# REDUCE LAP-HF II Pivotal Trial:

## *Primary Results*

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# Disclosure statement of financial interest

- Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below:

| Affiliation/Financial Relationship | Company |
|---|---|
| Grant/Research Support | **Corvia**, Pfizer |
| Consulting Fees/Honoraria | AstraZeneca, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Edwards Lifesciences, Eidos, Imara, Ionis, Merck, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Roche, Shifamed, and Tenaya |
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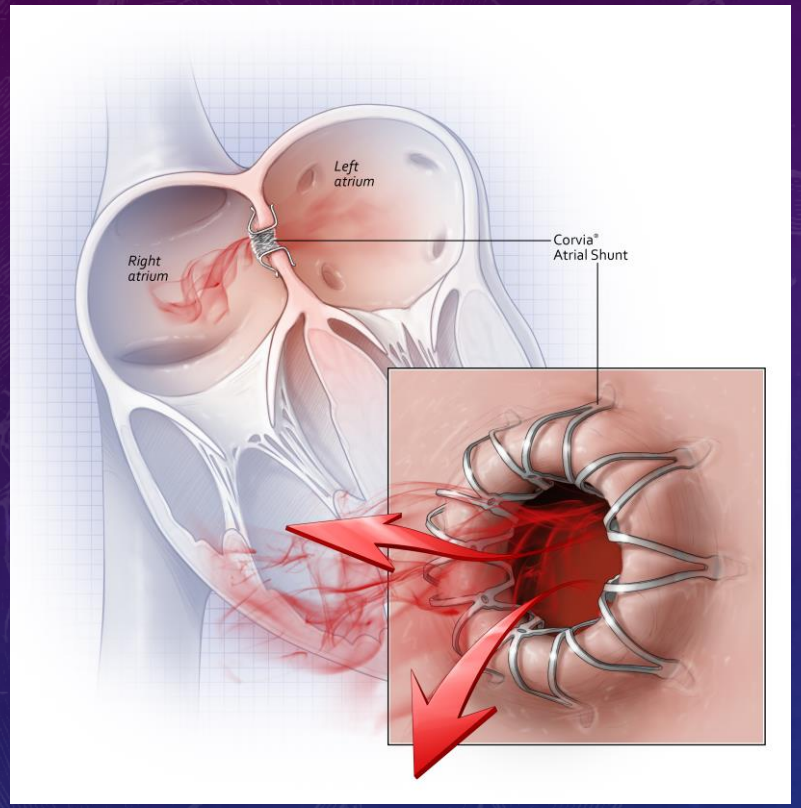
| Ownership/Founder | None |
| Intellectual Property Rights | None |
| Other Financial Benefit | None |

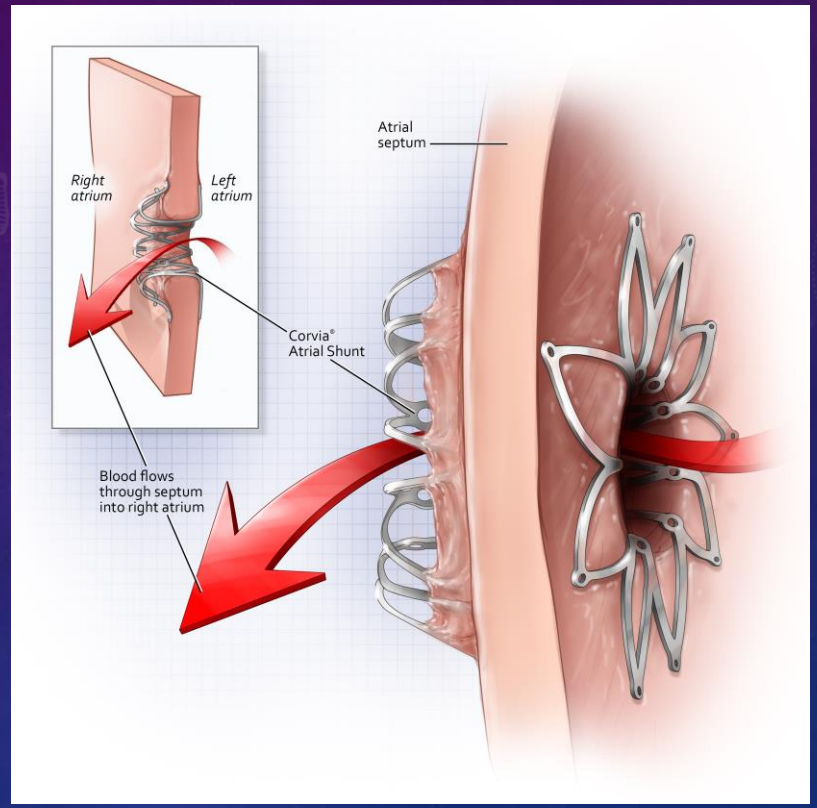
- Faculty disclosure information can be found in the app.

# REDUCE LAP-HF II study leadership

- **Steering committee:**
  - ✓ Sanjiv J. Shah, MD (co-PI)
  - ✓ Martin B. Leon, MD (co-PI)
  - ✓ Donald E. Cutlip, MD
  - ✓ Scott D. Solomon, MD
  - ✓ Dirk J. van Veldhuisen, MD, PhD
- **Sponsor:**
  - ✓ Jan Komtebedde, DVM
- **Former SC members:**
  - ✓ Laura Mauri, MD, MSc
  - ✓ Ted Feldman, MD

# Corvia Atrial Shunt




- **Self-expanding nitinol cage**
- **Double-disc, flush with LA septum**
- **Single, 8-mm shunt diameter**

**Proposed mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA → RA (Qp:Qs 1.2-1.3)**

Feldman T…Shah SJ. *Circ Heart Fail* 2016

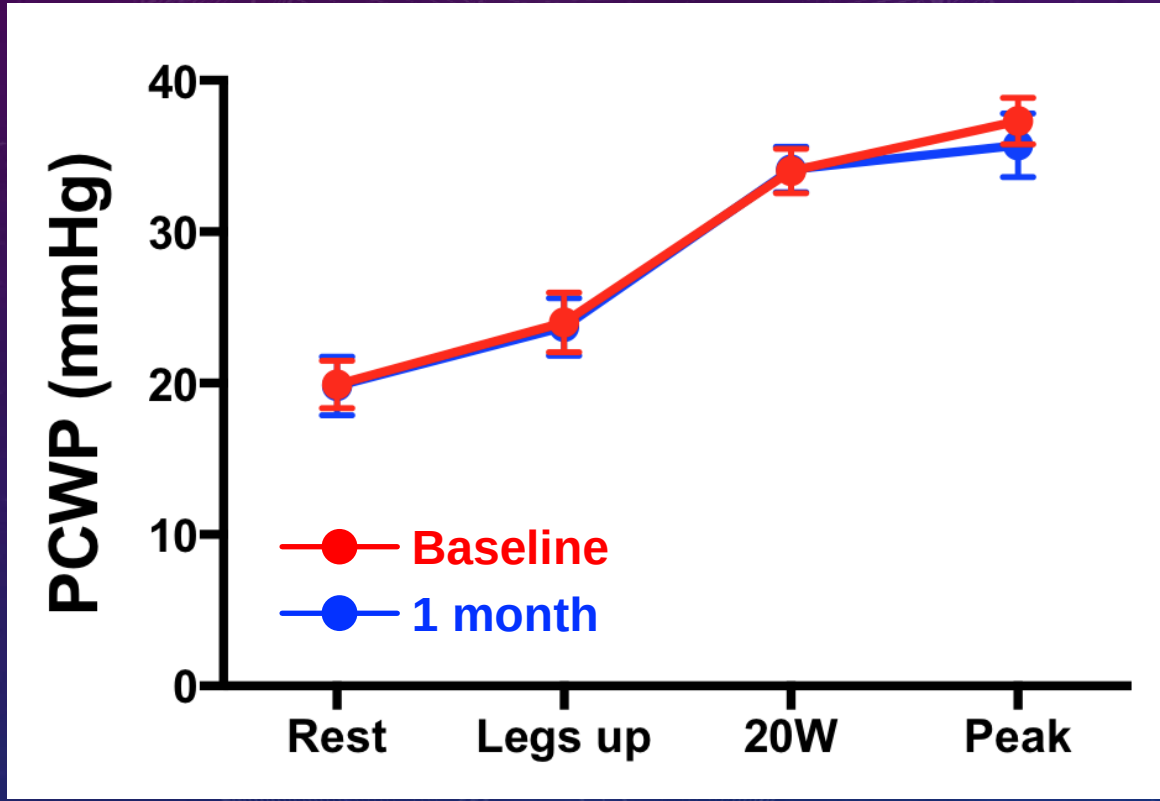
# Corvia clinical evidence pipeline

***Pilot Study → CE Mark Study → REDUCE LAP-HF I → REDUCE-LAP HF II***

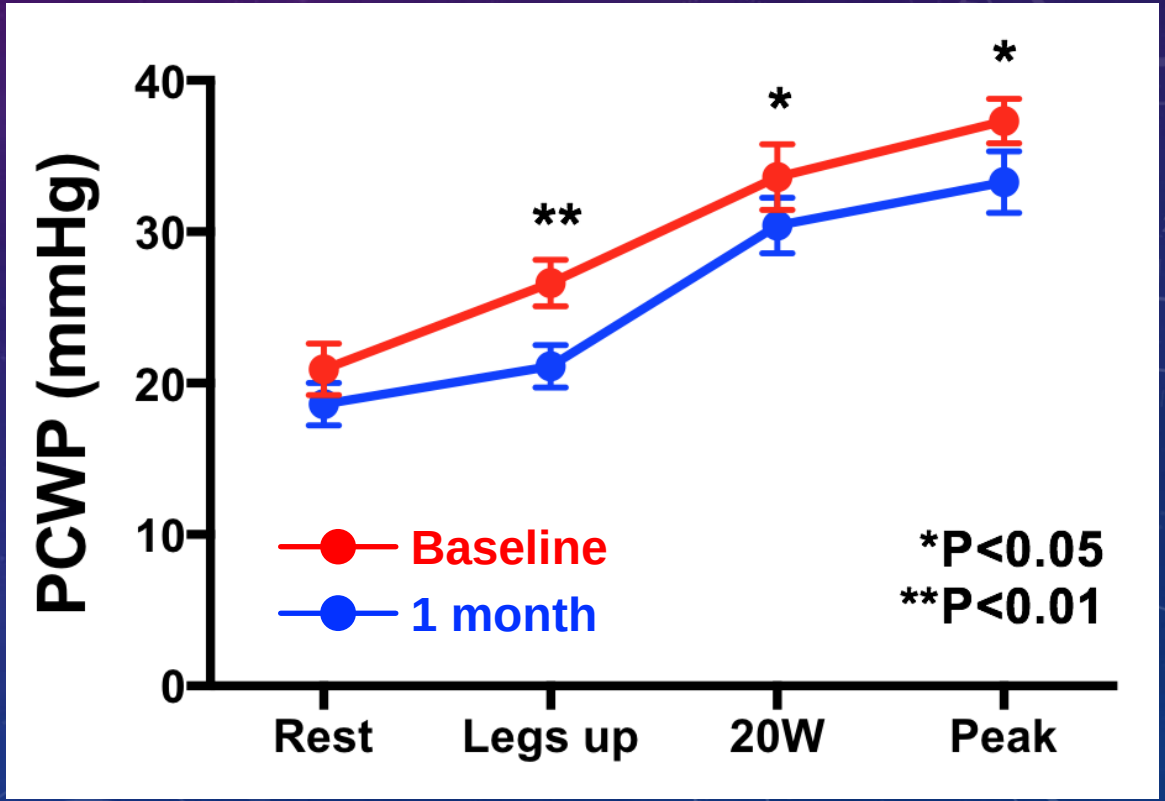
- **Pilot study (n=11):** non-randomized, single-arm
  - ✓ Completed (Søndergaard L, et al. *Eur J Heart Fail* 2014)
- **CE Mark Study (n=64):** non-randomized, single-arm
  - ✓ Completed (Hasenfuß G…Kaye D. *Lancet* 2016; Kaye D, et al. *ESC Heart Fail* 2019)
- **REDUCE LAP-HF I (n=44):** RCT mechanistic study
  - ✓ Completed (Feldman T…Shah SJ. *Circulation* 2017; Shah SJ, et al. *JAMA Cardiol* 2018)
- **REDUCE LAP-HF II (n=626):** RCT pivotal study
  - ✓ Completed (Shah SJ…Leon MB. *Lancet* 2022)

# REDUCE LAP-HF I RCT: ΔPCWP at 1 mo.

## CONTROL



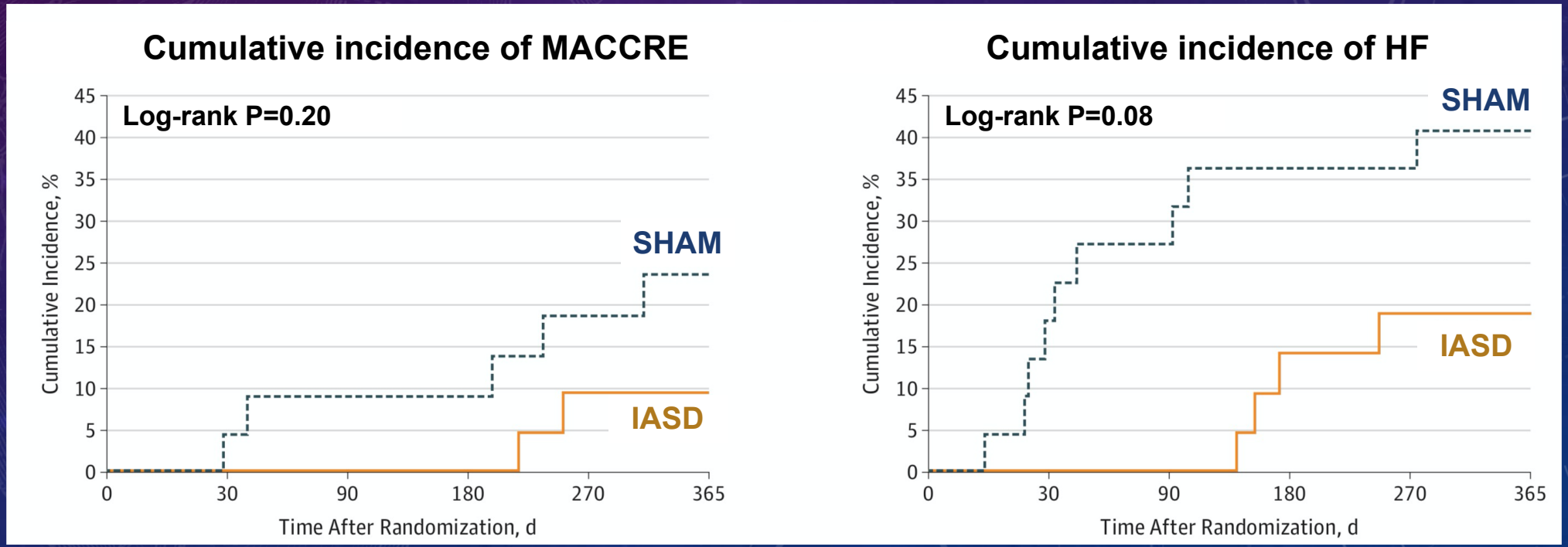

## CORVIA IASD




Feldman T…Shah SJ. *Circulation* 2018

# REDUCE LAP-HF I RCT: Outcomes at 1 yr.

| Endpoint | Atrial shunt device (N=21) | Sham procedure (N=22) | P-value |
|---|---|---|---|
| NYHA class | -1 (-1 to 0) | 0 (-1 to 0) | 0.08 |
| 6MWT distance, meters | +16 (-57 to 30) | +13.6 (-10 to 72) | 0.31 |
| KCCQ clinical summary score | +10.4 (-6.5 to 26.0) | +3.1 (-4.2 to 18.8) | 0.25 |




Shah SJ, et al. *JAMA Cardiol* 2018

# Hypothesis

- Placement of the Corvia Atrial Shunt in patients with HF, EF ≥40%, and exercise PCWP ≥25 mmHg, compared to sham control, will have:
  - ✓ Similar rates of CV death and non-fatal stroke
  - ✓ Lower rates of HF events (first and recurrent)
  - ✓ Improved health status (KCCQ)

Berry N…Shah SJ. *Am Heart J* 2020

# Design overview

- Prospective, multi-center, randomized (1:1), sham-controlled, blinded trial
  - ✓ 89 sites in US, Canada, Europe, Australia, Japan
  - ✓ Rigorous echocardiographic and invasive exercise hemodynamic screening
  - ✓ All patients underwent femoral venous access and visualization of the interatrial septum (ICE or TEE)
  - ✓ Cross-over allowed at 24 months

Berry N…Shah SJ. *Am Heart J* 2020

# Key inclusion/exclusion criteria

- Inclusion criteria:
  - ✓ History of chronic HF
  - ✓ Age ≥40 years
  - ✓ NYHA II or III symptoms
  - ✓ LVEF ≥40%
  - ✓ Exercise PCWP ≥25 mmHg
  - ✓ PCWP-RA pressure ≥5 mmHg
- Exclusion criteria:
  - ✓ Cardiac index <2.0 L/min/$m^2$
  - ✓ Previous EF <30%
  - ✓ CVA, TIA, DVT, PE in past 6 mo.
  - ✓ Greater than mild RV dysfunction/enlargement
  - ✓ Moderate or greater TR
  - ✓ Resting RA pressure >14 mmHg
  - ✓ Resting PVR >3.5 WU
  - ✓ BMI ≥45 kg/$m^2$
  - ✓ eGFR <25 ml/min/$m^2$

Berry N…Shah SJ. *Am Heart J* 2020

# Primary and secondary endpoints

- Primary efficacy endpoint:
  - ✓ Hierarchical composite endpoint:
    - ⇢ CV death or non-fatal ischemic stroke through 12 months
    - ⇢ Total HF events (first and recurrent) through 24 months
    - ⇢ Change in KCCQ overall summary score (baseline to 12 months)
- Secondary efficacy endpoints:
  - ✓ Total HF events through 24 months
  - ✓ Change in KCCQ overall summary score (baseline to 12 mo.)
  - ✓ Change in NYHA class (baseline to 12 mo.)

Berry N…Shah SJ. *Am Heart J* 2020

# Safety endpoints

- Composite safety endpoint (through 12 months):
  - ✓ Cardiovascular death
  - ✓ Non-fatal ischemic stroke
  - ✓ New-onset or worsening renal function (↓GFR >20 mL/min/1.73 $m^2$)
  - ✓ Major cardiac events: cardiac death, MI, cardiac tamponade, or emergency cardiac surgery
  - ✓ Thromboembolism (TIA, systemic embolization)
  - ✓ Newly acquired atrial fibrillation or atrial flutter
  - ✓ ≥30% in ↑RV size or ≥30% ↓TAPSE

Berry N…Shah SJ. *Am Heart J* 2020

# Statistical analysis

- Power calculation based on REDUCE LAP-HF I trial:
  - ✓ Assumptions:
    - ⇢ Combined CV death/CVA rate of 5% in each arm
    - ⇢ HF event rate of 0.39 per year in shunt arm, 0.50 per year in sham arm
    - ⇢ KCCQ improvement of +13 (SD 20) in shunt arm, +8 (SD 20) in sham arm
  - ✓ Sample size of n=304 per arm → 85% power, $\alpha$=0.05 (assumed a drop-out rate of 7.5% in each arm)
- Primary endpoint analysis:
  - ✓ Finkelstein-Schoenfeld hierarchical composite endpoint
    - ⇢ Combines time-to-event (CV death, CVA), recurrent (HF events), and continuous (KCCQ) endpoints
  - ✓ Win ratio (1 = neutral, >1 = treatment better, <1 sham better)

Berry N…Shah SJ. *Am Heart J* 2020

# Patient disposition flow chart

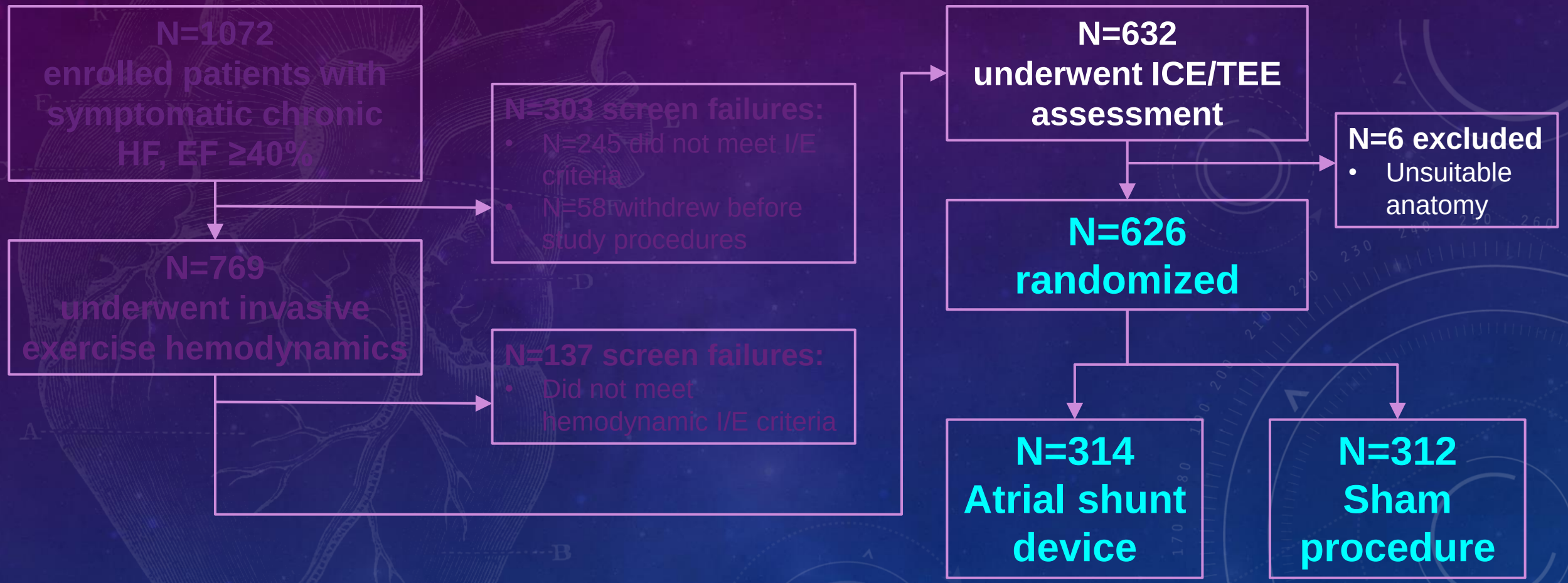
**N=1072**
**enrolled patients with symptomatic chronic HF, EF ≥40%**

**N=303 screen failures:**
- N=245 did not meet I/E criteria
- N=58 withdrew before study procedures

**N=769**
**underwent invasive exercise hemodynamics**

**N=137 screen failures:**
- Did not meet hemodynamic I/E criteria

# Patient disposition flow chart



# Baseline characteristics

- Older, majority (62%) women
- Multiple comorbidities
- Most (78%) NYHA class III
- Majority (93%) HFpEF (EF≥50%)
- Very poor health status (median KCCQ-OSS 46)
- ↓Exercise capacity, ↑NTproBNP
- **Median resting PCWP = 18 mmHg but 29% of enrolled patients had resting PCWP < 15 mmHg**
- **All patients had peak exercise PCWP ≥25 mmHg and 95% of patients had PCWP/CO ratio > 2.0**

# Baseline characteristics

| Characteristic | Atrial shunt device (N=314) | Sham procedure (N=312) |
|---|---|---|
| Age, years | 73 | 72 |
| Female | 64% | 59% |
| Body mass index, kg/m$^2$ | 31.6 | 32.2 |
| Hypertension | 89% | 87% |
| Diabetes | 37% | 37% |
| Atrial fibrillation | 50% | 53% |
| NYHA class III | 77% | 78% |
| HF hospitalization in last 12 mo. | 26% | 32% |
| NTproBNP, pg/ml (sinus rhythm) | 301 | 344 |
| NTproBNP, pg/ml (atrial fibrillation/flutter) | 1008 | 1230 |
| KCCQ-OSS | 46 | 45 |
| HFpEF (EF ≥50%) | 93% | 93% |

Median values shown for all continuous variables

# Baseline medications

| Medications | Atrial shunt device (N=314) | Sham procedure (N=312) |
|---|---|---|
| Loop diuretics | 83% | 81% |
| MRAs | 53% | 51% |
| SGLT2 inhibitors | 2% | 4% |
| Sacubitril/valsartan | 2% | 2% |
| ACE-inhibitors | 24% | 25% |
| Angiotensin receptor blockers | 39% | 37% |
| Beta-blockers | 70% | 70% |
| Oral anticoagulants | 47% | 52% |
| Aspirin | 37% | 40% |
| Other anti-platelet therapy | 11% | 12% |

# Echocardiography

| Echocardiographic parameters | Atrial shunt device (N=314) | Sham procedure (N=312) |
|---|---|---|
| LV ejection fraction, % | 60 | 60 |
| LV mass, g | 164 | 159 |
| LV GLS, % (absolute value) | 17.4 | 17.9 |
| E/A ratio | 1.1 | 1.1 |
| E/e' ratio (septal) | 14 | 14 |
| LA volume index, ml/m$^2$ | 33 | 31 |
| LA reservoir strain, % | 18 | 21 |
| TAPSE, mm | 20 | 20 |
| RA volume index, ml/m$^2$ | 26 | 24 |

Median values shown for all variables

***Of the overall cohort, 30% had abnormal LV GLS and 6% had abnormal TAPSE***

# Resting hemodynamics

| Hemodynamics | Atrial shunt device (N=314) | Sham procedure (N=312) |
|---|---|---|
| Heart rate, bpm | 70 | 70 |
| Systolic BP, mmHg | 144 | 143 |
| RA pressure, mmHg | 9 | 9 |
| PA mean, mmHg | 26 | 26 |
| PCWP, mmHg | 18 | 17 |
| PCWP-RAP gradient, mmHg | 9 | 8 |
| Cardiac output, L/min | 5.2 | 5.2 |
| PVR, WU | 1.5 | 1.5 |

Median values shown for all variables

***29% of patients had PCWP < 15 mmHg at rest (≥25 mmHg during exercise)***

# Exercise hemodynamics

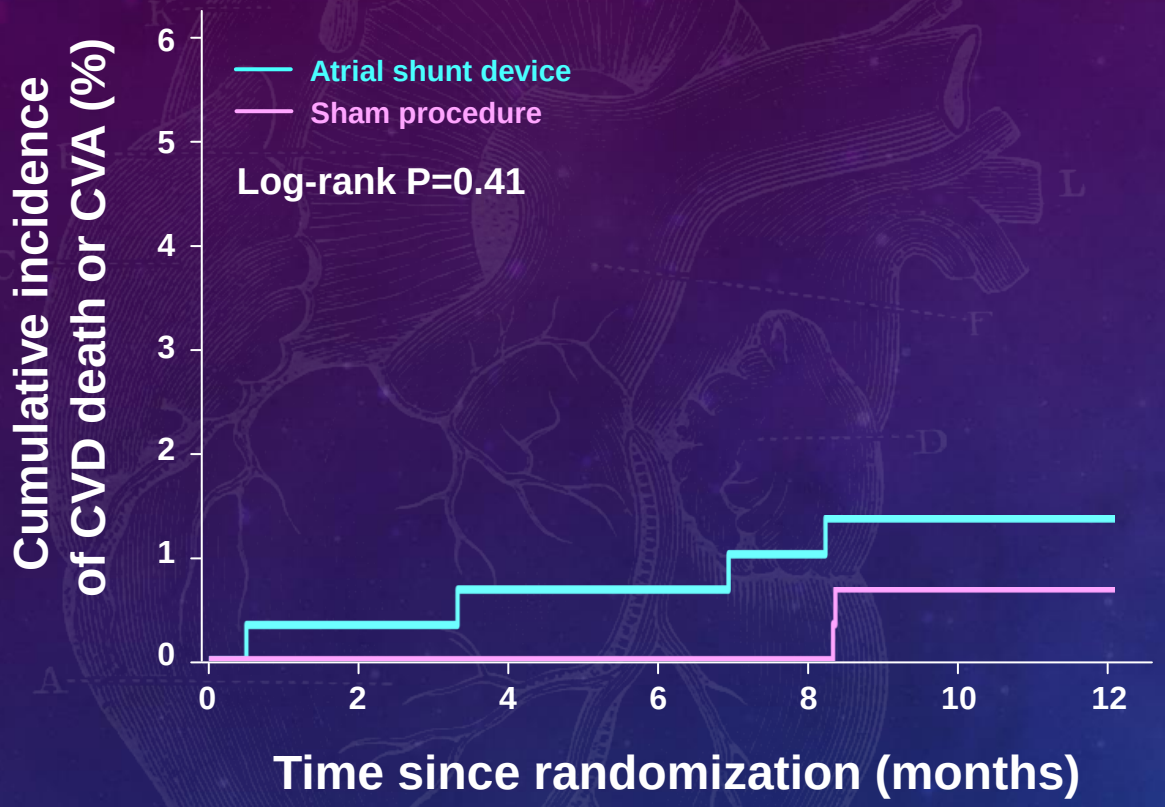
| Peak exercise hemodynamics | Atrial shunt device (N=314) | Sham procedure (N=312) |
|---|---|---|
| HR, bpm | 100 | 100 |
| SBP, mmHg | 154 | 156 |
| RAP, mmHg | 18 | 18 |
| PCWP, mmHg | 34 | 34 |
| PCWP-RAP gradient, mmHg | 16 | 16 |
| Cardiac output, L/min | 7.8 | 7.9 |
| PCWP/CO ratio (normal < 2.0) | 4.4 | 4.4 |
| PVR, WU | 1.3 | 1.3 |
| Workload, Watts | 40 | 40 |

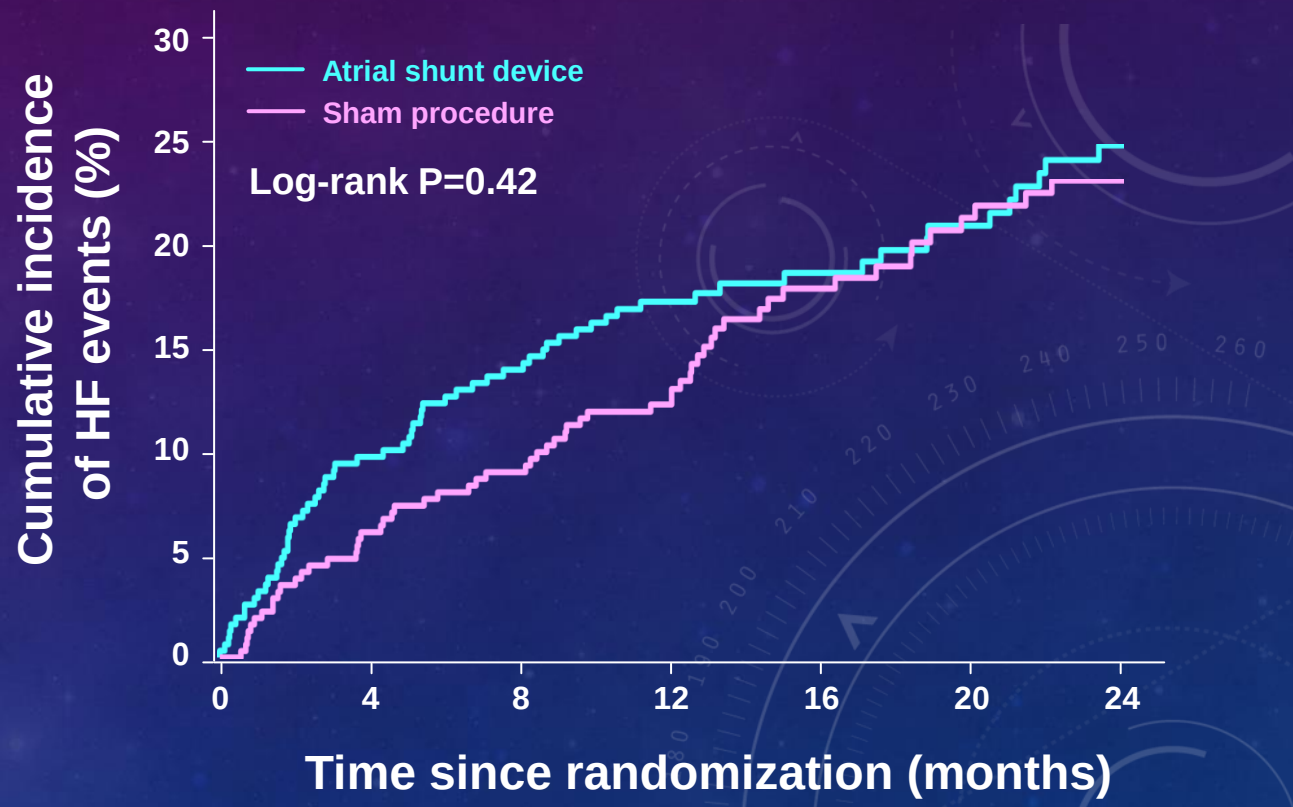
Median values shown for all variables

***95% of patients had abnormally high PCWP/CO ratio***

# RESULTS

# Primary composite endpoint




- Finkelstein-Schoenfeld p-value=0.85
- Win ratio: 1.0 (95% 0.8-1.2)

# Efficacy endpoints

| Efficacy endpoint | Atrial shunt device (N=309) | Sham procedure (N=312) | P-value |
|---|---|---|---|
| **CV death or non-fatal ischemic stroke** | 1% (4 events) | 1% (2 events) | 0.41 |
| **• CV death** | 1% (3 events) | 1% (2 events) | 0.65 |
| **• Non-fatal ischemic stroke** | <1% (1 event) | 0% (0 events) | 0.32 |
| **Total HF events per patient-year** | 0.28 | 0.25 | 0.45 |
| **Change in KCCQ-OSS** | 10.2 (-1.8, 26.8) | 9.4 (-2.1, 22.9) | 0.73 |
| **Change in NYHA class** | **-0.5 (-1.0, 0.0)** | **0.0 (-1.0, 0.0)** | **0.006** |

Modified intention-to-treat population (excludes 5 patients who did not receive shunt device in active treatment arm)

# Safety endpoints

| Safety endpoint | Atrial shunt device (N=309) | Sham procedure (N=312) | P-value |
|---|---|---|---|
| **Composite safety endpoint** | 38% | 31% | 0.11 |
| **New-onset worsening renal function** | 1% | 1% | 0.66 |
| **Major cardiac events** | **4%** | **1%** | **0.025** |
| • **Cardiac death** | 1% | 1% | 1.00 |
| • **Myocardial infarction** | 2% | <1% | 0.14 |
| • **Cardiac tamponade** | 1% | 0% | 0.95 |
| • **Emergency cardiac surgery** | <1% | 0% | 0.96 |
| **Embolic complications** | 0% | 0% | — |
| **Newly acquired atrial fibrillation/flutter** | 1% | 1% | 0.42 |
| **≥30% ↑RV size or ≥30% ↓TAPSE** | 30% | 25% | 0.15 |

Modified intention-to-treat population (excludes 5 patients who did not receive shunt device in active treatment arm)

# Additional results

- Vascular complications:
  - ✓ 18 events in 13 patients in atrial shunt arm (4% of patients; most of these events were access site hematomas)
  - ✓ 0 events in sham procedure arm
- Periodic blinding questionnaire at study visits:
  - ✓ In 96% of randomized patients, the patients and blinded study staff remained blinded to treatment allocation throughout the duration of the study

# Effect of COVID

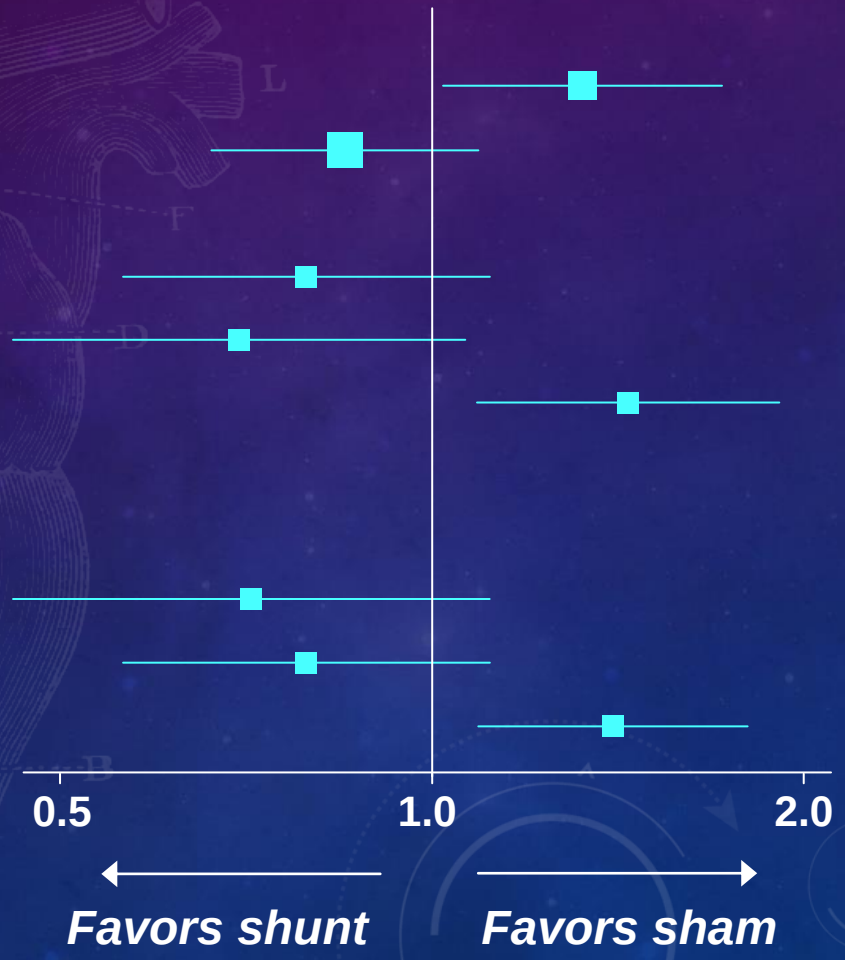
| Primary endpoint | Overall outcome | | Pre-COVID outcome | |
|---|---|---|---|---|
| | Win ratio (95% CI) | P-value | Win ratio (95% CI) | P-value |
| Composite endpoint | 1.0 (0.8, 1.2) | 0.85 | 1.1 (0.7, 1.5) | 0.78 |

| Components of the 1° endpoint | Atrial shunt device | Sham procedure | P-value | Atrial shunt device | Sham procedure | P-value |
|---|---|---|---|---|---|---|
| CV death/non-fatal ischemic CVA | 1% | 1% | 0.41 | 2% | 2% | 0.95 |
| Total HF events, per patient year | **0.28** | **0.25** | 0.45 | **0.36** | **0.38** | 0.82 |
| Mean change in KCCQ-OSS | +11.5 | +10.5 | 0.73 | +13.2 | +13.0 | 0.75 |

***HF event rates decreased in the COVID era, but there was no difference between treatment groups in the pre-COVID or COVID eras with respect to efficacy outcomes***

# Pre-specified subgroup analyses

| Subgroup | N | IRR (95% CI) | $P_{interaction}$ |
|---|---|---|---|
| **Sex** | | | 0.020 |
| • **Male** | **239** | **1.32 (1.01-1.71)** | |
| • Female | 382 | 0.85 (0.55-1.09) | |
| **RA volume index** | | | 0.012 |
| • Tertile 1 | 167 | 0.79 (0.57-1.11) | |
| • Tertile 2 | 168 | 0.70 (0.46-1.07) | |
| • **Tertile 3** | **168** | **1.43 (1.08-1.90)** | |
| **PA systolic pressure at 20W** | | | 0.002 |
| • Tertile 1 | 192 | 0.71 (0.46-1.11) | |
| • Tertile 2 | 202 | 0.80 (0.57-1.12) | |
| • **Tertile 3** | **202** | **1.40 (1.10-1.79)** | |




Statistical significance threshold: interaction p-value <0.05

# Summary

- Corvia Atrial Shunt treatment:
  - ✓ Reduces exercise PCWP compared to sham control
  - ✓ First atrial shunt therapy to complete phase 2 and 3 trials
- REDUCE LAP-HF II pivotal RCT (HF, EF ≥40%) with exercise hemodynamics (N=626): *largest device trial in HFpEF to date*
  - ✓ Majority (93%) HFpEF, typical HFpEF clinical characteristics
  - ✓ 29% had PCWP <15 mmHg at rest but ≥25 mmHg with exercise
- Placement of atrial shunt device did not reduce total rate of HF events or improve health status overall in HF with EF ≥40%
- **Subgroup analyses suggests a potential responder group**

# Clinical implications

ONE-SIZE-FITS-ALL APPROACH

**Heterogeneous group of patients with HFpEF**

**UNIFORM TREATMENT**

**IMPROVED**

**NO BENEFIT**

**WORSENED**

# REDUCE LAP-HF II: An enrichment trial

**Heterogeneous group of patients with HFpEF**

**REDUCE LAP-HF II:**
Enriched for hypothesized responders based on screening echo and exercise invasive hemodynamics

**TARGETED TREATMENT**

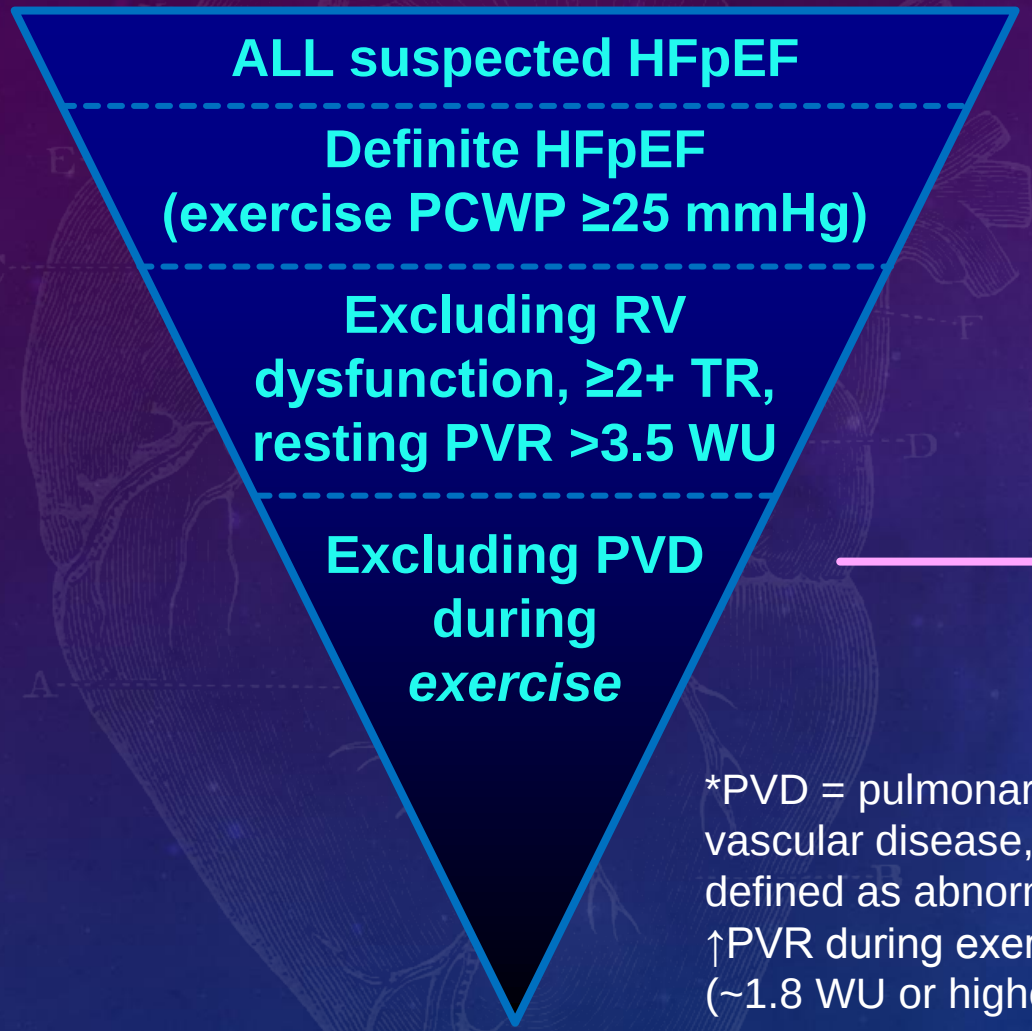
**IMPROVED (no exercise PVD)**

**NEUTRAL (overall)**

**WORSENED (exercise PVD)**

PVD = pulmonary vascular disease

# Future directions: ↑Precision medicine




**Most major pharma trials**

**REDUCE LAP-HF II trial**

**Large potential responder group for future trials of interatrial shunt devices (~67% of patients enrolled)**

*PVD = pulmonary vascular disease, defined as abnormal ↑PVR during exercise (~1.8 WU or higher)

# Simultaneous online publication

## Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial

*Sanjiv J Shah, Barry A Borlaug, Eugene S Chung, Donald E Cutlip, Philippe Debonnaire, Peter S Fail, Qi Gao, Gerd Hasenfuß, Rami Kahwash, David M Kaye, Sheldon E Litwin, Philipp Lurz, Joseph M Massaro, Rajeev C Mohan, Mark J Ricciardi, Scott D Solomon, Aaron L Sverdlov, Vijendra Swarup, Dirk J van Veldhuisen, Sebastian Winkler, Martin B Leon, on behalf of the REDUCE LAP-HF II investigators**

Shah SJ, et al. *Lancet* 2022

# Acknowledgements



- **Study patients and their families/caregivers**
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- Clinical events committee
  - ✓ Akshay Desai, MD; David Gossman, MD; Pablo Quintero, MD; David Thaler, MD
- Data safety monitoring board
  - ✓ Paul Hauptman, MD; Jeffrey Feinstein, MD; John Orav, PhD; Maggie Redfield, MD; Michael Rinaldi, MD
- Core labs
  - ✓ Echocardiography: Frank Silvestry, MD
  - ✓ Hemodynamics: Ethan Rowin, MD