Late Breaking Clinical Trials II
REDUCE LAP-HF II

Gerd Hasenfuß, MD

Clinic for Cardiology and Pneumology

Heart Center – University Medical Center Göttingen

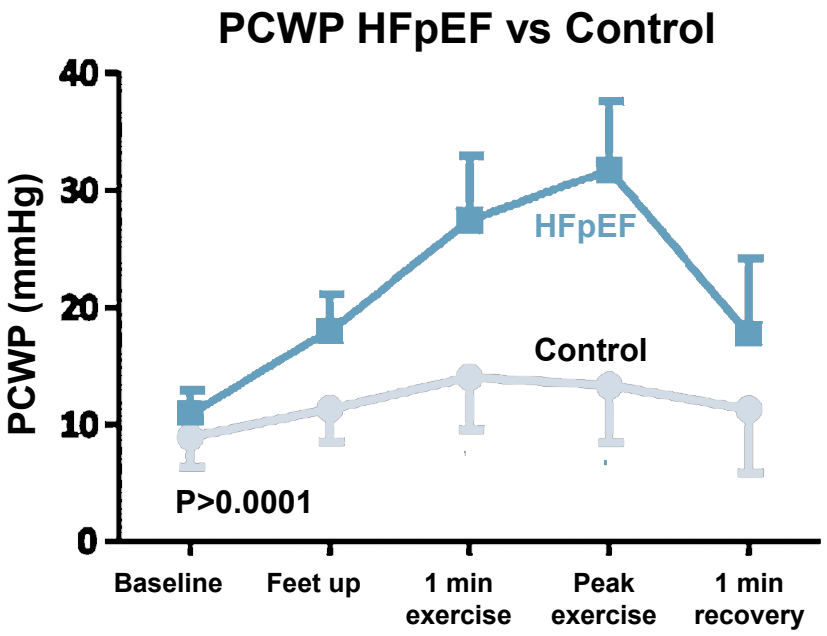
German Center for Cardiovascular Research

On behalf of the Steering Committee, Investigators and Research Staff

Conflicts of interest

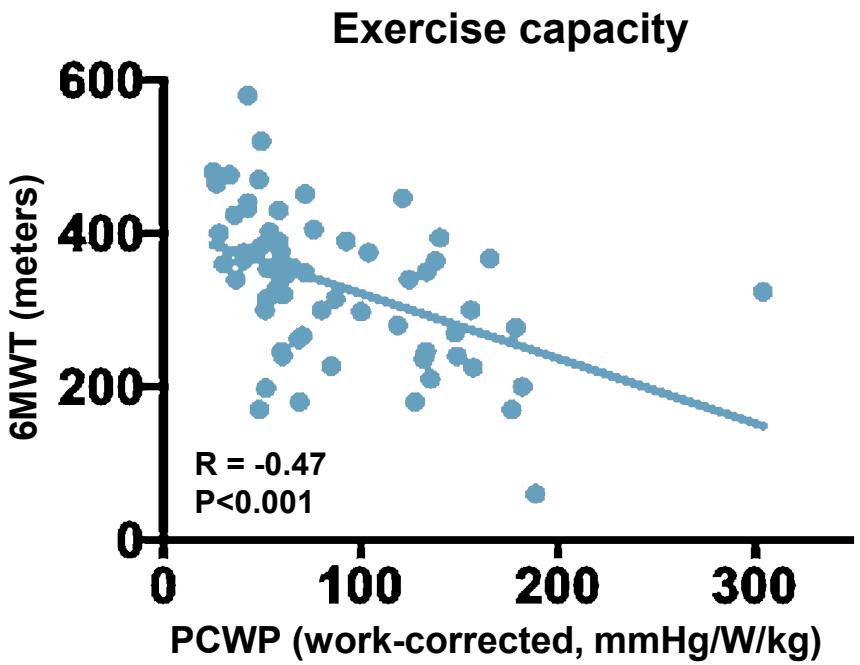
- Servier: Honorarium for presentations, Consultant
- Boehringer: Consultant
- Impulse Dynamics: Consultant, Honorarium for presentations
- Novartis: Consultant, Horonarium for presentations
- Pfizer: Horonarium for presentations
- AstraZeneca: Honorarium for presentations, Consultant
- Bayer: Honorarium for presentations
- Corvia: Consultant, no honorarium
- Vifor: Horonarium for presentations

High LA pressures impact QOL & survival



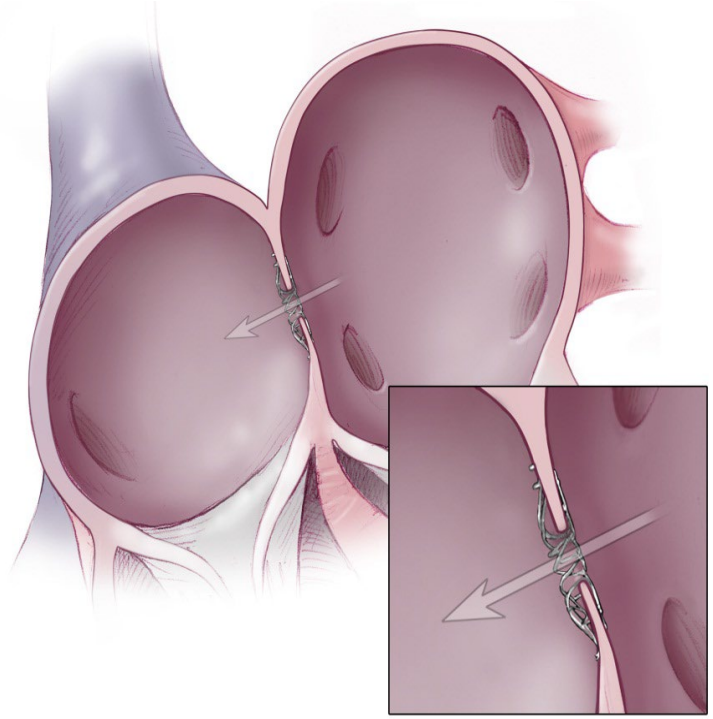
During exercise, HFpEF patients experience a significant rise in PCWP compared to control

Borlaug et al. Circ Heart Fail 2010



As PCWP rises, patient exercise capacity falls

Wolsk et al. Eur J Heart Fail 2017



Corvia Atrial Shunt: 8mm
Qp:Qs 1.27

Shunt allows blood to move from the higher pressure LA to the lower pressure more compliant right side, reducing LAP and pulmonary venous hypertension

REDUCE LAP-HF II – Study design
Phase III, multi-center, double-blind, Sham-controlled trial

PURPOSE: **Evaluate the clinical efficacy and safety of the Corvia Atrial Shunt to improve quality of life and reduce HF related symptoms and events in patients with HFpEF or HFmrEF**

Study Population
n=626 randomized

Symptomatic HF, ongoing GDMT, age ≥40, LVEF ≥40%, preserved RV function, elevated rest (≥15 mmHg) or exercise PCWP (≥25mmHg) with left-to-right gradient (≥5mmHg)

Atrial Shunt Treatment
n=314

Sham Control
n=312

Berry et al. Am Heart J 2020

PRIMARY ENDPOINT

Hierarchical composite of cardiovascular mortality or non-fatal, ischemic stroke through 12m, rate of total HF events (first and recurrent) through 24m & time to first HF event, change in KCCQ score between baseline & 12m

SECONDARY ENDPOINTS

- Composite safety endpoint (MACCRE)
- Rate of HF admissions or IV diuresis, through 24m
- Change in NYHA Class between baseline & 12m
- Change in KCCQ score between baseline & 12m

Shah et al. Lancet 2022

REDUCE LAP-HF II – Baseline characteristics

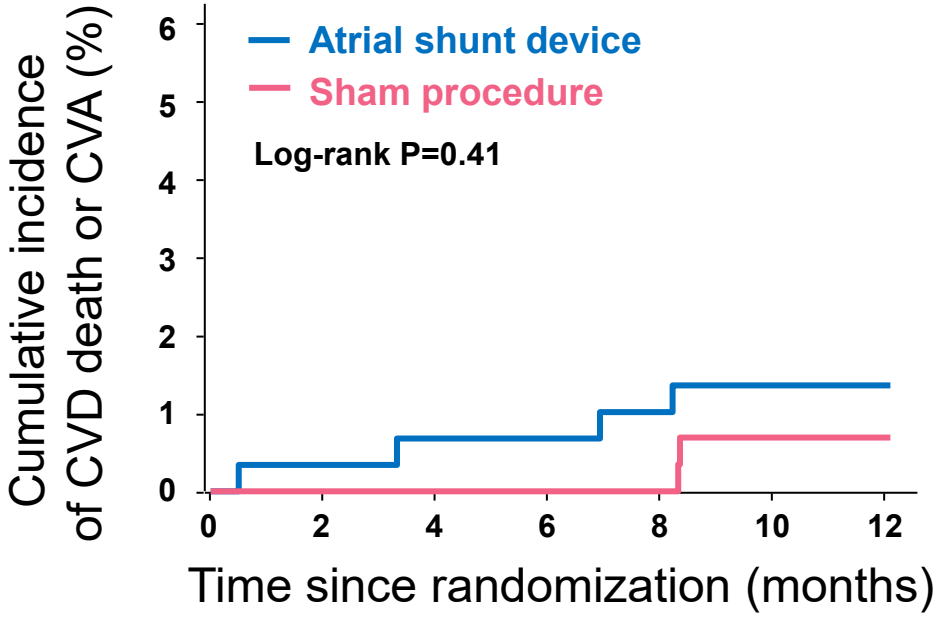
Characteristic	Atrial shunt device (n=314)	Sham procedure (n=312)
Age, years	73	72
Female	64%	59%
Body mass index, kg/m^2	31.6	32.2
Hypertension	89%	87%
Diabetes	37%	37%
Atrial fibrillation	50%	53%
NYHA class III	77%	78%
HF hospitalization in last 12 mo.	26%	32%
NTproBNP, pg/ml (sinus rhythm)	301	344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

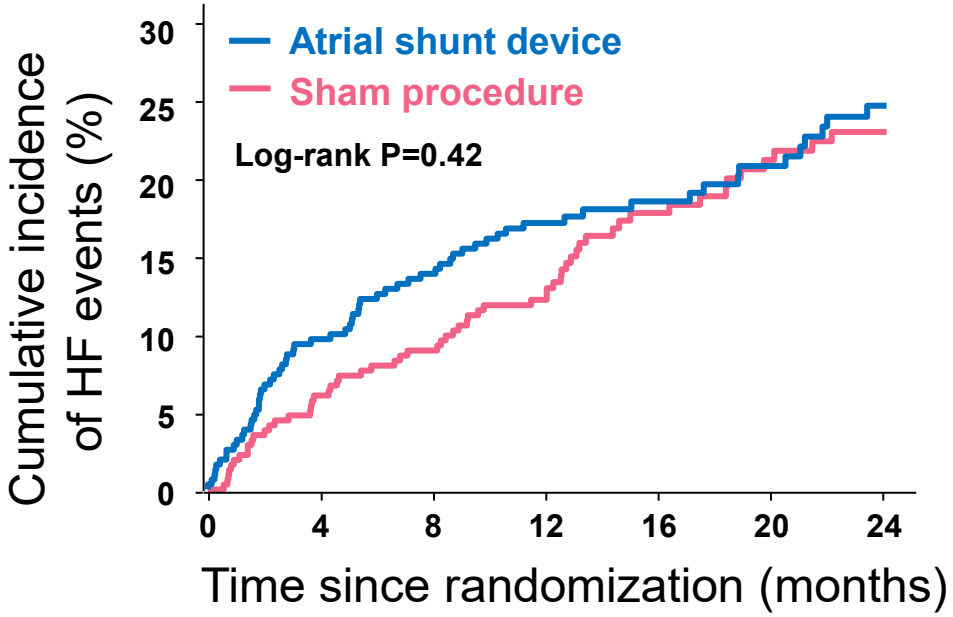
Median values shown for all continuous variables

REDUCE LAP-HF II – 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%

REDUCE LAP-HF II – Primary composite endpoint





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

REDUCE LAP-HF II – Primary results

Primary Endpoint	Win Ratio* (95% CI)	p-value
Composite Endpoint	0.98 (0.8, 1.2)	0.85

Efficacy Endpoints	Treatment (n=309)	Control (n=312)	p-value
CV death or non-fatal ischemic stroke	1% (4 events)	1% (2 events)	0.41
Cardiovascular 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 (Median (IQR)	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**

*In win ratio calculation, all patients are compared with each other in pairwise manner on values of the components in a hierarchical manner (1 = neutral, >1 = treatment better, <1 sham better)

Shah et al. Lancet 2022

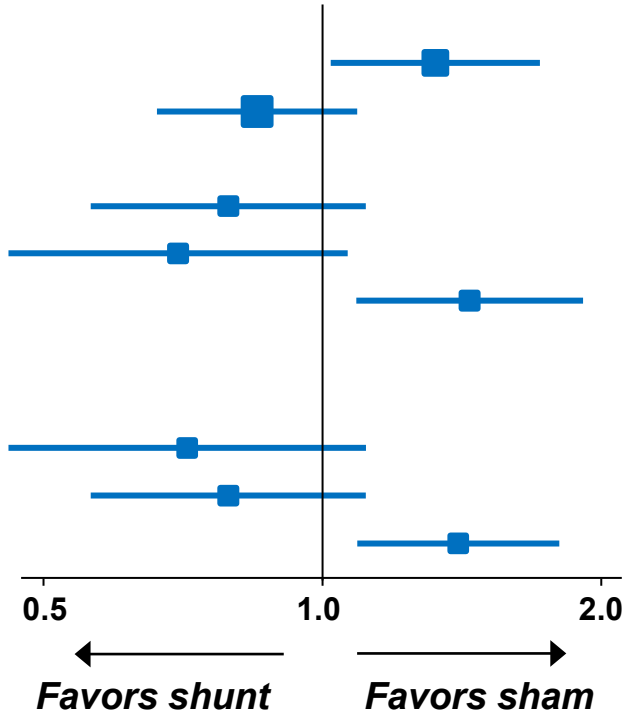
REDUCE LAP-HF II – Safety endpoints

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	7%	8%	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)

REDUCE LAP-HF II – Pre-specified subgroup analyses
Recurrent HF events

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

High peak PVR + pacemakers: Key factors in trial outcome

Systematic statistical analysis identified most significant variables affecting clinical efficacy

Prespecified Subgroup Analysis

Identified significant interactions….

- PA systolic pressure @ 20W exercise
- Indexed RA volume
- Sex

…which led to a focus on factors that affect PA pressure (most significant interaction)

- **Peak PVR**
- **Pacemakers**

[1]Upper tertile, which roughly corresponds to peak exercise in a healthy adult >55 years (≤1.8WU); [2]Includes CRT

Factors that Affect PA Pressure

PAs pressure = PCWP+ (CO x PVR)

Impact of atrial shunt

- ↓ LA unloading reduces pressure
- ↑ Shunting increases flow though the pulmonary vasculature
- ↓↑ Impacted by presence of pulmonary vascular disease

- Identified <u>exercise</u> PVR as having the most impact on clinical efficacy
  - With low exercise PVR (peak <1.74), win ratio 1.31
  - With high exercise PVR (peak ≥1.74 WU), win ratio 0.60

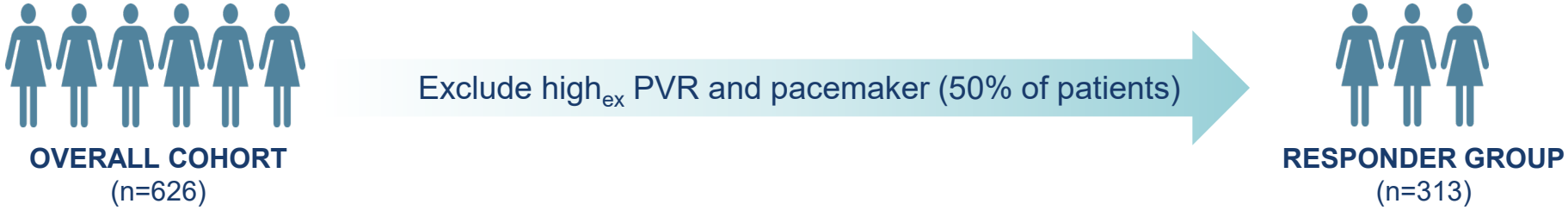
  2 subtypes of HFpEF: PVR ↘ PVR ↗
- Presence of a pacemaker result in a 3x increased risk of HF events

Responder group

Borlaug et al. Circulation 2022 (in press)

Primary endpoint in Responder group

Patients with normal exercise PVR (<1.74 WU) and no pacemaker derive significant HFH and QoL benefit



Subgroup	Variable	Treatment (N=161)	Sham Control (N=152)	Win Ratio	P-Value
Peak PVR < 1.74 no pacemaker	Composite Endpoint (KCCQ Threshold=5)			**1.5**	**0.004**
	CV death or non-fatal ischemic stroke	1.24% (2 events)	0% (0 events)	-	0.17
	Total HF events per 100 patient-years	**12**	**22**	**-**	**0.007**
	Change in KCCQ-OSS (Mean±SD)	**15.5 ± 22.2 (153)**	**10.0 ± 20.6 (141)**	-	**0.027**

Borlaug et al. Circulation 2022 (in press)

Summary

REDUCE LAP-HF II is the largest device therapy trial in HFpEF

- 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

Shah et al. Lancet 2022

- Patients with normal exercise pulmonary vascular resistance (PVR <1.74) and without a pacemaker derived significant clinical benefit from the shunt
  - 45% reduction in the rate of HF events
  - 55% greater improvement in KCCQ-OSS over sham including 40% more patients with >20 points improvement of KCCQ-OSS

Borlaug et al. Circulation 2022 (in press)

- A confirmatory randomized trial is under review by FDA
  - HFpEF, $PCWP_{Ex}$ ≥ 25 mmHg, LA/RA gradient ≥ 5mmHg, PVR_{Ex} < 1.75 WU, no Cardiac Rhythm Device

DGK.

DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

UNIVERSITÄTSMEDIZIN
GÖTTINGEN UMG

Herz
Zentrum
Göttingen

Thank you!

Patients
Site investigators
Committee members