A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure With Preserved or Mid-Range Ejection Fraction (REDUCE LAP-HF I):

1-Year Results from the Phase 2, Randomized, Blinded, Sham-Controlled Trial

Ted Feldman, M.D., MSCAI FACC FESC

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

August 27th, 2018

Ted Feldman MD, *MSCAI FACC FESC*

Disclosure Information

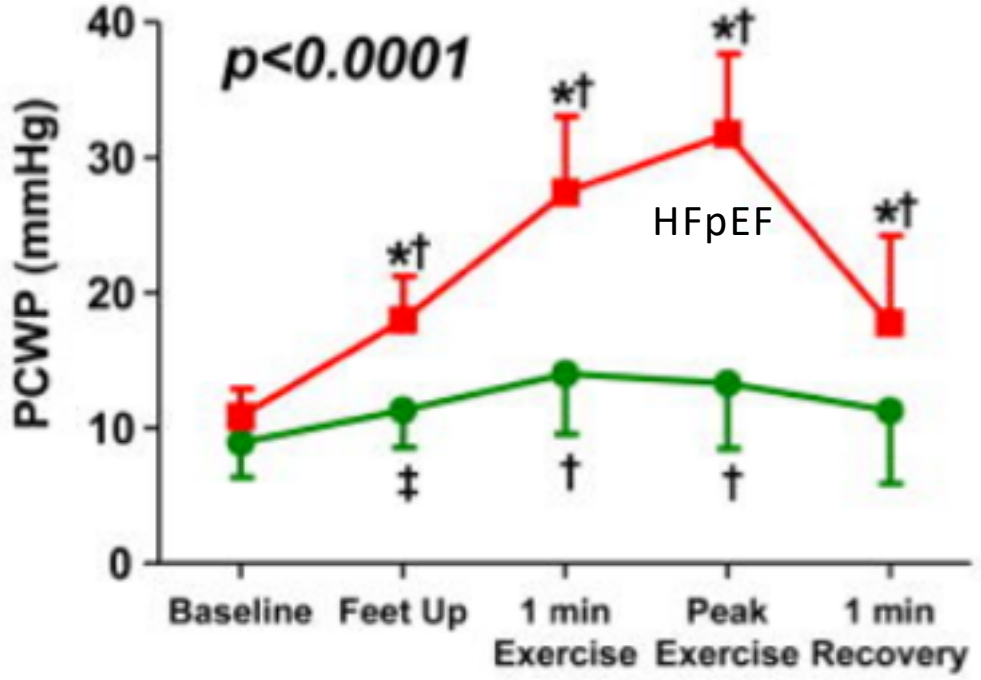
The following relationships exist:

Grant support: Abbott, BSC, Corvia Medical, Edwards, WL Gore
Consultant: Abbott, BSC, Edwards, WL Gore
Stock Options: Mitralign, Cardiac Dimensions

Off label use of products and investigational devices will be discussed in this presentation

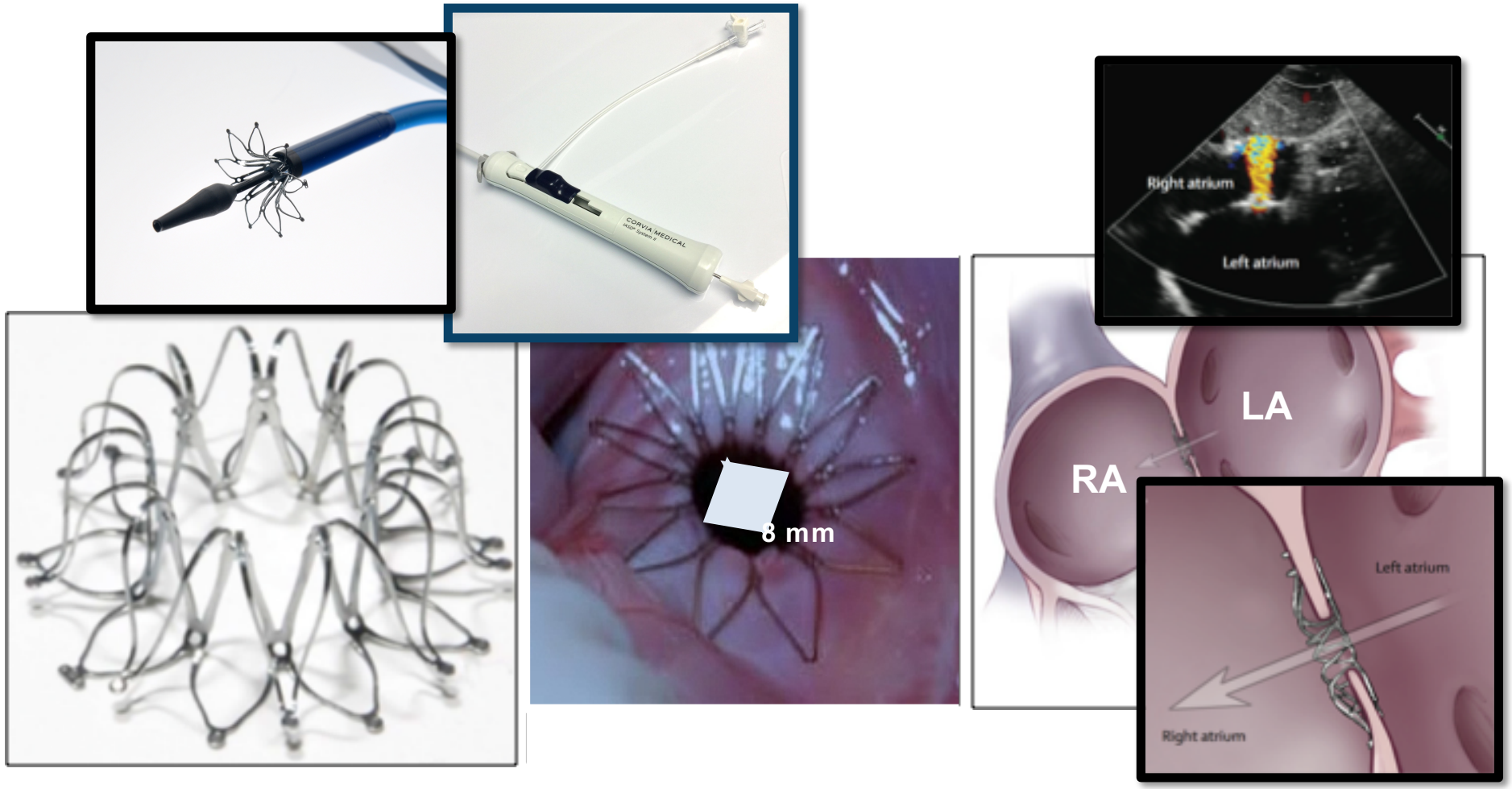
Introduction

- HFpEF (LVEF ≥ 50%) and HFmrEF (LVEF 40-49%):
  - Increasing in prevalence
  - High morbidity/mortality
  - No proven effective therapies
  - Heterogeneous syndromes
  - **Common pathophysiologic thread**
    ⇧*LA pressure at rest and with exercise*



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

InterAtrial Shunt Device (IASD®)



IASD proposed mode of action: dynamic LA decompression by shunting blood from LA
→ RA + systemic veins, at rest and particularly during exercise

NorthShore University HealthSystem
Evanston Hospital

Feldman T…Shah SJ: Circ Heart Fail. 2016 Jul;9(7) NCT02600234

Hypothesis

- Implantation of the IASD System II in patients with HF and EF ≥ 40% compared to sham control will result in:
  - Reduction in exercise PCWP (Mechanistic effect)
  - Improved symptoms and exercise capacity
  - No increase in major adverse cardiovascular, cerebral, or renal events (MACCRE)

Corvia Medical IASD® Clinical Studies

- Pilot study (N=11): non-randomized, single-arm
  - Completed (Søndergaard L et al. Eur J Heart Fail 2014; Malek et al. Int J Cardiol 2015)
- REDUCE LAP-HF (CE Mark) Study (N=64): non-randomized, single-arm
  - Completed (Hasenfuß Lancet 2016; Kaye Circ. HF 2016)
- **REDUCE LAP-HF I (N=44): RCT mechanistic study**
  - FDA approved IDE 30 Day Complete (*Feldman T… Shah SJ. Circulation. 2018;137:364–375)*
  - **1Y follow-up complete**
- REDUCE LAP-HF II (N=608): RCT pivotal study
  - FDA approved IDE; recruiting
- *HFrEF Feasibility study*
  - *FDA approved IDE; recruiting*
- *REDUCE LAP-HF III (N=100): Post-market Registry Germany*
  - *Recruiting*

NorthShore University HealthSystem
Evanston Hospital

REDUCE LAP-HF I RCT: Study Design

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

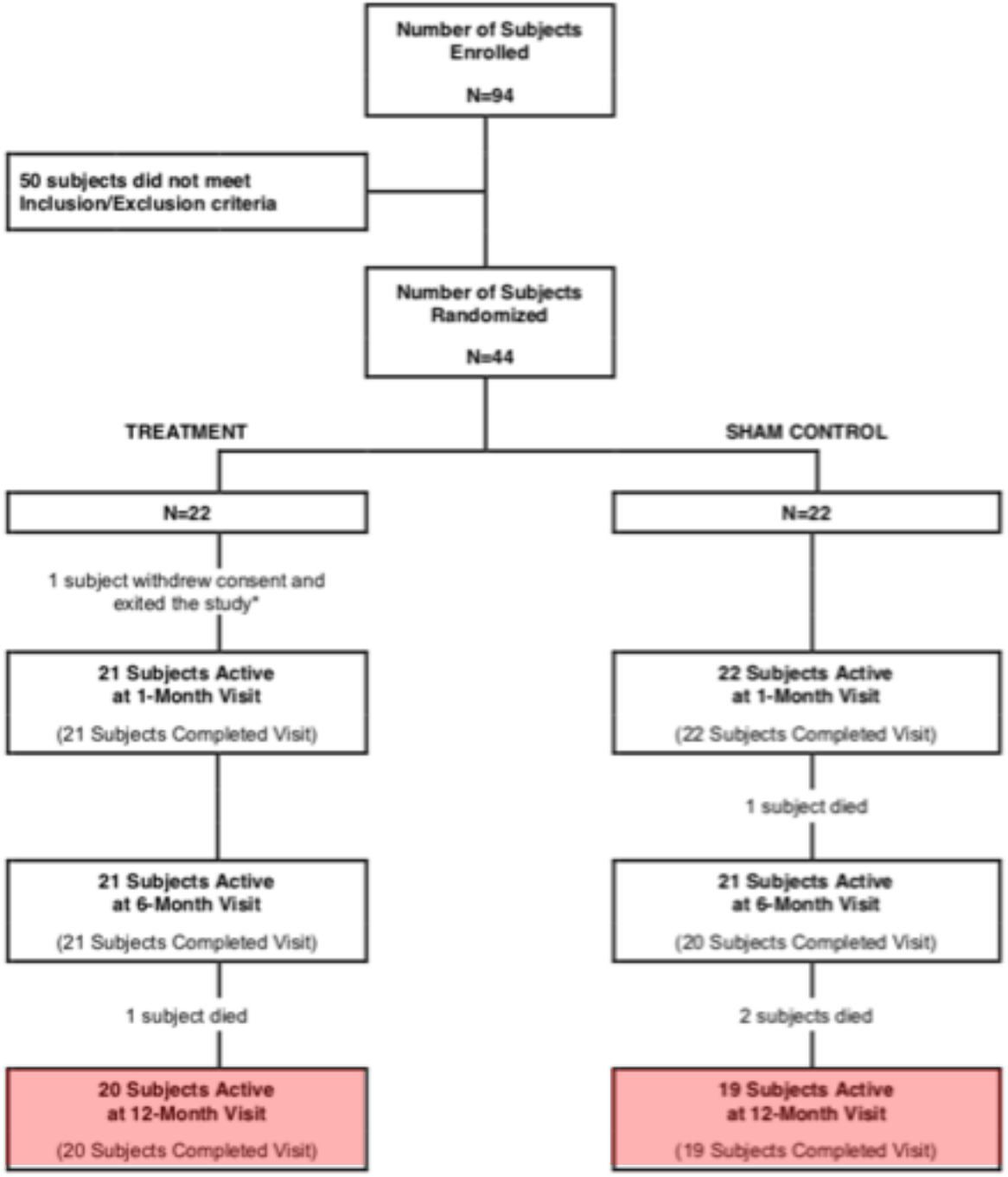
Primary and Secondary Outcomes: ITT

- Primary outcomes (30 days):
  - Mechanistic effect: *Reduction in exercise PCWP*
  - Safety: *Major adverse cardiac, cerebrovascular, or renal events (MACCRE)*
- Secondary outcomes (1 month):
  - Change in PCWP at peak exercise
  - Change in exercise duration
  - Change in PA pressures
- **Pre-specified for evaluation through 12-months (key outcome measures)**
  - MACCRE-composite of cardiovascular death, embolic stroke, device and/or procedure-related major adverse cardiac events, or new-onset or worsening of kidney dysfunction
  - HF hospitalization, including IV diuretics at a healthcare facility
  - Change from baseline in loop diuretic dose, left heart structure/function (by echocardiography), NYHA class, KCCQ and EQ-5D, and 6MWT distance
  - Echo core lab assessment of shunt flow

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 ⇧NT-pro BNP
  - 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

Patient flow



NorthShore University HealthSystem
Evanston Hospital

Results: Baseline characteristics (1)

Characteristic	IASD n=22	Control n=22	P-value
Age (years)	69.6±8.3	70.0±9.2	0.86
Male	64%	36%	0.13
Race			0.03
• African American	0%	18%	
• White	86%	82%	
• Other	14%	0%	
NYHA class III	100%	96%	0.32
Body mass index (kg/m^2)	35.2±6.4	35.1±9.1	0.98
Systolic BP (mmHg)	131±16	128±22	0.72
LV ejection fraction (%)	60±9	59±7	0.49

Results: Baseline characteristics (2)

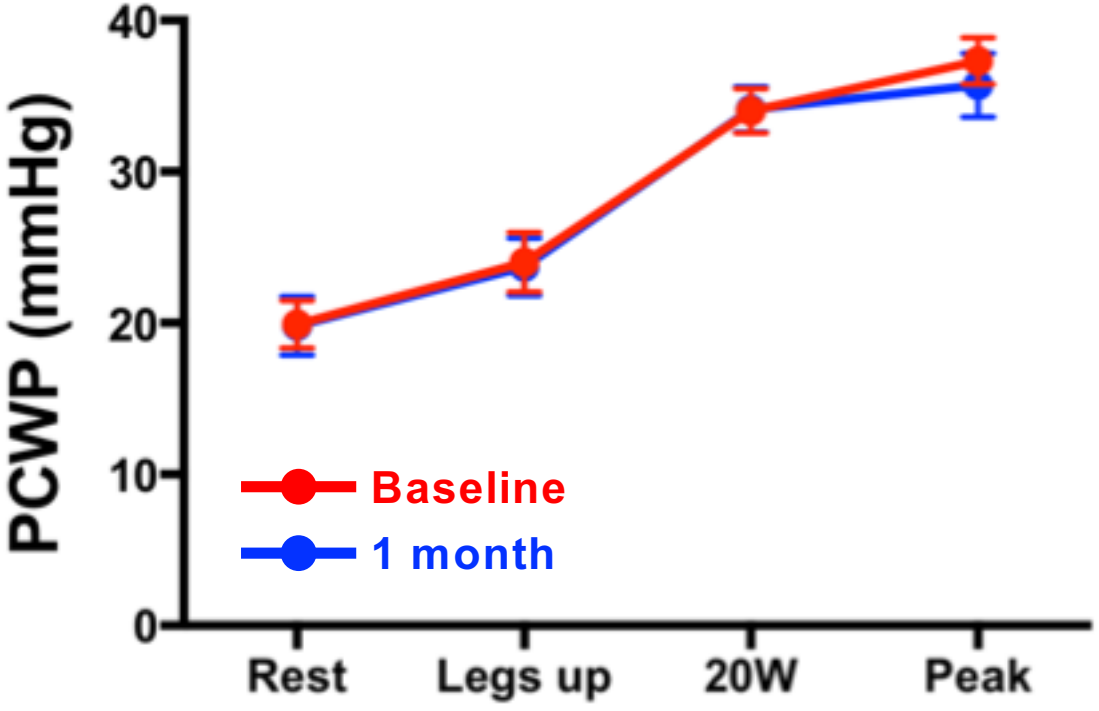
Characteristic	IASD	Control	P-value
Hypertension	82%	91%	0.66
Hyperlipidemia	73%	73%	1.00
Diabetes	55%	55%	1.00
Atrial fibrillation	55%	46%	0.76
Ischemic heart disease	23%	24%	1.00
COPD	14%	32%	0.28
Stroke	9%	14%	0.66
Loop diuretic dose (mg furosemide eq.)	93±99	113±90	0.42

Results: Baseline characteristics (3)

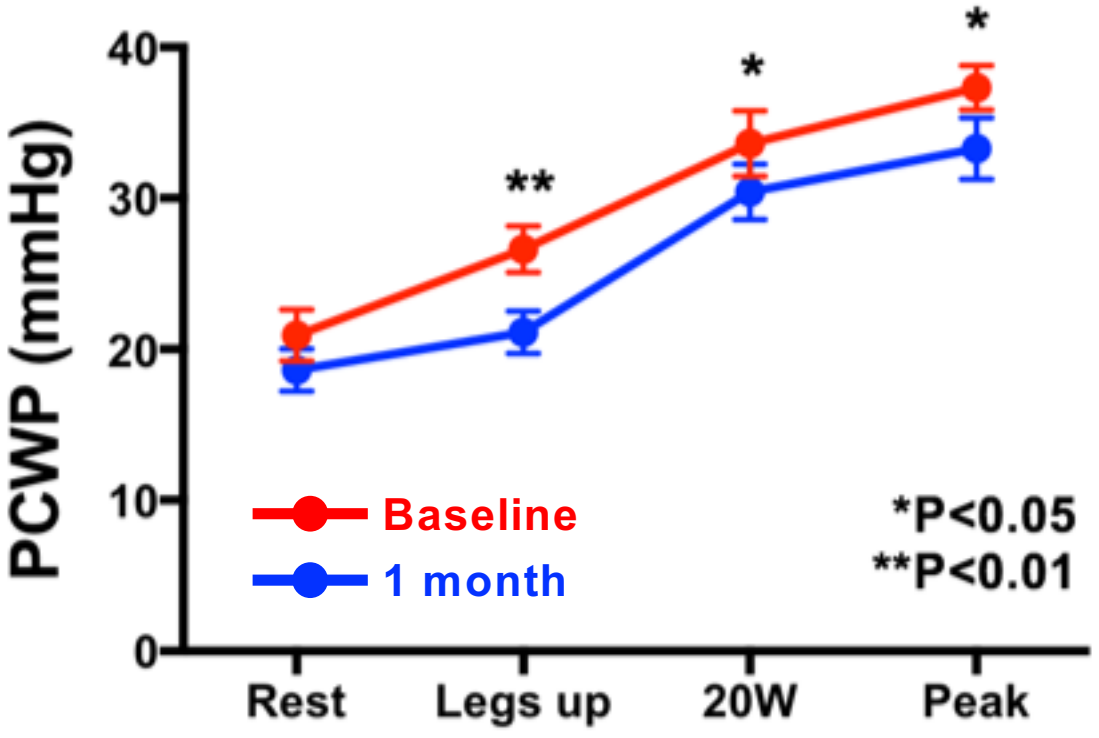
Baseline hemodynamics	IASD	Control	P-value
RA pressure (mmHg)	10.1±2.3	9.1±3.7	0.27
Mean PA pressure (mmHg)	30.2±9.5	28.4±8.6	0.52
Cardiac output (L/min/m²)	5.4±1.6	5.7±2.7	0.66
Pulmonary vascular resistance (WU)	2.19±1.52	1.74±1.45	0.32
PCWP, legs down (mmHg)	20.9±7.9	19.9±7.5	0.67
PCWP, legs up (mmHg)	26.6±7.1	24.0±9.3	0.32
PCWP, peak exercise (mmHg)	37.3±6.5	37.3±6.7	1.00
PCWP-RAP gradient at rest (mmHg)	10.8±5.6	10.9±7.3	0.95
Exercise duration (minutes)	7.4±3.1	8.9±4.0	0.18
Peak exercise workload (W)	42.3±19.5	41.8±16.2	0.93

Change in PCWP: Baseline to 1 month

CONTROL



IASD



NorthShore University HealthSystem
Evanston Hospital

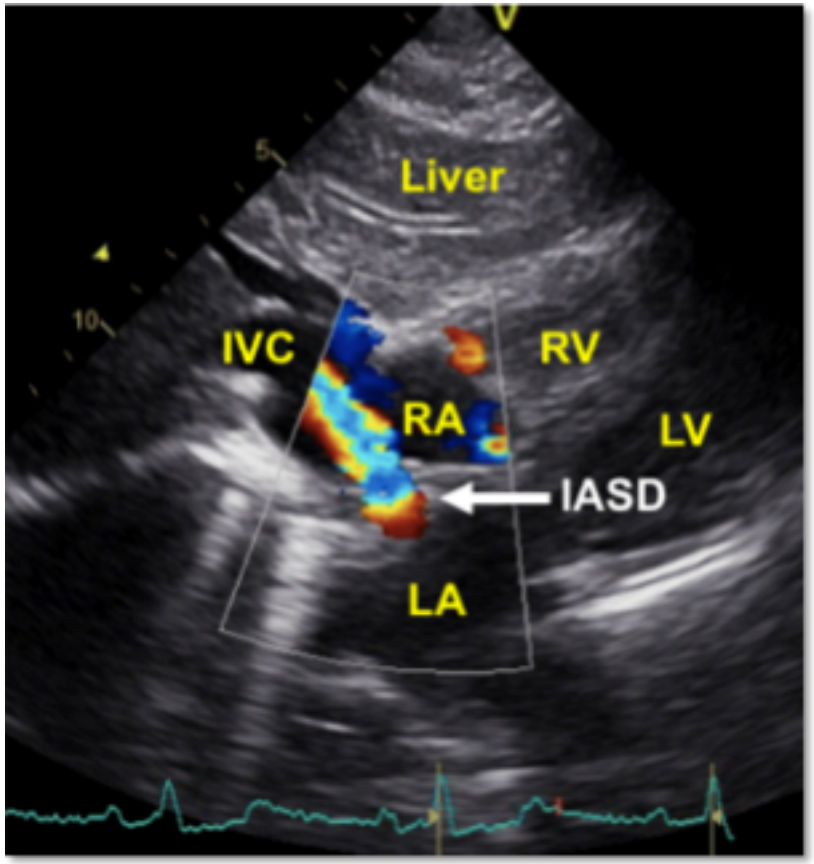
Feldman T… Shah SJ. Circulation. 2018;137:364–375

1 Year Results

Shunt Patency

- At 1 year, shunt patency was documented in all participants who received the IASD and were still alive (n=20)

- There was no evidence through 1 year in the IASD arm vs. control of:
  - Greater increases in number of diuretic medications (p=0.83)
  - Total daily loop diuretic dose (p=0.20)



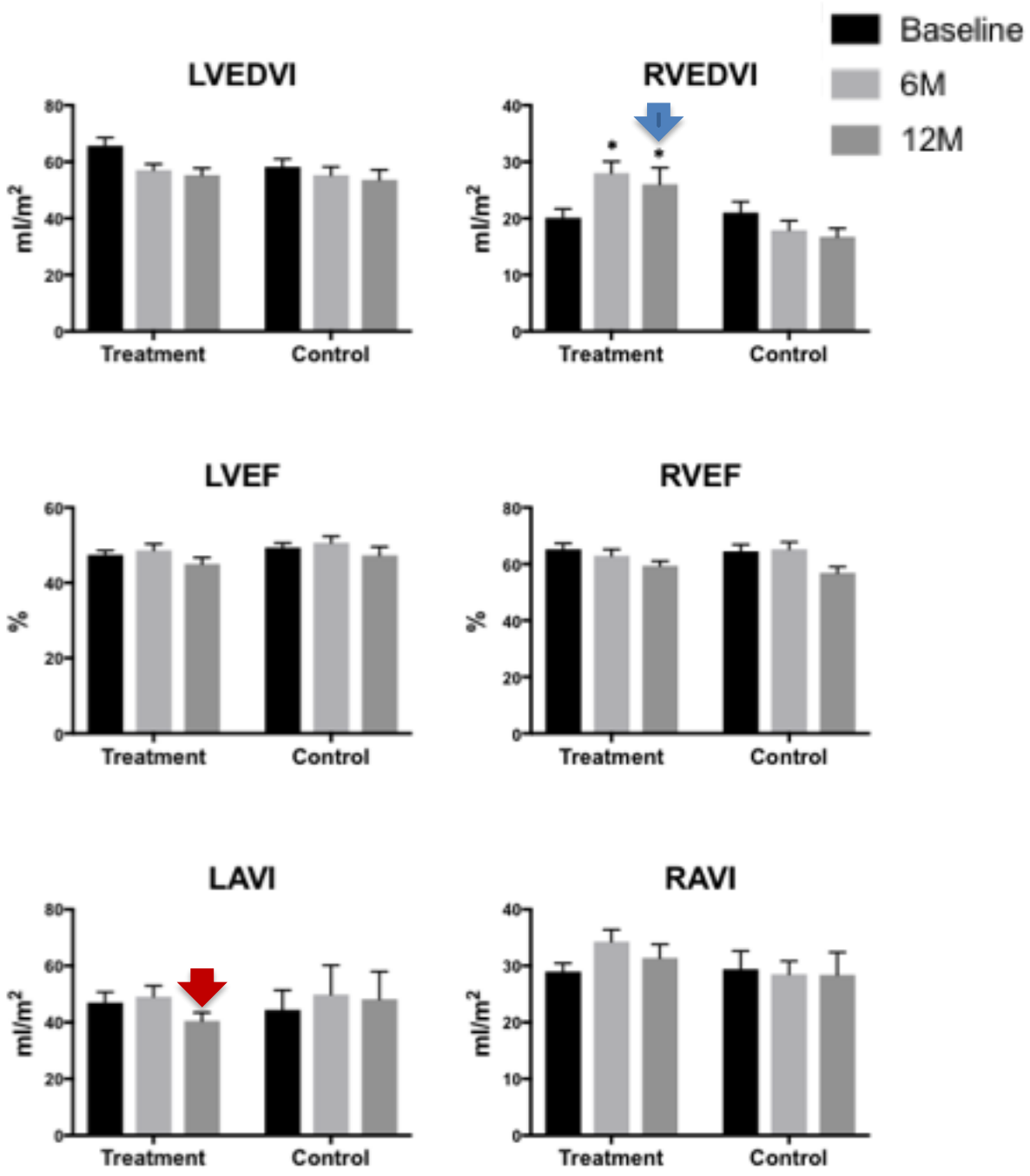
Left-to-Right Shunting Through a Patent IASD at 12 Months in a Study Participant

Baseline, 6-, and 12-Month Echocardiographic Parameters of Cardiac Structure and Function

- No significant change in left heart structure/function

- Trend towards greater reduction in LA volume index in IASD vs. control at 12 months (6.3±10.7 vs. 1.5±14.2 ml/m^2; p=0.078).

- Increase in RVEDV (p=0.01) without any change in RVEF in the IASD arm.



NorthShore University HealthSystem
Evanston Hospital

Key Secondary Outcome Measures at 12 Months* (1)

	IASD n=20	Control n=19	P-Value
Cardiovascular Death	4.8% (1/21)	4.5% (1/22)	1.000
95% CI	[0.1%,23.8%]	[0.1%,22.8%]	
Kaplan Meier Cumulative Incidence	4.8%	5.0%	0.986
95% CI	[0.0%,19.2%]	[0.0%,17.6%]	
Rate of total HF admissions/visits with IV diuretics (per patient-year)	0.22 (0.08,0.58)	0.63 (0.33,1.21)	0.064
Days alive and without hospitalization	353 (339,363)	340.5 (330,353)	0.161
Days alive without HF related hospitalization	359 (351,365)	351 (331,365)	0.167
Number of hospitalizations for a HF-related event per patient			0.087
0	85.7% (18/21)	63.6% (14/22)	
1	4.8% (1/21)	18.2% (4/22)	
2	0.0% (0/21)	4.5% (1/22)	
≥3	9.5% (2/21)	13.6% (3/22)	

NorthShore University HealthSystem
Evanston Hospital

**powered for primary and not for secondary outcome measures*

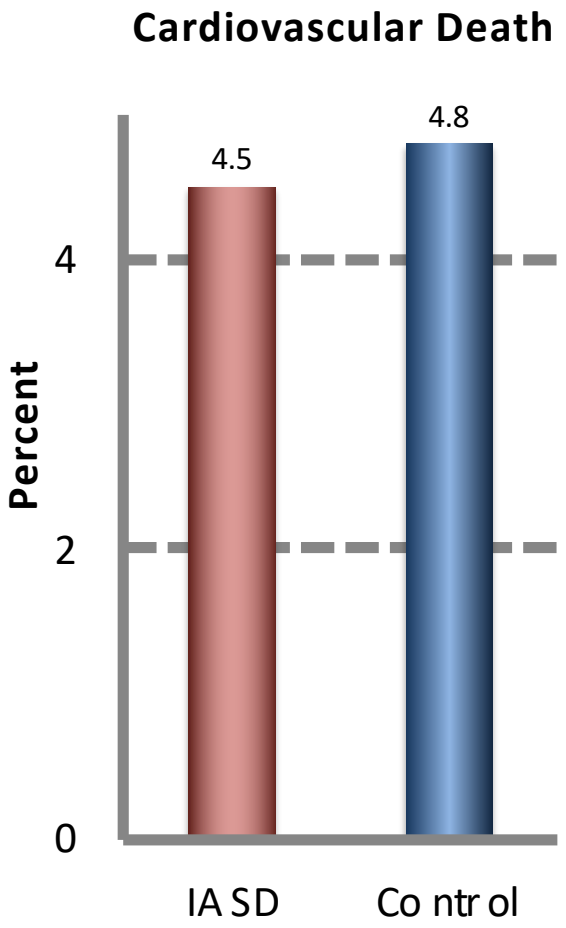
Key Secondary Outcome Measures at 12 Months* (2)

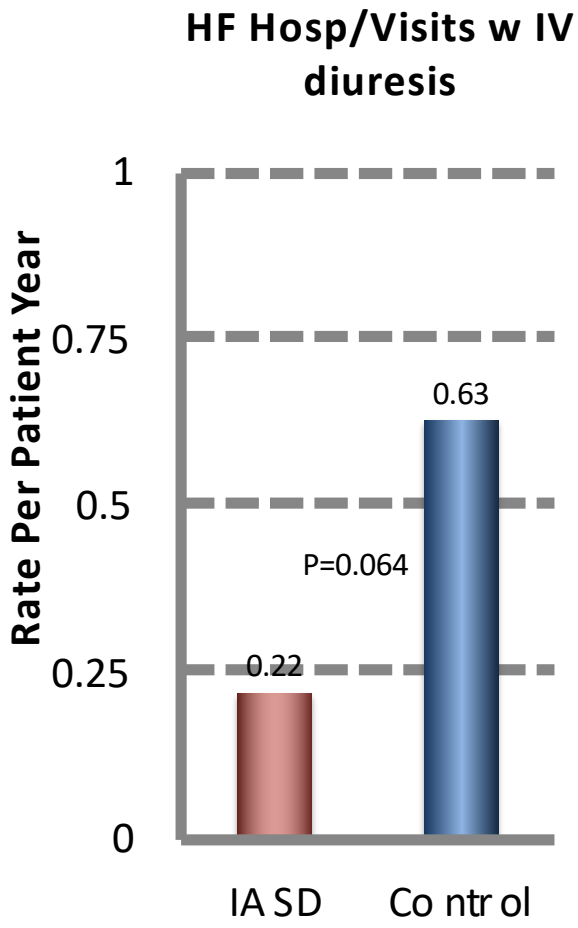
	IASD	Control	P-Value
Change in NYHA class (12M – baseline)	-1 (-1,0) [n=20]	0 (-1,0) [n=19]	0.083
Change in 6MWT distance (12M – baseline)	16 (-57,30) [n=20]	13.6 (-10,72) [n=19]	0.308
Change in QOL (12M – baseline)			
KCCQ	[n=20]	[n=19]	
Overall Summary score	+10.5 (0.7,18.8)	+8.1 (-5.7,20.6)	0.570
Clinical Summary score	+10.4 (-6.5,26.0)	+3.1 (-4.2,18.8)	0.827
EQ-5D score	0.0 (-0.2,0.1) [n=20]	0.0 (-0.1,0.2) [n=19]	0.814

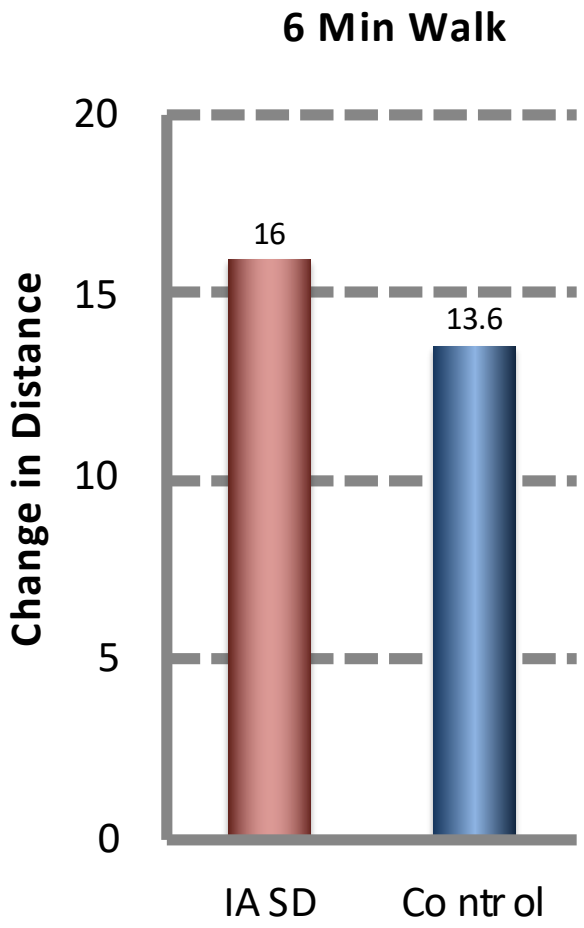
NorthShore University HealthSystem
Evanston Hospital

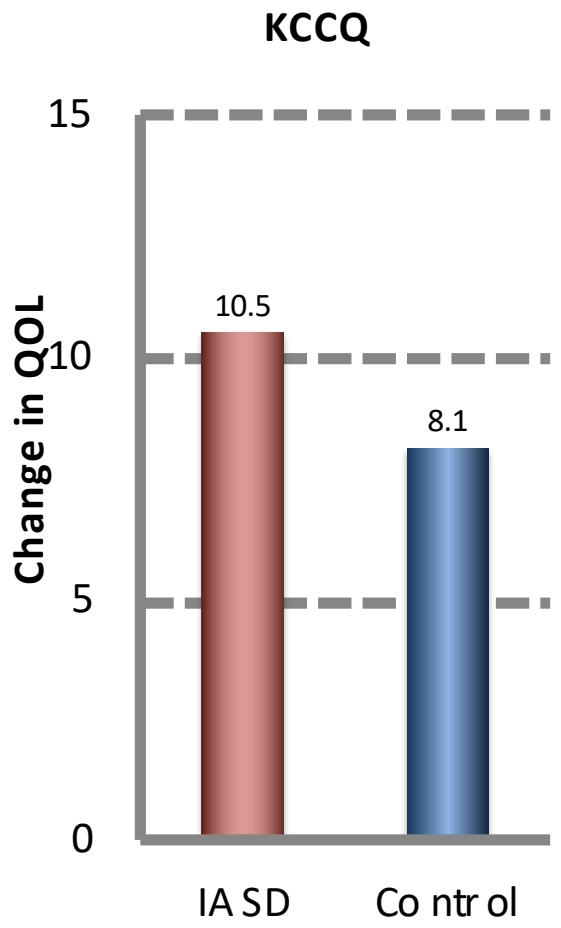
**powered for primary and not for secondary outcome measures*

Key Secondary Outcome Measures at 12 Months*







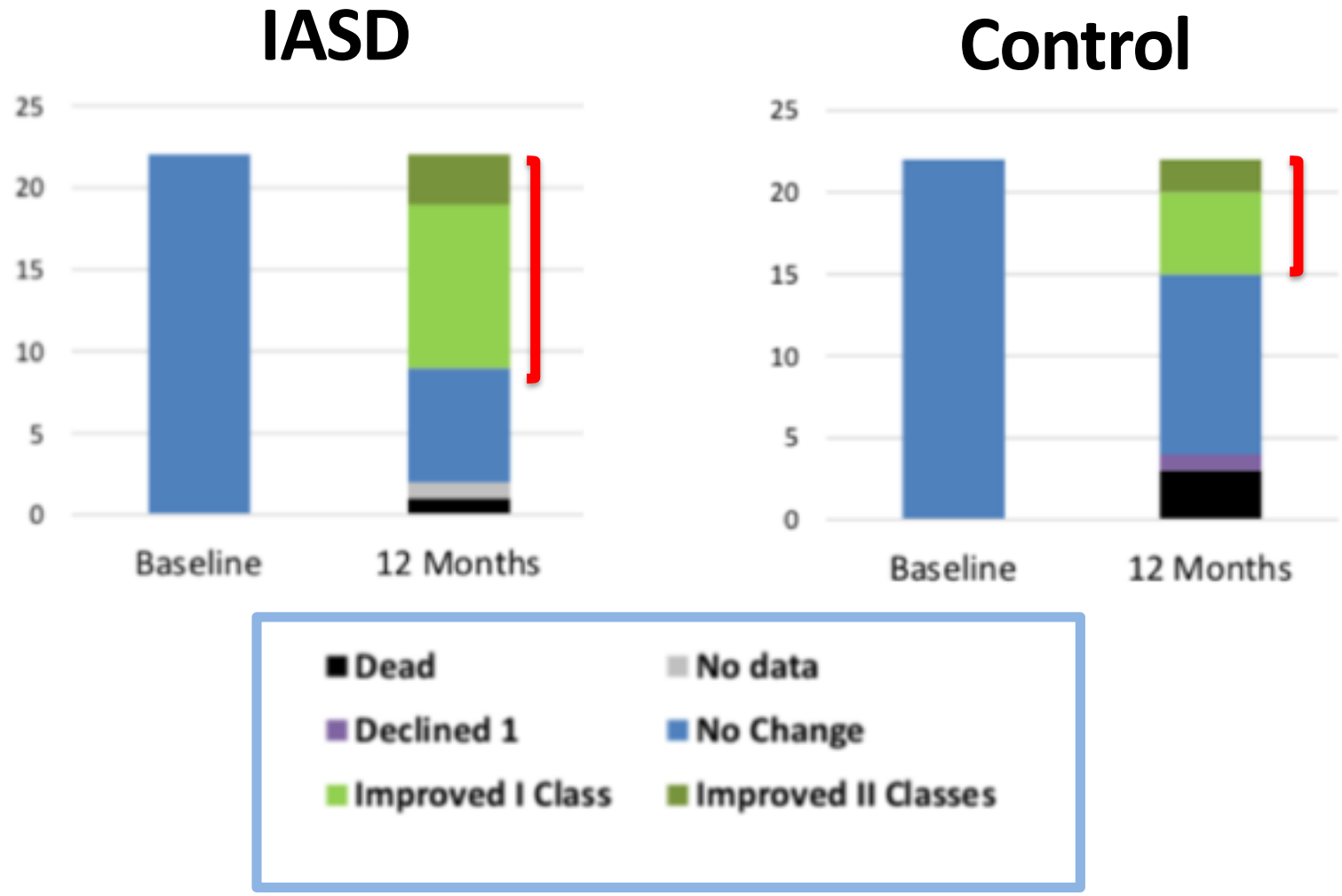


NorthShore University HealthSystem
Evanston Hospital

**powered for primary and not for secondary outcome measures*

N=39

Change in NYHA Functional Class: InterAtrial Shunt Device vs. Sham Control



NorthShore University HealthSystem
Evanston Hospital

Combined In- and Out-of-Hospital Events Through 12 Months (1)

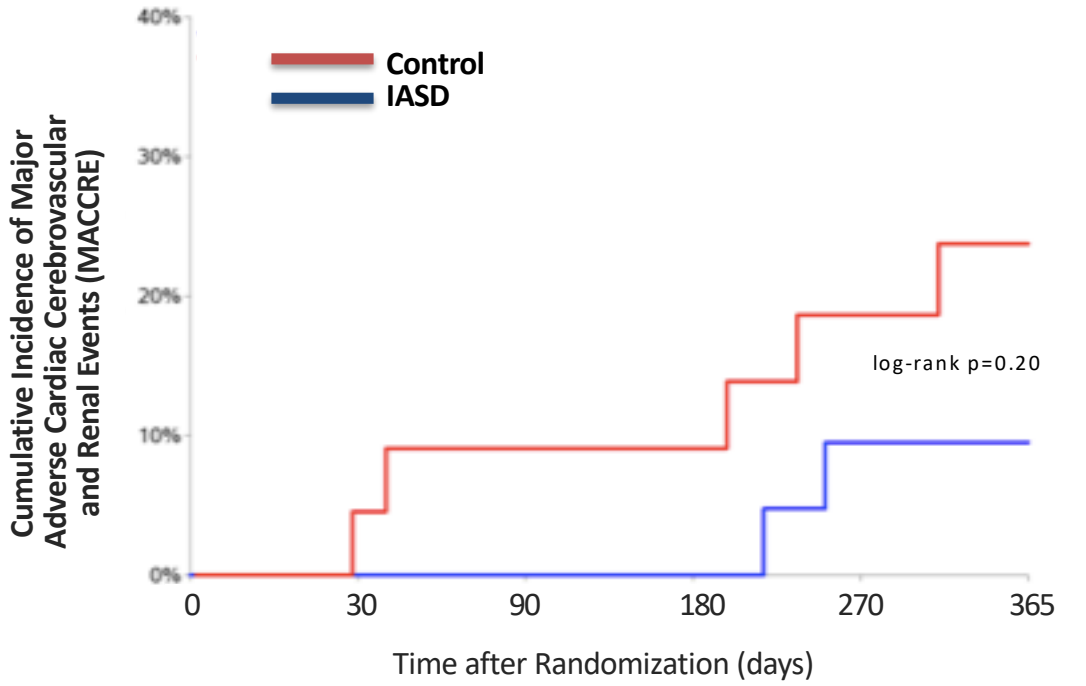
	IASD	Control	P Value
MACCRE	9.52% (2/21)	22.73% (5/22)	0.412
Cardiovascular Death	4.76% (1/21)	4.55% (1/22)	1.000
Embolic Stroke	0.00% (0/21)	0.00% (0/22)	--
Device/Procedure Related MACE	4.76% (1/21)	4.55% (1/22)	1.000
Renal Dysfunction (New Onset or Worsening)	4.76% (1/21)	13.64% (3/22)	0.607
MACE	4.76% (1/21)	13.64% (3/22)	0.607
Cardiac Death	4.76% (1/21)	4.55% (1/22)	1.000
Myocardial Infarction	0.00% (0/21)	9.09% (2/22)	0.488
Emergency Cardiac Surgery	0.00% (0/21)	0.00% (0/22)	--
Cardiac Tamponade	0.00% (0/21)	0.00% (0/22)	--

Combined In- and Out-of-Hospital Events Through 12 Months (2)

	IASD	Control	P Value
Death	4.76% (1/21)	13.64% (3/22)	0.607
Cardiovascular Death	4.76% (1/21)	4.55% (1/22)	1.000
Non-Cardiovascular Death	0.00% (0/21)	9.09% (2/22)	0.488
Heart Failure Event	47.62% (10/21)	45.45% (10/22)	1.000
Heart Failure Event Requiring IV Treatment	19.05% (4/21)	40.91% (9/22)	0.185
Cardiogenic Shock	4.76% (1/21)	0.00% (0/22)	0.488

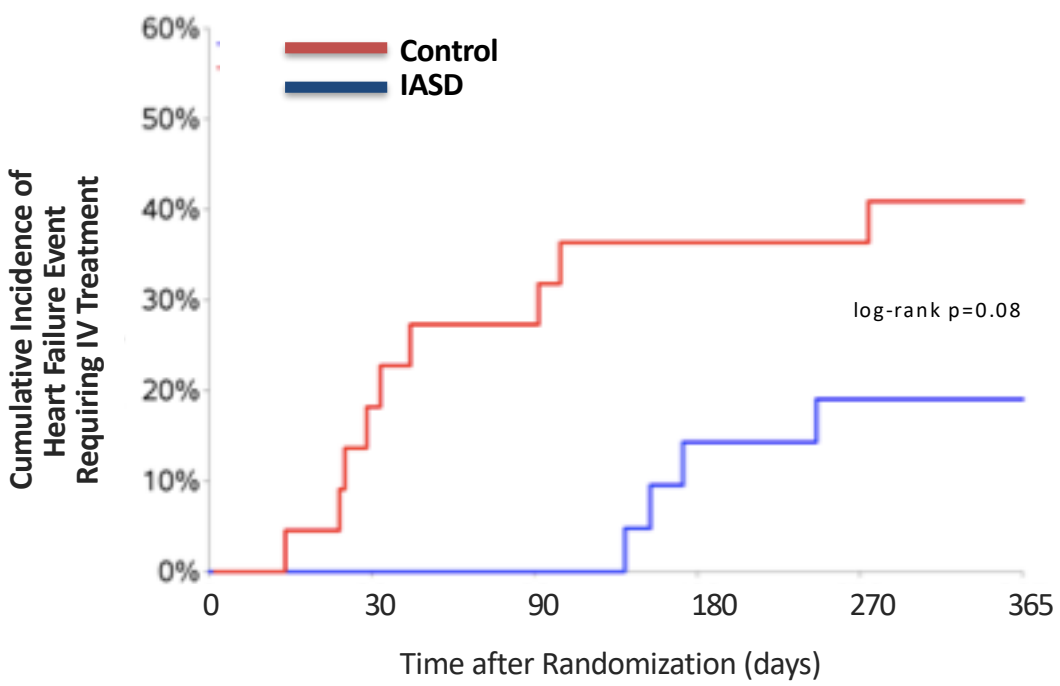
Cumulative Incidence of MACCRE and Heart Failure Events Requiring Intravenous Diuretic Treatment Through 12 Months

MACCRE



No. at risk						
Treatment:	22	21	21	21	21	14
Control:	22	22	21	20	19	12

Heart Failure Events



No. at risk						
Treatment:	22	21	21	21	18	12
Control:	22	22	18	16	14	11

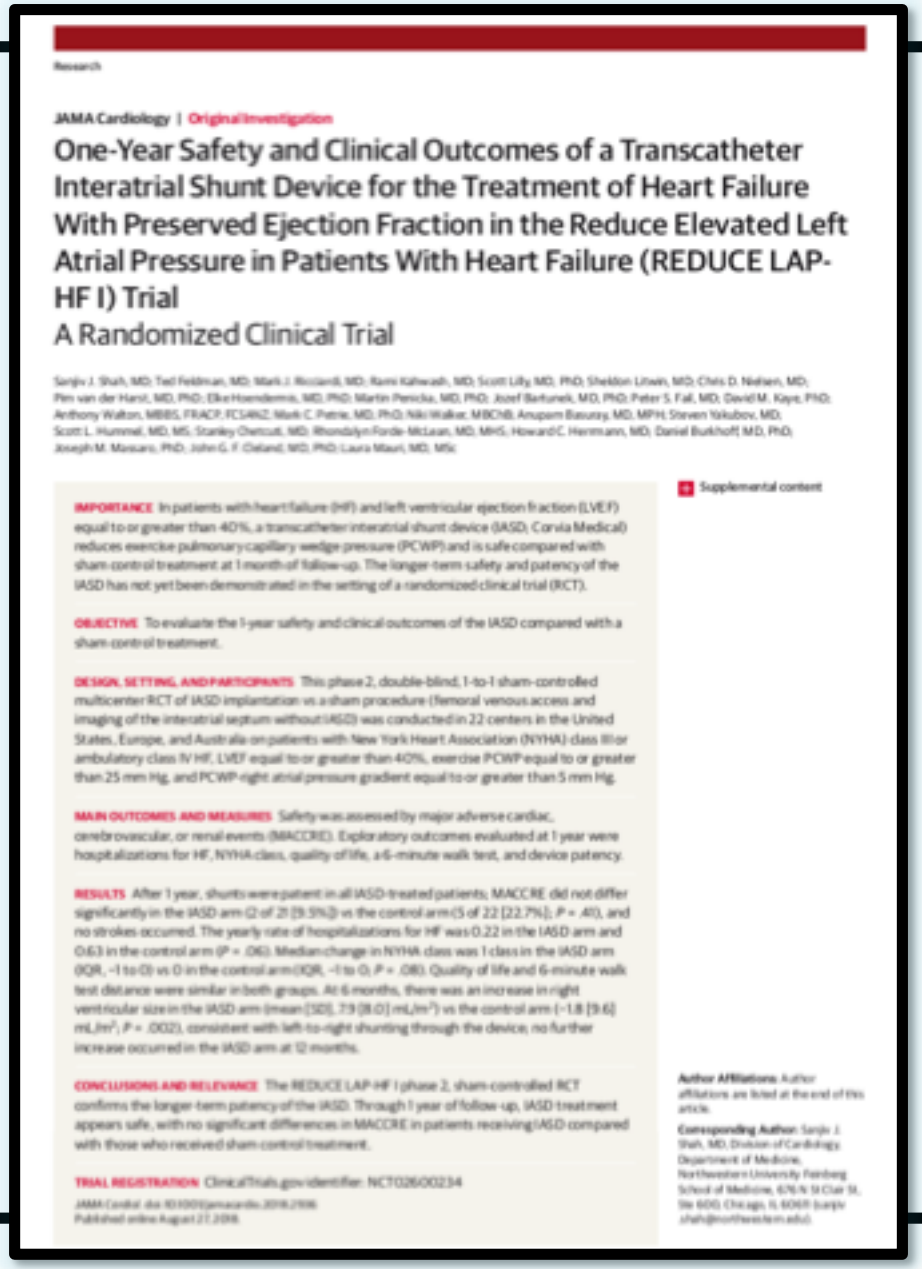
NorthShore University HealthSystem
Evanston Hospital

Conclusions

- REDUCE LAP-HF I confirms the 1 year patency of the IASD
- Through 1 year of follow-up IASD treatment compared to sham-control:
  - Appears safe
  - Is associated with favorable trends in
    - MACCRE
    - HF hospitalization
    - NYHA class

Summary

- First RCT of a device-based therapy in HFpEF and HFmrEF
- REDUCE LAP-HF I trial met its primary endpoint
  - Significantly reduced exercise PCWP at 1 month (P=0.028)
- Good safety profile through 12 months
- Beneficial clinical effects in HFpEF and HFmrEF through 12 months
- A larger pivotal trial to examine the effects of the IASD on clinical outcomes and QOL is warranted
- REDUCE LAP-HF II pivotal trial is underway (NCT03088033)



Research

JAMA Cardiology | Original Investigation

One-Year Safety and Clinical Outcomes of a Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial

A Randomized Clinical Trial

Supplemental content

IMPORTANCE In patients with heart failure (HF) and left ventricular ejection fraction (LVEF) equal to or greater than 40%, a transcatheter interatrial shunt device (IASD; Corvia Medical) reduces exercise pulmonary capillary wedge pressure (PCWP) and is safe compared with sham-control treatment at 1 month of follow-up. The longer-term safety and patency of the IASD has not yet been demonstrated in the setting of a randomized clinical trial (RCT).

OBJECTIVE To evaluate the 1-year safety and clinical outcomes of the IASD compared with a sham-control treatment.

DESIGN, SETTING, AND PARTICIPANTS This phase 2, double-blind, 1-to-1 sham-controlled multicenter RCT of IASD implantation vs a sham procedure (femoral venous access and imaging of the interatrial septum without IASD) was conducted in 22 centers in the United States, Europe, and Australia on patients with New York Heart Association (NYHA) class III or ambulatory class IV HF, LVEF equal to or greater than 40%, exercise PCWP equal to or greater than 25 mm Hg, and PCWP-right atrial pressure gradient equal to or greater than 5 mm Hg.

MAIN OUTCOMES AND MEASURES Safety was assessed by major adverse cardiac, cerebrovascular, or renal events (MACCRE). Exploratory outcomes evaluated at 1 year were hospitalizations for HF, NYHA class, quality of life, a 6-minute walk test, and device patency.

RESULTS After 1 year, shunts were patent in all IASD-treated patients; MACCRE did not differ significantly in the IASD arm (2 of 21 [9.5%]) vs the control arm (5 of 22 [22.7%]; $P = .41$), and no strokes occurred. The yearly rate of hospitalizations for HF was 0.22 in the IASD arm and 0.63 in the control arm ($P = .06$). Median change in NYHA class was 1 class in the IASD arm (IQR, −1 to 0) vs 0 in the control arm (IQR, −1 to 0; $P = .08$). Quality of life and 6-minute walk test distance were similar in both groups. At 6 months, there was an increase in right ventricular size in the IASD arm (mean [SD], 7.9 [8.0] mL/m^2) vs the control arm (−1.8 [9.6] mL/m^2; $P = .002$), consistent with left-to-right shunting through the device; no further increase occurred in the IASD arm at 12 months.

CONCLUSIONS AND RELEVANCE The REDUCE LAP-HF I phase 2, sham-controlled RCT confirms the longer-term patency of the IASD. Through 1 year of follow-up, IASD treatment appears safe, with no significant differences in MACCRE in patients receiving IASD compared with those who received sham-control treatment.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02600234

JAMA Cardiol. doi:10.1001/jamacardio.2018.2936
Published online August 27, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sanjiv J. Shah, MD, Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 N St Clair St, Ste 600, Chicago, IL 60611 (sanjiv.shah@northwestern.edu).

The JAMA Network

JAMA Cardiology

Shah SJ, Feldman T, Ricciardi M, et al.

One-Year Safety and Clinical Outcomes of a Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial: A Randomized Clinical Trial

Published online August 27, 2018
Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com