Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure: *Results From the REDUCE LAP-HF I Randomized Controlled Trial*

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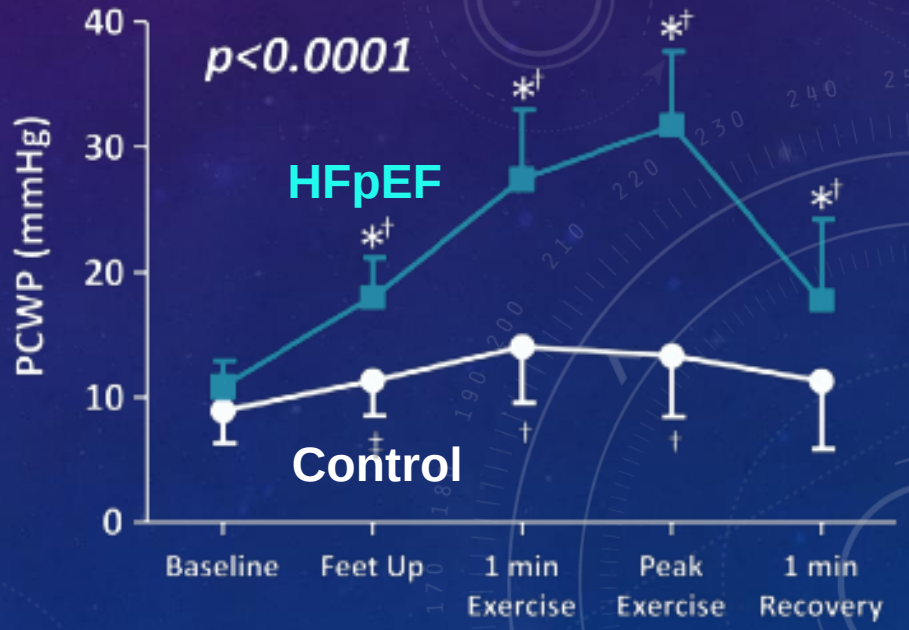
On behalf of the REDUCE LAP-HF I investigators and research staff

Introduction

- HFpEF (LVEF > 50%) and HFmrEF (LVEF 40-50%):
  - Increasing in prevalence
  - High morbidity/mortality
  - No proven therapies
  - Heterogeneous syndromes
  - Common pathophysiologic thread: ⇧*LA pressure at rest or with exertion*

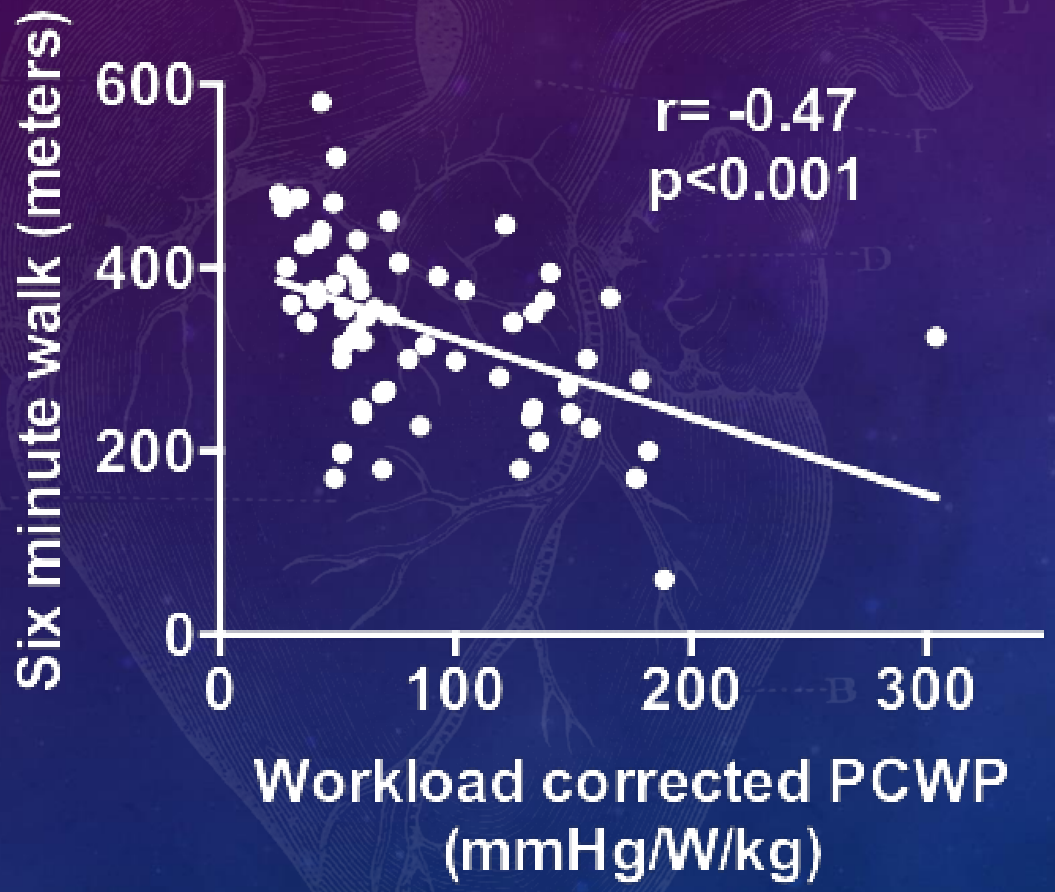


Borlaug BA, et al. *Circ Heart Fail* 2010

Importance of ⇧LA pressure in HFpEF

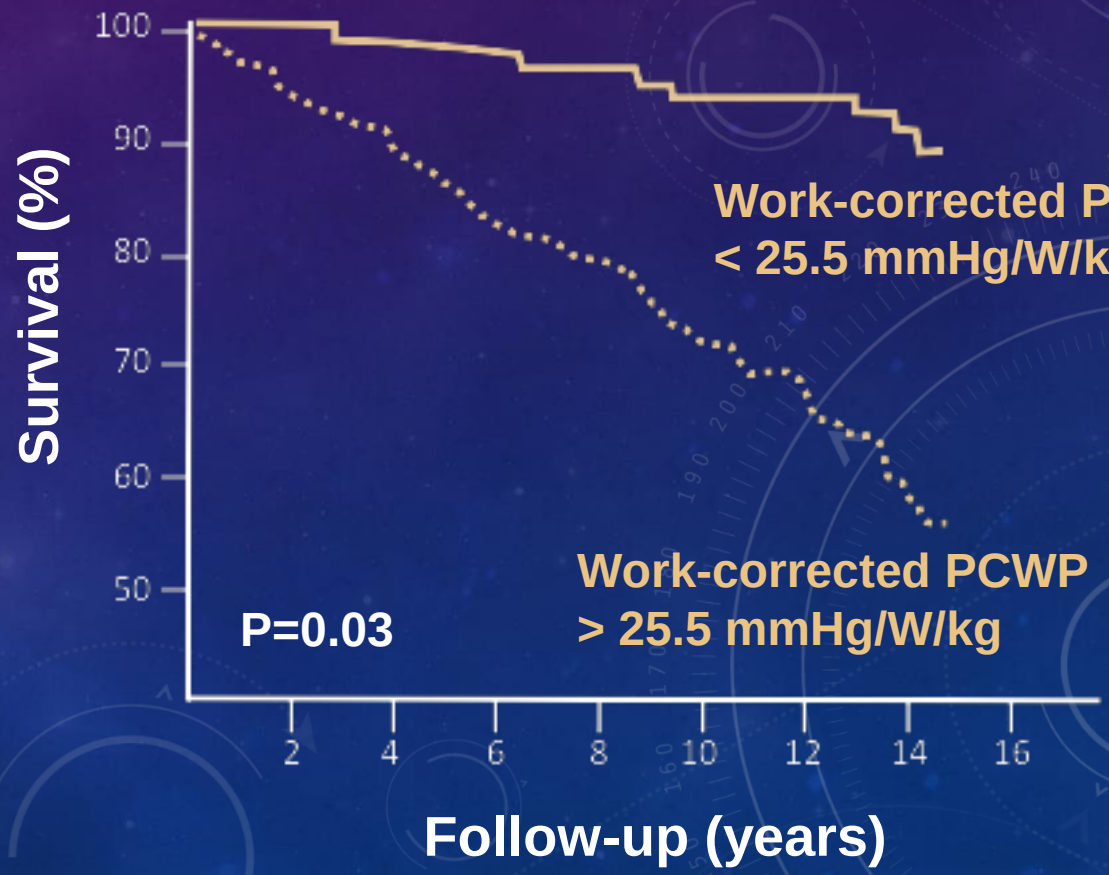
EXERCISE CAPACITY

Wolsk E…Gustafsson F. *EJHF* 2017

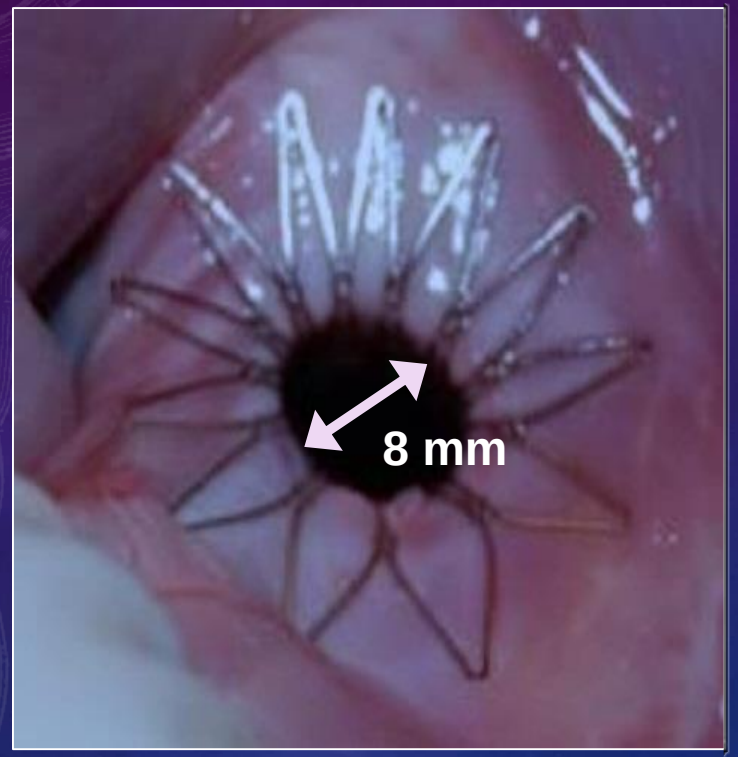


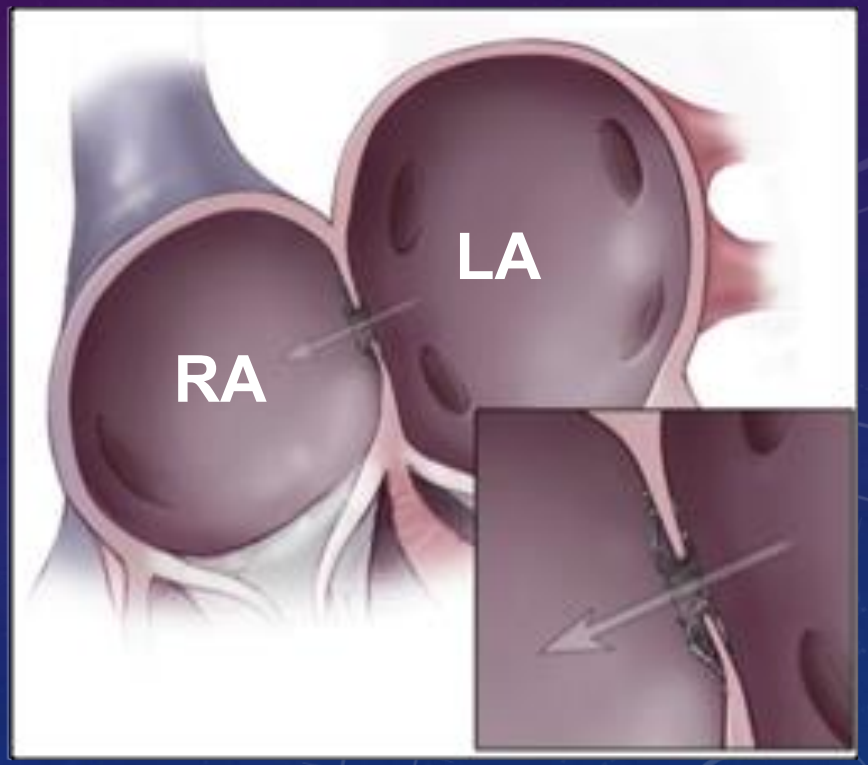
SURVIVAL

Dorfs S, et al. *Eur Heart J* 2014



InterAtrial Shunt Device



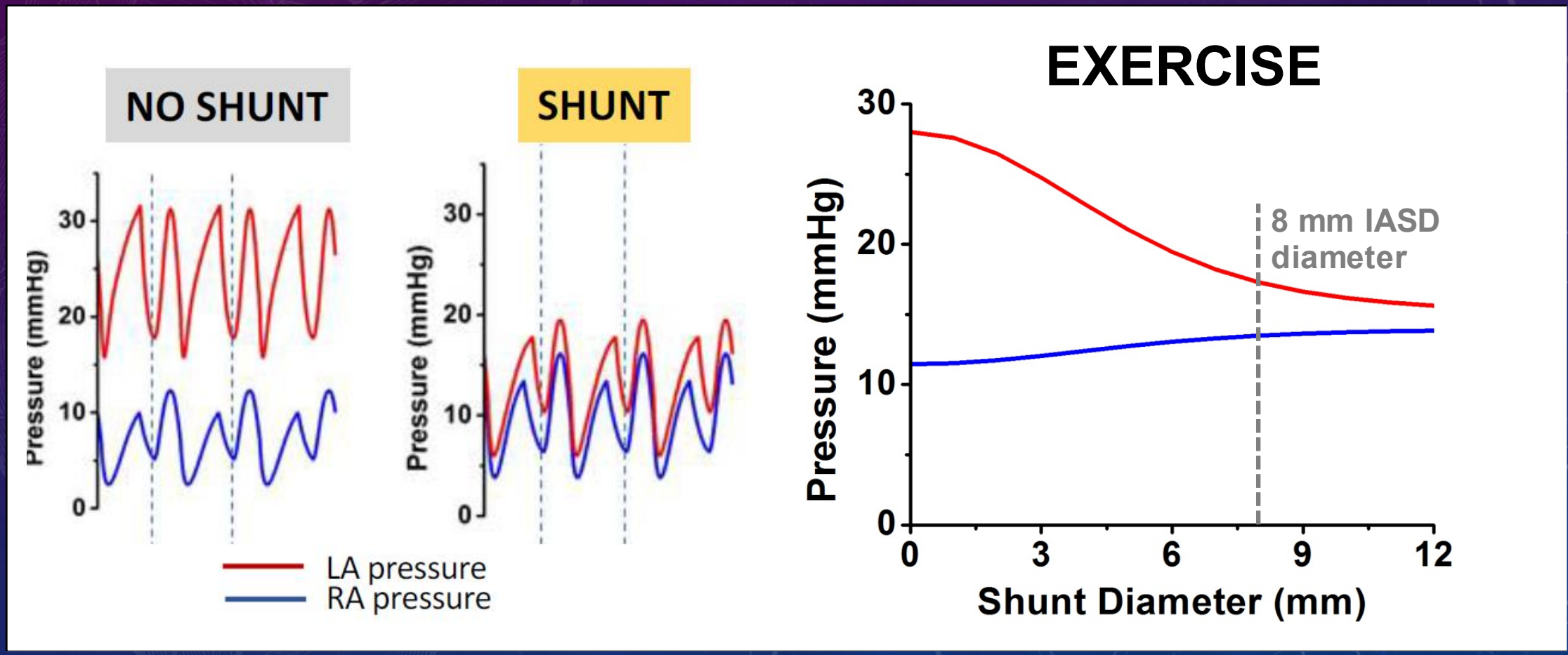


IASD proposed mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA → RA

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

InterAtrial Shunt Device

Simulation using exercise hemodynamic data from HFpEF patients



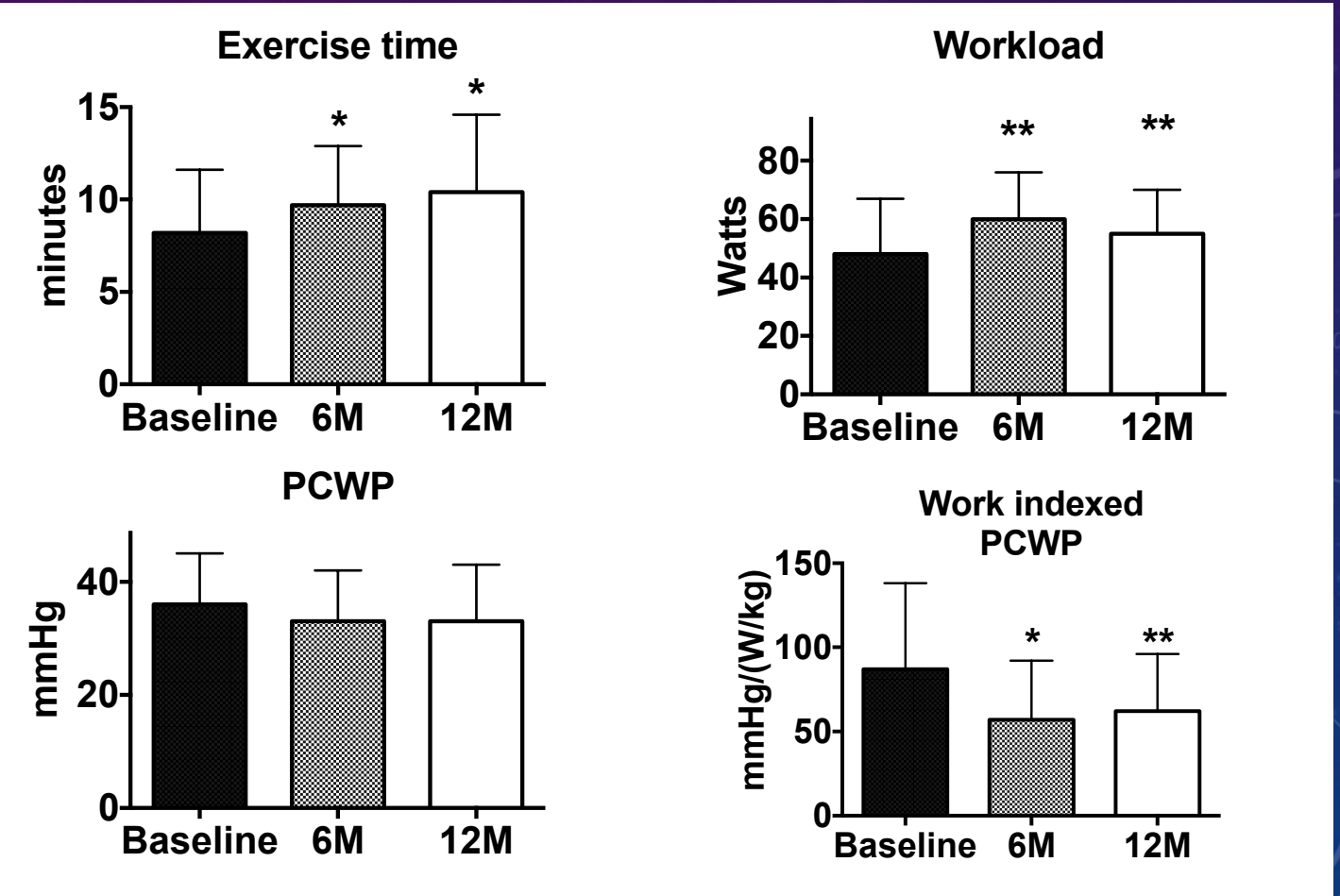
Kaye D…Burkhoff D. *J Card Fail* 2014

Results of IASD open-label study (n=64)

Inclusion criteria:

- Open label
- LVEF ≥ 40%,
- NYHA class II-IV
- Elevated PCWP
  - ≥ 15 mmHg (rest) or
  - ≥ 25 mmHg (supine bicycle exercise)

Acceptable safety profile at 12 months



*p<0.05, **p<0.01 vs. baseline

Hasenfuß G…Kaye D. *Lancet* 2016
Kaye D, et al. *Circ Heart Fail* 2016

Hypothesis

- At 1 month after randomization, compared to sham control, implantation of the IASD System II in patients with HF and EF ≥ 40% will result in:
  - Mechanistic effect: Reduction in exercise PCWP
  - Safety: No increase in major adverse cardiovascular, cerebral, or renal events (MACCRE)

REDUCE LAP-HF I RCT: Study Design

- Phase 2, randomized, sham-controlled trial
- Patient- and HF physician-blinded
- 1:1 randomization to IASD vs. sham control
  - Active treatment: Femoral venous access with ICE/TEE + transseptal IASD implantation
  - Sham control: Femoral venous access with examination of interatrial septum and LA with ICE/TEE
- Independent DSMB, CEC, hemodynamic core lab

Primary and Secondary Outcomes

- Primary outcomes (1 month):
  - Mechanistic effect: *Reduction in exercise PCWP*
  - Safety: *Major adverse cardiovascular, cerebral, or renal events (MACCRE)*
- Secondary outcomes (1 month):
  - Change in PCWP at peak exercise
  - Change in exercise duration
  - Change in PA pressures

Key inclusion/exclusion criteria

- Inclusion criteria:
  - Symptomatic HF
  - NYHA class III or ambulatory IV
  - LVEF ≥ 40%
  - HF hospitalization in prior 12 months *or* ⇧BNP (or ⇧NTproBNP)
  - Echo evidence of LV diastolic dysfunction
  - ⇧Exercise PCWP (≥ 25 mmHg)
  - ⇧PCWP-RAP gradient (≥ 5 mmHg)
- Exclusion criteria:
  - Stage D HF
  - Cardiac index < 2.0 L/min/m^2
  - Prior history of LVEF < 30%
  - Significant valve disease
    - ≥ 3+ MR, ≥ 2+ TR, ≥ 2+ AR
  - Significant RV dysfunction
    - TAPSE < 1.4 cm, RV > LV size, or RVFAC < 35%
  - RAP > 14 mmHg
  - PVR > 4 Wood units

Statistical Analysis

- Power calculation:
  - N=20 in each group to detect 6.0±7.2 mmHg greater reduction in exercise PCWP at 1 month in IASD group
  - Two-sided α=0.05 and power = 82%
- Primary outcome analysis:
  - Mixed effects model repeated measures (MMRM) analysis of covariance (ANCOVA)
  - Accounts for all available stages of exercise at both time points in all patients

Patient disposition flow chart

N=94 enrolled patients with symptomatic HF + LVEF > 40%

N=50 excluded patients:

- MI, PCI, or CABG in past 3 months (n=13)
- Significant untreated CAD (n=11)
- Hx of CVA, TIA, DVT, or PE (n=5)
- Resting RAP > 14 mmHg (n=5)
- Significant valvular disease (n=4)
- Severe CKD (n=2)
- Other (n=10)

N=44 randomized patients

CONTROL ARM (N=22)

IASD TREATMENT ARM (N=22)

N=22 patients active at 1 month

N=21 patients active at 1 month

N=1 patient withdrew consent after RA could not be accessed (occluded IVC filter)

Results: Baseline characteristics (1)

Characteristic	Control (N=22)	IASD (N=22)	P-value
Age (years)	70.0±9.2	69.6±8.3	0.86
Male	36%	64%	0.13
Race • African American • White • Other	 18% 82% 0%	 0% 86% 14%	0.03
NYHA class III	96%	100%	0.32
Body mass index (kg/m²)	35.1±9.1	35.2±6.4	0.98
Systolic BP (mmHg)	128±22	131±16	0.72
LV ejection fraction (%)	59±7	60±9	0.49

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Results: Baseline characteristics (2)

Characteristic	Control (N=22)	IASD (N=22)	P-value
Hypertension	91%	82%	0.66
Hyperlipidemia	73%	73%	1.00
Diabetes	55%	55%	1.00
Atrial fibrillation	46%	55%	0.76
Ischemic heart disease	24%	23%	1.00
COPD	32%	14%	0.28
Stroke	14%	9%	0.66
Loop diuretic dose (mg furosemide eq.)	113±90	93±99	0.42

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Results: Baseline characteristics (3)

Baseline hemodynamics	Control (N=22)	IASD (N=22)	P-value
RA pressure (mmHg)	9.1±3.7	10.1±2.3	0.27
Mean PA pressure (mmHg)	28.4±8.6	30.2±9.5	0.52
Cardiac output (L/min/m^2)	5.7±2.7	5.4±1.6	0.66
Pulmonary vascular resistance (WU)	1.74±1.45	2.19±1.52	0.32
PCWP, legs down (mmHg)	19.9±7.5	20.9±7.9	0.67
PCWP, legs up (mmHg)	24.0±9.3	26.6±7.1	0.32
PCWP, peak exercise (mmHg)	37.3±6.7	37.3±6.5	1.00
PCWP-RAP gradient at rest (mmHg)	10.9±7.3	10.8±5.6	0.95
Exercise duration (minutes)	8.9±4.0	7.4±3.1	0.18
Peak exercise workload (W)	41.8±16.2	42.3±19.5	0.93

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Results: Procedural characteristics

Procedural/device characteristic	Control (N=22)	IASD (N=22)	P-value
Device implantation attempted (%)	N/A	95.5%	—
Total procedure duration (minutes)	12.9±9.0	58.1±25.8	<0.001
Total fluoroscopy time (minutes)	5.3±3.6	23.3±13.0	<0.001
Total contrast agent administered (mL)	19.0±15.6	19.2±17.4	0.986
Device deficiency	N/A	4.5%	—
Device malfunction	N/A	4.5%	—
Device failure	N/A	0.0%	—
Device mal-deployment without embolization	N/A	4.5%	—

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PRIMARY OUTCOME RESULTS

Results: Efficacy outcomes at 1 month

Hemodynamic parameter (Change from baseline to 1 month)	**Control**	**IASD**	**P-value**
Primary outcome (exercise PCWP) • **PCWP at 20W (mmHg)***P=0.019 • **PCWP at 40W (mmHg)** • **PCWP at 60W (mmHg)**	 0.9±5.1 -1.9±4.3 -1.3±4.9	 -3.2±5.2 -1.0±4.5 -2.3±4.9	**0.028**
PCWP, legs up at rest (mmHg)	0.0±6.4	-5.0±5.7	0.024
PCWP, peak exercise (mmHg)	-0.5±5.0	-3.5±6.4	0.144
PCWP, workload-corrected (mmHg/W/kg)	10.3±45.9	-5.7±27.3	0.231
RV cardiac output at rest (L/min)	-0.5±1.4	1.6±1.3	<0.001
PVR at rest (Wood units)	0.17±1.57	-0.76±1.59	0.102
PVR during exercise (Wood units)	0.31±1.64	-0.29±1.22	0.051

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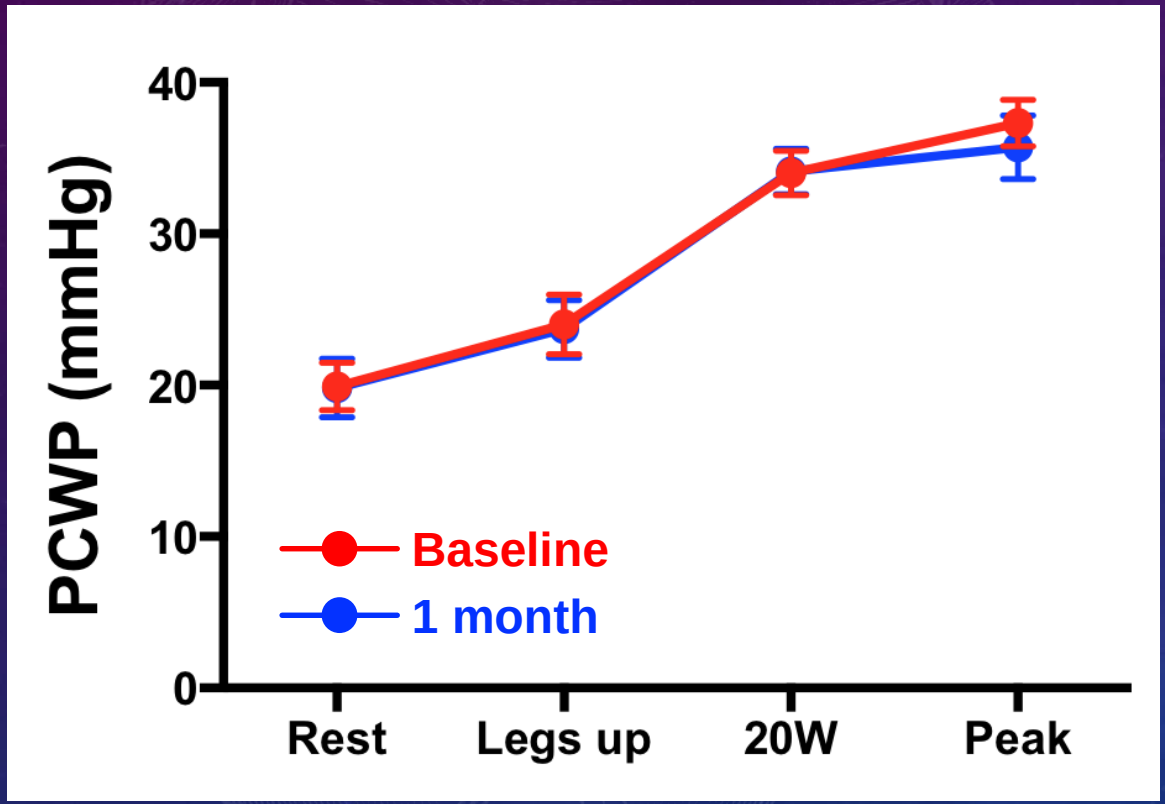
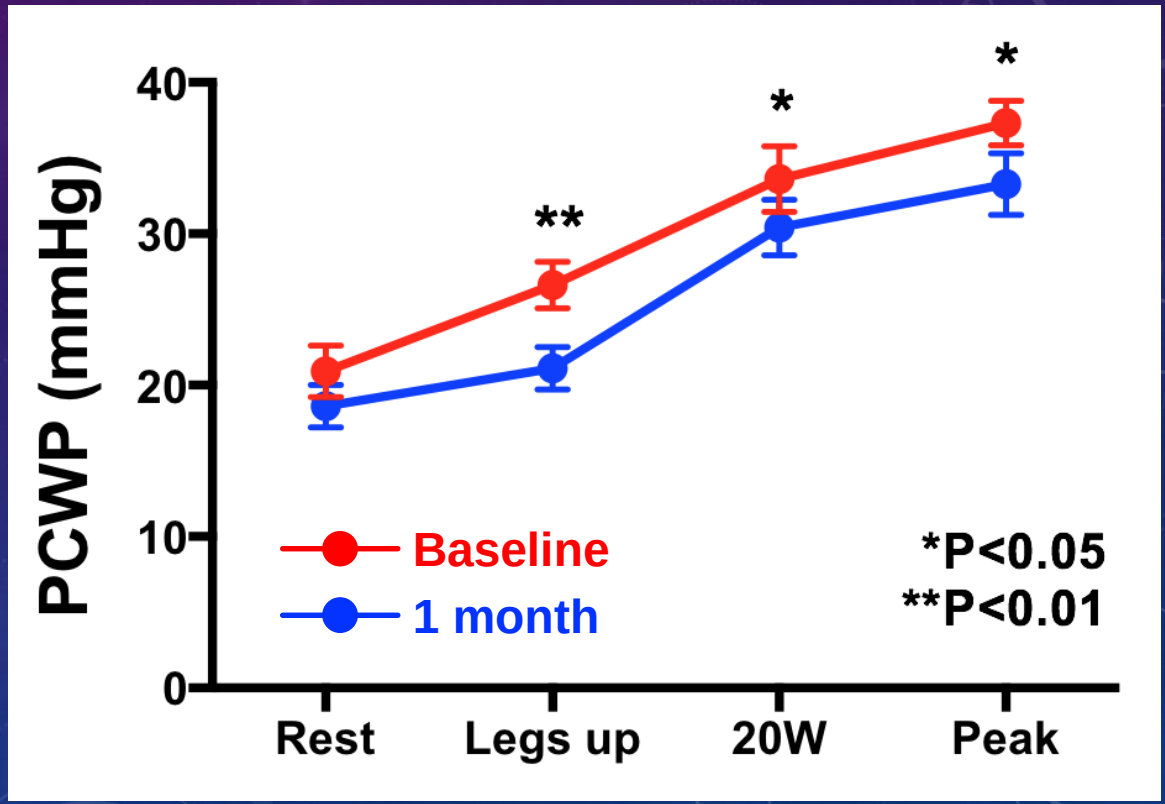
Change in PCWP: Baseline to 1 month

CONTROL



IASD



Results: Safety outcomes at 1 month

Adverse event	Control (N=22)	IASD (N=22)	P-value
MACCRE	4.6% (1 renal event)	0%	1.00
Death	0%	0%	—
New-onset atrial fibrillation/flutter	0%	0%	—
Stroke or TIA	0%	0%	—
Systemic embolization	0%	0%	—
HF event requiring IV treatment	9.1%	0%	0.49
Cardiac perforation	0%	0%	—
Device embolization or occlusion	0%	0%	—
Major vascular complication	0%	0%	—

Summary

- First RCT of a device-based therapeutic in HFpEF
- REDUCE LAP-HF I trial met its primary endpoint
  - Significantly reduced exercise PCWP at 1 month (P=0.028)
- Good safety profile at 1 month
- Demonstrates beneficial mechanistic effect of IASD
- IASD could have beneficial clinical effects in HFpEF/mrEF
- A larger pivotal trial to examine effects of IASD on QOL, exercise capacity, and clinical outcomes is warranted
- REDUCE LAP-HF II pivotal trial is underway (NCT03088033)

Circulation

American Heart Association®

ORIGINAL RESEARCH ARTICLE

A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction (REDUCE LAP-HF I): *A Phase 2, Randomized, Sham-Controlled Trial*

Ted Feldman, Laura Mauri, Rami Kahwash, Sheldon Litwin, Mark J. Ricciardi, Pim van der Harst, Martin Penicka, Peter S. Fail, David M. Kaye, Mark C. Petrie, Anupam Basuray, Scott L. Hummel, Rhondalyn Forde-McLean, Christopher D. Nielsen, Scott Lilly, Joseph M. Massaro, Daniel Burkhoff, Sanjiv J. Shah

on behalf of the REDUCE LAP-HF I investigators and research staff

Full study details published today online in Circulation

http://circ.ahajournals.org