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Left atrial decompression to treat heart failure

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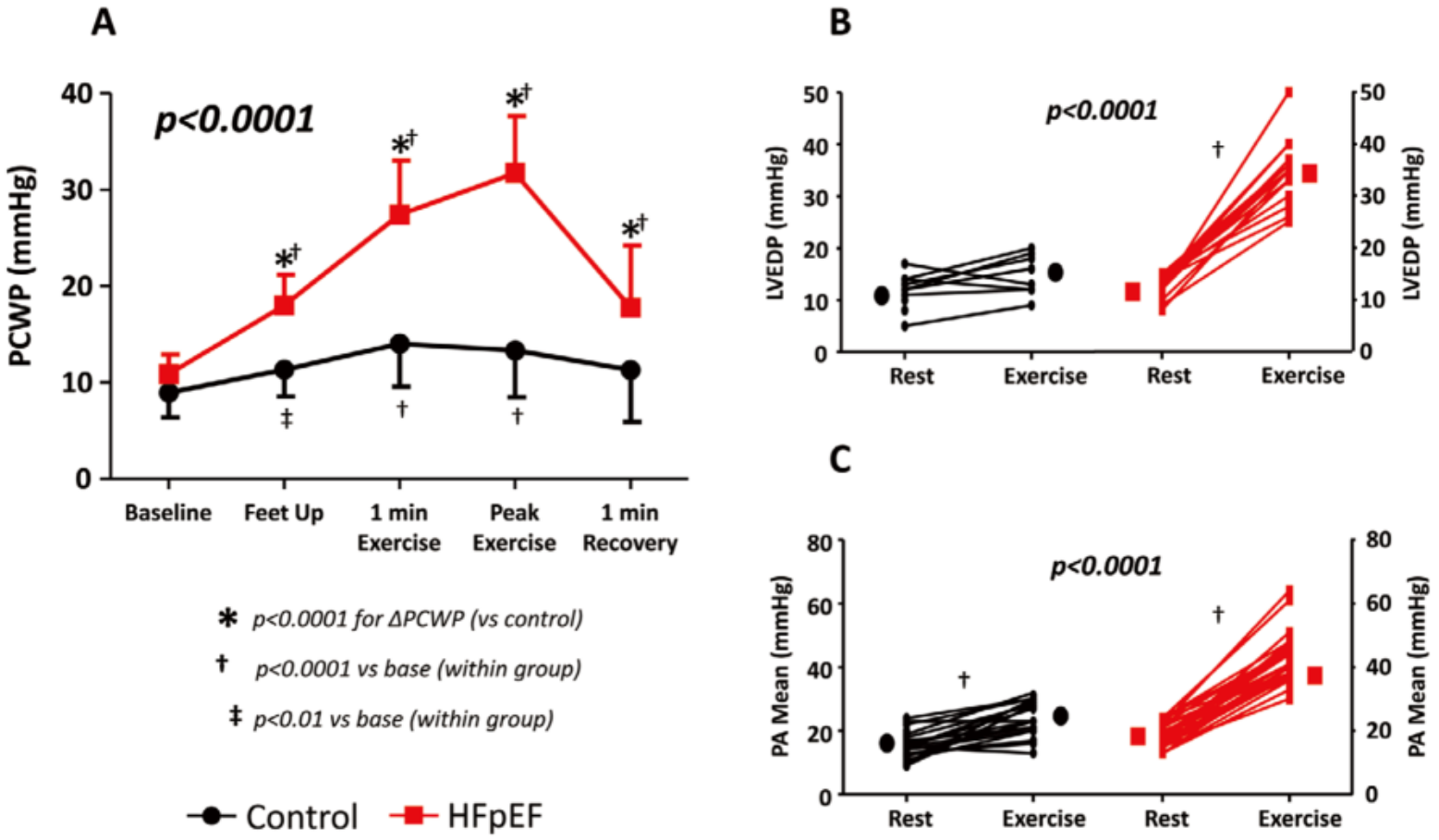
Presenter disclosure information
Gerd Hasenfuss

Corvia	Consulting, lectures, Study PI
Servier	Consulting, honorarium for lectures
Impulse Dynamics	Consulting, honorarium for lectures, Co-PI
Novartis	Consulting, honorarium for lectures
AstraZeneca	Honorarium for lectures
Vifor Pharma	Consulting, honorarium for lectures
Berlin Chemie	Honorarium for lectures

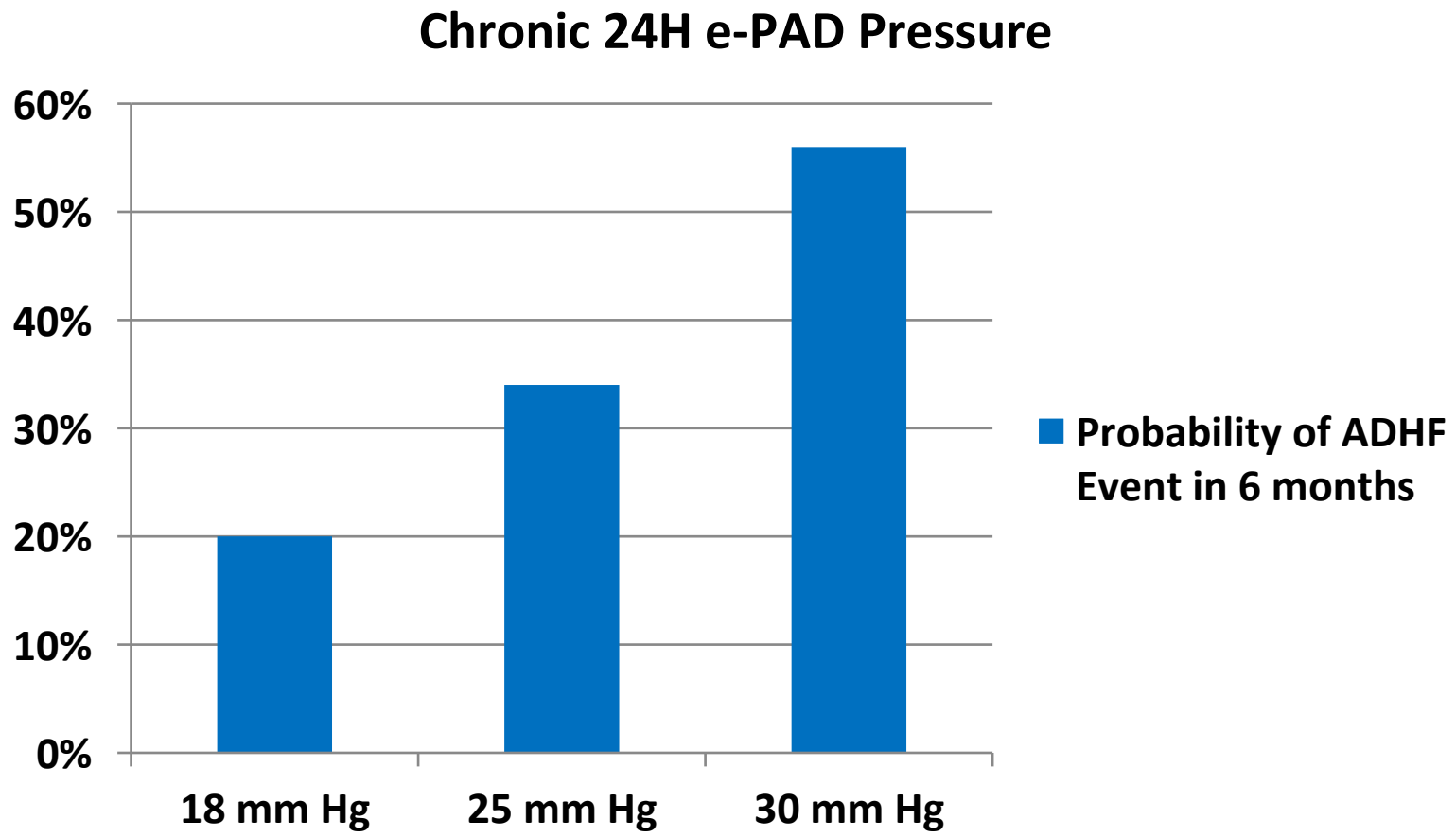
Mechanisms of exercise intolerance in HFpEF



PCWP rises quickly and profoundly and may be the key mechanism underlying effort intolerance

Borlaug, Circ J 2014

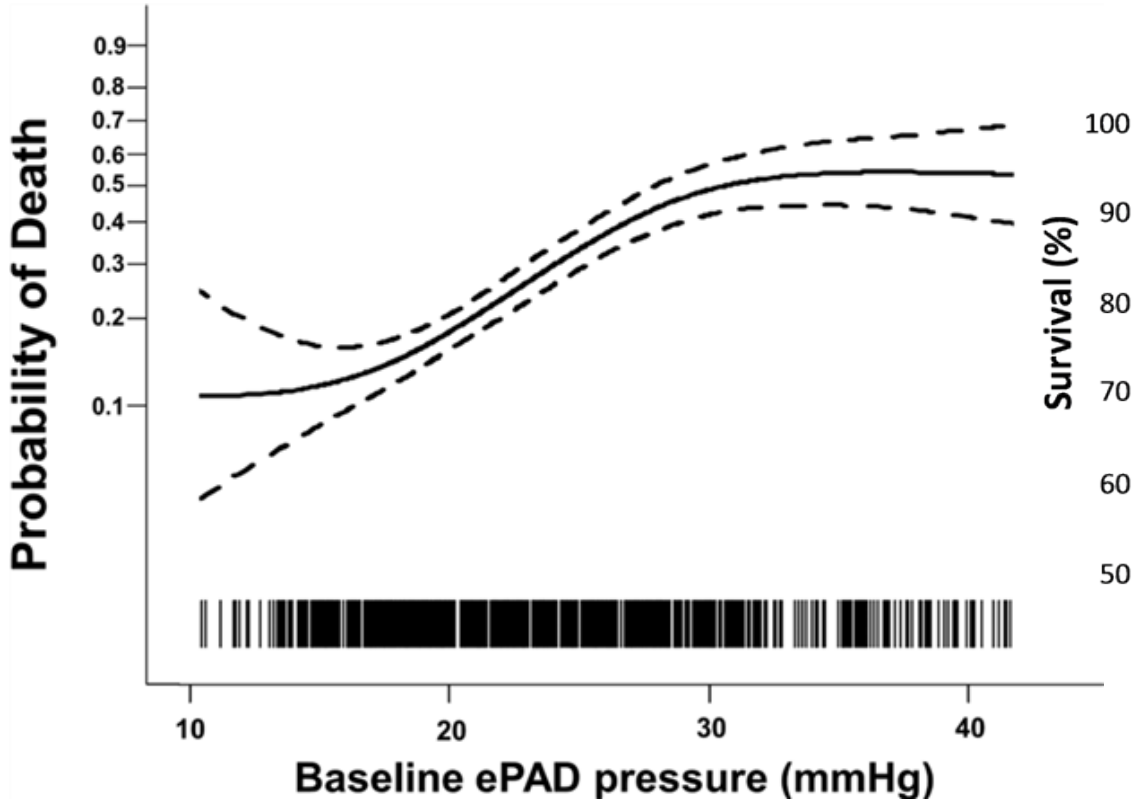
COMPASS-HF trial
HFpEF subgroup analysis

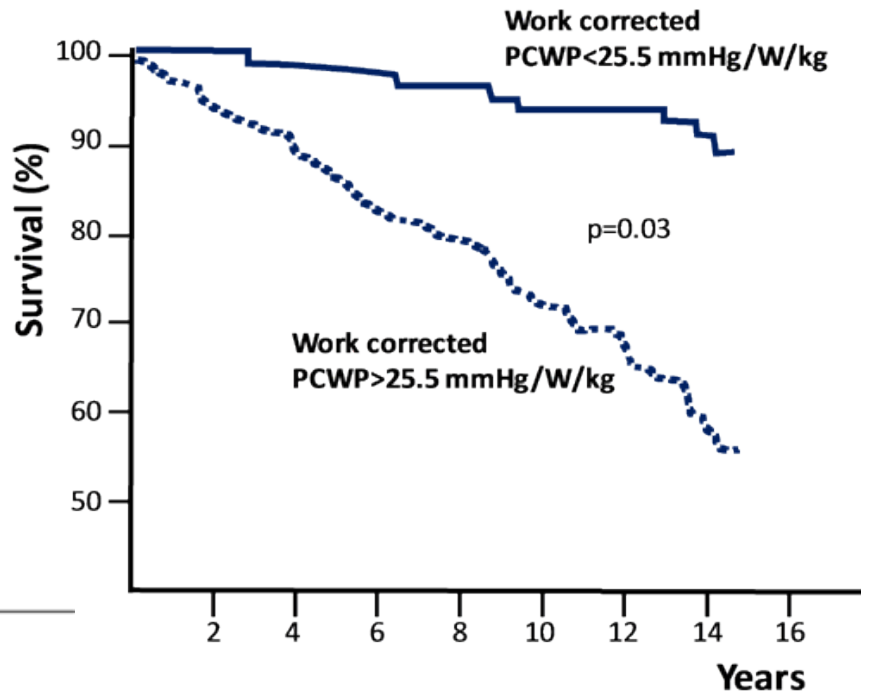


Implantable PA device to monitor diastolic PAP (Surrogate for LAP)
A 5 mm Hg (17 ± 7 to 22 ± 7) increase in estimated resting minimum PA diastolic P in HFpEF patients was associated with development of Acute Decompensated HF (ADHF)

Zile et al., Circ. Heart Fail 2017

Baseline and exercise filling pressures & mortality

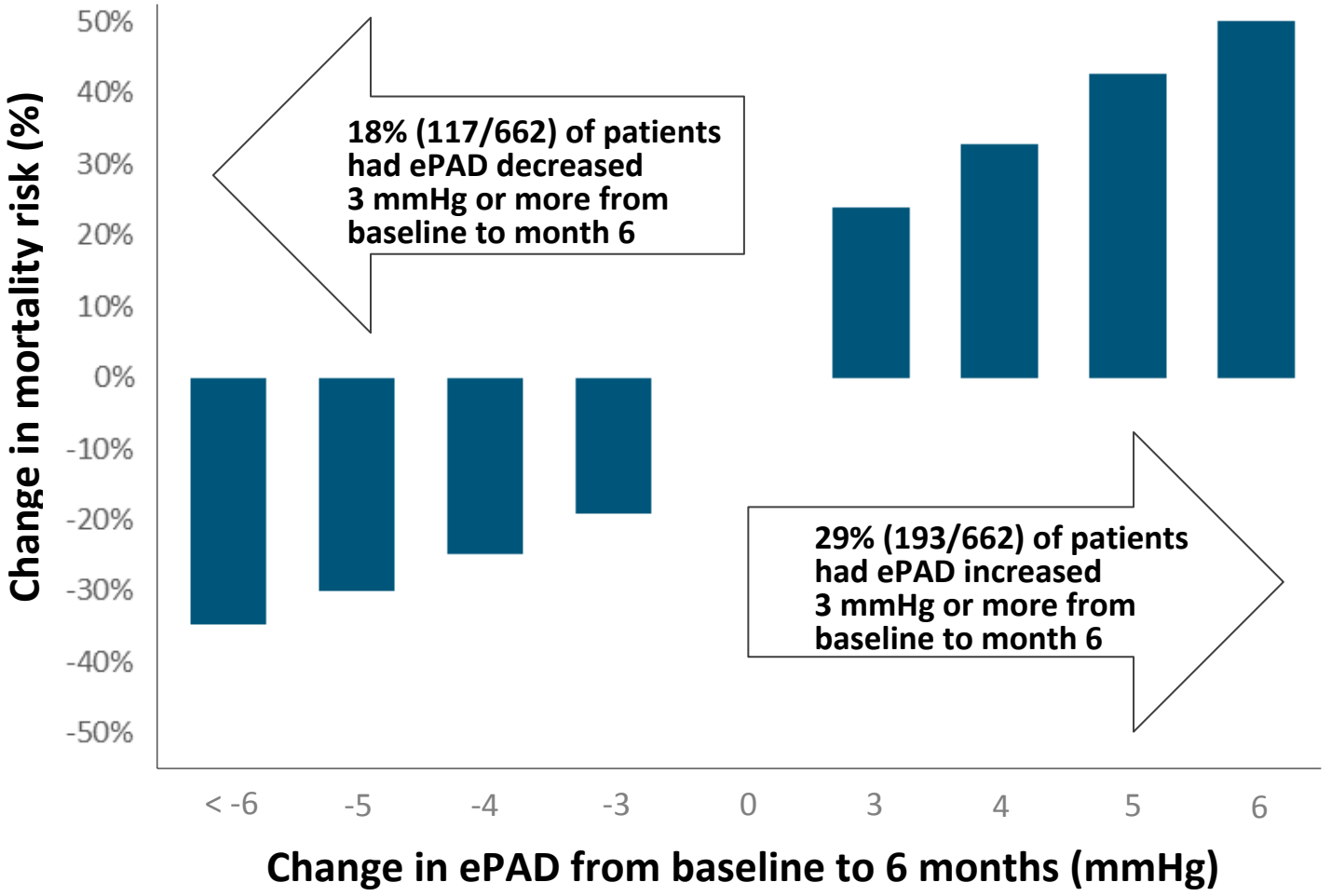




Over a range of ePAD* (≈15–35mm Hg), baseline pressure is directly related to probability of mortality.

Zile et al., Circ. Heart Fail 2017
Dorfs et al., Eur Heart J 2014

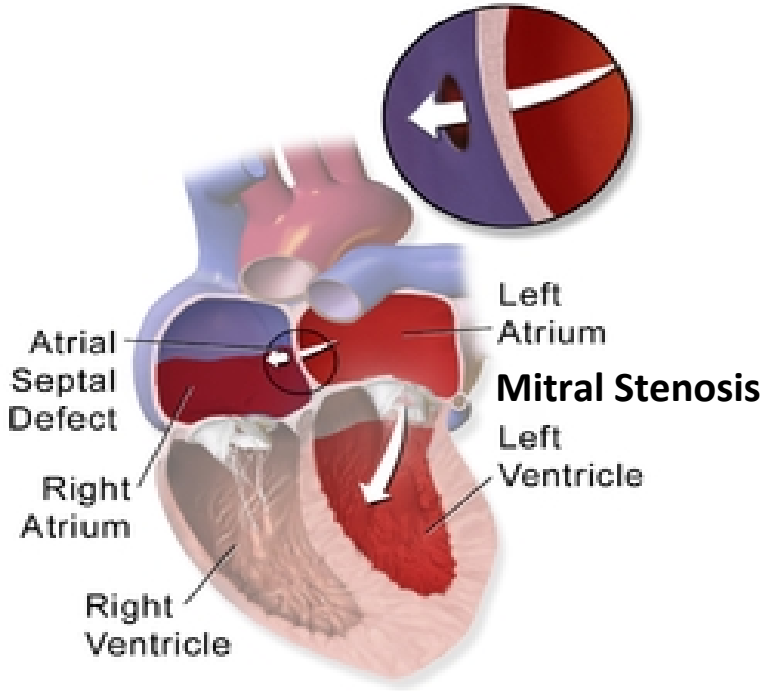
Mortality & small filling pressure (ePAD*) changes



Zile et al., Circ. Heart Fail 2017

Lutembacher´s Syndrome: Congenital ASD + Mitral Stenosis

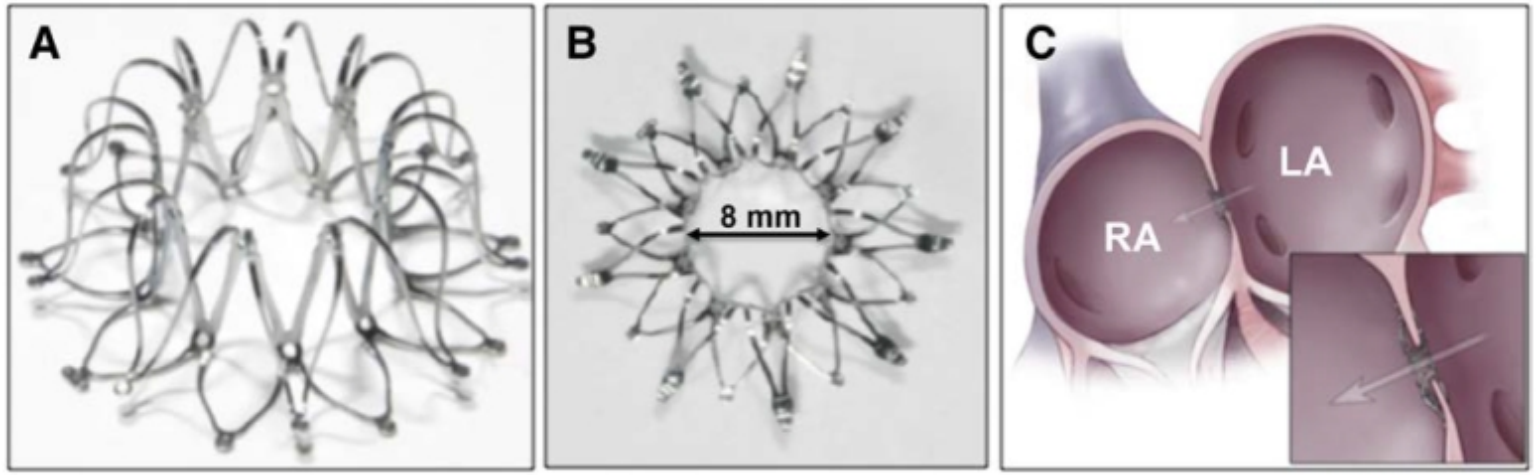
In 1916, Lutembacher described the combination of mitral stenosis (which mimics the hemodynamic pathophysiology of HFpEF), and an ASD

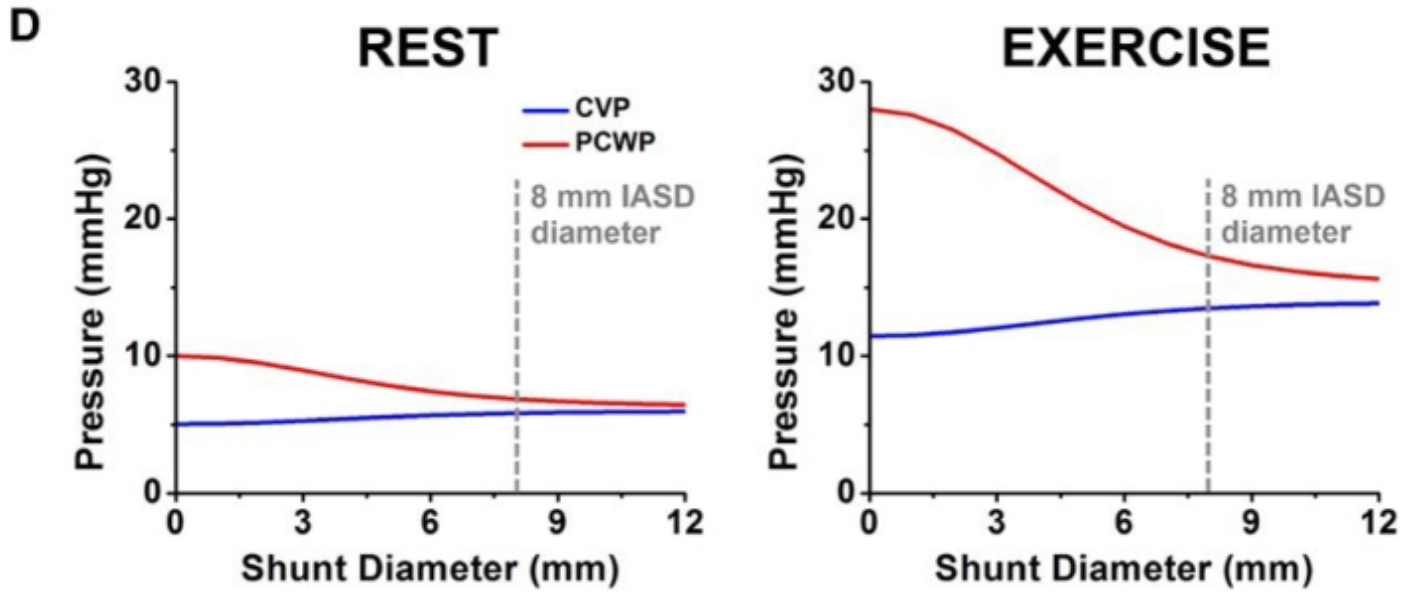


Heart with Atrial Septal Defect

Patients with this syndrome had fewer symptoms and better outcomes

InterAtrial Shunt Device (IASD®)





Kaye et al., J Card Fail 2014

REDUCE LAP-HF TRIAL

- **REDUCE LAP-HF TRIAL:**
  - **A study to evaluate the DC Devices, Inc. IASD® System II to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure**
  - Multicenter, open-label, single-arm, phase 1 trial

- **Symptomatic HFpEF (64 patients)**
- **Preserved EF (> 40%)**
- **PCWP ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise**
- **CVP ≤ 14 mmHg, TAPSE ≥ 14 mm**

- **Monitored by independent DSMB, and CEC**
- **Independent Core-Laboratories**
  - **Echo**
  - **Hemodynamic**
  - **Sub-studies: Cardiac MRI, CPET**

- **Co-Primary endpoints: Safety and device performance at 6 months, three year clinical follow-up**

Hasenfuss et al., Lancet 2016

Baseline demographics (n=64)

Age (Y)	69 ± 8.3
Male/Female (n)	22/42
LVEF (%)	47 ± 7
NYHA (n, II/III/IV)	18/46/0
BMI (kg/m^2)	33 ± 6
MLWHF score	49 ± 20
NT-Pro BNP (pg/ml) 271 SR; 1176 AF	377 (222-925)
Permanent AF (%)	36
CAD (%)	24
Hypertension (%)	81
Diabetes (%)	33
Musculoskeletal (%) / Rheumatologic (%)	35/20
COPD (%)	9

*Data are mean ± SD, except *NT-BNP (median, IQR).*

Hasenfuss et al., Lancet 2016

Resting echocardiographic / hemodynamic data

LV end diastolic volume index (ml/m^2)	68 ± 13
LV mass index (g/m^2)	119 ± 36
LA diastolic volume index (ml/m^2)	34 ± 17
RV diastolic volume index (ml/m^2)	22 ± 9
RA volume index (ml/m^2)	35 ± 17
E/A ratio	1.3 ± 0.8
E/e' ratio	13.9 ± 5.9
TAPSE (mm)	20 ± 4
Mean RA Pressure (mmHg)	9 ± 4
Mean PA Pressure (mmHg)	25 ± 7
Mean PCWP (mmHg)	17 ± 5
TD Cardiac output (l/min)	5.5 ± 1.6

Hasenfuss et al., Lancet 2016

Primary safety endpoint (n=64 Pts, 6 months)

- **MACCE event rate at 6 months:**
  - **Death rate: 0%**
  - **Stroke rate: 0%**
  - **MI rate: 0%**
  - **Systemic embolic event rate: 0%**
  - **Implant removal rate: 0%**
- **No patient met the Primary safety endpoint**

Hasenfuss et al., Lancet 2016

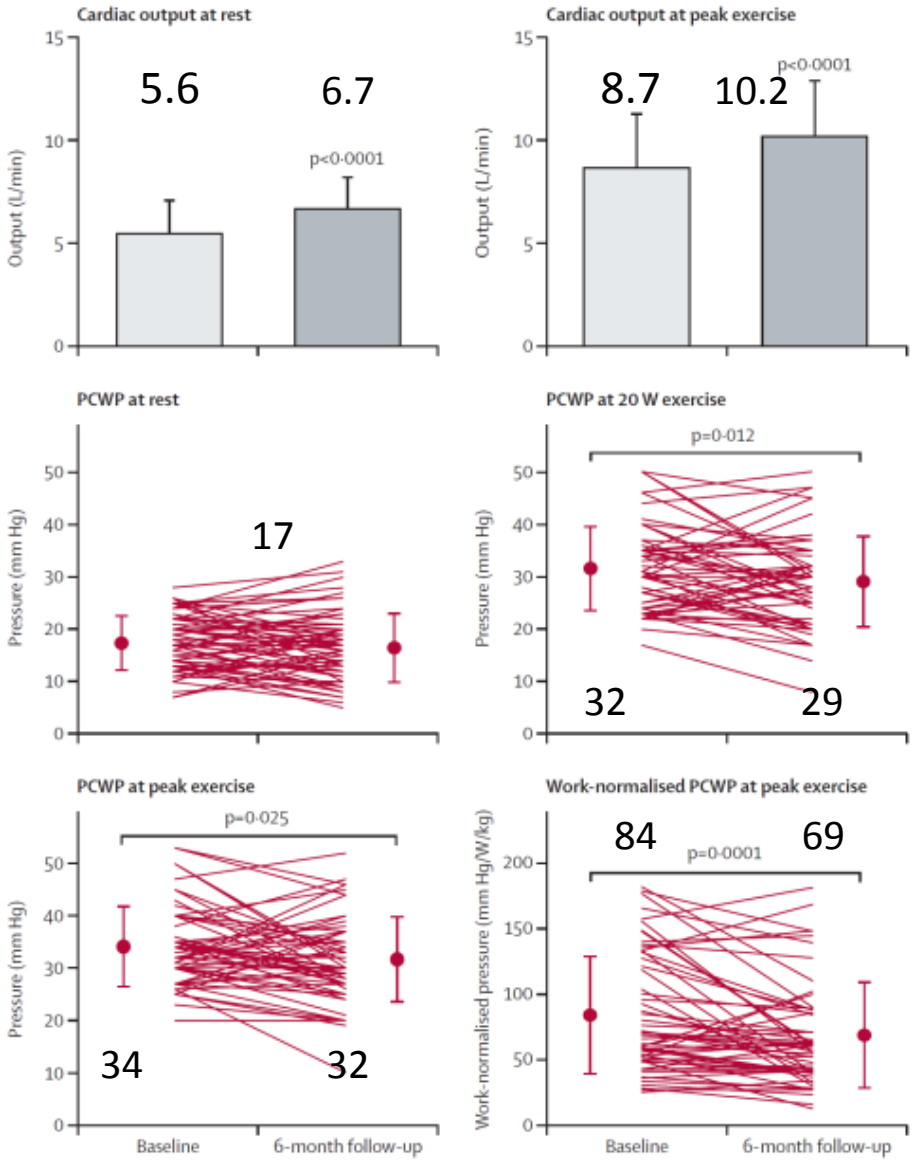
Primary device performance endpoints

- The % of subjects who have successful device implantation, defined as deployment at the intended location during the index procedure:
  - Overall success rate: 96.7% (64/66)

- The % of subjects with reduction of PCWP; and demonstration of L→R flow through the device <u>at 6 months</u>:
  - Echo L→R flow: 100%
    - 1 not analyzable
  - Reduction of PCWP 71% (42/59)

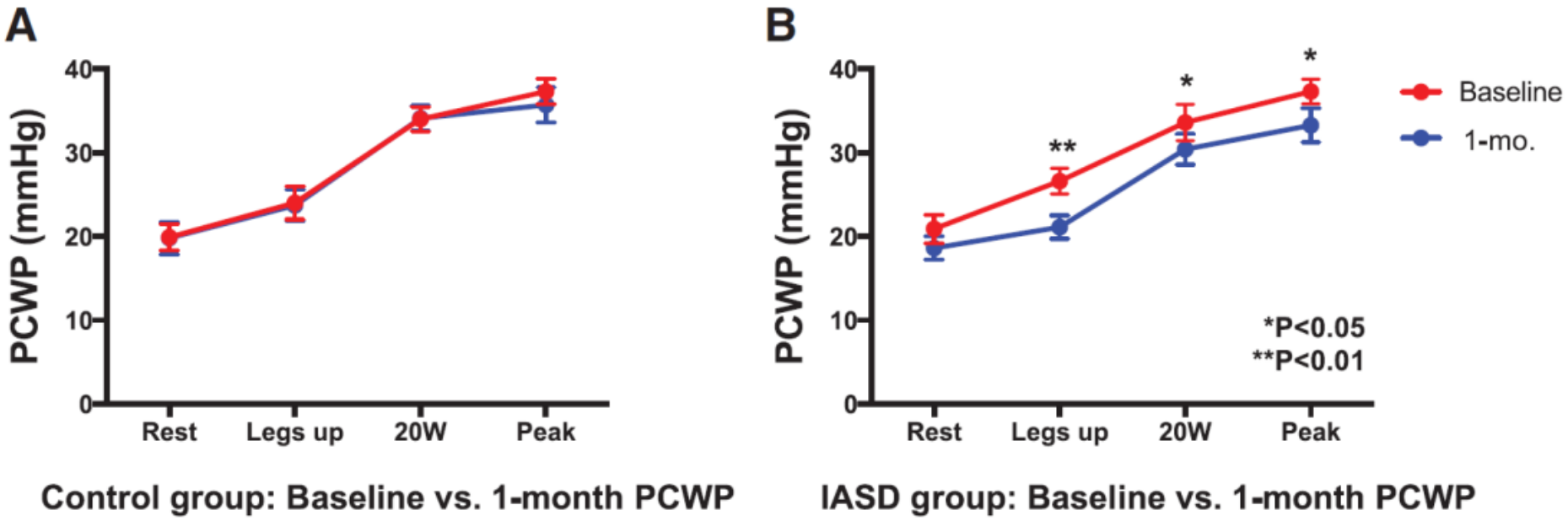
Hasenfuss et al., Lancet 2016

Cardiac output and PCWP at rest and exercise at baseline and 6-month follow-up



Hasenfuss et al., Lancet 2016

Sham controlled trial
Pulmonary capillary wedge pressure during exercise hemodynamic testing

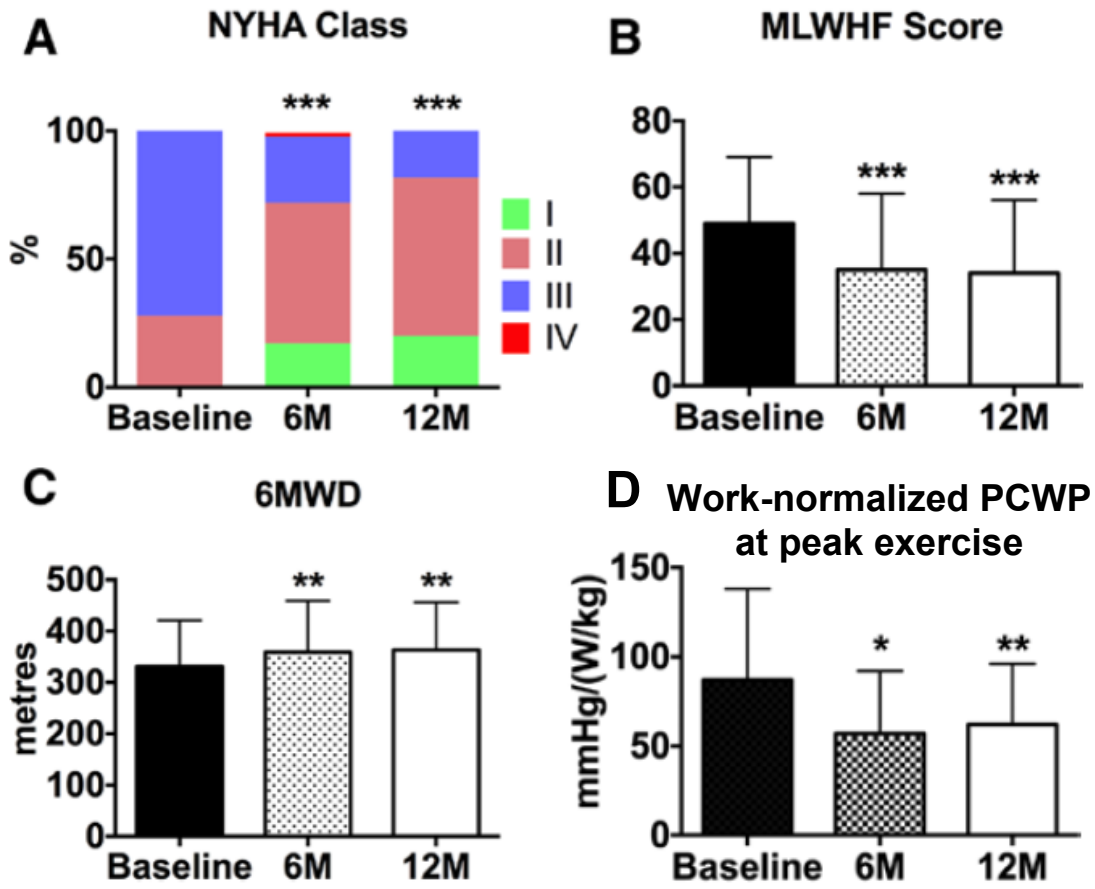


Control group: Baseline vs. 1-month PCWP

IASD group: Baseline vs. 1-month PCWP

Feldman et al., Circulation 2018

Reduce LAP-HF
6 and 12 month clinical results



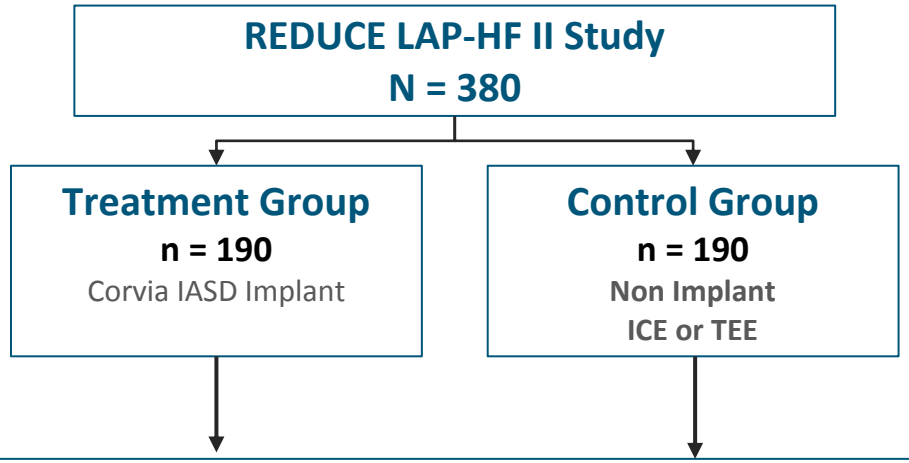
Kaye et al., Circ Heart Fail 2016

Right heart hemodynamics/function 6 months after IASD

Parameter	6M vs. baseline	*P* value
Op:Qs	1.27 vs. 1.06	0.0004
RA pressure (mmHg)	11±5 vs. 9±4	0.027
TAPSE	20±4 vs. 20±4	n.s.
PVR (Wood)	1.1 vs. 1.3	n.s.
RVDVI (ml/m^2)	27±11 vs. 22±9	0.0001
RAVI (ml/m^2)	40±22 vs. 35±17	0.0145

Approved Pivotal trial

MULTICENTER, PROSPECTIVE, 1:1 RANDOMIZED, SHAM CONTROLLED, DOUBLE BLINDED TRIAL



ENDPOINTS

The Primary endpoint is a composite of:

- Cardiovascular mortality or non-fatal, ischemic stroke through 6 months; and
- Change in KCCQ score between baseline and 6 months.

The first powered secondary efficacy endpoint is

- The change in 6MWT distance between baseline and 6 months

The second powered secondary efficacy endpoint is a composite of:

- Cardiovascular mortality or non-fatal ischemic stroke through 12 months; and
- Rate of total (first plus recurrent) HF admissions, healthcare facility visits for IV diuresis for HF through 12 months; and
- Change in KCCQ score between baseline and 12 months.

The Primary and the Second powered secondary endpoint will be analyzed using the Finkelstein-Schoenfeld methodology

Conclusions

Reduction of LAP (PAP) by generating left to right shunt with IASD may be an effective therapeutic approach in HFpEF (HFmrEF)

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Thank you!