Long-Term Effects of Atrial Shunt Device on Cardiac Structure and Function in HFpEF and HFmrEF

Results from the REDUCE LAP-HF II Randomized Clinical Trial

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The REDUCE LAP-HF II trial was funded by Corvia Medical, Inc. Clinicaltrials.gov identifier: NCT03088033

Disclosures

Research funding:

- ---> NIH U54 HL160273, R01 HL140731, R01 HL149423
- ---> AstraZeneca, Corvia, Novartis, Pfizer

Consulting / advisory board / steering committee:

---> Abbott, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Edwards Lifesciences, Eidos, Gordian, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, and Tenaya



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%
- ---> N=626 randomized (largest interventional HFpEF trial to date)
 - All patients underwent exercise RHC with peak exercise PCWP ≥25 mmHg
- ---> Primary outcome: hierarchical composite (win ratio)
 - CV death, non-fatal ischemic CVA, HF events, KCCQ overall 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])



Responder subgroup

• Pre-specified + post-hoc subgroup analyses:

- ---> Identified a potential responder subgroup:
 - Large subgroup: 50% of randomized patients (n=313)
 - Peak exercise PVR <1.74 WU + no pacemaker/ICD</p>
 - After 12 months of follow-up: Beneficial treatment response





HF events by responder status

24-month recurrent HF events analysis



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Longitudinal echo completion rates

- Echo required at baseline and 1-, 6-, 12-, 24-month visits
- Interpreted centrally at Univ. of Pennsylvania echo core lab





Shunt patency, flow direction



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Shunt patency rates during follow-up

- At each follow-up echo time point, there were some patients in whom shunt patency could not be evaluated on echo due to:
 - ---> Poor acoustic windows
 - ---> Color Doppler flow across septum missing

no. 24 mo.
% 71%
% 13%*
% 9%*
% 7%



*Approximately half of those not evaluable or not completed at Month 24 had a patent shunt at Month 12

Shunt patency, flow direction



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In shunt group (n=309):

- → 98% with evaluable echo at 24 months had a patent shunt
 → All echos with patent shunts showed LA→RA shunting except for 2 echos with bidirectional shunting
 → No isolated R→L shunting
 → Caveats:
 - Echos done in supine position
 - No exercise echo
 - Valsalva maneuver only done on the 1-month echo

Effect of shunt on echo parameters

• Statistical analysis:

---> Primary analysis :

- Modified intention-to-treat population (n=621)
 - 5 patients randomized to shunt did not undergo shunt implantation
- Change in key echo parameters in shunt vs. sham groups
- Mixed model repeated measures (MMRM) analyses
 - Allows inclusion of all patients at all time points
- ---> Secondary analyses:
 - Subgroup analyses in responders and non-responders (+interaction)
 - Comparison of shunt vs. sham on prevalence of markers of moderate or greater RV systolic dysfunction at 12- and 24-month visits



LV volume/systolic function parameters





LV diastolic function parameters





LA volume/function parameters





RV volume, RA size parameters





RV systolic function parameters





Valvular regurgitation parameters





Echo hemodynamic parameters





Effect of atrial shunt on cardiac structure/function

Summary of changes over time (compared to sham)	Interpret
LV and LA get smaller	Shunt is unloadir
LV longitudinal systolic function gets better	Shunt is unloadir
LA emptying fraction gets better	Shunt is unloa
LA pressure goes down	Shunt is unloa
Degree of MR goes down (-0.2 grades)	Shunt is unloa
RA and RV get larger	Shunt is working
Degree of TR goes up (+0.2 grades)	Effect of RA/R
No difference in PASP and RA pressure between groups	Shunt ≠ hemody
No difference in RV systolic function between groups	RV function is



ng left heart ng left heart ading LA ading LA ading LA g (LA \rightarrow RA) V dilation namic stress preserved



Responders vs. non-responders

Mean Z-score (SD of difference [shunt-sham]) across all post-randomization time points (1, 6, 12, 24 months) **RV/LV** ratio¹ **RVESV**^T **RVEDV**[†] **RVEF** A velocity **RA** pressure **Cardiac output** E/A ratio PASP **Responders Non-responders** Lateral a' velocity 0.2 0.4 0.6 0.8 1.0 -0.2 -0.4 0.0

- Z-score method used to compare across echo parameters on a uniform scale
- Top 10 most differential treatment responses (responders vs. non-responders) shown
- 4 echo parameter treatment effects were significantly different between responders vs. non-responders (P_{interaction} <0.05):
 - ---> RV/LV volume ratio, RV end-systolic volume, RV end-diastolic volume, transmitral A velocity

*P<0.05 vs. sham, **P<0.01 vs. sham, ***P<0.001 vs. sham. \dagger Interaction P<0.05



Responders vs. non-responders



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 <p>
 ↑Left heart unloading + ↑LA function →
 ↓RV enlargement + ↑RV systolic function →
 ↑delivery of shunted blood through lungs
 = preserved LV cardiac output
 ↓MPROVED
 ₀UTCOMES

PPM = permanent pacemaker; †Interaction P<0.05

Responders vs. non-responders



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- Responders (peak PVR <1.74 and no PPM/ICD):
 ↑Left heart unloading + ↑LA function →
 ↓RV enlargement + ↑RV systolic function →
 ↑delivery of shunted blood through lungs
 = preserved LV cardiac output
- Non-responders (peak PVR ≥1.74 <u>or</u> PPM/ICD): ↑PV enlargement but no improvement in

 \uparrow RV enlargement but no improvement in RV systolic function $\rightarrow \downarrow$ left heart unloading, \downarrow improvement in LA function $\rightarrow \downarrow$ delivery of shunted blood through lungs

= \uparrow **RA pressure +** \downarrow **LV cardiac output**



PPM = permanent pacemaker; †Interaction P<0.05

Prevalence of RV dysfunction at follow-up

• Significant RV systolic dysfunction defined based on presence of 1 or more of the following 4 markers:

- ---→ **RVEF <40%**
- ---> RV tissue Doppler s' velocity <9 cm/s
- ---> TAPSE <1.4 cm
- ---> Greater than mild RV dysfunction (qualitative grading)
- Analysis done on 12- and 24-month echos



Prevalence of RV dysfunction at follow-up

• RV systolic dysfunction defined based on presence of 4 markers: RVEF <40%, RV s' <9 cm/s, TAPSE <1.4 cm, or >mild RV dysfunction (qualitative)



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Take home points

• **REDUCE LAP-HF II trial of Corvia Atrial Shunt Device:**

- ••• Overall neutral but subgroup analyses identified large responder group with peak exercise PVR <1.74 WU + no pacemaker/ICD: ↓HF events, ↑KCCQ improvement
- ---> The most comprehensive echo evaluation to date in a pivotal HFpEF RCT
- 98% shunt patency at 24 months in patients with evaluable echos
- Effect of atrial shunt device (vs. sham) on echo parameters:
 - \longrightarrow \downarrow LV size, \uparrow LV function, \downarrow LA pressure, \uparrow LA function
 - \rightarrow \uparrow RV size, \uparrow RA size, with no evidence of worse RV systolic function
- Responder subgroup: More favorable changes in cardiac structure/function compared to non-responders (supports responder hypothesis and mechanism)
- RESPONDER-HF: Ongoing RCT of Corvia Atrial Shunt in responder population



Acknowledgements

- Patients enrolled in the REDUCE LAP-HF II trial
- U. Penn Echo Core Lab:
 - ---> Frank Silvestry, MD
 - ---> Bonnie Ky, MD
 - ---> Amanda (Laney) Smith, RDCS
- REDUCE LAP-HF II trial site PIs and study coordinators



