Heart Failure Devices

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Disclosures

• Abbott – Honoraria (prior)
• Alleviant – support to institution/trial
• Ancora (Accucinch) – Eligibility committee for CORCINCH-HF trial
• BrioHealth Solutions - Honoraria
• CVRx (Baroreceptor activation therapy) – Consulting
• Daxor – Advisory board
• Edwards Lifesciences – Support to institution/trial
• Medtronic – Eligibility committee for TTVR trial

Topics

• Atrial shunts
• LV remodeling
• Baroreceptor activation therapy
• Preload reduction in cardiogenic shock
HFpEF – Lutembacher syndrome

• Hallmark is effort intolerance
• Profound/brisk increase in LA pressure during exercise
• Lutembacher syndrome (1916)
  • Combination of mitral stenosis and secundum ASD
  • Originally described 1750 by Johann Friedrich Meckel, Sr.

Interatrial Shunting in Heart Failure: Why It Should Work

• Patients with mitral valve stenosis and an atrial septal defect (ASD) have fewer symptoms than patients with an intact septum\(^1\)
• Closure of ASDs in patients with unrecognized left ventricular dysfunction results in elevated LAP and pulmonary edema\(^2\)
• Pre-clinical animal studies demonstrate hemodynamic, echocardiographic, and survival benefits with interatrial shunting\(^3\)
• First-in-human / clinical pilot studies support the safety, feasibility, and potential effectiveness of interatrial shunting in heart failure\(^4\)\(^-\)\(^10\)

1. Lutembacher R. Arch Mal Coeur 1916
8. Rodés-Cabau J, et al. JACC Intv 2018
Shunt devices in human trials

<table>
<thead>
<tr>
<th>Device/procedure</th>
<th>Corvia</th>
<th>V-Wave</th>
<th>Occlutech</th>
<th>Edwards</th>
<th>Alleviant</th>
<th>NoYA</th>
<th>InterShunt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Implant</td>
<td>Implant</td>
<td>Implant</td>
<td>Implant</td>
<td>Procedure</td>
<td>Procedure</td>
<td>Procedure</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Nitinol stent</td>
<td>Nitinol/PTFE hourglass</td>
<td>Nitinol braid with central orifice</td>
<td>Tubular nitinol device with retention arms</td>
<td>Coring catheter</td>
<td>RF catheter</td>
<td>Cutting catheter</td>
</tr>
<tr>
<td><strong>Shunt flow</strong></td>
<td>LA → RA</td>
<td>LA → RA</td>
<td>LA → RA</td>
<td>LA → CS</td>
<td>LA → RA</td>
<td>LA → RA</td>
<td>LA → RA</td>
</tr>
<tr>
<td><strong>Shunt size</strong></td>
<td>8 mm</td>
<td>5.1 mm</td>
<td>4, 6, 8, 10 mm</td>
<td>7 mm</td>
<td>6 mm</td>
<td>4-12 mm</td>
<td>6 mm</td>
</tr>
<tr>
<td><strong>Development stage</strong></td>
<td>Pivotal RCT complete, follow-up confirmatory RCT in responder subgroup ongoing</td>
<td>Pivotal RCT enrollment complete, follow-up ongoing</td>
<td>Pivotal RCT enrollment ongoing</td>
<td>Phase 2 feasibility/mechanistic RCT ongoing</td>
<td>Pivotal RCT enrollment ongoing</td>
<td>Open-label trial ongoing</td>
<td>Small pilot studies in humans</td>
</tr>
</tbody>
</table>

Summary from William Gray, MD (Lankenau)

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**Background: REDUCE LAP-HF II Trial**

- Pivotal, phase 3, international, multicenter, sham-controlled RCT of Corvia Atrial Shunt Device in patients with HF and LVEF ≥40%
  - NYHA II-IV, GDMT, age ≥40, LVEF ≥40%, preserved RV fn
  - Ex RHC with peak exercise PCWP ≥25mmHg, L-R gradient >5mmHg
- Primary outcome: hierarchical composite (win ratio)
  - CV death, non-fatal ischemic CVA, HF events, KCCQ summary score

- N=626 randomized 1:1 to shunt (n=314) vs. sham (n=312)
- Overall trial was neutral (win ratio = 1.0 [95% CI 0.8-1.2])
**REDUCE LAP-HF II Responder Subgroup**

- Post hoc, pre-specified analysis:
  - Large subgroup: 50% of randomized patients (n=313)
  - Peak exercise PVR <1.74 WU + no pacemaker/ICD
  - After 12 months of follow-up: Beneficial treatment response

![Graph showing responder group comparisons](image)

- **Responder Group (shunt vs. sham)**
  - ↑Win ratio = 1.43 (p=0.009)
  - ↓HF events (IRR 0.49, P=0.035)
  - ↑KCCQ (+5.9 points; =0.01)

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**HF events by shunt responder status**

- 24-month recurrent HF events analysis

  **RESPONDERS (win ratio = 1.36)**
  - IRR 0.48 (95% CI 0.45-0.92)
  - P=0.027

  **NON-RESPONDERS (win ratio = 0.73)**
  - IRR 2.22 (95% CI 1.29-3.85)
  - P=0.004

![Graph showing cumulative HF events](image)
**Responder Status: Serial Echocardiographic Changes**

- Four echo parameter treatment effects were significantly different between responders vs. non-responders ($P_{\text{interaction}} < 0.05$):
  - Lower RV/LV volume ratio
  - Lower RVESV, RVEDV
  - Higher transmitional A velocity

**RESPONDER-HF (NCT05425459):** Ongoing RCT of Corvia Atrial Shunt in Responder Gp: NYHA II-IV, LVEF>40%, GDMT, ExPVR<1.75, No Pacemaker
Effects of IASD on the heart

- LV and LA get smaller: Avoid HCM, avoid low output states
- RV and RA get bigger: Avoid vulnerable RV, overt RV failure, RA failure
- Tricuspid annulus will dilate: Avoid moderate or greater TR
- Blood needs to get back to left heart: Avoid pulmonary vascular disease, tricuspid/pulmonary valve obstruction

Echo evaluation for optimal candidate

- Left atrial enlargement (LA size > RA size)
- Interatrial septum bows from left to right
**Echo evaluation for optimal candidate**

RVOT notching on PW Doppler is associated with high PVR: unlikely to benefit from interatrial shunting!

**ALLAY-HF**

Safety and Efficacy of the Alleviant System for No-Implant Interatrial Shunt Creation in Patients with Chronic Heart Failure

Figure 2. Alleviant Catheter (Distal Assembly)

- CERAMIC BEARING
- ELECTRODE (CUTTING EDGE)
- TISSUE ANCHOR
- 12FR CATHETER BODY (PRECURVED)
- TIP SHAFT
- ATRAUMATIC TIP

Figure 6. Alleviant System (Procedure Overview)

A – Catheter is advanced over guidewire into LA; B – Device tip is opened and slowly retracted under image guidance until electrode resides in RA; C – A short pulse of RF energy is applied to cut target tissue; D – Guidewire and catheter (with occluded tissue) are withdrawn, leaving a durable passageway to permit LA-to-RA shunt flow (arrow).
Preliminary Data (EFS)

• N=32, 20F, mean age 67, mean BMI 35.4

• Technical success in 100% with mean size 7.1 ± 0.8 mm

• No major CV AEs, 10 SAE’s in 6/32, none deemed device or procedure related (1 died d/t COVID, 1 died d/t breast cancer, 3 HF hospitalization with IV diuretics)
Secondary Effectiveness (6 mos)

- Mean NTproBNP:
  - 1050 ± 908 to 682 ± 502
  - 69% improvement in NYHA functional class
- Mean 6MW:
  - 260 ± 64 to 366 ± 75
- KCCQ Overall:
  - 31 ± 14 to 58 ± 18

**ALLAY-HF**

**Enrollment underway…**

<table>
<thead>
<tr>
<th>Name</th>
<th>Safety and Efficacy of the Alleviant System for No-Implant Interatrial Shunt Creation in Pts with Chronic HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Multicenter, randomized, double-blinded, adaptive, sham-controlled</td>
</tr>
<tr>
<td>Size</td>
<td>400 - 700 patients (adaptive/Bayesian)</td>
</tr>
<tr>
<td>Patient Population</td>
<td>HFpEF and HFmrEF, identified with exercise hemodynamics</td>
</tr>
</tbody>
</table>
| Primary Endpoint (Composite, Hierarchical) | Time to CV mortality  
HF events  
KCCQ |
| Key Inclusion | Symptomatic HFpEF/HFmrEF (LVEF ≥ 40%)  
NYHA Class II, III or ambulatory IV  
Elevated PCW during exercise RHC (≥ 25 mmHg)  
Exercise PVR < 1.8 WU  
Ongoing stable guideline-directed medical therapy |
| Key Exclusion | Advanced HF  
Presence of a pacemaker  
Evidence of right heart dysfunction |
Left atrium to coronary sinus shunting
An alternative approach to chronic left atrial decompression

ALT FLOW early feasibility study design
A prospective, multi-center, single-arm study

Objective: To evaluate initial clinical safety, device functionality, and effectiveness of the APTURE transcatheter shunt system

Key Inclusion Criteria
- Chronic Symptomatic HF, NYHA Class II-IV, AND
- HF event requiring IV Lasix in prior 12 months, OR
- Elevated BNP (>500 pg/mL, >150 pg/mL for AF) or NT-pro-BNP (>150 pg/mL; >450 pg/mL for AF) in prior 6 months
- Stable GDMT for HF and co-morbidities
- PCWP > 15 mmHg at rest with LAP > RAP by 5 mmHg, OR PCWP > 25 mmHg during supine ergometer exercise stress test with LAP > RAP by 10 mmHg.
- Site PVR < 5 WU

Key Exclusion Criteria
- Severe HF
- Hemodynamic instability or inotrope infusion within 6 months
- Stage D HF or on transplant waiting list
- LVEF < 20%
- Significant untreated coronary, carotid or valvular disease (e.g., MR > 3+ or TR > 2+, AS > moderate)
- CRT initiation, MI or Stroke within 6 months
- Serum Creatinine > 2.5 mg/dL or eGFR > 25 ml/min/1.73 m²
- GFR < 50 or > 450 mL
- HOCM or infiltrative cardiomyopathy
- More than mild RV dysfunction
Pre-Specified Endpoint Assessments

All Enrolled Patients (N=116):
- Performance outcomes
- MACCRE and Reintervention (30d)

Device Implanted Patients (N=105)
- Shunt patency at one year

Analysis Population (N=95):
- All implanted patients with LVEF > 40%
- Outcomes Assessment up to 1-year for total population and subgroups
  - Clinical
  - Hemodynamic
  - Functional
  - Quality of Life

ALT-FLOW EFS
Patient flow and endpoints

CAUTION: Investigational device. Limited by Federal (or USA) law to investigational use.

30-day safety endpoint: all enrolled patients
MACCRE* plus reintervention

<table>
<thead>
<tr>
<th>Safety Endpoint</th>
<th>Total Cohort N=116</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCRE or Reintervention</td>
<td>2.6% (3/116)</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>0.0% (0/116)</td>
</tr>
<tr>
<td>Stent Occlusion/Thrombosis</td>
<td>0.0% (0/116)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0.9% (1/116)</td>
</tr>
<tr>
<td>AKI Stage 3</td>
<td>0.0% (0/116)</td>
</tr>
<tr>
<td>Death</td>
<td>0.0% (0/116)</td>
</tr>
<tr>
<td>Reintervention</td>
<td>2.6% (3/116)</td>
</tr>
</tbody>
</table>

3 Patients with 4 Events:
- (1) Embolization with surgical retrieval, with (2) post-surgical stroke
- (3) Surgical reintervention for tamponade and CS repair
- (4) Percutaneous Drainage of tamponade and CS covered stent

Successful shunt implantation achieved in 90.5%
(All Enrolled Patients: 105/116)

Shunt patency per Echocardiography CoreLab
100% at one year
(Device Implanted patients: 105/105)
## Baseline patient characteristics
### Analysis population

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>N=95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>71 ± 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33 ± 8</td>
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<tr>
<td>Hypertension</td>
<td>87%</td>
<td></td>
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<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>59%</td>
<td></td>
<td></td>
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<tr>
<td>COPD</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CABG / PCI</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker / ICD</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Stroke / TIA</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>9%</td>
<td></td>
<td></td>
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<tr>
<td>Primary HFH within 1 yr</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous measures - mean ± SD.

### NYHA functional class and health status
### Paired changes from baseline – analysis population

**NYHA Class**

- **Baseline n=71**
  - Class I: 8%
  - Class II: 25%
  - Class III: 32%
  - Class IV: 35%
- **6 months**
  - Class I: 27%
  - Class II: 32%
  - Class III: 27%
  - Class IV: 30%
- **1 year**
  - Class I: 26%
  - Class II: 32%
  - Class III: 16%
  - Class IV: 31%

**Health Status (KCCQ-OSS)**

- **Baseline n=69**
  - Good to Excellent: 6%
  - Fair to Good: 30%
  - Poor to Fair: 6%
  - Death: 0%
- **6 months**
  - Good to Excellent: 3%
  - Fair to Good: 28%
  - Poor to Fair: 6%
  - Death: 0%
- **1 year**
  - Good to Excellent: 6%
  - Fair to Good: 31%
  - Poor to Fair: 6%
  - Death: 0%

NYHA = New York Heart Association; Health Status category based on Quartile of KCCQ-OSS Score (0-100).

CAUTION: Investigational device. Limited by Federal (or USA) law to investigational use.
Baseline hemodynamics
Analysis population – core lab data

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort</th>
<th>PVR ≤ 2</th>
<th>PVR &gt; 2</th>
<th>p-value PVR ≤ 2 vs. PVR &gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP</td>
<td>20.1 ± 8.25 (93)</td>
<td>19.8 ± 8.11 (69)</td>
<td>20.9 ± 8.77 (24)</td>
<td>0.59</td>
</tr>
<tr>
<td>RAP</td>
<td>9.6 ± 4.69 (95)</td>
<td>9.2 ± 4.67 (91)</td>
<td>10.5 ± 4.87 (24)</td>
<td>0.26</td>
</tr>
<tr>
<td>PASP</td>
<td>44.2 ± 15.60 (94)</td>
<td>39.3 ± 11.68 (69)</td>
<td>57.8 ± 17.71 (24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean PA</td>
<td>28.1 ± 9.68 (94)</td>
<td>25.6 ± 7.79 (69)</td>
<td>35.6 ± 11.05 (24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR (Site)</td>
<td>2.1 ± 0.94 (94)</td>
<td>1.8 ± 0.79 (68)</td>
<td>3.0 ± 0.72 (24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac Index (Thermoregulation)</td>
<td>2.5 ± 0.51 (95)</td>
<td>2.6 ± 0.51 (69)</td>
<td>2.2 ± 0.48 (24)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

20W Exercise

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>PCWP</td>
<td>35.1 ± 8.41 (84)</td>
<td>35.1 ± 8.24 (62)</td>
<td>35.2 ± 9.08 (22)</td>
<td>0.96</td>
</tr>
<tr>
<td>RAP</td>
<td>18.7 ± 7.68 (89)</td>
<td>18.0 ± 6.19 (65)</td>
<td>21.0 ± 9.27 (22)</td>
<td>0.16</td>
</tr>
<tr>
<td>PASP</td>
<td>71.3 ± 17.81 (80)</td>
<td>67.6 ± 14.57 (57)</td>
<td>81.4 ± 21.89 (22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean PA</td>
<td>46.6 ± 10.71 (79)</td>
<td>44.8 ± 8.73 (56)</td>
<td>51.7 ± 13.66 (22)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Continuous measures - mean ± SD (n).

*DOI: 10.1183/13993003.00879-2022

Presence or absence of Pulmonary Vascular Disease (PVD) at rest defined using ESC/ERS 2022* criteria.

Baseline resting PVR > 2 WU

CAUTION: Investigational device. Limited by Federal (or USA) law to investigational use.

PCWP at 20 watts exercise (PCWP 20W)
Paired comparisons vs. baseline – analysis population

Mean Change [95% CI] -5.1 [-7.4, -2.7] p < 0.0001
Mean Change [95% CI] -5.7 [-8.6, -2.9] p < 0.001

All values in mmHg.

CAUTION: Investigational device. Limited by Federal (or USA) law to investigational use.
ALT-FLOW Early Feasibility Study - Conclusions

In patients with chronic symptomatic HF and elevated PCWP at rest and/or exercise with an LVEF > 40%, the APTURE transcatheter shunt demonstrated:

- High implant success rate with low 30-day MACCRE or reintervention,
- Clinically meaningful improvements in HF symptoms and overall health status at one year,
- Significant and durable reductions in PCWP at 20-W exercise through 6 months,
- Overall consistency in favorable responses for changes from baseline in exercise PCWP and KCCQ-OSS among multiple analyzed subgroups, and
- No evidence of adverse effects on right heart volumes, hemodynamics, function, or RV-PA coupling.

Presented at THT 2024 (Zahr F on behalf of ALT FLOW study team)
Trial Comparison

<table>
<thead>
<tr>
<th></th>
<th>ALLAY</th>
<th>ALT-FLOW 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing/Leads</td>
<td>No leads allowed</td>
<td>RV ok, none in CS</td>
</tr>
<tr>
<td>PVR</td>
<td>Resting excludes PVR &gt;3.5</td>
<td>Excludes &gt; 5</td>
</tr>
<tr>
<td></td>
<td>PVR &lt; 1.8 at 25W exercise</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Covered</td>
<td>CMS approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Private payors likely to refuse due to randomization</td>
</tr>
<tr>
<td>RHC</td>
<td>Screening</td>
<td>Baseline and 6-month exercise RHC</td>
</tr>
<tr>
<td>Requires diuretic</td>
<td>Yes, stable 2 weeks</td>
<td>No, but stable for 4 weeks</td>
</tr>
<tr>
<td>Resting RHC requirements</td>
<td>RAP &lt;15 PCWP &gt; RAP</td>
<td>PCWP &gt; RAP by 5</td>
</tr>
</tbody>
</table>

Please consider...

• Is this an option for a persistently symptomatic HFpEF patient?
• Would an exercise RHC be helpful clinically?
• Measure LVEDP
• Does echo suggest high left – and normal right-sided filling pressures?
## LV Remodeling Therapy Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Carvedilol</th>
<th>CRT</th>
<th>MV Repair</th>
<th>MV Replace</th>
<th>MitraClip</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSENSUS</strong></td>
<td>Doughty et al</td>
<td>Abraham et al</td>
<td>Acker et al</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Konstam et al</td>
<td>1 Year</td>
<td>6 months</td>
<td>N Eng J Med 370</td>
<td>1 year</td>
<td></td>
<td>Mitra-fr</td>
</tr>
<tr>
<td></td>
<td>+4</td>
<td>+5</td>
<td>+3.0</td>
<td>0</td>
<td>0</td>
<td>-3</td>
</tr>
<tr>
<td><strong>Δ EF (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Δ ESV (mL)</strong></td>
<td>-13</td>
<td>-32</td>
<td>-25.6</td>
<td>-7</td>
<td>-5</td>
<td>+1</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>31%</td>
<td>65%</td>
<td>10%</td>
<td>Not Evaluated</td>
<td>Not Evaluated</td>
<td>No Effect</td>
</tr>
<tr>
<td>(% risk reduction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death or HF Hosp</strong></td>
<td>50%</td>
<td>27%</td>
<td>18%</td>
<td>Not Evaluated</td>
<td>Not Evaluated</td>
<td>No Effect</td>
</tr>
</tbody>
</table>

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### Device Description: Carillon

- 18 patients randomized
- 5 additional have completed screening
- 80 total consented
- 49 sites active
- 11 sites being activated

Kapadia S, THT 2024
ALIVE Trial: Baseline and Follow-Up Left Ventricular End-Systolic Volume Index Results

<table>
<thead>
<tr>
<th>A</th>
<th>ITT Population (N=127)</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N=84</td>
<td>N=43</td>
</tr>
<tr>
<td>Visit Interval</td>
<td>LVEV Index (mL/m²)</td>
<td>Change from Baseline</td>
<td>LVEV Index (mL/m²)</td>
</tr>
<tr>
<td>Baseline</td>
<td>96.7 ± 35.2</td>
<td>-</td>
<td>89.0 ± 35.6</td>
</tr>
<tr>
<td>(94)</td>
<td>(41)</td>
<td></td>
<td>(50, 179)</td>
</tr>
<tr>
<td></td>
<td>88 (72, 112)</td>
<td></td>
<td>80 (52, 117)</td>
</tr>
<tr>
<td>1-Month Follow-up</td>
<td>75.3 ± 31.4</td>
<td>-22.0 ± 25.8</td>
<td>84.8 ± 35.5</td>
</tr>
<tr>
<td></td>
<td>(69)</td>
<td>(-125, 23)</td>
<td>(54)</td>
</tr>
<tr>
<td></td>
<td>(22, 102)</td>
<td></td>
<td>(25, 100)</td>
</tr>
<tr>
<td></td>
<td>75 (52, 94)</td>
<td></td>
<td>75 (64, 119)</td>
</tr>
<tr>
<td>1-Year Follow-up</td>
<td>69.7 ± 28.8</td>
<td>-27.1 ± 28.4</td>
<td>69.1 ± 27.4</td>
</tr>
<tr>
<td></td>
<td>(64)</td>
<td>(-48, 40)</td>
<td>(56)</td>
</tr>
<tr>
<td></td>
<td>(30, 170)</td>
<td></td>
<td>(81, 123)</td>
</tr>
<tr>
<td></td>
<td>65 (51, 80)</td>
<td>-24 ± 46, 48</td>
<td>65 (47, 87)</td>
</tr>
</tbody>
</table>

Data presented as mean ± std (n); [min, max]; median [25th percentile, 75th percentile].
Based on Core Lab data for subjects with available measurements.
*For follow-up comparison of the change in LVEV (delta from baseline).
ALIVE Trial: Primary Safety End Point

<table>
<thead>
<tr>
<th>Endpoint Result</th>
<th>Total Events (N)</th>
<th>Revivent + OMT Patients (%) N=84</th>
<th>One-Sided 97.5% Upper Confidence Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite MAE at 30 days</td>
<td>30</td>
<td>15 (17.9%)</td>
<td>27.7%</td>
</tr>
<tr>
<td>All-Cause Death¹</td>
<td>3</td>
<td>3 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Placement of Mechanical Support Device Intra- or Post-op²</td>
<td>10</td>
<td>8 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Emergent Cardiac Surgery</td>
<td>7</td>
<td>7 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Prolonged Mechanical Ventilation¹</td>
<td>9</td>
<td>8 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Renal Failure</td>
<td>3</td>
<td>3 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Clinically Important Stroke (Rankin Score of 4 or higher)</td>
<td>0</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Post hoc: Composite MAE at 30 days
Device (Surgical only LV-LV approach) 3/23 (13%)
Device (Hybrid RV-LV approach) 12/60 (20%)

The primary 30-day safety endpoint was met (MAE 15/84 (17.9%); one-sided 97.5% upper confidence limit 27.7%; p<0.0001).

ALIVE Trial: Primary Composite Efficacy Endpoint Results

A

COMPOSITE HIERARCHY (% Wins)

CV Death 2.2% 8.7%
HF Hospitalization 6.0% 11.7%
GMWT 14.6% 26.2%
MLHF 7.4% 10.1%
NYHA Class 2.9% 1.3%

B

Composite Efficacy Endpoint

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>REVIVENT</th>
<th>CONTROL</th>
<th>Win ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>83</td>
<td>42</td>
<td>1.13</td>
<td>0.320</td>
</tr>
</tbody>
</table>

Anchor Configuration

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>REVIVENT</th>
<th>CONTROL</th>
<th>Win ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-LV vs. Control</td>
<td>23</td>
<td>42</td>
<td>1.32</td>
<td>0.182</td>
</tr>
<tr>
<td>RV-LV vs. Control</td>
<td>60</td>
<td>42</td>
<td>1.06</td>
<td>0.393</td>
</tr>
</tbody>
</table>

The primary 12-month hierarchal composite efficacy endpoint was not met (win ratio 1.13; p=0.32)
The AccuCinch System Procedure in 3 Steps

**ACCESS**
- LV ACCESS USING THE ACCUCINCH GUIDE CATHETER
- LV FREE WALL GUIDEWIRE PLACEMENT WITH THE ACCUCINCH NAVCATH

**DELIVERY**
- ADVANCEMENT OF THE ACCUCINCH TRACCATH
- DELIVERY OF THE ACCUCINCH IMPLANT

**CINCH**
- COMPLETION OF THE ACCUCINCH PROCEDURE BY CINCHING AND ACUTELY REDUCING THE SIZE OF THE LEFT VENTRICLE

Acute Implantation ➔ LV Wall Integration

- Cadaver / Immediately post implant
- Clinical / 10 days post implant
- Preclinical / 90 days post implant
- Clinical / 90 days post implant
Acute LV Reduction ➔ Biological Reverse Remodeling

Immediate Post-Procedure

Post-Cinch LV Wall

Pre-Cinch LV Wall

Cardiac CT

Baseline

12-Months Post Procedure

Improvement in LV Volume, QoL & Exercise Capacity

Significant, Progressive Left Ventricle Volume Reduction (LVEDV)

<table>
<thead>
<tr>
<th>Time</th>
<th>Change in LVEDV (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Month</td>
<td>-10.1 mL</td>
</tr>
<tr>
<td>3-Months</td>
<td>-23.5 mL</td>
</tr>
<tr>
<td>6-Months</td>
<td>-31.9 mL</td>
</tr>
<tr>
<td>12-Months</td>
<td>-39.3 mL</td>
</tr>
</tbody>
</table>

p<0.001 (n=31)

Clinically Significant Improvement in Quality of Life (KCCQ)

19.0 Points (p<0.001 vs Baseline)

> 5 points*

Clinically Significant Improvement in Exercise Capacity (6MWT)

47.7 Meters (p=0.003 vs Baseline)

> 32 meters*

*Thresholds of clinical significance

Mean ± SE; Jorde, U. & Hamid, N. / TVT 2022
Improvement in Events Post-Procedure

<table>
<thead>
<tr>
<th>Events (n=41 Subjects)</th>
<th>12 Mo. Pre-Procedure</th>
<th>12 Mo. Post-Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Heart Transplant</td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td>LVAD</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>32 Events in 21 Subjects</td>
<td>5 Events in 3 Subjects</td>
</tr>
</tbody>
</table>

Composite Event Rate (per patient month)

- Pre-Procedure: 0.065
- Post-Procedure: 0.011

p<0.0001

The CORCINCH-HF Study / IDE Pivotal Trial (NCT04331769)

**DESIGN:** Prospective, randomized, open-label, multi-center clinical safety and efficacy investigation in patients with symptomatic HFrEF

**RANDOMIZATION:** 1:1 - Treatment with the AccuCinch System plus GDMT or GDMT alone

**ENROLLMENT:** 400 randomized subjects at up to 80 centers, globally

**ENDPOINTS:** Safety & efficacy evaluated when 250 subjects reach 6-mo follow-up, and when 400 subjects reach 12-mo follow-up

**KEY ELIGIBILITY CRITERIA**

- **LVEF:** 20-40%
- **NYHA:**
  - II with HF hosp. in the past 12 mo.
  - III
  - IV ambulatory
- **LVEDD:** ≥ 55 mm
- **MR:** ≤ 2+

**Study Leadership**

**Chairman:**
Martin Leon, MD

**Co-Principal Investigators:**
Mark Reisman, MD
Ulrich Jorde, MD
CORCINCH-HF Study Eligibility Guide

HFrEF
LVEF ≤ 40

ARNI
(or ACEi/ARB)

SGLT2i

MRA

Beta-Blocker

Maximally Tolerated Dose
+ additional Rx
and/or ICD when indicated

Persistent Symptoms

NSR
QRS >150ms
LBBB

+ CRT

Persistent Symptoms

+ LBBB

MR ≥ 3+
TEER

Persistent Symptoms

Refer to the CORCINCH-HF Protocol for the complete list of inclusion/exclusion criteria

GDMT produces modest improvements in QOL

KCCQ Score

Clinically Meaningful
5 Points

6.1
Interv.

3.3
Control

2.8
Diff

p<0.001

5.8
Interv.

4.1
Control

1.7
Diff

p=n.s

PARADIGM-HF³

(ARNI)

-2.9
Interv.

-1.6
Control

-1.6
Diff

p<0.001

DAPA-HF¹

(SGLT2i)

EMPEROR-Reduced²

(SGLT2i)


GDMT produces modest improvements in QOL
**Autonomic nervous system in heart failure**

- Decreased Baroreceptor Signaling
- Elevated sympathetic tone
- Decreased parasympathetic tone

- Heart Rate Remodeling
- Diuresis Renin Secretion
- Vasodilation Blood Pressure

---

Adapted from Lewis G et al, Developments in Exercise Capacity Assessment in Heart Failure Clinical Trials and the Rationale for the Design of METEORIC-HF. Circ Heart Fail. 2022 May; 15(5):510-524

GDMT produces modest improvements in exercise capacity

- β-blockers
- SGLT2i
- ACE/ARB
- ARNI
- MRA

<table>
<thead>
<tr>
<th>Class I</th>
<th>~Class IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS &lt; 150</td>
<td>RBS &gt; 150</td>
</tr>
<tr>
<td>Narrow QRS</td>
<td>Intermediate QRS</td>
</tr>
</tbody>
</table>

- Sample size weighted average % change in exercise capacity
- n = # of studies

---

Creager MA, Creager SJ. J Am Coll Cardiol. 1994;23(2):401-5

---

GDMT produces modest improvements in exercise capacity
Baroreceptor activation therapy (BAT) elements

- Designed to deliver electrical stimulation to carotid baroreceptors to increase baroreceptor signaling

Implantable Pulse Generator (IPG) & Carotid Sinus Lead

Study Details
- N = 11 patients
- Single center
- NYHA III, EF < 40%
- GDMT
- Barostim delivered for 6m

BAT decreases sympathetic tone

Muscle Sympathetic Nerve Activity (bursts/min)

Study Details
- Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac hemodynamics in heart failure: a proof-of-concept study
BeAT-HF Inclusion/Exclusion Criteria

Key Inclusion/Exclusion Criteria

- NYHA Functional Class III
- Left ventricular ejection fraction ≤35%
- Six-minute hall walk distance: 150-400m
- Elevated NT-proBNP or previous HF hospitalization
- Stable optimal medical therapy ≥4 weeks
- CRT-eligible subjects are excluded
- No restriction on AF, QRS width or concomitant devices

BeAT-HF baseline demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Barostim (n=163)</th>
<th>Control (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Screening (years)</td>
<td>63 ± 11</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>28 (17.2%)</td>
<td>35 (21.9%)</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>120 (73.6%)</td>
<td>116 (72.5%)</td>
</tr>
<tr>
<td>Heart failure and physical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 16</td>
<td>121 ± 16</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74 ± 10</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>75 ± 10</td>
<td>75 ± 11</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>31 ± 5</td>
<td>31 ± 5</td>
</tr>
<tr>
<td>eGFR</td>
<td>62.5 ± 16.3</td>
<td>61.1 ± 18.9</td>
</tr>
<tr>
<td>NYHA: Class III</td>
<td>155 (95.1%)</td>
<td>151 (94.4%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27 ± 6</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>6 Minute Walk (m)</td>
<td>314 ± 66</td>
<td>300 ± 71</td>
</tr>
<tr>
<td>QOL</td>
<td>53 ± 24</td>
<td>51 ± 24</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>736 (474, 1057)</td>
<td>704 (442, 1044)</td>
</tr>
<tr>
<td>&gt;=1 HF Hospitalization</td>
<td>66 (40.5%)</td>
<td>79 (49.4%)</td>
</tr>
<tr>
<td>Number of HF Hospitalizations</td>
<td>0.6 ± 0.9</td>
<td>0.7 ± 0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Morbidities</th>
<th>Barostim (n=163)</th>
<th>Control (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>104 (63.8%)</td>
<td>107 (66.9%)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>53 (32.5%)</td>
<td>66 (41.3%)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>29 (17.8%)</td>
<td>37 (23.1%)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>45 (27.6%)</td>
<td>43 (26.9%)</td>
</tr>
<tr>
<td>Type II Diabetes</td>
<td>74 (45.4%)</td>
<td>80 (50.0%)</td>
</tr>
</tbody>
</table>

Heart failure treatment

<table>
<thead>
<tr>
<th>Number of Meds</th>
<th>4.0 ± 1.3</th>
<th>4.1 ± 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I / ARB / ARNI</td>
<td>143 (88%)</td>
<td>129 (81%)</td>
</tr>
<tr>
<td>ARNI</td>
<td>57 (35%)</td>
<td>43 (27%)</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>152 (93%)</td>
<td>147 (92%)</td>
</tr>
<tr>
<td>MRA</td>
<td>74 (45%)</td>
<td>64 (40%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>138 (85%)</td>
<td>139 (87%)</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>4 (2.5%)</td>
<td>9 (5.6%)</td>
</tr>
<tr>
<td>ICD</td>
<td>125 (77%)</td>
<td>127 (79%)</td>
</tr>
</tbody>
</table>
**BeAT-HF two-phase trial design**

**Pre-Market Phase as Breakthrough Device**
- Met safety and all effectiveness endpoints
  - Safety
  - 6-month symptom improvement
  - NT-proBNP at 6 months

**Post-Market Phase for Labeling Expansion**
- Confirmed safety and effectiveness endpoints of Pre-Market Phase. Primary endpoint of CV death and hospitalization was not met. Additional effective analysis suggest favorable effect of Barostim therapy
  - Safety
  - 6,12,24-month symptom improvement
  - CV death and HF hospitalization
  - All-cause death, LVAD or transplant
  - Win ratio - mortality, morbidity & QOL

**FDA**
- FDA approval 2019
- FDA labeling expansion 2023
- Published 2020

---

**BeAT-HF symptom improvement at 12 months**

**Exercise capacity (6MHW)**
- BAT: 41 Meters
- Control: 39 Meters
- Diff: +2 Meters

**Quality of life (MLWHF)**
- BAT: 4-9 Points
- Control: 3-4 Points
- Diff: +1 Point

**NYHHA class**
- BAT: 73%
- Control: 61%
- Diff: +12%

---

1 Data from different studies and different patient populations may not be directly comparable.
Reduction in all-cause death, LVAD or transplant

Patients in the BAT arm had a 34% reduction in all-cause death or the use of LVAD or heart transplant.

BeAT-HF safety

**MANCE-Free Rate**

97% MANCE-Free Rate

**6-month MANCE (System or Procedure-Related)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Barostim Subjects (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Events</td>
</tr>
<tr>
<td>CV Death</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>0</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0</td>
</tr>
<tr>
<td>Acute Decompensated HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive Crisis</td>
<td>0</td>
</tr>
<tr>
<td>Severe Complication of HF Treatment</td>
<td>0</td>
</tr>
<tr>
<td>Systemic and Pulmonary Thromboembolism</td>
<td>0</td>
</tr>
<tr>
<td>Infection Requiring Explant</td>
<td>2</td>
</tr>
<tr>
<td>Cranial Nerve Damage</td>
<td>0</td>
</tr>
<tr>
<td>Non-Elective Major Restorative Procedures</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
</tr>
</tbody>
</table>

BeAT-HF: Serious cardiovascular events at 6 months

Potential Reduction in Serious Cardiovascular Events

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Barostim (n=125)</th>
<th>Control (n=134)</th>
<th>Relative Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Events</td>
<td>Event Rate*</td>
<td>Number of Events</td>
</tr>
<tr>
<td>Cardiac Arrhythmia/ Cardiac Arrests</td>
<td>8</td>
<td>0.054</td>
<td>18</td>
</tr>
<tr>
<td>MI/Angina</td>
<td>5</td>
<td>0.034</td>
<td>10</td>
</tr>
<tr>
<td>Hypotension/ Syncope</td>
<td>2</td>
<td>0.014</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>0.101</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

* Events per patient-year of follow-up

p-value = 0.023

Not a powered endpoint

Sample BAT Titration Schedule

<table>
<thead>
<tr>
<th>@ Implant</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical device amplitude</td>
<td>1mA</td>
<td>2mA</td>
<td>4mA</td>
<td>6mA</td>
</tr>
<tr>
<td>Drug titration</td>
<td>Δ Diuretic</td>
<td>Δ Diuretic</td>
<td>Δ Diuretic</td>
<td>Δ Diuretic ± NH Blockade</td>
</tr>
<tr>
<td>Assessment</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Device and drug titration is physician-directed
MHI Experience To Date

- 4 implants, another ~3 approved and pending
- Must have proBNP <1600
- High rate of payors refusing coverage
- I want to acknowledge Dr. Haglund for spearheading, Dr. Jim for implanting, and HF nurses (Emily Bernstein RN and Ruwayda Mohamed RN) for extensive efforts to organize process and program and Stephanie Garrison for PA support
MCS: Innovative Technologies for Cardiogenic Shock
Optimizing MCS with Mechanical Cardiac Preload Reduction

Intermittent SVC Occlusion

Kapur NK et al, Catheter Cardiovasc Interv 2019
Site Initiation Visit TOMORROW!

SVC Occlusion in Subjects With Acute Decompensated Heart Failure (VENUS-HF)

ClinicalTrials.gov ID: NCT038366079

Sponsor: Abiomed Inc.

Outcome Measures

<table>
<thead>
<tr>
<th>Change History</th>
<th>See all versions of this study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (Current)</td>
<td>Freedom from Major Adverse Events through 90 days post-discharge [Time Frame: 90 days post-discharge]</td>
</tr>
<tr>
<td></td>
<td>MAE is defined as death, myocardial infarction, major thromboembolic event, vascular damage requiring surgical intervention, hemorrhagic stroke or prolongation of heart failure-related hospitalization attributable to the preCARDIA device or procedure.</td>
</tr>
<tr>
<td>Primary (Original)</td>
<td>Freedom from Major Adverse Events through 30 days [Time Frame: 30 days]</td>
</tr>
<tr>
<td></td>
<td>MAE is defined as death, myocardial infarction, major thromboembolic event, vascular damage requiring surgical intervention, hemorrhagic stroke or prolongation of heart failure-related hospitalization attributable to the preCARDIA device or procedure.</td>
</tr>
</tbody>
</table>

Inclusion Criteria:
- NYHA Class III-IV heart failure
- Subjects with inadequate diuresis
- Stage C-D systolic heart failure

Exclusion Criteria:
- Active myocardial ischemia or acute coronary syndrome (ACS)
- Severe aortic or mitral valve insufficiency
- Severe peripheral vascular disease
Thank you!