outpatient care, but 82% of HF events were in-hospital admissions
- Early CRT intervention reduces the relative risk of recurrent heart failure events by 43% (p=0.001) in high risk NYHA Class I and II pts with LBBB.


*Left bundle branch block (LBBB) was not an inclusion parameter for the MADIT-CRT trial. However, a significant interaction between treatment and bundle branch block morphology was detected. Further analyses revealed that LBBB is an objective discriminator of patient benefit from CRT-D regardless of other baseline characteristics.
One-third of patients do not experience the full benefit of CRT.$^{1-6}$

<table>
<thead>
<tr>
<th>Study/Device</th>
<th>% Improved Clinical Composite Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE$^1$</td>
<td>67%</td>
</tr>
<tr>
<td>MIRACLE ICD$^2$</td>
<td>52%</td>
</tr>
<tr>
<td>MIRACLE II ICD$^3$</td>
<td>58%</td>
</tr>
<tr>
<td>InSync III Marquis$^4$</td>
<td>67%</td>
</tr>
<tr>
<td>PROSPECT$^5$</td>
<td>69%</td>
</tr>
<tr>
<td>FREEDOM$^6$</td>
<td>67%</td>
</tr>
</tbody>
</table>

*AV optimised only

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CURRENT HF MANAGEMENT IS INADEQUATE FOR IDENTIFYING AND MANAGING CONGESTION LEADING TO DECOMPENSATION

Identifying congestion early will lead to early treatment, prevent hospitalizations and slow the progression of HF.

- 90% of HF hospitalizations present with symptoms of pulmonary congestion.¹,²
- Post-hoc analysis of 463 acute decompensated HF patients from DOSE-HF and CARRESS-HF trials showed:
  - 40% of patients are discharged with moderate to severe congestion.³
  - Of patients decongested at discharge, 41% had severe or partial re-congestion by 60 days.³

Congestion state at discharge

- Absent or mild congestion
- Moderate to severe congestion

Congestion state of patients discharged without congestion at 60-day follow-up³

- Maintained decongestion
- Partial recongestion
- Relapse to severe congestion

INCREASES IN FILLING PRESSURE START THE CYCLE OF WORSENING HEART FAILURE SYNDROMES

- Pulmonary Artery Pressure

<table>
<thead>
<tr>
<th>Left Heart Failure</th>
<th>Right Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Left Atrial Pressure</td>
<td>↓ Cardiac Output</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>Confusion</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Jaski BE, “Basics of Heart Failure A Problem Solving Approach”
Data from clinical evaluations has poor sensitivity and predictive value in determining hemodynamic profile

Capomolla, 2005. N = 366

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate of</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP</td>
<td>RAP</td>
<td>48</td>
<td>78</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td>10</td>
<td>94</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Pulse Press</td>
<td>Cardiac Index</td>
<td>27</td>
<td>69</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>S3</td>
<td>PCWP</td>
<td>36</td>
<td>81</td>
<td>69</td>
<td>54</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>50</td>
<td>73</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>Rales</td>
<td></td>
<td>13</td>
<td>90</td>
<td>60</td>
<td>48</td>
</tr>
</tbody>
</table>

Table adapted from Capomolla S, et al. Eur J Heart Failure, 2005.
TIM-HF TRIAL: TELEMONITORING OF WEIGHT AND BLOOD PRESSURE DO NOT REDUCE READMISSION OR MORTALITY

- Randomized study of 710 patients
- Primary Endpoint: Total Mortality
- Control Group: Standard-of-care (no telemonitoring)
- Treatment Group: Telemonitoring of weight and BP information
- Results: No difference in all-cause death or HF hospitalizations

<table>
<thead>
<tr>
<th>End Point</th>
<th>Telemonitoring n = 354 (%)</th>
<th>Usual care n = 356 (%)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>15.3</td>
<td>15.4</td>
<td>0.97 (0.67-1.41)</td>
<td>0.87</td>
</tr>
<tr>
<td>Cardiovascular-related mortality</td>
<td>11.3</td>
<td>12.9</td>
<td>0.86 (0.56-1.31)</td>
<td>0.49</td>
</tr>
<tr>
<td>All-cause readmission</td>
<td>54.2</td>
<td>50.3</td>
<td>1.12 (0.91-1.37)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Koehler F et al, Circulation 2011
IS THERE VALUE IN FREQUENT MONITORING OF WEIGHT, SYMPTOM AND BP TO MONITOR DECOMPENSATION?

Frequent monitoring of weight, symptoms, BP has mixed results in reducing mortality and hospitalization.

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Mean age</th>
<th>Type of interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg 2002 (WHARF)¹</td>
<td>280/280</td>
<td>59</td>
<td>Wt. and symptoms</td>
<td>Significant reduction in mortality with no difference in readmission rates</td>
</tr>
<tr>
<td>Bondmass 2001¹</td>
<td>164/164</td>
<td>61</td>
<td>Wt., BP, HR and oxygen saturation</td>
<td>Fewer HF readmissions with reduced length of stay compared to nurse visit group</td>
</tr>
<tr>
<td>Gattis 1999 (PHARM study)²</td>
<td>181</td>
<td>67</td>
<td>symptoms</td>
<td>Significant reduction in mortality</td>
</tr>
<tr>
<td>Rainville 1999²</td>
<td>34</td>
<td>70</td>
<td>symptoms</td>
<td>Significant reduction in hospitalization</td>
</tr>
<tr>
<td>Massie 2001¹</td>
<td>147/147</td>
<td>69</td>
<td>Wt., vital signs and symptoms</td>
<td>No significant difference in outcome</td>
</tr>
<tr>
<td>Cleland 2005 (TEN-HMS)²</td>
<td>426</td>
<td>67</td>
<td>Wt., BP, symptoms, ECG</td>
<td>No difference in hospitalization, significant difference in mortality</td>
</tr>
<tr>
<td>Barth 2001²</td>
<td>34</td>
<td>75</td>
<td>symptoms</td>
<td>No difference in hospitalization</td>
</tr>
<tr>
<td>Riegel 2002²</td>
<td>358</td>
<td>74</td>
<td>symptoms</td>
<td>No difference in hospitalization</td>
</tr>
<tr>
<td>Laramee 2003²</td>
<td>287</td>
<td>71</td>
<td>symptoms</td>
<td>No difference in hospitalization</td>
</tr>
<tr>
<td>De Busk 2004²</td>
<td>462</td>
<td>72</td>
<td>symptoms</td>
<td>No difference in hospitalization</td>
</tr>
<tr>
<td>Tsuyuke 2004²</td>
<td>276</td>
<td>72</td>
<td>symptoms</td>
<td>No difference in hospitalization</td>
</tr>
<tr>
<td>Riegel 2006²</td>
<td>134</td>
<td>72</td>
<td>symptoms</td>
<td>No difference in hospitalization</td>
</tr>
</tbody>
</table>

Boston Scientific sensors enable the early detection of heart failure decompensation symptoms

Sensors are intended to represent typical in-office tests and questions

<table>
<thead>
<tr>
<th>Our Sensors:</th>
<th>What Clinicians ask/do during a physical exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Sounds</td>
<td>Listen to the heart S3 heart sound</td>
</tr>
<tr>
<td>Heart Sounds</td>
<td>Listen to the heart for S1 heart sound</td>
</tr>
<tr>
<td>Thoracic Impedance</td>
<td>Take chest X-ray for signs of pulmonary edema</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>“Are you out of breath? Have difficulty breathing?”</td>
</tr>
<tr>
<td>Activity Level</td>
<td>“Are you able to get your mail/go upstairs?”</td>
</tr>
<tr>
<td>Weight</td>
<td>“Have you gained weight?” (check leg or abdominal swelling)</td>
</tr>
<tr>
<td>Night Heart Rate</td>
<td>Is resting heart rate elevated?</td>
</tr>
</tbody>
</table>

KEY:
- New to Resonate Platform
- Unique to BSC
Thoracic Impedance

Thoracic impedance
- is a measure of lung resistance between RV coil and Pulse Generator
- correlates with pulmonary capillary wedge pressure
- decreases with thoracic congestion.


Thoracic impedance may decrease prior to a heart failure decompensation.
Monitoring intrathoracic impedance (OptiVol™ algorithm, Medtronic) with an audible alert did not improve mortality and increased HF hospitalizations.

Diagnostic: Heart Sound

• Evaluation of device measured Heart Sounds in patients with versus without Heart Failure Events.¹
  – *Device-based S3 was significantly louder in patients with heart failure events.*
  – *Auscultated S3 heart sounds were mostly absent, and were no different between patient groups.*

Heart sounds are measured from the accelerometer and reveal signs of elevated filling pressure and weakened ventricular contraction via S3 and S1 heart sounds.

Worsening heart failure may be associated with an increase in S3 or a decrease in S1, or both.
## Diagnostic: Heart Sound

Device-based S3 heart sounds were strongly correlated with echo parameters in CRT-D patients.¹

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low S3</th>
<th>High S3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (cm)</td>
<td>5.57</td>
<td>6.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>134.8</td>
<td>182.6</td>
<td>0.005</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>4.35</td>
<td>5.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>83.5</td>
<td>134.6</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>41.5</td>
<td>28.4</td>
<td>0.004</td>
</tr>
<tr>
<td>LAEDV (mL)</td>
<td>72.1</td>
<td>101.1</td>
<td>0.006</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>62.8</td>
<td>89.0</td>
<td>0.006</td>
</tr>
<tr>
<td>EDT (ms)</td>
<td>279.5</td>
<td>193.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDR (m/s²)</td>
<td>2.63</td>
<td>5.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.89</td>
<td>1.49</td>
<td>0.020</td>
</tr>
<tr>
<td>E/E’ septal ratio</td>
<td>13.2</td>
<td>19.4</td>
<td>0.003</td>
</tr>
<tr>
<td>E’ septal (cm/s)</td>
<td>5.31</td>
<td>4.29</td>
<td>0.162</td>
</tr>
</tbody>
</table>

¹Klodas M et al. S3 Amplitude Measured Using A CRT-D Is Correlated To Echocardiographic Filling Parameters In Heart Failure Patients J Card Fail 2013; 19 (8Suppl); S67.
Multisensor Algorithm

- Diagnostics in ICDs and CRT-Ds with associated remote monitoring systems may provide an opportunity to better identify worsening status, but technology to date has used single sensors with high false-detection rates or required manual review of multiple measures, limiting utility and adoption.¹

- New approach seeks to use new device sensors to emulate what physicians do in their clinical assessment - evaluate multiple signs and symptoms² and utilize multiple diagnostics in ambulatory evaluation.

New + existing biometric sensors in ICD and CRT-D

Automatically evaluate signs & symptoms of Heart Failure

- Elevated filling pressure
- Tachypnea
- Dyspnea on exertion
- Dyspnea at rest
- Fluid accumulation and Pulmonary edema
- Orthopnea or Paroxysmal Nocturnal Dyspnea
- Atrial fibrillation
- Tachycardia

Automated, ambulatory heart failure status indicator available remotely or in-clinic

1 Conraads VM et al., Eur Heart J, 2011:32(18),2266-73.
2 Heart Failure Practice Guideline, Journal of Cardiac Failure, 2010:16(6),e137
MultiSENSE Clinical Trial

International multi-center, non-randomized, feasibility study to collect chronic ambulatory data simultaneously from multiple sensors in implantable devices in order to develop algorithms for the early detection of worsening HF

Enrollment and follow-ups complete as of Jan 2015

900 Patients with market-released devices converted for research and followed for approximately 1 year
Primary Results from the MultiSENSE Study

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

- International, multi-center, non-randomized, clinical study designed to develop and prospectively evaluate a multi-sensor index and alert for the early detection of worsening heart failure
- New sensors created with enhanced components and novel data collection and processing techniques

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
- History of appropriate Tachy therapy 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

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:
- hospitalizations with a **secondary** cause of HF,
- outpatient visits with a primary cause of HF and augmented **oral** medication changes,
- HFEs that did not meet sensor **data availability** criteria or occurred within 45 days of device conversion

**Unexplained Alerts**

- All other alerts

Boehmer, J et al., JACC-HF, 2017;5(3),2 1 6 – 2 5
Multisense study

Combined into a single, simple index with alert

.png

Issues alert when index crosses threshold

Physician programmable threshold

Creates a high performing composite indicator for detecting worsening of heart failure using multiple physiologic measurements
Primary Results from the MultiSENSE Study

• Endpoint 1: **Sensitivity** for detecting usable heart failure events >40%
• Endpoint 2: **Unexplained alert rate** (UAR) per patient year <2.0

• **HeartLogic threshold** is configurable to user’s preference for sensitivity and specificity
• By increasing sensitivity the UAR decreases

Boehmer, J et al., JACC-HF, 2017;5(3),2 1 6 – 2 5
Primary Results from the MultiSENSE Study

Data was used to develop individual physiologic sensor trends and a multi-sensor composite alert for worsening heart failure

Development Group
500 patients
Used to develop the algorithm

Test Group
400 patients
Used to prospectively validate algorithm

Enrolled (n=974)

Allocated to Development Group (n=531)
- Withdrawn before conversion visit (n=28)
- Died before conversion visit (n=0)
- Withdrawn at conversion visit (n=3)

SRD Conversion (n=500)
- Died (n=24)
- Withdrawn – Explanted / OOS (n=7)
- Withdrawn – Other (n=1)

SRD Reconversion (n=488)

Allocated to Test Group (n=443)
- Withdrawn before conversion visit (n=38)
- Died before conversion visit (n=1)
- Withdrawn at conversion visit (n=4)

SRD Conversion (n=400)
- Died (n=12)
- Withdrawn – Explanted / OOS (n=3)
- Withdrawn – Other (n=0)

SRD Reconversion (n=385)

## 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>
</tr>
<tr>
<td>United States [N (%)]</td>
<td>Yes</td>
<td>491 (92)</td>
<td>362 (82%)</td>
<td>&lt;0.0001</td>
</tr>
<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>
</tr>
<tr>
<td>Renal Disease [N (%)]</td>
<td>Yes</td>
<td>143 (27)</td>
<td>101 (23)</td>
<td>0.13</td>
</tr>
<tr>
<td>Ischemic Etiology [N (%)]</td>
<td>Yes</td>
<td>277 (52)</td>
<td>217 (49)</td>
<td>0.31</td>
</tr>
<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>
</tr>
<tr>
<td>LVEF (%)</td>
<td>Mean ± SD</td>
<td>29.3 ± 11.5</td>
<td>29.7 ± 11.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>Mean ± SD</td>
<td>121 ± 19</td>
<td>125 ± 19</td>
<td>0.009</td>
</tr>
<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>
</tr>
<tr>
<td>Concomitant Medications [N (%)]</td>
<td>Ace-</td>
<td>436 (83)</td>
<td>354 (81)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Inhibitors/ARBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beta Blockers</td>
<td>490 (94)</td>
<td>405 (93)</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>399 (76)</td>
<td>340 (78)</td>
<td>0.50</td>
</tr>
<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

*HeartLogic™ is pending FDA Approval.*
Why a Multisensor Approach: Two observed cases

**Patient A**

**Patient B**

Which patient had the Heart Failure Admission?

---

**Thoracic Impedance (RV-Can)**
Why a Multisensor Approach: Two observed cases

**Patient A**
(True Positive)

Multisensor changes before a HF Admission

**Patient B**
(False Positive)

Impedance change only with NO event

---

Goal for multisensor data to be combined into a single alert
MultiSENSE Study Results

HeartLogic™ Composite Index calculated daily using:
- First and third heart sounds
- Thoracic impedance
- Respiration rate
- Ratio of respiration rate to tidal volume
- Heart rate
- Patient activity

HeartLogic Index of 16 selected as nominal threshold
- Higher threshold reduces sensitivity
- Lower threshold increases unexplained alerts

Average HeartLogic Index Trend in MultiSENSE Study for Patients with and without Heart Failure Events

Patients with HFE
- * Beginning 29 days pre-event the HeartLogic Index was higher (p<0.05) than baseline average (-180 to -90 days) [1]

Patients without HFE


MultiSENSE Primary Endpoint

At threshold of 16 both endpoints met:
- Sensitivity 70% [55.4 - 82.1%]
- Unexplained Alert Rate 1.47 [1.32 - 1.65]
Median time from alert to Heart Failure Event was 34 days.

Endpoints also met at thresholds 14, 18, 20, 22

Performance of HeartLogic Index at Multiple Thresholds

Primary Endpoints Met
Sensitivity = 70% [55.4 - 82.1%]
Unexplained Alert Rate = 1.47 [1.32-1.65]
Median Time to HFEs – 34 days
FPR = 1.56 [1.41-1.77]

No comparison to other technologies!


Event Rate Ratio Presented as a LBCT at ESC-HF 2017

- At nominal HeartLogic Threshold = 16
  - HF Event Rate was 10X higher in the IN Alert State than OUT of Alert State
- 17% of patient-days IN Alert State
- HeartLogic was a better prognosticator than a baseline NT-proBNP.

NOTE: Event rate ratio calculation
HeartLogic alert used in combination with an intermittent measure of NT-proBNP, enable clinicians to identify high risk patients of HF decompensation in a timely manner.

Event Rate Ratio compared to lowest risk group:
- LOW NT-proBNP, IN HL alert: 23.5
- HIGH NT-proBNP, OUT HL alert: 8.0
- HIGH NT-proBNP, IN HL alert: 50.0

NOTE: Event rate cut off
Limitations

• 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).

*HeartLogic™ is pending FDA Approval
### Background

**Background:** The MultiSENSE study followed 900 heart failure (HF) patients with a CRT device for up to 1 year. Episodes of HF decompensations were collected and adjudicated as worsening HF events (HFE) by a panel of clinicians. Devices collected daily duration in atrial tachyarrhythmia (AADur) as time above atrial tachyarrhythmia trigger rate.

AADur is a quantitative measure of how much atrial arrhythmia has been present in a patient. It has been hypothesized that HF decompensation is related to atrial arrhythmia.

### Objective

**Objective:** We examined the relationship of AADur to HFE.

### Methods

**Methods:** Patients with no valid AADur measurements are excluded from analysis. For patients with valid AADur measures, we found an average Atrial Arrhythmia Burden (AADur/day). Patients were grouped as HFE Group 0 (no decompensations) or HFE Group 1 (≥ 1 decompensations). We compared AADur/day between HFE groups. We also compared AADur/day in the periods prior to HFE versus other times in the same patients.

### Results

**Results:** Of 900 enrolled patients, 869 patients had valid AADur measurements and were included in the analyses. Patients that decompensated (Group 1) had significantly (p = 0.0005) higher AADur/day than those that did not (Group 0). The table below shows the AADur/day (mean ± SD) in minutes.

<table>
<thead>
<tr>
<th>Period</th>
<th>Pts</th>
<th>AADur/day PreEvent</th>
<th>AADur/day OtherTimes</th>
<th>Mean Difference</th>
<th>Wilcoxon p</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 days</td>
<td>96</td>
<td>129.5 min</td>
<td>124.1 min</td>
<td>5.3±19.3 min</td>
<td>0.0547</td>
</tr>
<tr>
<td>42 days</td>
<td>96</td>
<td>133.8 min</td>
<td>122.9 min</td>
<td>10.9±19.8 min</td>
<td>0.0602</td>
</tr>
<tr>
<td>28 days</td>
<td>96</td>
<td>138.5 min</td>
<td>122.4 min</td>
<td>16.0±21.9 min</td>
<td>0.0816</td>
</tr>
<tr>
<td>21 days</td>
<td>96</td>
<td>138.8 min</td>
<td>122.7 min</td>
<td>16.1±23.5 min</td>
<td>0.0698</td>
</tr>
<tr>
<td>14 days</td>
<td>96</td>
<td>140.3 min</td>
<td>122.7 min</td>
<td>17.6±24.2 min</td>
<td>0.0282</td>
</tr>
<tr>
<td>7 days</td>
<td>96</td>
<td>143.6 min</td>
<td>122.7 min</td>
<td>20.9±24.7 min</td>
<td>0.0152</td>
</tr>
</tbody>
</table>

### Results (continued)

The table at the top of the next column shows AADur/day (mean ± SE) during pre-event periods from 7-days to 56-days versus other times in the same patients.

In a period closest to the HFE (7-days), the patient’s AADur/day was 17% greater than other times in the same patients, (143.6 minutes vs 122.7 minutes). In a longer pre-event period (14-days), the AADur/day was 14% greater than other times. In a 56-day pre-event period, it was only 4% greater than other times. Thus, the AADur/day becomes more pronounced as it approached the HFE.

### Conclusions

Patient that decompensated had an increased AF burden compared to patients that did not decompensate. This burden became more pronounced in the weeks before HFE.
Preliminary experience with the multisensor HeartLogic algorithm for heart failure monitoring: a retrospective case series report

Alessandro Capucci1,2, Luca Santini3, Stefano Favale3, Domenico Pecora4, Barbara Petracchi5, Leonardo Calò6, Giulio Molon7, Laura Cipolletta1, Valter Bianchi8, Valentina Schirripa9, Vincenzo E. Santobuono9, Carmelo La Greca8, Monica Campari9, Sergio Valsecchi9, Fabrizio Ammirati3 and Antonio D’Onofrio8

ESC Heart Failure, 2019

- From December 2017 to April 2018, HeartLogic was activated in 67 patients
- At the time of activation, HeartLogic initialization had been completed in 58 patients
- Daily index values were available for analysis over a mean observation period of 5±3 months (a total of 24 person-years)

Baseline clinical parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total N=58</th>
<th>Alerts N=16</th>
<th>No Alerts N=42</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>47 (81)</td>
<td>13 (81)</td>
<td>34 (80)</td>
<td>0.980</td>
</tr>
<tr>
<td>Age, years</td>
<td>71±9</td>
<td>72±11</td>
<td>70±9</td>
<td>0.773</td>
</tr>
<tr>
<td>Ischemic etiology, n (%)</td>
<td>21 (37)</td>
<td>7 (44)</td>
<td>14 (33)</td>
<td>0.461</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>153±25</td>
<td>147±24</td>
<td>156±25</td>
<td>0.340</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>Class I, n (%)</td>
<td>2 (4)</td>
<td>1 (6)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Class II, n (%)</td>
<td>29 (50)</td>
<td>4 (25)</td>
<td>26 (62)</td>
<td></td>
</tr>
<tr>
<td>Class III, n (%)</td>
<td>26 (44)</td>
<td>11 (69)</td>
<td>14 (33)</td>
<td></td>
</tr>
<tr>
<td>Class IV, n (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>30±8</td>
<td>26±6</td>
<td>31±8</td>
<td>0.016</td>
</tr>
<tr>
<td>AF History, n (%)</td>
<td>23 (40)</td>
<td>9 (56)</td>
<td>14 (34)</td>
<td>0.111</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>18 (30)</td>
<td>3 (21)</td>
<td>9 (22)</td>
<td>0.010</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>9 (17)</td>
<td>3 (21)</td>
<td>6 (16)</td>
<td>0.675</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>14 (24)</td>
<td>6 (36)</td>
<td>8 (20)</td>
<td>0.142</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>48 (82)</td>
<td>13 (80)</td>
<td>35 (83)</td>
<td>0.851</td>
</tr>
<tr>
<td>b-Blocker use, n (%)</td>
<td>55 (94)</td>
<td>13 (84)</td>
<td>42 (100)</td>
<td>0.004</td>
</tr>
<tr>
<td>ACE-inhibitor use, n (%)</td>
<td>32 (55)</td>
<td>10 (62)</td>
<td>22 (53)</td>
<td>0.489</td>
</tr>
<tr>
<td>Diuretic use, n (%)</td>
<td>53 (92)</td>
<td>16 (100)</td>
<td>37 (87)</td>
<td>0.149</td>
</tr>
</tbody>
</table>
HeartLogic_Preliminary experience

HeartLogic index crossed the threshold value (set by default to 16) **24 times** in 16 patients
- **0.99 alerts/pt-year**

Time in the alert state (i.e. the number of weeks above the threshold): 153 weeks
- **12% of the total observation period**

- 5 HF hospitalizations in 3 patients (0.21 per patient-year)
- 5 unplanned in-office visits in 3 patients for HF (symptoms and signs of clinical deterioration of HF)
- 5 patients reported symptoms or signs of HF at the time of 5 scheduled visits
- 10 additional HeartLogic alerts (7 patients) after discontinuation or reduction of prescribed HF therapy or after events with a direct impact on clinical status or on sensor data collection

**MULTISENSE:**
- Alert rate: ~1.6 alerts/year
- % days at LOW risk: 83%
HeartLogic_Preliminary experience

**HeartLogic performance:**
- Rate of unexplained alerts: 0.41 per patient-year #
- Positive predictive value: 58% (14/24)

# considering therapy discontinuations as «unexplained alerts»

<table>
<thead>
<tr>
<th></th>
<th>Early-warning time (days)</th>
<th>Time spent in the alert state (days)</th>
<th>Maximum HeartLogic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF hospitalizations</td>
<td>38 [15-61]</td>
<td>70 [61-71]</td>
<td>40 [28-40]</td>
</tr>
</tbody>
</table>

- The early warning window was longer in cases of major HF hospitalizations → disease progression that may finally result in a fully decompensated status
- When patients or physicians could identify early worsening of HF by detecting initial signs or symptoms, prompt management prevented further worsening; this resulted in shorter duration of the alert state and was associated with a lower maximum HeartLogic index value.

**MULTISENSE:**
- UAR: 1.47 per patient-year
- PPV: 11.3%

**Contributing sensors:**

<table>
<thead>
<tr>
<th>Sensors with worsening on the day of the alert threshold crossing</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>84%</td>
</tr>
</tbody>
</table>
HeartLogic_Preliminary experience

Conclusion:

✓ In this first description of the use of HeartLogic in clinical practice, the algorithm demonstrated its ability to detect gradual worsening of HF.

✓ Among the sensed parameters that contribute to the calculation of the HeartLogic index, accelerometer-based heart sounds seemed to correlate well with HF status.

✓ The strong association between HeartLogic alerts and HF-related clinical events in our study is consistent with the high sensitivity in early detection of worsening HF demonstrated in the validation phase of the MultiSENSE study.

✓ Activation of the associated alert may allow clinical worsening to be detected early and enable action to be taken in patients who are deteriorating but not yet critical, thereby potentially preventing severe events.
## Heart Failure Diagnostic and Management
### Competitor Information

<table>
<thead>
<tr>
<th>Boston Scientific</th>
<th>Abbott</th>
<th>Medtronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HeartLogic</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td><strong>CardioMEMS</strong>&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td><strong>OptiVol</strong>&lt;sup&gt;8,9,10&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Proactive Composite Alert</strong></td>
<td>□ Multiple Sensors</td>
<td>□ Single Sensor Only</td>
</tr>
<tr>
<td><strong>Sensor(s)</strong></td>
<td>Heart sounds&lt;br&gt;Thoracic impedance&lt;br&gt;Respiration rate&lt;br&gt;Activity&lt;br&gt;Heart rate</td>
<td>Pulmonary arterial pressure</td>
</tr>
<tr>
<td><strong>Time to HFE, days</strong></td>
<td>34 days (median)</td>
<td>Not reported*</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>70%</td>
<td>22.5%</td>
</tr>
<tr>
<td><strong>Alerts, per pt-year</strong></td>
<td>Less than 2***</td>
<td>200+</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>Resonate Platform&lt;br&gt;(ICD / CRT-D)</td>
<td>Separate implant</td>
</tr>
<tr>
<td><strong>Data Transmission</strong></td>
<td>Automatic measurements and wireless download</td>
<td>Daily for several minutes on special pillow</td>
</tr>
</tbody>
</table>

*CHAMPION Trial sub analysis shows time course of decompensation of filling pressure increasing occurring between 30 - 20 days.

**Sensitivities are for thoracic impedance trending only and are the closest value comparisons for HL.

***Results from different clinical studies are not directly comparable. Definitions of sensitivity and false/unexplained alerts vary by study. Performance data presented as published: not adjusted for differences in study population, event definition, and event classification. Information provided for educational purposes only."
WHAT’S NEXT?

- Can we set up a specific reaction to a multiparametric alarm?
  
  (Heartlog Registry, on going)

- What is the best therapeutic tool if any to react efficaciously?
  
  (increasing the diuretic dosage only?)

- Do we need a new organization setting to take care of the increasing on line home informations?
Thank you for kind attention