What (Else) Have We Learned From REDUCE-LAP II?

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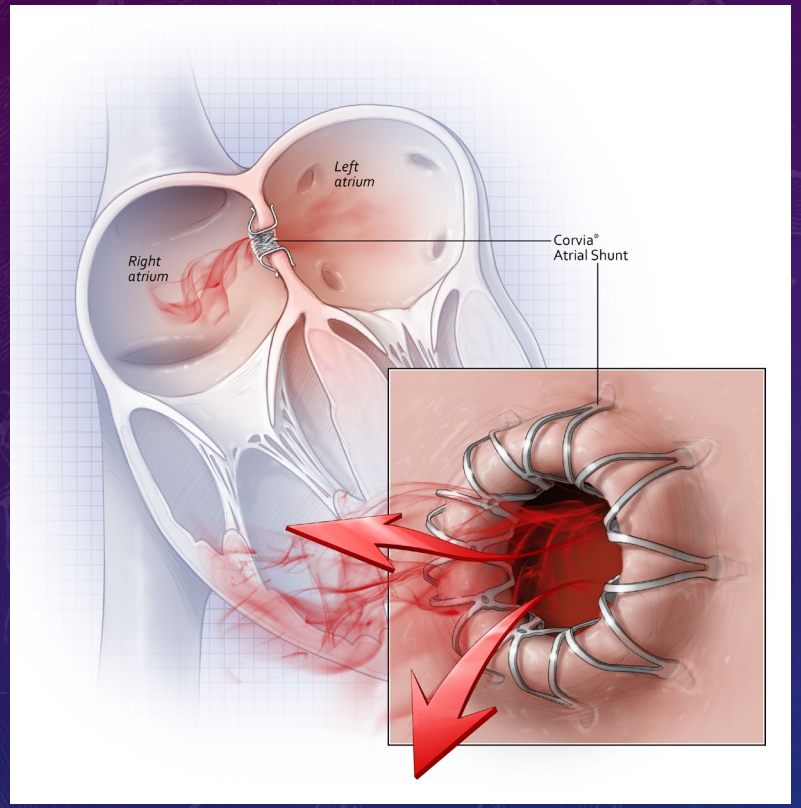
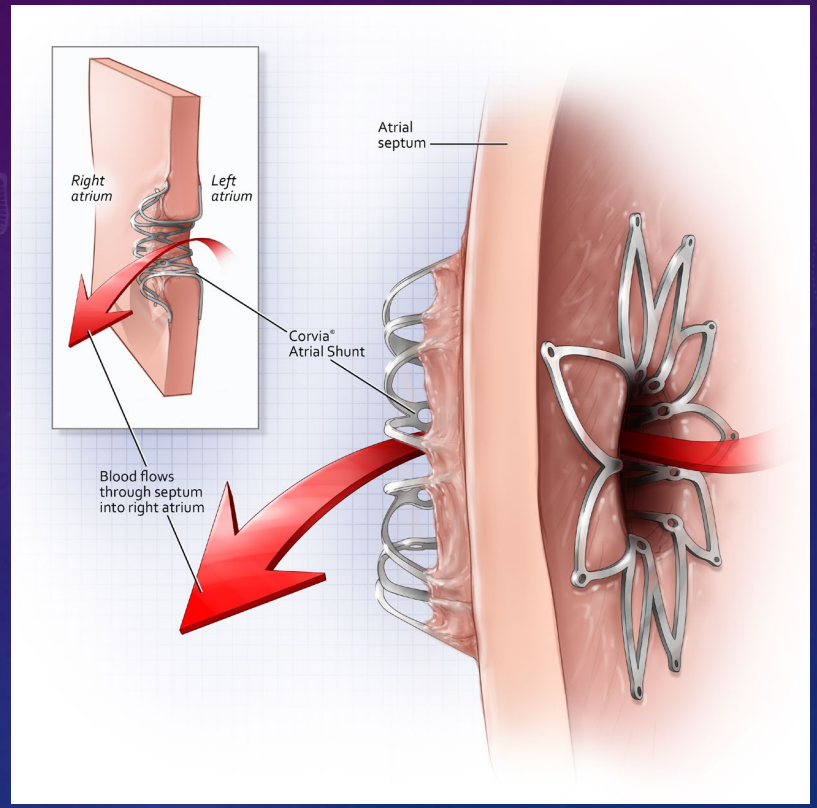
Corvia Atrial Shunt





- **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)

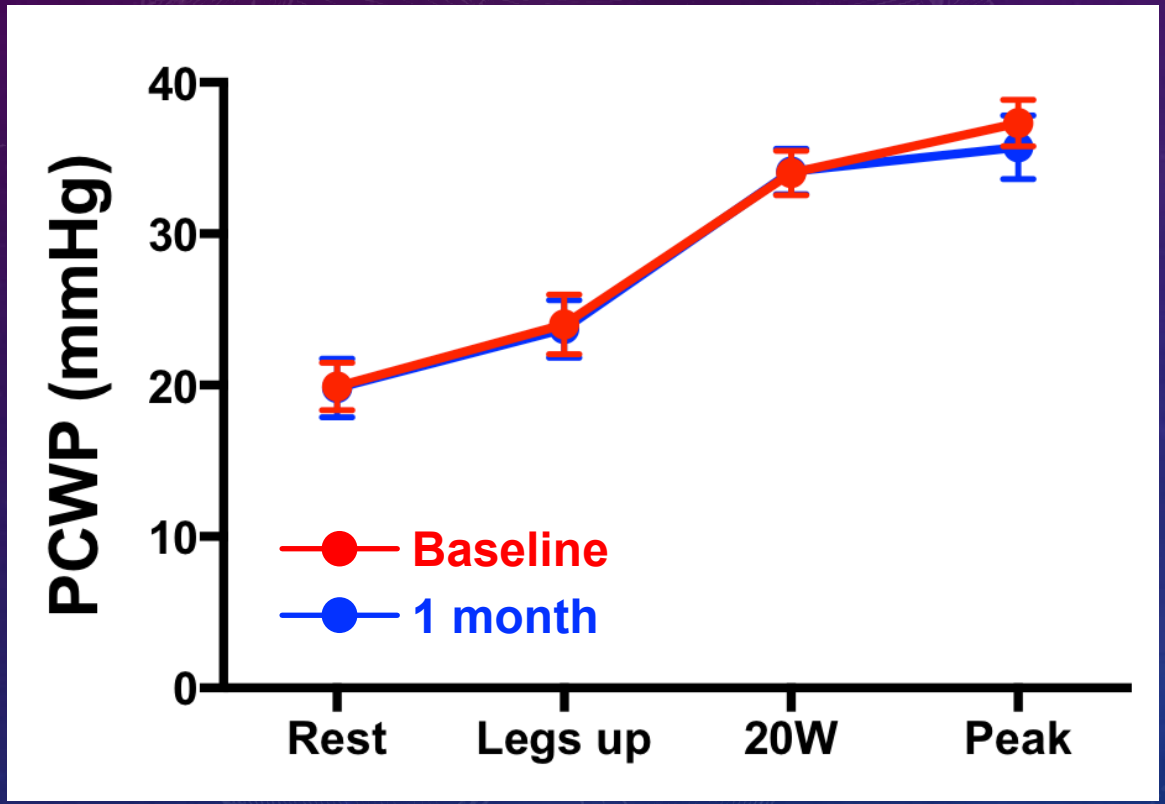
Feldman T…Shah SJ. *Circ Heart Fail* 2016

Corvia vs. other interatrial shunts

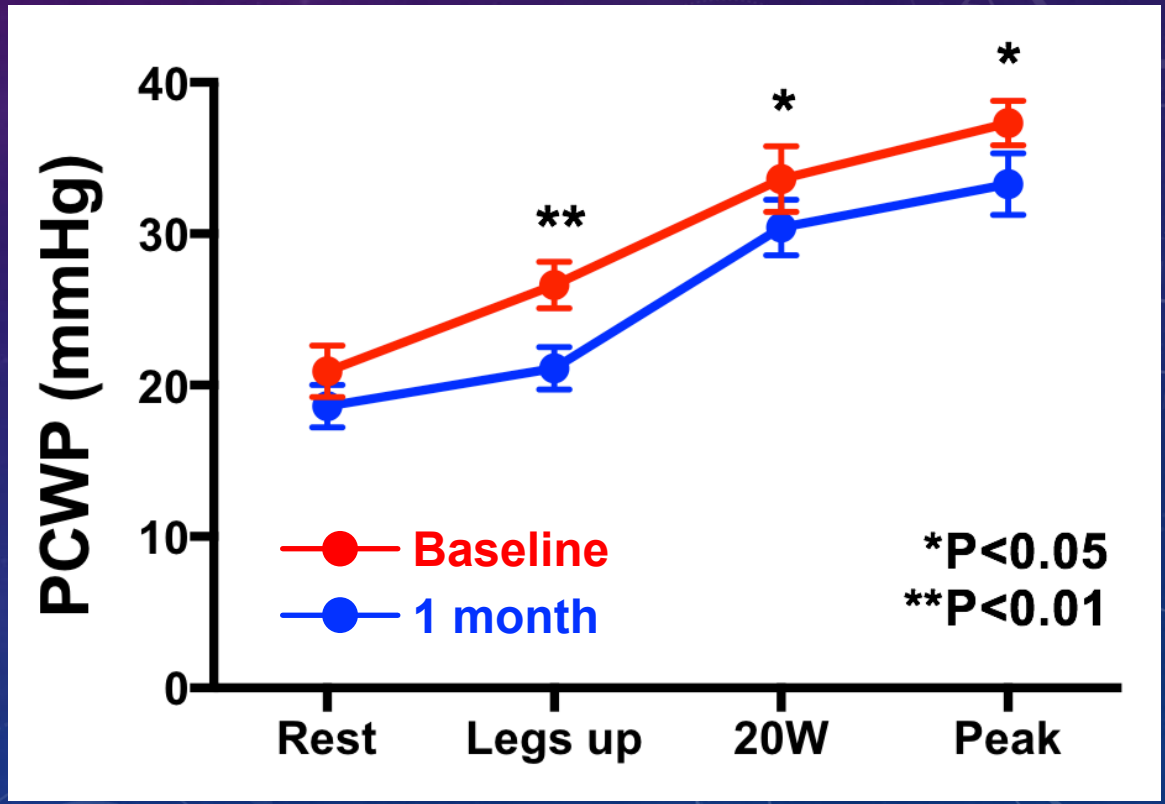
Parameter	Corvia Atrial Shunt Device	Other shunt devices/procedures
Device type	Interatrial shunt device	Interatrial shunt, LA→CS shunt
Device vs. procedure	Device (self-expanding nitinol cage, double-disc, flush with LA septum)	Variety of device designs and procedures (i.e., ASD creation without device)
ASD size	8 mm shunt, single size	Various sizes, ± customizable
Mechanistic, Phase 2 RCT	↓Exercise PCWP vs. sham	No RCT data yet
Development stage	Pivotal Phase 3 trial enrollment complete	Various stages (pilot/feasibility to ongoing Phase 3 trial)
Phase 3 trial design	Exercise RHC in all patients	No exercise RHC in Phase 3 trial

REDUCE LAP-HF I trial: ↓LA pressure

CONTROL



CORVIA IASD



Feldman T…Shah SJ. *Circulation* 2018

REDUCE LAP-HF II trial design

- 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
  - ✓ Gold-standard diagnosis of HFpEF, trial enriched with patients expected to benefit most from shunt therapy
  - ✓ Excluded patients unlikely to benefit from shunt treatment

Berry N…Shah SJ. *Am Heart J* 2020

Key inclusion/exclusion criteria

- Inclusion criteria:
  - ✓ **Gold-standard diagnosis of HFpEF, enriched to benefit from shunt therapy**
  - ✓ 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:
  - ✓ **Exclude patients unlikely to benefit from shunt therapy**
  - ✓ 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**

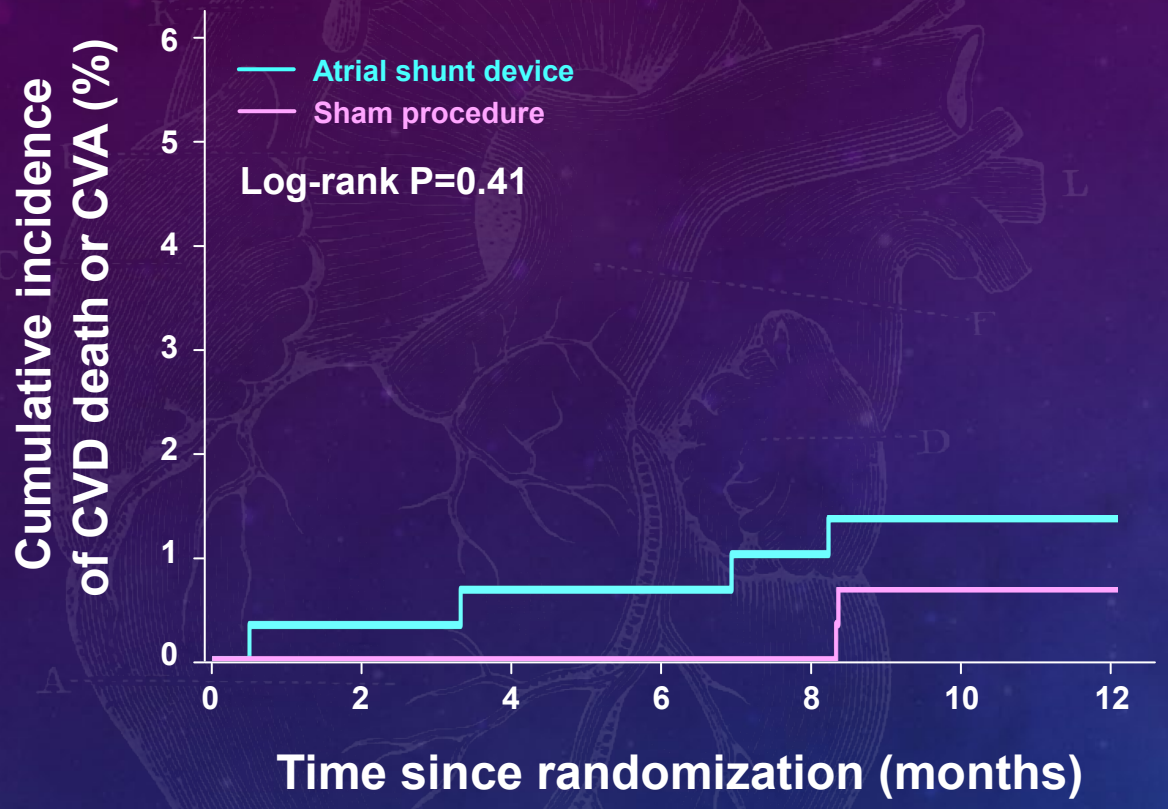
Berry N…Shah SJ. *Am Heart J* 2020

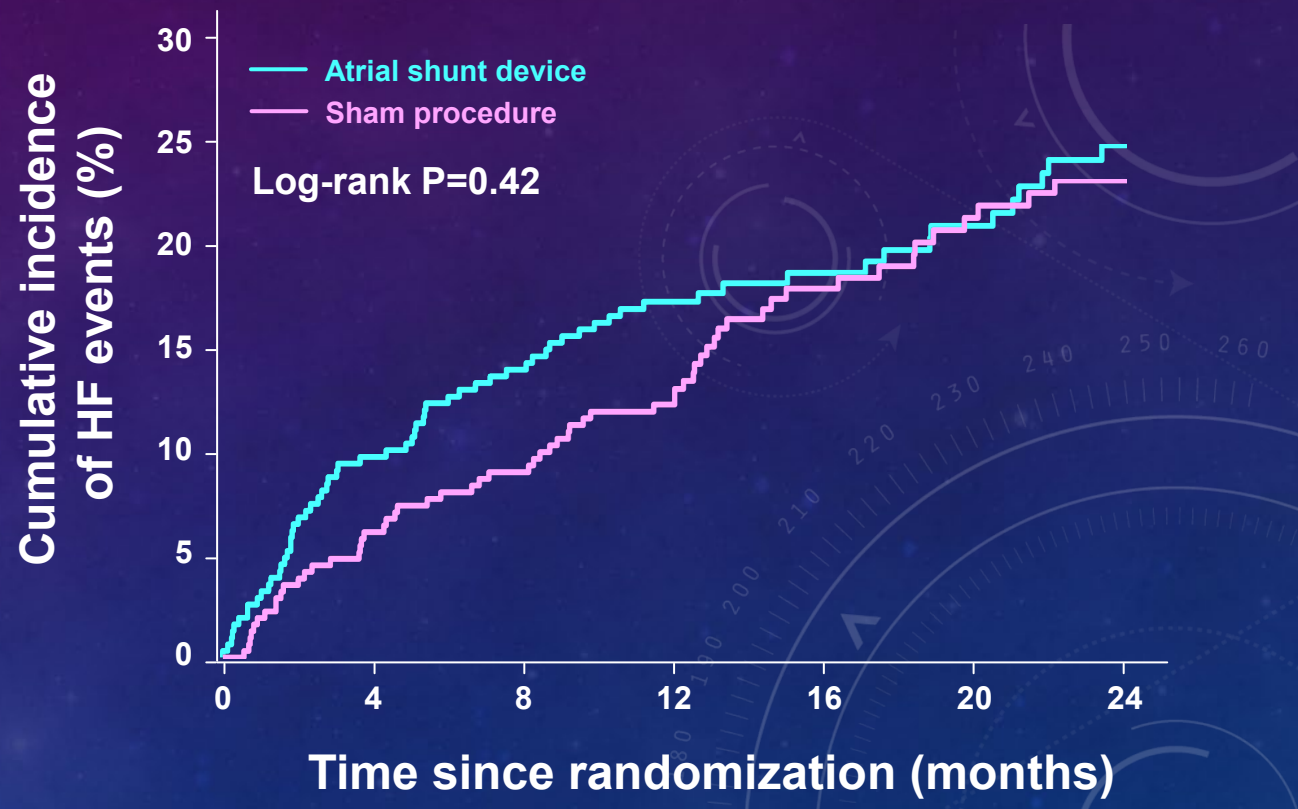
REDUCE II: Baseline characteristics

Characteristic	All patients (n=626)
Age, years	72
Female	62%
Diabetes mellitus	37%
Atrial fibrillation	52%
Pacemaker	15%
Median LVEF, %	60
HFmrEF (EF 40-49%)	7%
NYHA class III	77%
HF hospitalization in last 12 mo.	27%
Median NTproBNP, pg/ml	405
Median KCCQ-CSS	46
Median 6MWD, meters	301
Median eGFR, ml/min/1.73 m^2	57

- Older, majority women
- Multiple comorbidities
- Most NYHA class III
- Majority (93%) HFpEF (EF≥50%)
- Very poor health status
- ↓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)

Primary composite endpoint

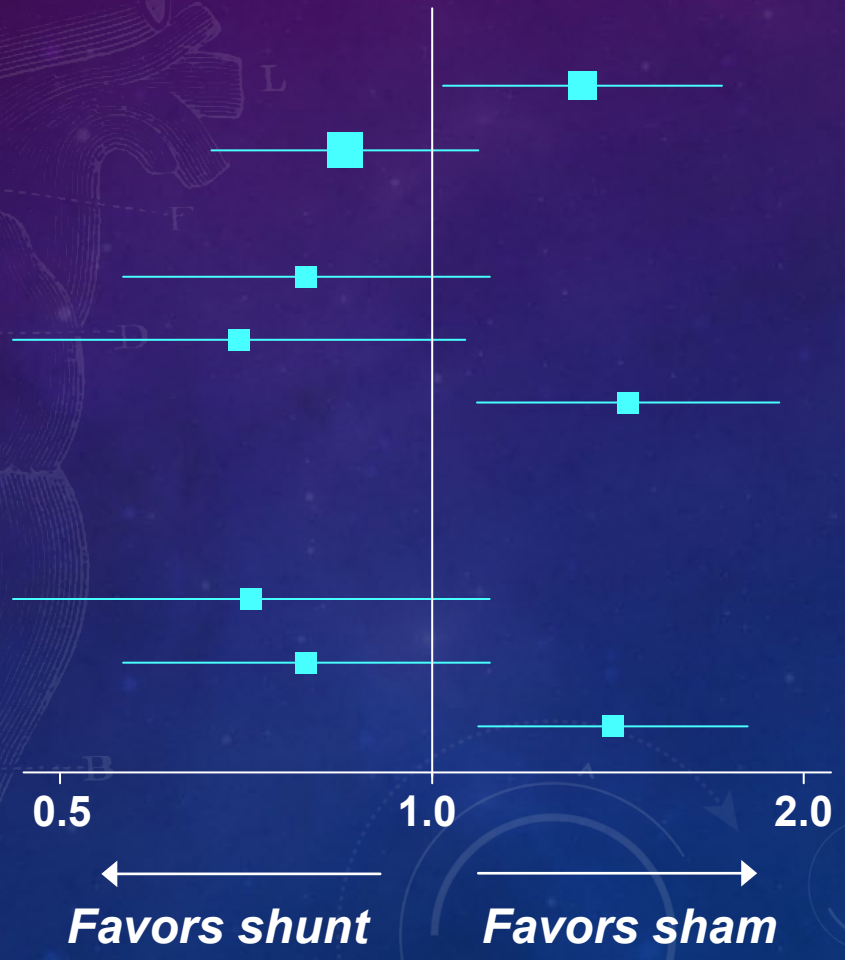




- Finkelstein-Schoenfeld p-value=0.85
- Win ratio: 1.0 (95% 0.8-1.2)

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

Shah SJ, et al. *Lancet* 2022

Gender differences in REDUCE LAP-HF II

- Women and men: similar rest and exercise PCWP, PVR
- Women:
  - ✓ Less AF, diabetes, CAD, prior HF hospitalization
  - ✓ Worse KCCQ-OSS: 44 vs. 51 (P=0.0002)
  - ✓ Small cardiac chamber volumes, higher LVEF
  - ✓ Better LV, RV, LA, and RA strain
- Similar overall win ratio (1.03 in women, 0.95 in men)
- Women had less recurrent HF events in response to the atrial shunt device (vs. sham): incidence rate ratio 0.77 vs. 2.19 (P=0.02)

Borlaug BA…Shah SJ. *Circulation* 2022
Lam CSP…Shah SJ. *ESC-HFA* 2022 [abstract]

Connecting the dots: gender, RA volume

Differences by gender:

Characteristic	Women (n=385)	Men (n=241)	P-value
Permanent pacemaker	16.4% (63/385)	22.0% (53/241)	0.078
RA volume index (ml/m^2)	25.6±11.8 (311)	31.9±14.1 (195)	<0.001

*After excluding patients with pacemakers, there are no longer any sex differences in response to atrial shunt treatment

Differences by RA volume index:

Characteristic	RA volume ≤29.7 ml/m^2 (N=336)	RA volume >29.7 ml/m^2 (N=170)	P-value
Female	73.2% (246/336)	38.2% (65/170)	<0.001
Permanent pacemaker	11.7% (39/333)	28.2% (48/170)	<0.001

Borlaug BA…Shah SJ. *Circulation* 2022
Lam CSP…Shah SJ. *ESC-HFA* 2022 [abstract]

Pacemaker vs. no pacemaker

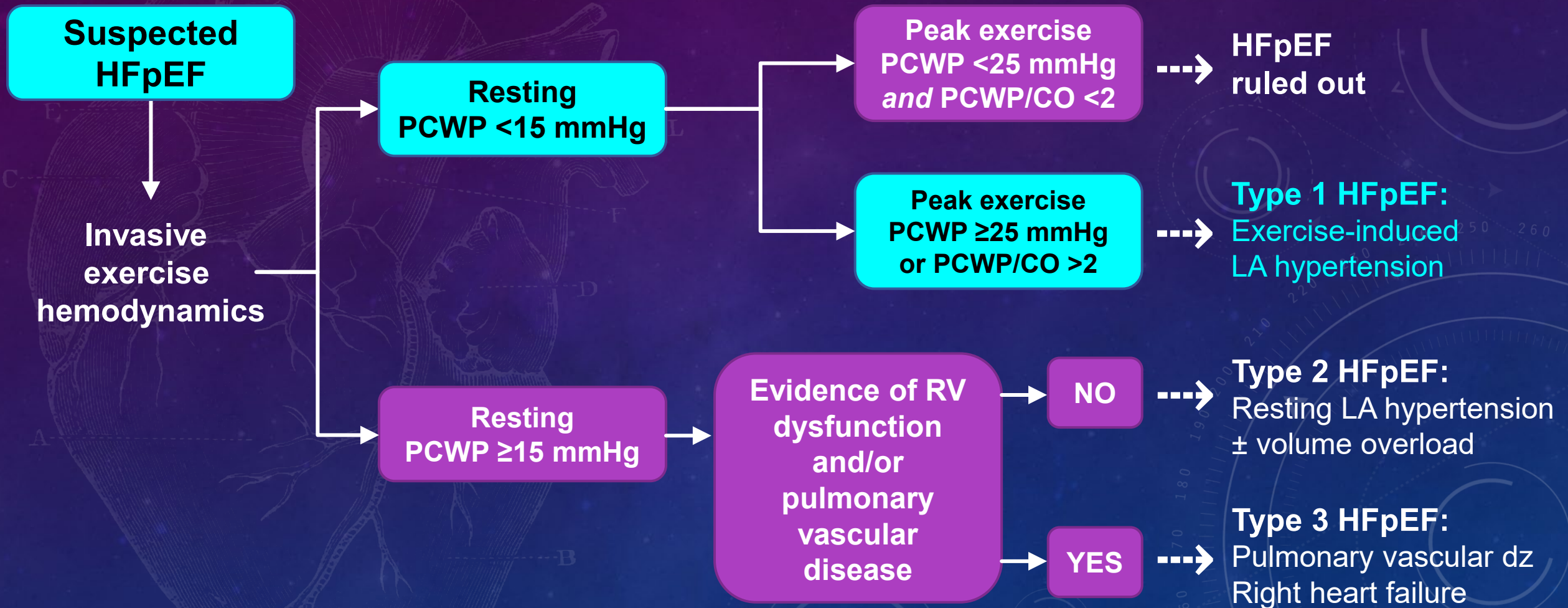
	No pacemaker (n=510)	Pacemaker (n=116)	P-value
Age (years)	72	74	0.03
Men (%)	37	46	0.08
Obesity (%)	63	52	0.02
Diabetes (%)	39	28	0.04
AF or flutter (%)	47	81	<0.001
Loop diuretics (%)	82	84	0.64
LVEF (%)	55	50	<0.001
Moderate or more TR (%)	11	24	<0.001
RAVI (ml/m^2)	24	33	<0.001
RAP rest	9	10	0.004
PVR (peak exercise)	1.3	1.4	0.76

Petrie M…Shah SJ. *ESC-HFA* 2022 [abstract]

Pacemaker vs. no pacemaker

Subgroup	Variable	Statistic	Atrial Shunt	Sham Control	Incidence Rate Ratio	Win Ratio	P-value
No pacemaker N=504	Primary efficacy endpoint	Win ratio	-	-	-	1.13 (0.91, 1.40)	0.23
	HF event	Rate per person year	0.26	0.27	1.06 (0.66, 1.71)	-	0.81
	Change in KCCQ OSS at 12 months	Mean±SD	11.3 (-2.3, 27.3)	8.3 (-2.6, 22.1)	-	-	0.32
Pacemaker N=115	**Primary efficacy endpoint**	**Win ratio**	**-**	**-**	**-**	**0.63 (0.40, 1.01)**	**0.05**
	HF event	**Rate per person year**	**0.40**	**0.23**	**2.19 (1.00, 4.75)**	**-**	**0.05**
	Change in KCCQ OSS at 12 months	Mean±SD	7.7 (-0.4, 20.3)	10.7 (-1.8, 23.2)	-	-	0.71

Phenotype-guided approach to HFpEF



Exercise-induced LA hypertension (EILAH)

- EILAH (vs. resting LA hypertension [RELAH]):
  - ✓ 29% of REDUCE LAP-HF II patients
  - ✓ Younger, less comorbidities, less AF, less pacemakers
  - ✓ Lower NTproBNP, better 6MWD, less abnormal cardiac structure/function, less abnormal hemodynamic at rest/exercise

Exercise hemodynamics (median values)	**Resting PCWP <15mmHg (n=182)**	**Resting PCWP ≥15mmHg (n=436)**	**P-value**
Peak RAP (mmHg)	15	19	<0.001
Peak PCWP (mmHg)	30	36	<0.001
Peak CI (L/min/m²)	4.0	3.6	0.001
Peak PVR (WU)	0.67	1.14	0.001
Peak PVR <1.74 WU	78%	62%	<0.001

Exercise-induced LA hypertension (EILAH)

- EILAH (vs. resting LA hypertension [RELAH]):
  - ✓ 29% of REDUCE LAP-HF II patients
  - ✓ Younger, less comorbidities, less AF, less pacemakers
  - ✓ Lower NTproBNP, better 6MWD, less abnormal cardiac structure/function, less abnormal hemodynamic at rest/exercise
  - ✓ ***Trend to greater reduction in HF events in EILAH vs. RELAH in response to the atrial shunt***
    - ⇢ EILAH: IRR 0.54 [95% CI 0.27-1.53]
    - ⇢ RELAH: IRR 1.44 [95% CI 0.92-2.25]
    - ⇢ Interaction P=0.11

Take home points

- REDUCE LAP-HF II pivotal RCT (HF, EF ≥40%) with exercise hemodynamics (N=626): ***Largest device trial in HFpEF to date***
- Placement of atrial shunt did not reduce total rate of HF events or improve health status overall in HF with EF ≥40%: ***Pre-specified subgroup analyses showed that women, smaller RA volume, and lower exercise PA systolic pressure did better with the shunt***
- Gender differences and RA volume: explained by pacemaker effect: ***Patients with pacemakers did worse with the device***
- 29% of patients in the trial had resting PCWP <15 mmHg (EILAH): ***More likely to be in responder groups, possible greater benefit***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