# HFpEF in Focus: Scientific Rationale for the RESPONDER-HF Trial

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CRF<sup>®</sup> TECHNOLOGY AND HEART FAILURE THERAPEUTICS

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# **Corvia Atrial Shunt Device**



- Self-expanding nitinol cage
- Double-disc, flush with LA septum
- Single, 8-mm shunt diameter
- REDUCE LAP-HF I: ↓Exercise PCWP at 1 month

# Proposed mode of action: dynamic decompression of overloaded LA by shunting blood from LA $\rightarrow$ RA (Qp:Qs 1.2-1.3)



# **REDUCE LAP-HF II (n=626): Primary results**





Shah SJ, et al. Lancet 2022

### Are atrial shunts harmful in HFpEF?

### **RELIEVE-HF HFpEF group (LVEF ≥40%)**





Stone GW, et al. Circulation 2024

# **REDUCE LAP-HF II: Pre-specified subgroups**





Shah SJ, et al. *Lancet* 2022

# **REDUCE LAP-HF II: Responder analyses**

### Pre-specified + post-hoc subgroup analyses:

- ---> Identified a potential responder 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





Borlaug BA...Shah SJ Circulation 2022

### Effect of shunt on KCCQ across peak exercise PVR



Change in KCCQ from baseline to 12 months



Borlaug BA...Shah SJ. Circulation 2022

# **Peak PVR vs.** \Delta **PCWP-** \Delta **RAP difference**



- Prior to randomization, patients with ↑peak exercise PVR had:
   → ↓Augmentation of PCWP
   → ↑Augmentation of RAP
- Which leads to lower △ PCWP-△ RAP difference during exercise
  - ---> In patients with ↑peak PVR, RA pressure is rising much more relative to the rise in LA pressure
  - $\longrightarrow$  Not optimal for L $\rightarrow$ R shunting



# **Peak PVR vs.** \Delta **PCWP-** \Delta **RAP difference**



- Therefore, patients with ↑PVR at peak exercise have ↓PCWP-RAP gradient at peak exercise
  Conversely, patients with ↓PVR at peak exercise have↑PCWP-RAP gradient during exercise, which is
  - optimal for  $L \rightarrow R$  shunting and unloading of the LA
- May explain why \U224 PVR<sub>peak</sub> (<1.74 WU) were treatment responders

# Importance of recognizing latent PVD in HFpEF





Oakland HT, Shah SJ. JACC Heart Fail 2023

### **REDUCE LAP-HF II: Responder analyses**

### 2-year HF event rate analysis: atrial shunt vs. sham



♥<u>CRF'</u> TH1

Borlaug BA...Shah SJ. Circulation 2022; Gustafsson F...Shah SJ. JACC Heart Fail 2024

# Efficacy and safety of atrial shunts in HFpEF

### **Depends on phenotype...**





# Efficacy and safety of atrial shunts in HFpEF

#### **Depends on phenotype...**





# Longitudinal echocardiographic analysis



• **Responders** (peak PVR <1.74 <u>and</u> no PPM/ICD):  $\uparrow$  Left heart unloading +  $\uparrow$  LA function  $\rightarrow$   $\downarrow$  RV enlargement +  $\uparrow$  RV systolic function  $\rightarrow$   $\uparrow$  delivery of shunted blood through lungs = preserved LV cardiac output

**PPM = permanent pacemaker;** †Interaction P<0.05



Patel RB...Shah SJ. JAMA Cardiol 2024

# Longitudinal echocardiographic analysis



- **Responders** (peak PVR <1.74 <u>and</u> no PPM/ICD):  $\uparrow$  Left heart unloading +  $\uparrow$  LA function  $\rightarrow$   $\downarrow$  RV enlargement +  $\uparrow$  RV systolic function  $\rightarrow$   $\uparrow$  delivery of shunted blood through lungs = preserved LV cardiac output  $\Longrightarrow$  MPROVED OUTCOMES
- **Non-responders** (peak PVR  $\geq$  1.74 or PPM/ICD):

↑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 = ↑RA pressure +  $\downarrow$ LV cardiac output



PPM = permanent pacemaker; †Interaction P<0.05

Patel RB...Shah SJ. JAMA Cardiol 2024

### **REDUCE LAP-HF II: 5-year primary results\***





### **Responder group: Components of the win ratio**

Outcome at 5 years	Responders (n=313)		P-valuo
	Atrial shunt	Sham control	r-value
CV death or non-fatal	9.3	10.0	0.61
ischemic stroke (95% CI)	(2.3-16.3)	(0.0-20.0)	0.01
CV death	7.4	7.6	0.66
(95% CI)	(1.1-13.7)	(0.0-16.6)	0.00
Non-fatal ischemic stroke	1.9	1.5	0 02
(95% CI)	(0.0-5.4)	(0.0-7.9)	0.02
Total rate of HF events	10	15	0.014
per 100 patient years	10	10	0.014
Delta KCCQ	19.4	7.2	0.007
(median [IQR])	(8.1, 36.7)	(-9.8, 19.7)	0.007
Win ratio	1.44 (0.98, 2.12)		0.066



### **Responder group: Cumulative HF events at 5 years**





### **Responder group: ΔKCCQ-OSS** (baseline to 60 months)





# **RESPONDER-HF:** Trial design

#### **REDUCE LAP-HF II**

#### 50% of population benefited significantly despite overall neutral trial



**OVERALL POPULATION** (n=626) Neutral primary outcome (win ratio=1)



#### **RESPONDER GROUP** (n=313)

Positive outcome (win ratio=1.5, p=0.004) in patients with normal exercise PVR (<1.74 WU) and no cardiac rhythm device

#### **RESPONDER-HF**

**Confirmatory trial to validate Responder Group** outcomes observed in REDUCE LAP-HF II

Randomized, double-blinded, **Study Design** sham-controlled Enrolling Q4 '22 Status Approximately 60 sites **Clinical Sites Participants** 260 randomized 1:1 Population



#### HFpEF & HFmrEF (EF≥40%)

#### **Primary Composite Endpoint**

- Rate of total HF events up to 24 months, analyzed when last randomized patient reaches 12 months
- KCCQ change from baseline to 12 months

#### **Major Secondary Endpoint**

Cardiovascular mortality through 12 months



# **RESPONDER-HF: Screening committee**



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

### **RESPONDER-HF: Screening committee**



Example of a patient who was screened out of RESPONDER-HF by screening committee despite meeting all noninvasive I/E criteria



# **RESPONDER-HF: Screening committee**

#### Echocardiographic evidence of significant pulmonary vascular disease







### Conclusions

- Corvia Atrial Shunt Device:
  - ---> Reduces exercise PCWP
  - → ↓**HF events and** ↑**health status in responders** (Ex. PVR <1.74 + no PM/ICD)
  - → **↑HF events and ↓health status in non-responders** (Ex. PVR ≥1.74 WU <u>or</u> PM/ICD)
- HFpEF is heterogeneous: one size does not fit all!
- Exercise-based phenotyping: critical for patient evaluation
- RELIEVE-HF HFpEF group: sick patients with exaggerated nonresponder phenotype → poor response to atrial shunt
- Both REDUCE LAP-HF II and RELIEVE-HF provide strong rationale for RESPONDER-HF confirmatory trial

