Multizentrische klinische Ergebnisse und laufende klinische Studien

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Führt die IASD Implantation…

- zu einer Rechtsherzbelastung?
- zu mehr Schlaganfällen?
- zu einem dauerhaften li.-re. Shunt?
- zu reduziertem LAP?
- zu einer Verbesserung der Symptomatik?
- Zu weniger Krankenhauseinweisungen?

Ist die IASD Implantation…

Sicher ?

Effektiv ?
### Purpose
Evaluate Corvia Atrial Shunt safety and performance for patients with elevated left atrial pressure who remain symptomatic despite appropriate medical management.

### Enrollment
Subjects enrolled at 21 sites in the UK, Netherlands, Belgium, France, Germany, Austria, Denmark, Czech Republic, Australia, and New Zealand.

### Follow-up
Patients will be followed for 1 year and then annually for 3 years after index procedure and implant.

### Endpoints
1. **Safety endpoints:**
   - MACCE or systemic embolic event (excl. pulmonary thromboembolism), or
   - Explant within 6 months of implant

2. **Device performance endpoints:**
   - Successful implant (deployed at intended location during index procedure)
   - PCWP reduction & proof of left to right flow through the device at 6 months

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*2 patients not implanted as a result of 1) trans-septal puncture complication without further sequelae, and 2) perceived unsuitable atrial septal anatomy*
### MACCE EVENT

<table>
<thead>
<tr>
<th>Event</th>
<th>Six Months %</th>
<th>One Year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>4.7 (3/64)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1.5 (1/64)</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systemic Embolic Event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Implant Removal</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### EFFECTIVENESS

<table>
<thead>
<tr>
<th>Event</th>
<th>Six Months %</th>
<th>One Year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L→ R Shunt Flow (ECHO)</td>
<td>100 (49/49)</td>
<td>100 (48/48)</td>
</tr>
<tr>
<td>R→ L Shunt Flow (ECHO)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QP:QS</td>
<td>1.27 ± 0.24</td>
<td>1.28 ± 0.25</td>
</tr>
</tbody>
</table>

Implantation of an interatrial shunt device was successful, safe and well tolerated, reduces left atrial pressure during exercise and may be a novel strategy for the management of HFpEF.

- Sustained improvements in:
  - NYHA class (P<0.001)
  - QOL – MLWHF (P<0.001)
  - 6-minute walk distance (P<0.01)
- Sustained reduction in workload-corrected exercise PCWP at 6 months and one year (p<0.01)
- 95% survival at one year
- Sustained device patency confirmed at 6 months and one year by left-to-right shunting
- No evidence of device-related complications
REDUCE LAP-HF | study design

**Phase 2, randomized, blinded, sham-controlled trial**

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<th>Purpose</th>
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<th>Endpoints</th>
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<tbody>
<tr>
<td>Evaluate the peri-procedural safety and potential effectiveness (mechanistic effect) of the Corvia Atrial Shunt in HF patients with LVEF &gt;40%, elevated left sided filling pressures, and who remain symptomatic despite optimal Guideline Directed Medical Therapy (GDMT).</td>
<td>22 centers across the US, Europe, &amp; Australia.</td>
<td>at 1 month and then annually for a total of 5 years after index procedure or implant.</td>
<td>• Change in supine exercise PCWP compared to control group at 1 month</td>
</tr>
<tr>
<td></td>
<td>Participants enrolled n = 94</td>
<td></td>
<td>• % of patients that experience major adverse cardiac, cerebrovascular embolic, or renal events (MACCRE)</td>
</tr>
<tr>
<td></td>
<td>Participants randomized n = 44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Endpoints**

- Change in supine exercise PCWP compared to control group at 1 month
- % of patients that experience major adverse cardiac, cerebrovascular embolic, or renal events (MACCRE)

**Participants enrolled**

- n = 94

**Participants randomized**

- n = 44

**Treatment n = 22**

**Control n = 22**

*1 pt exited the study*


*primary objective: to evaluate mechanistic efficacy (lowering of PCWP with exercise) and periprocedural safety*
A 3mmHg reduction in PCWP has been reported to decrease mortality\(^2\).

REDUCE LAP-HF I – 12 months: safety profile


*P=NS, for safety outcomes at 12 months
DGK. REDUCE LAP-HF I – 12 months: secondary outcomes


- **6 Min Walk**
  - IASD: 16
  - Control: 13.6

- **KCCQ**
  - IASD: 10.5
  - Control: 8.1

- **HF Hosp Visits with IV diuresis**
  - IASD: 0.22
  - Control: 0.63

65% fewer HF events with iv diuresis per patient year
REDUCE LAP-HF I – 12 months: timing of events

A MACRE

Log-rank $P = .20$

Cumulative Incidence, %

<table>
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<tr>
<th>Time After Randomization, d</th>
<th>Treatment</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>30</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>90</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>180</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>270</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>365</td>
<td>14</td>
<td>12</td>
</tr>
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B Heart failure events requiring intravenous treatment

Log-rank $P = .08$

Cumulative Incidence, %

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<td>365</td>
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REDUCE LAP-HF I – safety after 12 months

Safety

- Device patency confirmed in all patients
- No device embolization / migration
- No strokes or transient ischemic attacks in the IASD-treated patients
- None of the IASD-treated participants developed persistent or permanent atrial fibrillation or atrial flutter through 12 months
- No differences in major adverse cardiac, cerebrovascular, or renal events (MACCRE)
- RV size slightly enlarged at 6 months, but stable at 12 months. RV function preserved.

Right ventricular and pulmonal effects

No change in RV parameters between 6- and 12-months post implant¹

¹Kaye D, et al. *Circ Heart Fail* 2016;
²Obokata et al, *JACC*, 2019

Shunt implant correlated with increases in pulmonary blood flow (Qp), pulmonary artery oxygen saturation, pulmonary artery compliance (PAC), and reduction in arterial elastance (pulmonary Ea).

Patients with increased PAC had a significant increase in exercise duration.²

Improved pulmonary vascular function may be due to enhanced perfusion of pulmonary circulation or pulmonary vasodilation due to increased blood oxygen content.²
Anticoagulation

- All get ASA 81 mg po qd indefinitely
- If on anticoagulation (e.g., DOAC, warfarin, clopidogrel) continue for at least 6 months
- If not on anticoag, Rx with clopidogrel x 6 mo.

Open-label study (n=64) showed low risk of stroke through 4 years of follow-up.¹

<table>
<thead>
<tr>
<th>Freedom from CVA</th>
<th>Pilot study (n=11)</th>
<th>REDUCE LAP-HF (n=64)</th>
<th>REDUCE LAP-HF I (n=22)</th>
<th>Combined (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>100%</td>
<td>98.5%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>2 year</td>
<td>100%</td>
<td>98.5%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>3 year</td>
<td>100%</td>
<td>98.5%</td>
<td>95.5%</td>
<td>98%</td>
</tr>
<tr>
<td>4 year</td>
<td>100%</td>
<td>97%^</td>
<td>95.5%</td>
<td>96%</td>
</tr>
<tr>
<td>5 year</td>
<td>100%</td>
<td>97%^</td>
<td>TBD</td>
<td>---</td>
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¹ Median FY 44.4M ² Median FU of 68.7M

Similar results across 3 studies with a combined 96% freedom from CVA through 4 years of follow-up.³⁻⁵

Corvia IASD trials - summary

**Pilot Study**
Observational study  
(n=11)

**REDUCE LAP-HF**
Observational study  
(n=64)

**REDUCE LAP-HF I**
Randomized, blinded, sham-controlled trial  
(n=44)

**REDUCE LAP-HF II**
Randomized, blinded, sham-controlled trial  
(n=626)

**OBJECTIVE**
Evaluate device safety & potential benefit at 30 days.

**RESULTS**
Evidence of significant PCWP drop and procedural safety at 30 days.1 NYHA & QoL improvements at 1 year.2

**OBJECTIVE**
Understand device safety & therapy performance in larger patient cohort.

**RESULTS**
Evidence of sustained PCWP drop and device patency at 6 & 12 months. Sustained symptom, 6MWT, QoL improvement through 3 years.3-5

**OBJECTIVE**
Evaluate peri-procedural safety & device effectiveness against control arm.

**RESULTS**
Demonstrated mechanistic effect. Improvement in HF events, symptoms, QoL vs. control at 1 year. 100% shunt patency at 1 year.6,7

**OBJECTIVE**
Evaluate safety & clinical efficacy against control arm in powered study.

**RESULTS**
Available 2022.

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IASD therapy ist technisch sicher durchführbar und sicher hinsichtlich Rechtsherzbelastung und Schlaganfallrisiko. Sie führt zu einer relevanten Senkung des LAP und zeigt vielversprechende Ergebnisse zu HF Symptomatik und Hospitalisierung.
# REDUCE LAP-HF II study design

## Purpose
Evaluate the clinical efficacy and safety of the Corvia Atrial Shunt in HF patients with LVEF >40%, elevated left sided filling pressures, and who remain symptomatic despite optimal Guideline Directed Medical Therapy (GDMT).

## Enrollment
Up to 60 US sites and 28 sites in Europe, Australia and Japan. Start date was Q2 2017. Enrollment is complete.

## Follow-up
1 year and annually for a total of 5 years after index procedure or implant. Cross-over to treatment group allowed at ≥24 months post-control procedure. If patient crosses over they are followed for an additional 5 years.

## Primary Endpoint
- Composite of:
  - Cardiovascular mortality or first non-fatal, ischemic stroke through 12m
  - Rate of HF admissions or IV diuresis, up to 24m
  - Change in KCCQ score between baseline & 12m

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**Randomization completed – Results expected in 2022**

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| Evaluate the clinical efficacy and safety of the Corvia Atrial Shunt in HF patients with LVEF >40%, elevated left sided filling pressures, and who remain symptomatic despite optimal Guideline Directed Medical Therapy (GDMT). | Up to 60 US sites and 28 sites in Europe, Australia and Japan. Start date was Q2 2017. Enrollment is complete. | 1 year and annually for a total of 5 years after index procedure or implant. Cross-over to treatment group allowed at ≥24 months post-control procedure. If patient crosses over they are followed for an additional 5 years. | Composite of:
- Cardiovascular mortality or first non-fatal, ischemic stroke through 12m
- Rate of HF admissions or IV diuresis, up to 24m
- Change in KCCQ score between baseline & 12m |

**Randomization completed – Results expected in 2022**

**Berry et al. Am Heart J, 2020**
### Purpose
Collect post market data in consecutive patients treated with the Corvia Atrial Shunt to further evaluate efficacy, safety and quality of life outcomes as a new treatment for patients with heart failure in a “real world” practice setting.

### Enrollment
Up to 500 subjects treated at up to 50 sites in Europe.

### Follow-up
Patients will be followed for 1 year and then annually for 5 years after index procedure and implant.

### Select Outcome Measures
- Implant procedure failures
- Device and or procedure related serious adverse cardiac events through 30 days
- Embolic stroke through 60 months
- All cause, CV and HF related mortality through 60 months
- Newly acquired persistent or permanent AF or atrial flutter through 60 months.
- NYHA, KCCQ, EQ-5D, 6MWT at all follow-up timepoints
- HF hospitalizations through 60 months
Vielen Dank!

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