Interatrial Shunting for the Treatment of Heart Failure Across the Spectrum of LVEF – HFrEF and HFpEF

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Disclosure

• I disclose a material financial interest related to my compensation as CEO of V-Wave Ltd.

I attest that I will comply with ACCME Standards for Commercial Support of Continuing Medical Education to ensure that this CME activity is free of commercial bias or appearance thereof.

I will base all clinical recommendations on evidence that is accepted within the profession of medicine as adequate justification in the care of patients.

All scientific research referred to in support of a patient care recommendation will conform to generally accepted standards of experimental design, data collection, and analysis.

I will not discuss any unlabeled uses of products.
Dear Mentors, Mentees, Colleagues and Friends
─ Celebrating 4 Decades at Cedars-Sinai
Preventing Acute Decompensated HF
A huge Unmet Clinical Need

>1M
Annual US hospital admissions for ADHF

Re-hospitalization
25% At 1 month
50% At 6 months

NYHA Class III mortality:
1 year ~20%; 3 year ~50%

>90%
of admissions present to hospital with lung congestion due to elevated Left Atrial Pressure (LAP)

Elevated LAP: Cause of Lung Congestion, Worsening Symptoms, and Hospitalizations in Heart Failure

Regardless of Left Ventricular Ejection Fraction!

- LAP often highly variable over the course of a day
- Increase of LAP precedes clinical events, averaging >25 mmHg for several days before admission or death
- Lowering LAP improves clinical outcomes

Evidence Supporting Inter-Atrial Shunt Therapy in Chronic Heart Failure

• Patients with mitral stenosis and an ASD (Lutembacher syndrome) have fewer symptoms of pulmonary congestion than patients with an intact septum

• Closure of ASDs in patients with unrecognized left ventricular dysfunction results in elevated LAP and pulmonary edema

• Pre-clinical animal studies demonstrate hemodynamic, echocardiographic, and survival benefits with interatrial shunting

• First-in-human and clinical pilot studies support the safety, feasibility, and potential effectiveness of interatrial shunting in heart failure
Interatrial Shunt Devices in Clinical Development

Caution: all devices are investigational and not commercially available in any country

V-Wave Shunt (5mm), Israel/US
FDA BDD pivotal international RCT

Corvia IASD II (8mm), US
FDA BDD pivotal international RCT

Occlutech AFR (6-10mm), Germany
EU feasibility study

NoYa RF-based Interatrial Shunt System, China

Edwards LA-CS Shunt (7 mm), US
Canadian feasibility study

And, likely many more to come!
A Small Shunt can Regulate LAP in HFpEF and HFrEF


LV Diastolic Filling Curves

When LAP rises, shunt flow increases lowering LVEDV, LVEDP, and LAP

When LAP falls, shunt flow falls rapidly


V-Wave Shunt Flow
5-mm shunt at 65 bpm
Interatrial Shunting Self-Regulates LAP 24/7
Standard care & pressure-guided management have delays & failure points

- Many patients do not tolerate or are refractory to pharmacological therapies that lower LAP
- Pharmacological therapies may not fully address the dynamic increases in LAP during HF exacerbations, exercise, or changes in venous capacitance

Abraham WT. In: Topol & Teirstein eds., Textbook of Interventional Cardiology (7th Edition), 2016
Interatrial Shunt Device in Microembolization Model of Ischemic Heart Failure

N=21 sheep
14 V-Wave 5 mm Shunts
7 Controls

A small shunt (Qp:Qs 1.2) significantly improved:
LA, LV, RA, PA pressures LV systolic & diastolic function, and survival

A “Device Effect” is the likely cause of observations

*  p<0.05 vs. Control
** p<0.01 vs. Control
†  p<0.05 vs. Baseline

Eigler, et al. Cardiac Unloading with an Implantable Shunt in Heart Failure. Structural Heart 2017
Corvia First REDUCE LAP-HF Trial

- Prospective, non-randomized study
- Symptomatic HF (N=64)
- Preserved EF (>40%)
- Elevated PCWP at rest (>15 mmHg) or during exercise (>25 mmHg)
- Monitored by independent DSMB and CEC
- Assessed by independent Core-Laboratories
  - Echo
  - Hemodynamic
- Three-year clinical follow-up
  - One year complete

First REDUCE-LAP Trial Results

Corvia REDUCE LAP HF I: Mechanistic RCT

**Objectives**

Evaluate device safety and mechanistic effect in heart failure patients with LV EF≥40% who are symptomatic despite optimal therapy

Measure 6- and 12-month exploratory efficacy endpoints

Inform design of Pivotal IDE trial

**Design**

N=44, randomized 1:1 Treatment vs. Sham Control

Primary Endpoint: Powered for mechanistic effect @1M: exercise PCWP reduction

Exploratory Endpoints (out to 12 months)

- safety
- clinical efficacy

**Results**

- Met Primary Endpoint
- Safe procedure
Key Efficacy Measure: Exercise PCWP

Feldman et al. REDUCE LAP-HF I, CIRC. Nov 2017
V-Wave First-in-Human (FIH) Studies

Total 38 pts (30 HFrEF, 8 HFpEF)
6 sites (Canada, EU, Israel)
Median FU 28 months (18-48 months)

Major Inclusion Criteria

- Chronic HF, ischemic or non-ischemic etiology
- HFrEF and HFpEF
- NYHA class III or ambulatory class IV
- On GDMT and device therapies
- HF-hospitalization or elevated BNP/NT-proBNP

V-Wave FIH Procedural Success and Safety

Procedural success: 38/38 (100%)

- Procedure time: 72 ± 24 min
- Median LOS: 1 days (IQR: 1-2)

Safety

Procedure-related major adverse events in 1 pt (2.6%)
- 1 pericardiocentesis
- 0 deaths, strokes, MIs, or device embolization's

1-year adverse events
- 2 deaths (CV, non-device-related)
- 0 strokes or MIs
Shunting Improves Functional Outcomes

NYHA Class*

QoL Change*

6MWT Change (m)*

* \( p < 0.04 \) (baseline vs. follow-up)

Rodes-Cabau J, et al. JACC Intv 2018

Interatrial Shunts | 2019
Shunting May Improve Clinical Outcome
HF-Hospitalization Rates for First Year: V-Wave (n=38) vs IHM Studies

**St. Jude LAP Sensor Study***

Treatment (# of events = 80)
Control (# of events = 155)

HR = 0.57 (0.40, 0.83), p = 0.003

**CardioMEMS – CHAMPION Study**

Treatment (# of events = 127)
Control (# of events = 189)

HR = 0.69 (0.51, 0.94), p = 0.017


Shunt Valve Function deteriorated by 12 Months (TEE)

A. Widely Patent
B. Stenotic; narrowed/skewed
C. Occluded Shunt

<table>
<thead>
<tr>
<th></th>
<th>Patent (n=18)</th>
<th>Stenotic/Occluded (n=18)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vena Contracta</td>
<td>3.1 [3.0-3.8] mm</td>
<td>0 (0-2.5) mm</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>1.17±0.12 mm</td>
<td>1.05±0.12 mm</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Patients with patent shunts had higher baseline risk

Patients with patent shunts were:
- older
- worse comorbidity profile
- poorer exercise capacity
- lower LVEF
- worse hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Patent Shunts (N=18 at 12 mos)</th>
<th>Stenotic Shunts (N=18 at 12 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±9</td>
<td>64±9</td>
</tr>
<tr>
<td>DM / HTN / AFIB, %</td>
<td>78 / 82 / 71*</td>
<td>61 / 83 / 41</td>
</tr>
<tr>
<td>eGFR, mL·min⁻¹·1.73 m⁻²</td>
<td>49±16*</td>
<td>60±22</td>
</tr>
<tr>
<td>6-Minute Walk Distance, m</td>
<td>264±106*</td>
<td>328±105</td>
</tr>
<tr>
<td>Maggic Risk Score 1-yr mortality</td>
<td>25±9*</td>
<td>16±8</td>
</tr>
<tr>
<td>Frequency LVEF ≥ 0.40, %</td>
<td>22.2</td>
<td>16.7</td>
</tr>
<tr>
<td>LVEF HFrEF</td>
<td>23±7*</td>
<td>29±6</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>23±6**</td>
<td>19±9</td>
</tr>
<tr>
<td>Cardiac Index, L·min⁻¹·m⁻²</td>
<td>2.2±0.4*</td>
<td>2.5±0.5</td>
</tr>
</tbody>
</table>

*P<0.1, **P<0.05

One patient with a patent shunt at 12 months developed shunt closure by 24 months.
Hemodynamic Changes by Shunt Patency at 1-Year F/U

Patients with patent shunts were had more severe HF and worse prognosis at baseline:

- Older
- ↑ AF
- ↓ eGFR
- ↓ 6MWT
- ↓ LVEF
- ↑ PCWP, ↓ CO
- ↑ Maggic Risk Score 25% vs. 16% 1-yr mortality
Shunt patency was associated with improved late morbidity and mortality outcomes
Patients with patent shunt at 1-yr had stable right heart function (Qp:Qs = 1.17±0.12 mm, n=18)

<table>
<thead>
<tr>
<th>PATENT SHUNTS</th>
<th>Abnormal reference</th>
<th>Baseline</th>
<th>12-Month</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV Global Longitudinal Systolic Strain</td>
<td>&gt;-20%</td>
<td>-12.2 ± 5.3</td>
<td>-14.5 ± 5.4</td>
<td>0.052</td>
</tr>
<tr>
<td>RV Longitudinal Free Wall Systolic Strain</td>
<td>&gt;-20%</td>
<td>-12.9 ± 5.3</td>
<td>-17.1 ± 8.1</td>
<td>0.051</td>
</tr>
<tr>
<td>RV End-Diastolic Diameter (Base)</td>
<td>&gt;4.1 cm</td>
<td>4.4 ± 1.2</td>
<td>4.6 ± 0.8</td>
<td>0.165</td>
</tr>
<tr>
<td>RV End-Diastolic Diameter (Mid)</td>
<td>&gt;3.5 cm</td>
<td>3.6 ± 1.0</td>
<td>3.4 ± 0.4</td>
<td>0.670</td>
</tr>
<tr>
<td>RV End-Diastolic Length</td>
<td>&gt;8.3 cm</td>
<td>8.4 ± 0.9</td>
<td>8.9 ± 1.3</td>
<td>0.127</td>
</tr>
<tr>
<td>TAPSE</td>
<td>&lt;17mm</td>
<td>16.8 ± 3.4</td>
<td>17.0 ± 4.1</td>
<td>0.853</td>
</tr>
<tr>
<td>Tricuspid Annulus Tissue Doppler S'</td>
<td>&lt;9.5 cm/s</td>
<td>8.8 ± 2.2</td>
<td>9.2 ± 1.8</td>
<td>0.581</td>
</tr>
<tr>
<td>Tricuspid Annulus Tissue Doppler e'</td>
<td>&lt;7.8</td>
<td>9.4 ± 3.7</td>
<td>10.4 ± 4.0</td>
<td>0.519</td>
</tr>
<tr>
<td>RV Tei Index</td>
<td>&gt;0.54</td>
<td>0.53 ± 0.17</td>
<td>0.51 ± 0.16</td>
<td>0.918</td>
</tr>
<tr>
<td>Tricuspid Regurgitation grade (1-7):</td>
<td>3.8 ± 1.5</td>
<td>4.0 ± 1.6</td>
<td>0.709</td>
<td></td>
</tr>
<tr>
<td>PAP systolic pressure</td>
<td>&gt;25 mmHg</td>
<td>50.0 ± 11.7</td>
<td>46.2 ± 8.8</td>
<td>0.241</td>
</tr>
</tbody>
</table>

Source: Laval University Echo Core Lab
V-Wave Gen 2 Shunt “valveless”

- Interatrial Shunts
- Hourglass shape
- Secure and atraumatic septal retention
- Minimal ID 5.1 mm with venturi efficiency
- Full ePTFE encapsulation
- Channels flow
- Prevents late lumen loss
- Self-expanding Nitinol frame

Right Atrium — Interatrial septum — Left Atrium
Gen 2 valveless shunts had no late lumen loss after 6 month in non-diseased ovine model (2-3 mmHg L-R gradient)

Gen 1 “valved” at 3 months

Gen 2 “valveless” at 6 months
V-Wave RELIEVE-HF Pivotal RCT design

**Design**
- RCT, double-blind (patient and HF team)
- 400 randomized and 150+ roll-in patients at up to 100 sites (US, Canada, EU and Israel)
- 2-year anticipated enrollment schedule; Primary Analysis 1 year after last patient enrolled
- Adaptive design with interim analysis allowing randomization up to 600 patients

**Study Population**
- NYHA functional class III or ambulatory class IV HF irrespective of LVEF, with hx of HF hospitalization or elevated NT-proBNP, in the setting of GDMT

**Endpoints**
- Primary Effectiveness: Finkelstein-Schoenfeld hierarchical comparison of mortality, transplant/LVAD, HF hospitalization or equivalent, and 6MWT
- Primary Safety: Performance criteria for device-related MACNE
- Health economic metrics
RELIEVE – HF RCT Enrollment Design

Preliminary Screen & Eligibility Committee

Final Screen in Cath Lab If Pass TEE/RHC

Roll-In Arm 1-3 pts per site 100 pts

Fail Screen Exit Study

Randomize 1:1 400 pts*

Shunt Arm

Sham Control Arm

FU clinic visits at 1, 3, 6, 12, 18, 24 M and telephonic contacts at 9, 15, 21 M

Primary Analysis when last randomized patient at 12 M. Unblinding at 24 M or at Primary Analysis

Unblinded

TEE at 6 and 12 M for patency

Shunt

ROLL-IN ARM (Unblinded) ~ 100 patients

(PART1) RANDOMIZED ACCESS Blinded

(PART2) OPEN ACCESS – Unblinded, Control option to crossover to Treatment if eligible

Annual FU of implanted patients for 5 years

* Up to 600 pts per interim analysis

ROLL-IN ARM (Unblinded) ~ 100 patients

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Conclusions

• Interatrial shunting is feasible, safe, and associated with promising efficacy data in terms of hemodynamics, functional improvement, and reduction of cardiovascular events, in HFrEF and in HFpEF patients

• Ongoing and future randomized controlled pivotal trials designed to confirm the safety and effectiveness of interatrial shunting may support the addition of this approach to our armamentarium of heart failure therapies