# Current and Promising Approaches to HFpEF

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### What is HFpEF?

- Signs and symptoms of HF
- Preserved LVEF (≥50%)
- Objective evidence of elevated LV filling pressures at rest or during exercise
  - ✓ ↑BNP, LA enlargement/dysfunction, ↑PCWP (> 15 mmHg at rest, > 25 mmHg with exercise), ↑PCWP/CO slope (> 2.0)
- Evidence of a cardiac-predominant problem
- Exclude: infiltrative, genetic, valvular, toxin, pericardial, ischemic etiology

### H<sub>2</sub>FPEF score

	Clinical Variable	Variable Values					
ш	Heavy	Body mass index > 30 kg/m <sup>2</sup>	2				
H <sub>2</sub>	Hypertensive	2 or more antihypertensive medicines	1				
F	Atrial Fibrillation	Paroxysmal or Persistent	3				
Р	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1				
Е	Elder	Age > 60 years	1				
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1				
	Sum (0-9)						
Total Points 0 1 2 3 4 5 6 7 8							
Probability of HFpEF 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95							

- Dyspnea on exertion, normal EF
- HFpEF vs. non-cardiac dyspnea?
- Intermediate pre-test probability

Nomogram below table for probability of HFpEF based on score:

- A score of 4 or higher = 70% probability of HFpEF
- A score of 5 or higher = >80%
   probability of HFpEF
- A score of 7 or higher = >95% probability of HFpEF

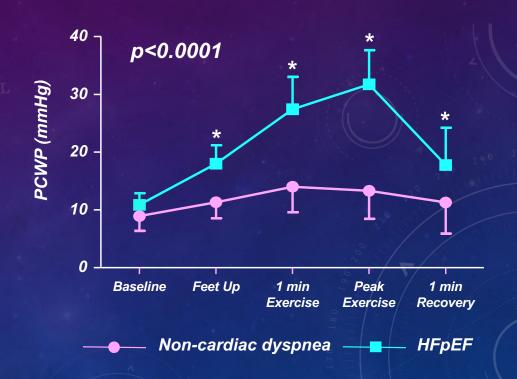
Reddy YN...Borlaug BA. Circulation 2018

### HFpEF: û û PCWP with minimal exercise

When in doubt about the HFpEF diagnosis:

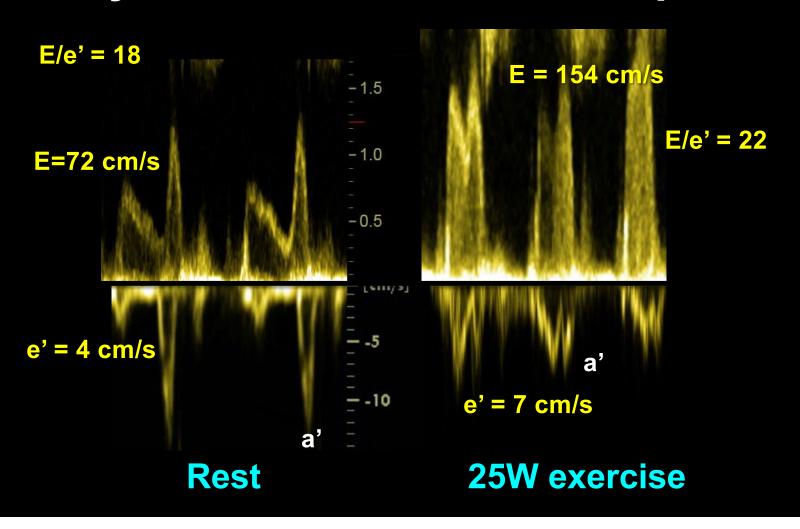
Perform right heart catheterization and perturb the system!

- Exercise
- Passive leg raise
- Volume challenge

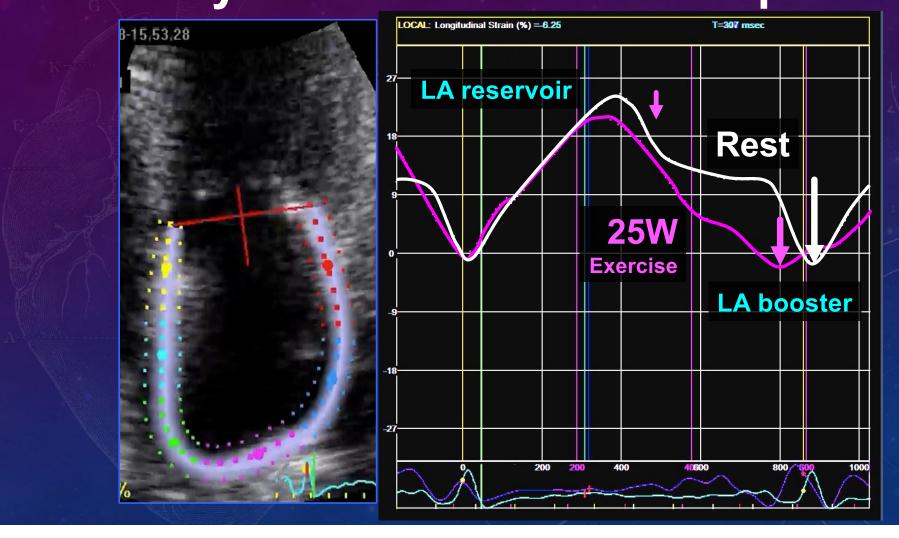


Borlaug B, et al. Circ Heart Fail 2010

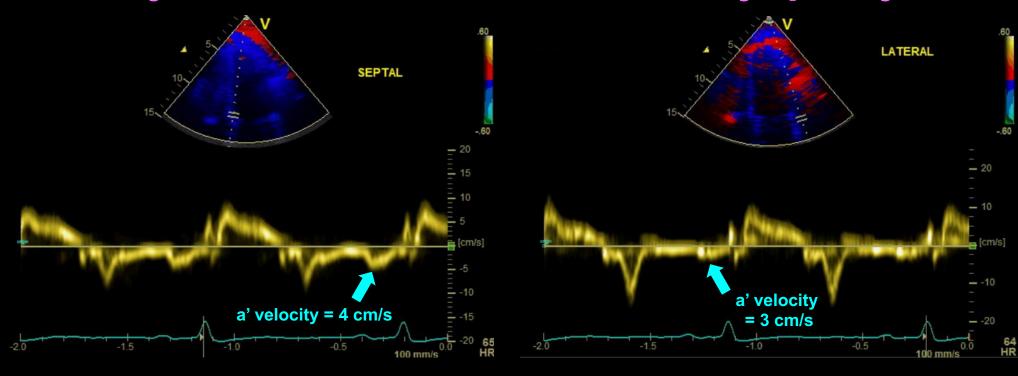
### 72-year-old woman with HFpEF



### 72-year-old woman with HFpEF

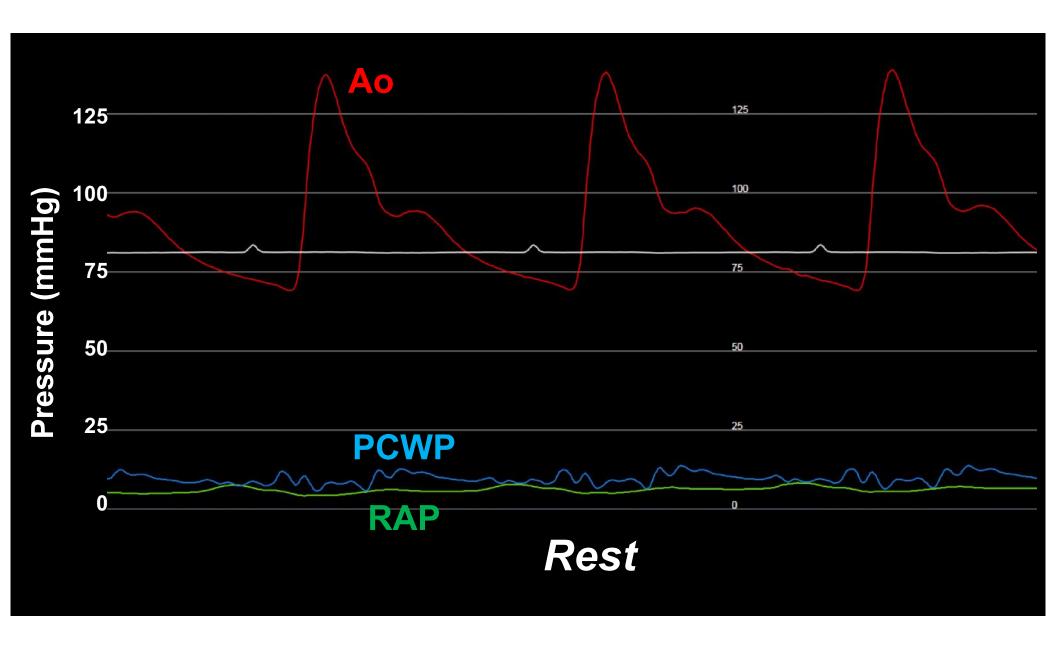


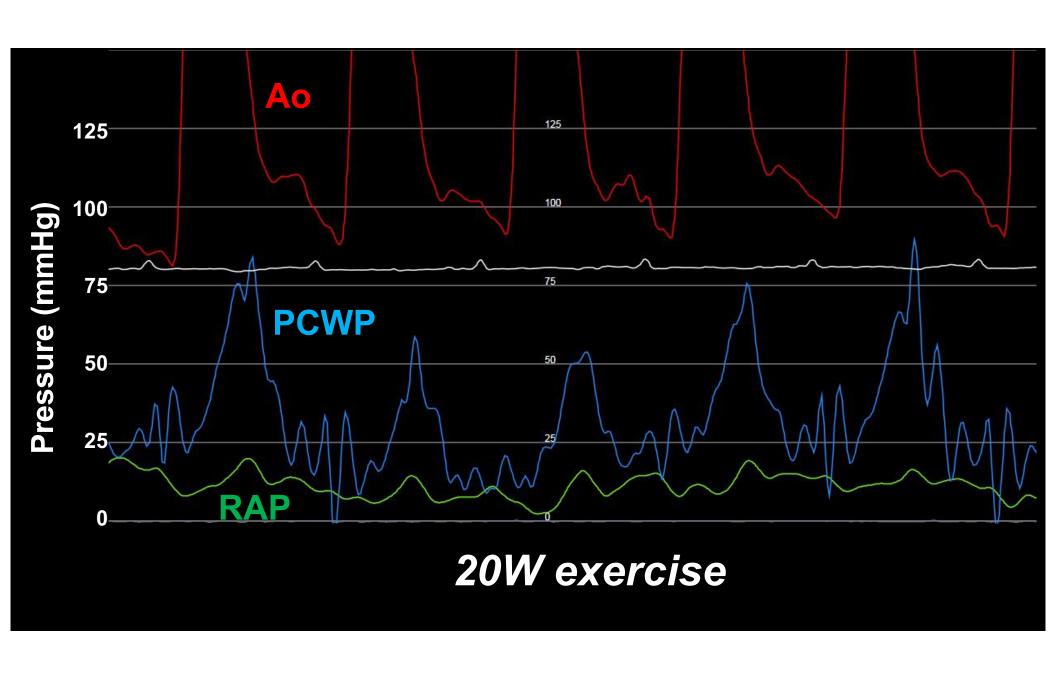
### 3 years later: overt left atrial myopathy

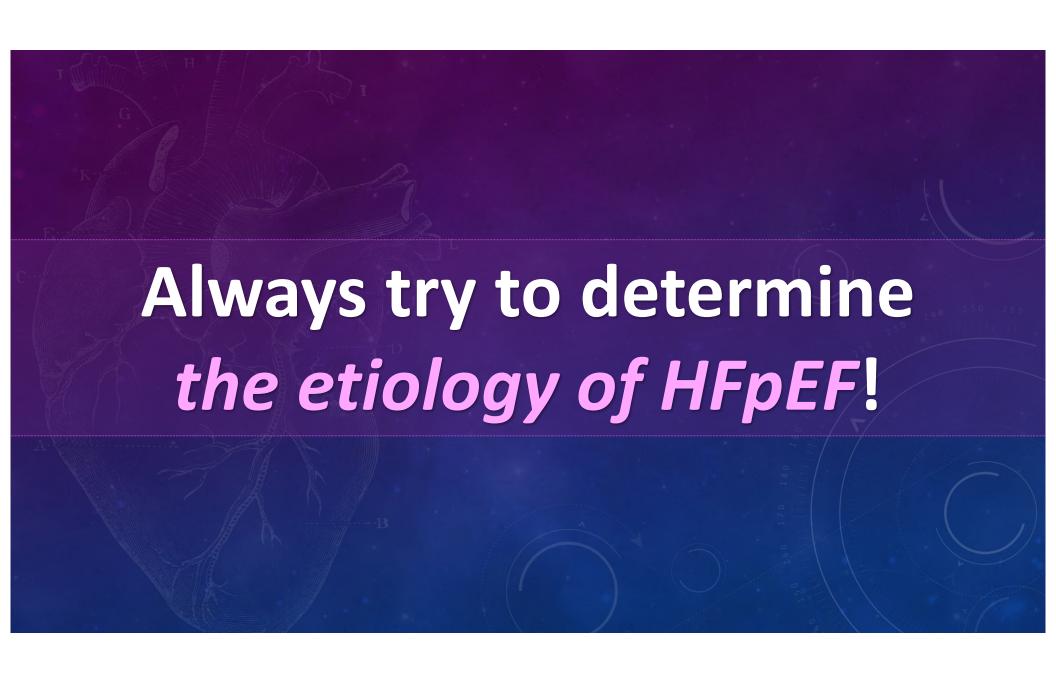


**Septal TDI** 

**Lateral TDI** 







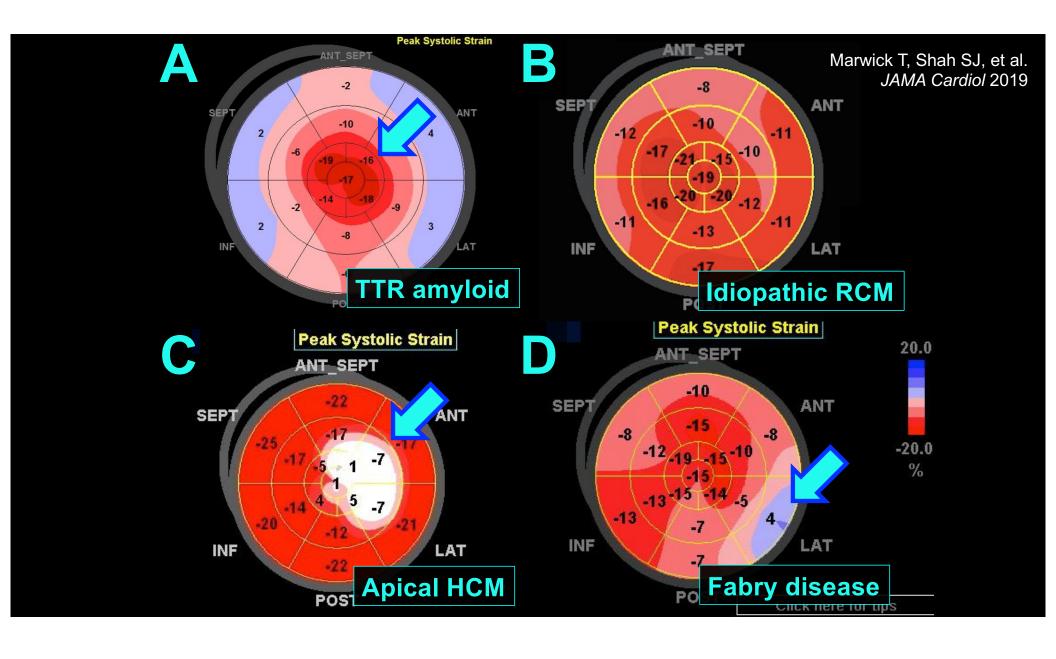
# Differential diagnosis of HFpEF

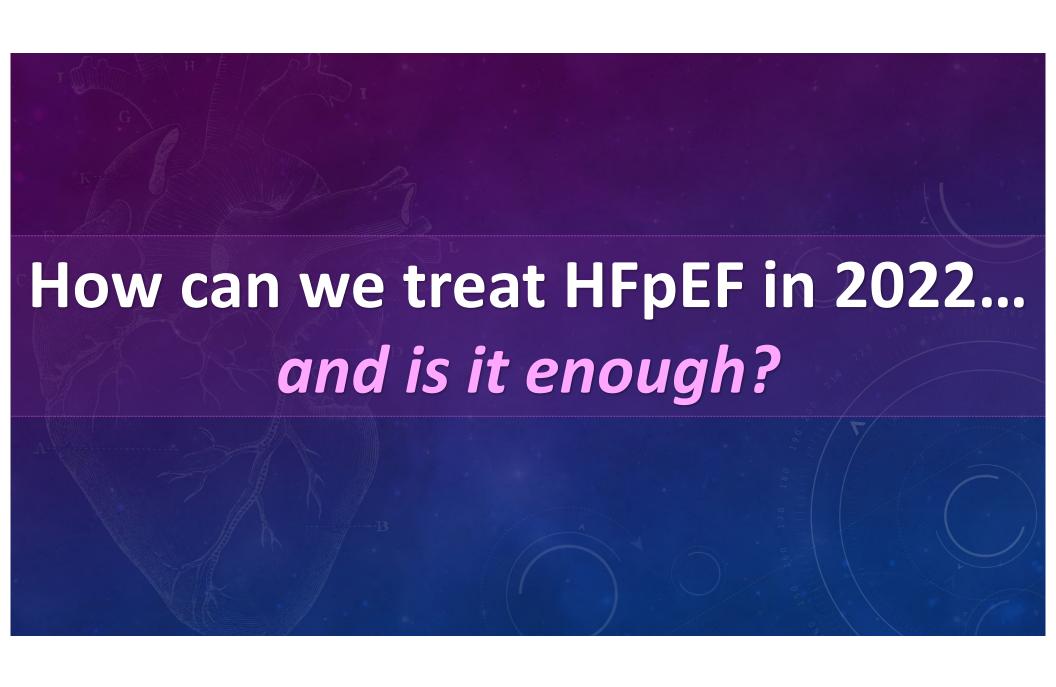
	Etiology	Diagnostic tools	Treatment		
F	Cardiac amyloidosis	Monoclonal proteins, radionuclide scintigraphy, biopsy	Tafamidis (for transthyretin amyloidosis) or chemotherap (for light-chain amyloidosis); avoid neurohormonal antagonists		
	Hypertrophic cardiomyopathy	Echocardiography, cardiac MRI	$\beta\textsc{-Blockers}$ , calcium-channel blockers or septal-reduction therapies (for obstructive cardiomyopathy); avoid vasodilators		
C c c H	Cardiac sarcoidosis	Cardiac MRI, FDG-PET, biopsy	Immunosuppressive agents		
	Constrictive pericarditis	Echocardiography, cardiac MRI or CT imaging, invasive haemodynamic measurements	Pericardiectomy		
	Valvular heart disease <sup>a</sup>	Echocardiography, invasive haemodynamic measurements with ventriculography	Surgical or percutaneous valve interventions		
	Coronary artery disease <sup>a</sup>	Invasive coronary angiography, stress imaging <sup>b</sup> or CT imaging	Revascularization, aspirin, statins, $\beta\text{-blockers}$ and nitrates		
	High-output heart failure Evaluate for arteriovenous shunts and liver disease		Treatments directed at the cause of high cardiac output (such as fistula ligation for shunts, liver transplantation for cirrhosis)		
	Myocarditis	Cardiac MRI, endomyocardial biopsy	Immunosuppressive agents for some types (such as giant cell myocarditis or eosinophilic myocarditis)		
	Toxins <sup>a</sup>	Assessment of clinical history, blood testing, endomyocardial biopsy	Removal of offending toxin (such as alcohol, cocaine, chemotherapy or radiation therapy, or heavy metals)		

Borlaug BA.
Nat Rev Cardiol 2020

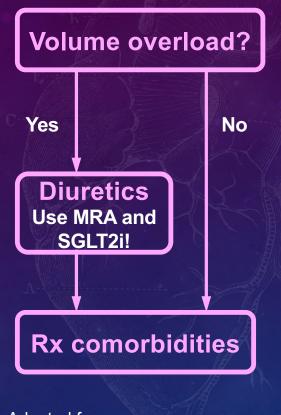
# HFpEF: Know your zebras

- HFpEF: Diagnostic mystery until proven otherwise
- Careful history, physical examination, and review the echo yourself!
- Some clues to zebras:
  - ✓ HFpEF in younger pt (age < 55)
  - ✓ Low H<sub>2</sub>FPEF score in setting of overt HFpEF (e.g., HF hosp., ↑BNP)
  - ✓ Kussmaul's sign: ↑JVP with inspiration
  - ✓ Diastolic septal bounce, variation in mitral inflow
  - ✓ Speckle-tracking strain bullseye map patterns





# HFpEF treatment algorithm (1)

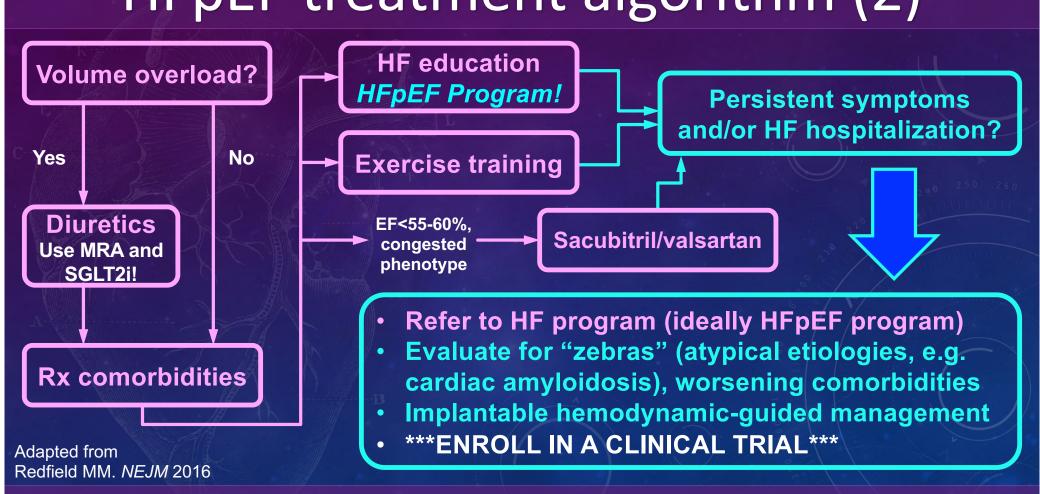


Adapted from Redfield MM. *NEJM* 2016

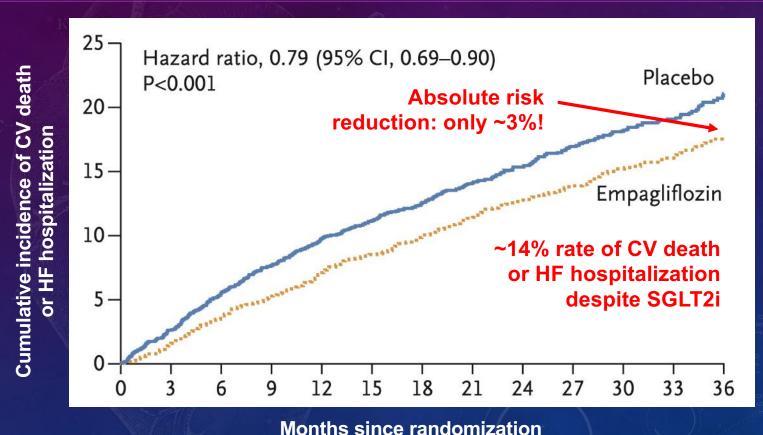
# HFpEF treatment algorithm (2)



# HFpEF treatment algorithm (2)



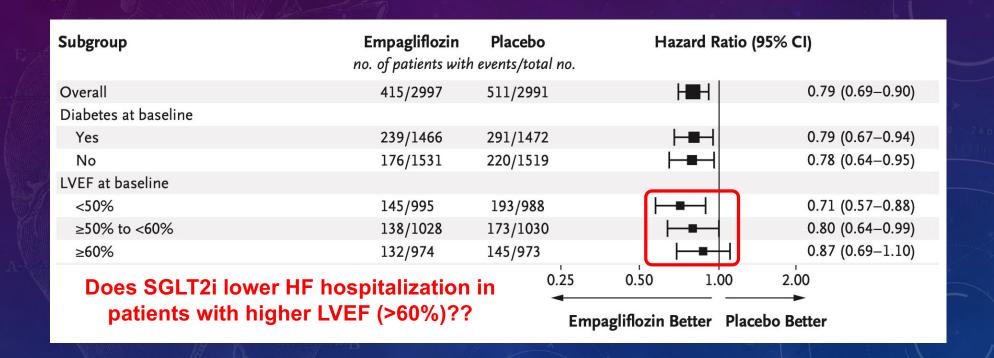
### **EMPEROR-Preserved: Results**



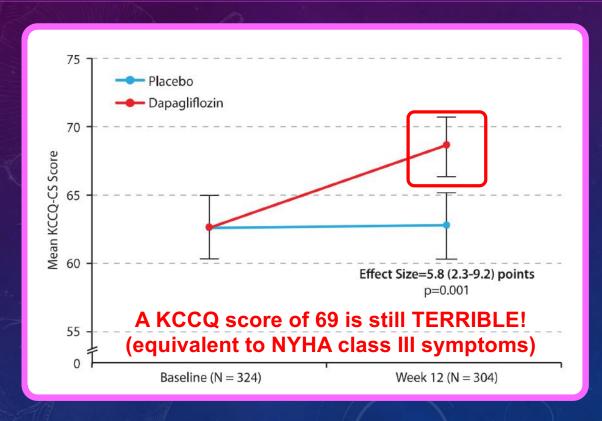
- N=5988
- Empagliflozin vs. placebo
- HF with LVEF > 40%
- (n=4005 [67%] with LVEF ≥ 50%)
- Primary outcome driven by HF hospitalizations
- Only +1.32-point improvement in KCCQ vs. placebo at 52 weeks

Anker S, et al. NEJM 2021

### **EMPEROR-Preserved: Results**

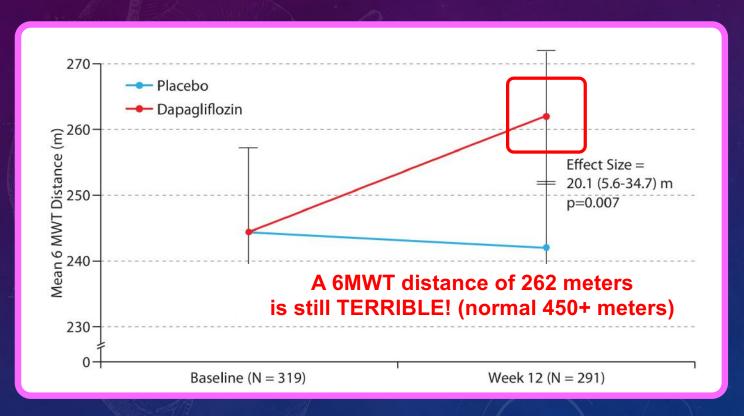


### PRESERVED-HF Results: KCCQ



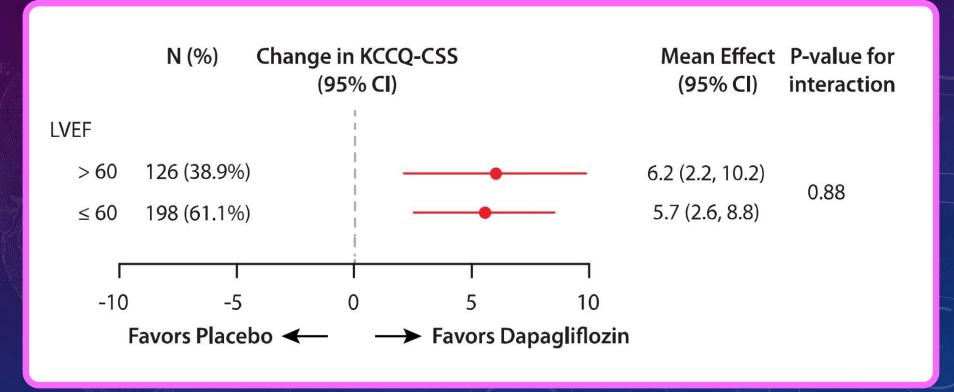
- N=324
- Dapagliflozin vs. placebo
- HF with LVEF ≥ 45%
- +5.8-point improvement in KCCQ vs. placebo

### PRESERVED-HF Results: 6MWT



- N=324
- Dapagliflozin vs. placebo
- HF with LVEF ≥ 45%
- +5.8-point improvement in KCCQ vs. placebo
- +20.8-meter
   improvement in
   6MWT distance vs.
   placebo

### PRESERVED-HF Results: KCCQ

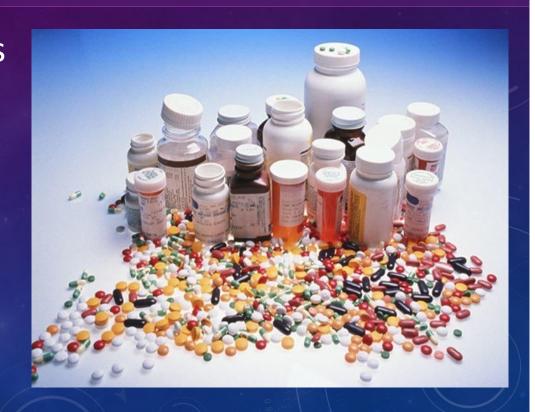


### Additional SGLT2i trials in HFpEF

- EMPERIAL-Preserved (n=315):
  - ✓ No significant difference in KCCQ total symptom score
  - ✓ No significant difference in 6MWT distance
  - ✓ No significant difference in congestion score
- DETERMINE-Preserved (n=504):
  - ✓ No significant difference in KCCQ total symptom score
  - ✓ No significant difference in KCCQ physical limitation score
  - ✓ No significant difference in 6MWT distance

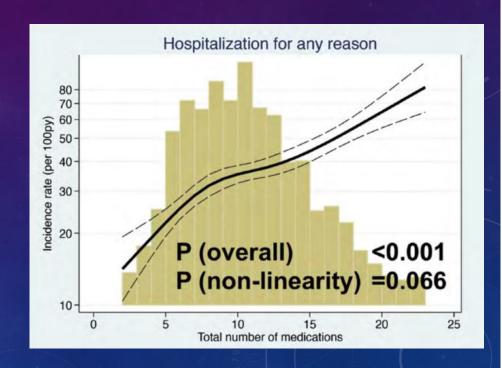
### HF patient med adherence: dismal

- In a study of 219 HF patients (42% were HFpEF):
  - √ 41% were non-adherent to medications
  - ✓ Non-adherence to meds: associated with HR 2.19 for cardiac hospitalization or death (p=0.006)



# HFpEF: huge polypharmacy problem

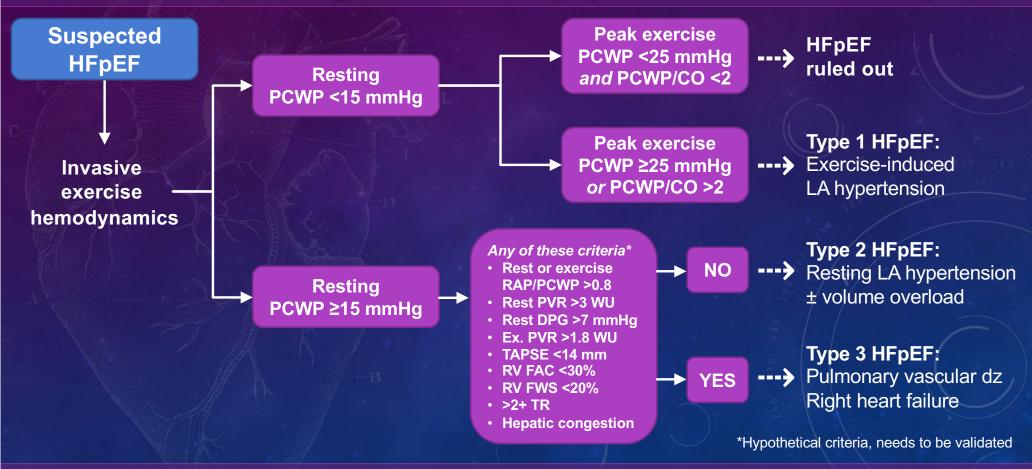
- Hyper-polypharmacy in HFpEF: the TOPCAT trial (n=1758):
  - √ 93% met criteria for polypharmacy (defined as 5+ meds)
  - √ 54% of patients in TOPCAT were taking 10+ meds at baseline (hyper-polypharmacy)
  - ✓ Hyper-polypharmacy:
     HR 1.22 (95% Cl, 1.05-1.41) for
     all-cause hospitalizations after
     multivariable adjustment (P=0.009)



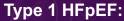
Minamisawa M, et al. Circ Heart Fail 2021



# Phenotype-guided approach to HFpEF



# Device-based therapeutics for HFpEF



Exercise-induced LA hypertension

### Interatrial shunts

(Corvia, V-Wave, Occlutech, Alleviant, etc)

### Type 2 HFpEF:

Type 3 HFpEF:

Right heart failure

Pulmonary vascular dz

Resting LA hypertension ± volume overload

Implantable PA

Implantable PA compliance

enhancer (Aria CV) baroreceptor stimulation
Implantable PA
monitoring

(CardioMEMS, Endotronix)

Carotid

Aortic arch stimulation (Enopace)

Implantable closed-loop diuretic systems (Sequana, Reprieve)

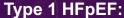
Intermittent SVC occlusion (preCARDIA)

### Renal denervation

(ReCor, Medtronic)

Splanchnic nerve ablation (Axon Therapies) Vagal nerve stimulation (Anthem) Diaphragmatic pacing (VisCardia) Cardiac plexus stimulation (Cardionomic)

# Device-based therapeutics for HFpEF



Exercise-induced ---> LA hypertension

### Interatrial shunts

(Corvia, V-Wave, Occlutech. Alleviant, etc)

### Type 2 HFpEF:

Resting LA hypertension ± volume overload

**Implantable** PA monitoring

> (CardioMEMS, **Endotronix**)

Carotid baroreceptor stimulation (CVRx)

> **Aortic arch** stimulation (Enopace)

**Implantable** closed-loop diuretic systems (Sequana, Reprieve)

Intermittent **SVC** occlusion (preCARDIA)

### Type 3 HFpEF: Pulmonary vascular dz

Right heart failure

**Implantable** PA compliance enhancer

(Aria CV)

(Axon Therapies)

Vagal nerve stimulation (Anthem)

**Diaphragmatic** pacing (VisCardia)

Cardiac plexus stimulation (Cardionomic)

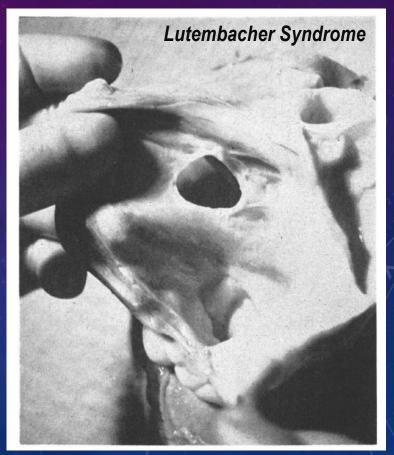
Renal denervation

(ReCor, Medtronic)

Splanchnic nerve ablation

### ASD in the setting of mitral stenosis

- Congenital ASD in the setting of mitral stenosis
  - Decompression of high LA pressure
  - Large reservoir: right atrium, great veins, hepatic veins



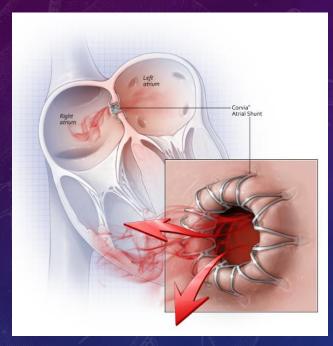


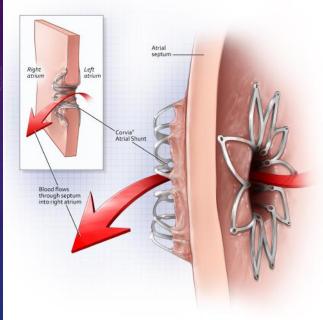
# Interatrial shunt devices/procedures

Device	Corvia	V-Wave	Occlutech	Edwards	Alleviant	NoYA	InterShunt
E				DE C			240 250 260
Туре	Implant	Implant	Implant	Implant	Procedure	Procedure	Procedure
Description	Nitinol stent	Nitinol/PTFE hourglass	Nitinol braid with central orifice	Tubular nitinol device with retention arms	Coring catheter	RF catheter	Cutting catheter
Shunt flow	LA → RA	LA → RA	LA → RA	LA → CS	LA → RA	LA → RA	LA → RA
Shunt size	8 mm	5.1 mm	4, 6, 8, 10 mm	7 mm	6 mm	4-12 mm	4 mm
Development stage	Phase 3 RCT	Phase 3 RCT	Open-label studies	FIH complete	Animal studies	FIH complete	FIH complete

\*CS = coronary sinus; FIH = first in human

### 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)

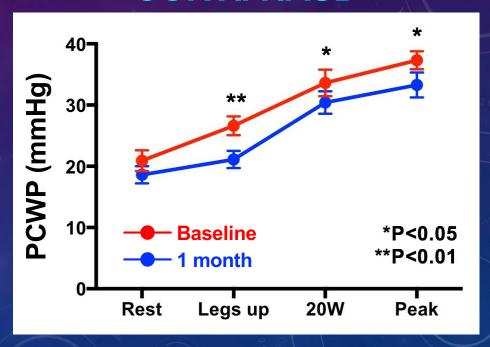
Feldman T...Shah SJ. Circ Heart Fail 2016

### REDUCE LAP-HF | RCT: △PCWP at 1 mo.

### **CONTROL**

# Baseline Rest Legs up 20W Peak

### **CORVIA IASD**



Feldman T...Shah SJ. Circulation 2018

### REDUCE LAP-HF II trial design

- Prospective, multi-center, randomized (1:1),
   sham-controlled, blinded trial (n=626 randomized)
  - √ 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

# 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

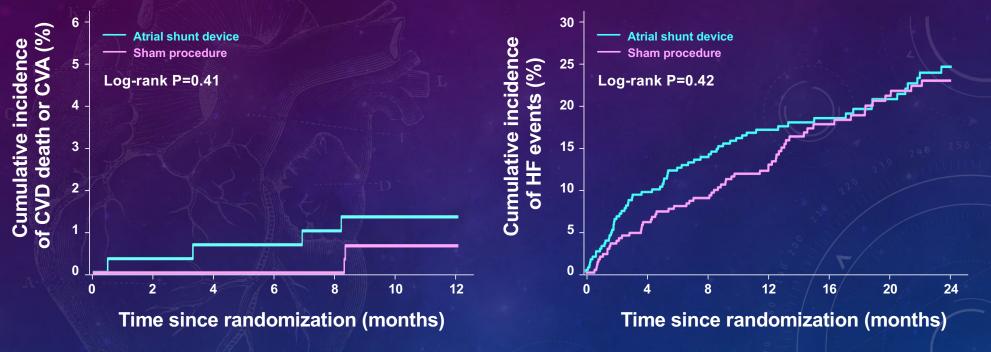
- Exclusion criteria:
  - ✓ Exclude patients unlikely to benefit from shunt therapy
  - ✓ Cardiac index <2.0 L/min/m²
  - ✓ Previous EF <30%
  - ✓ CVA, TIA, DVT, PE in past 6 mo.
  - ✓ Greater than mild RV dysfunction/enlargement
  - ✓ Moderate or greater TR
  - ✓ Resting RA pressure >14 mmHg
  - ✓ Resting PVR >3.5 WU

# Baseline characteristics (n=626)

- Older, majority (62%) women
- Multiple comorbidities
- Most (78%) NYHA class III (very sick, debilitated)
- Majority (93%) HFpEF (EF≥50%)
- Very poor health status (median KCCQ 46)
- ↓Exercise capacity, ↑NTproBNP
- All patients had peak exercise LA pressure ≥25 mmHg, confirming the diagnosis of HFpEF

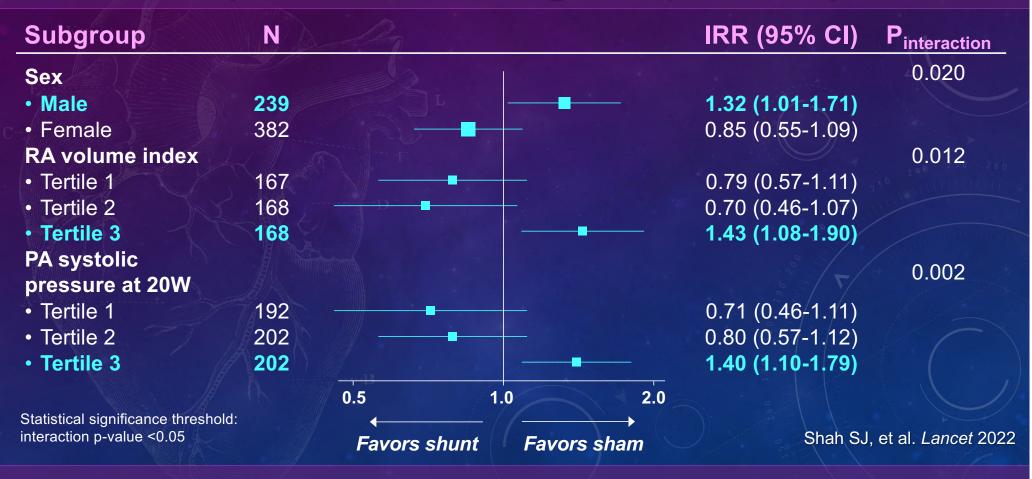
Shah SJ, et al. Lancet 2022

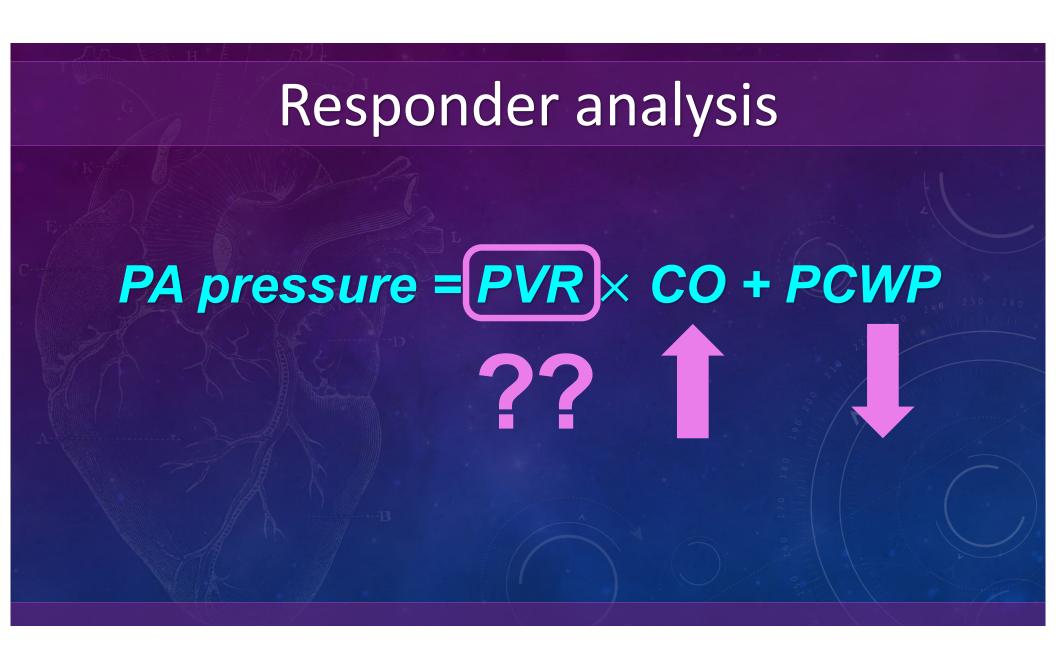
# Primary composite endpoint



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

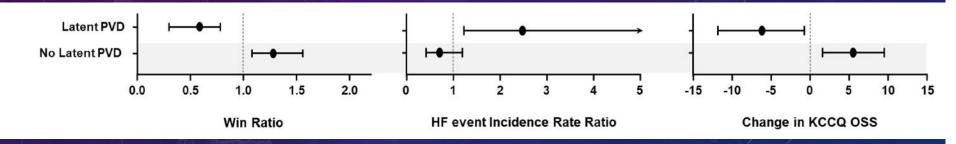
# Pre-specified subgroup analyses





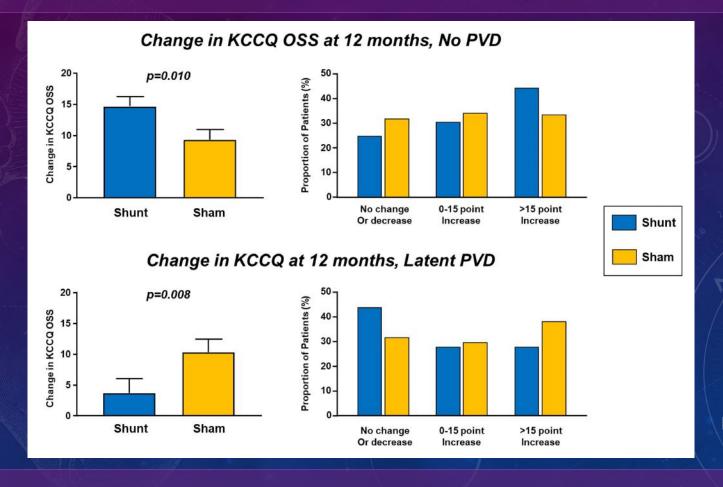
# Responder analysis

Latent PVD = peak exercise PVR ≥1.74 WU



Borlaug BA...Shah SJ. Circulation 2022

### Effect of shunt on KCCQ by ± latent PVD



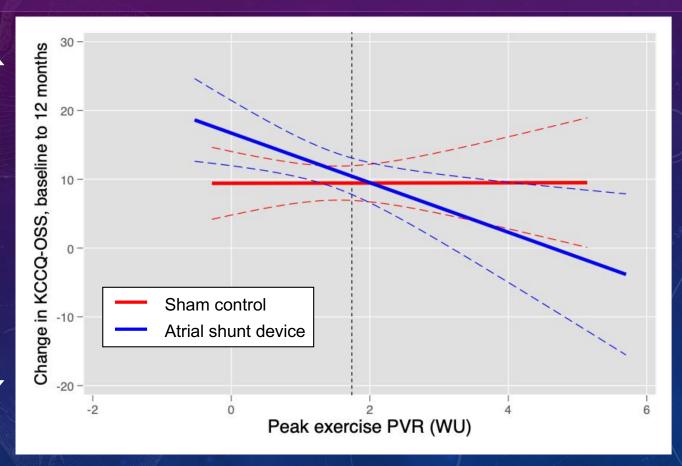
Borlaug BA...Shah SJ.

Circulation 2022

## Effect of shunt on KCCQ by peak exercise PVR

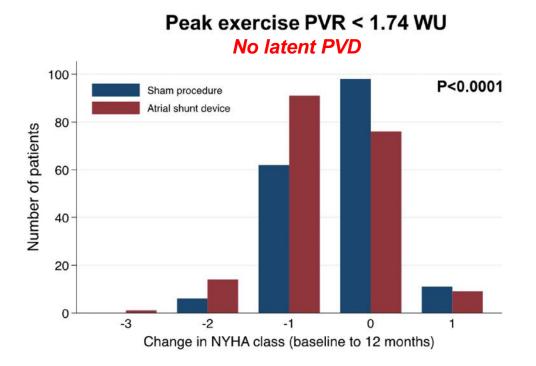


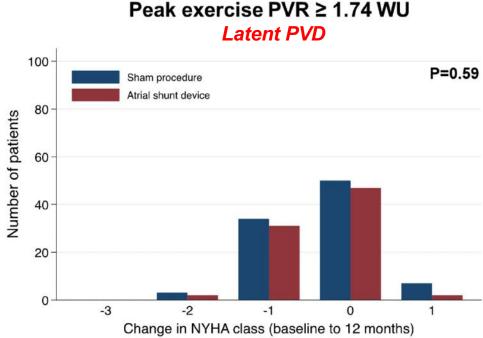
Health status



Borlaug BA...Shah SJ. Circulation 2022

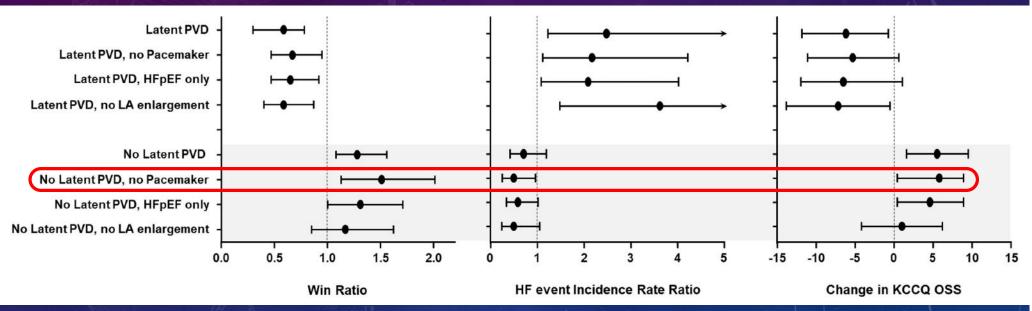
## Effect of shunt on NYHA class by ± latent PVD





# Responder analysis

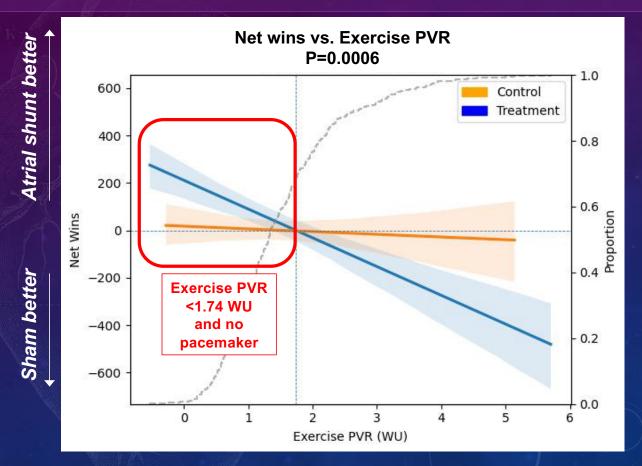
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Borlaug BA...Shah SJ.

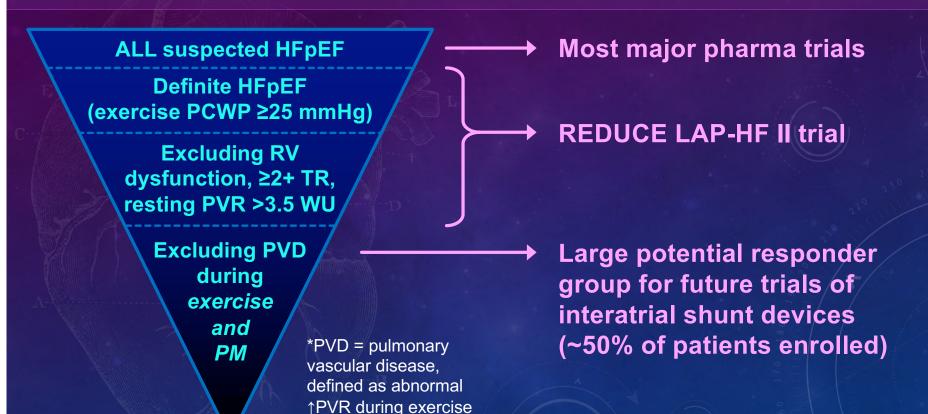
Circulation 2022

### Overall efficacy of shunt by peak exercise PVR



- ~50% of patients had exercise PVR <1.74 and no pacemaker
- These patients had more "wins" when treated with atrial shunt device (↓HF hospitalizations and ↑health status)
- Opposite was true in those with exercise PVR ≥1.74 or pacemaker

## Future directions: 1 Precision medicine

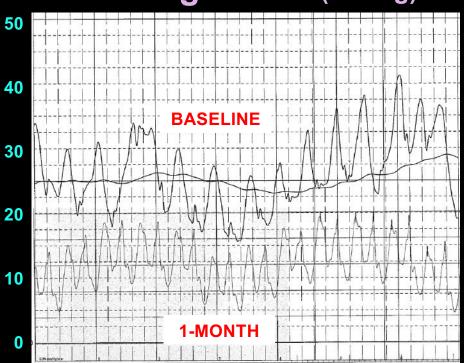


(~1.8 WU or higher) PM = pacemaker

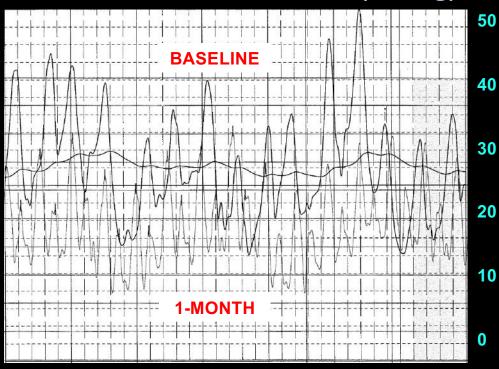
### 72-year-old woman with HFpEF, LA myopathy

PARTICIPATED IN REDUCE LAP-HF I RCT: RANDOMIZED TO SHUNT DEVICE





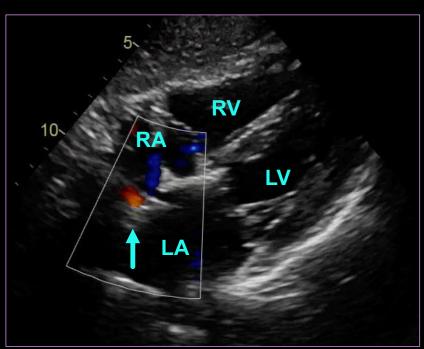
#### Peak exercise PCWP (mmHg)



### 72-year-old woman with HFpEF, LA myopathy

PARTICIPATED IN REDUCE LAP-HF I RCT: RANDOMIZED TO SHUNT DEVICE

#### Subcostal view



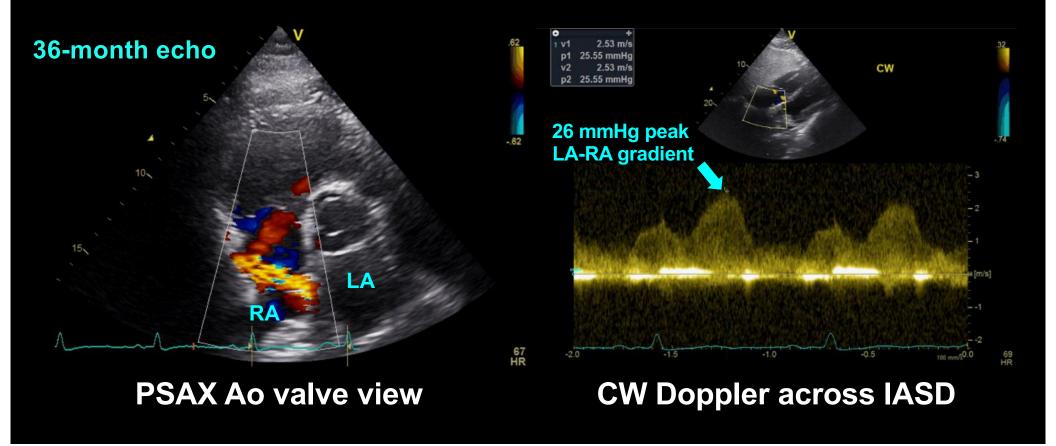
12-month echo

#### **Subcostal view (zoomed)**



### 72-year-old woman with HFpEF, LA myopathy

PARTICIPATED IN REDUCE LAP-HF I RCT: RANDOMIZED TO SHUNT DEVICE



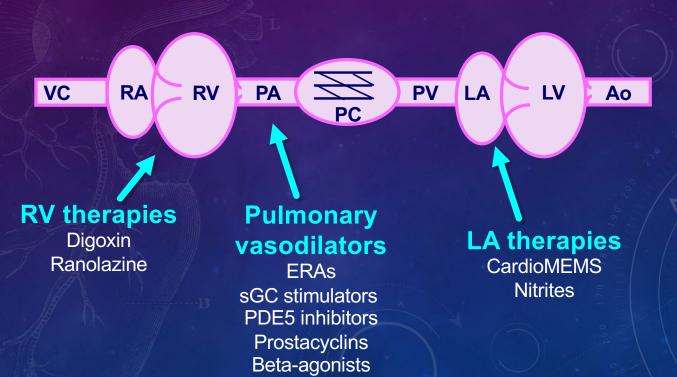
# Take home points

- Despite recent successful RCTs in HFpEF, still a big unmet need: HFpEF is underdiagnosed, ↑HF hospitalizations, poor health status
- Medication non-adherence and hyper-polypharmacy are big problems in HFpEF patients: Need alternate solutions
- Once euvolemic at rest, patients with HFpEF are still very symptomatic and have 11 exercise PCWP: Role for device therapies?
- Corvia Atrial Shunt: \(\frac{\mathbb{Exercise PCWP compared to sham control}\)
- 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%: Subgroup analyses suggests a potential responder group (exercise PVR < 1.74 WU, no pacemaker)</li>



## Is PH-HFpEF treatable? OLD NEWS

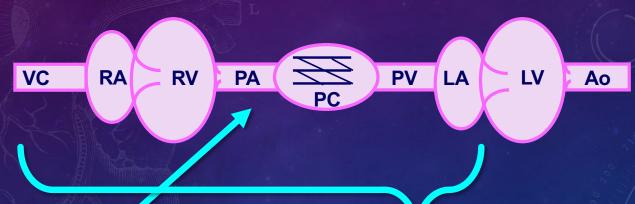
### Treatment targets: LA, PA, RV



## Is PH-HFpEF treatable? **NKOTB**

Treatment targets: LA, PA, RV, SBV





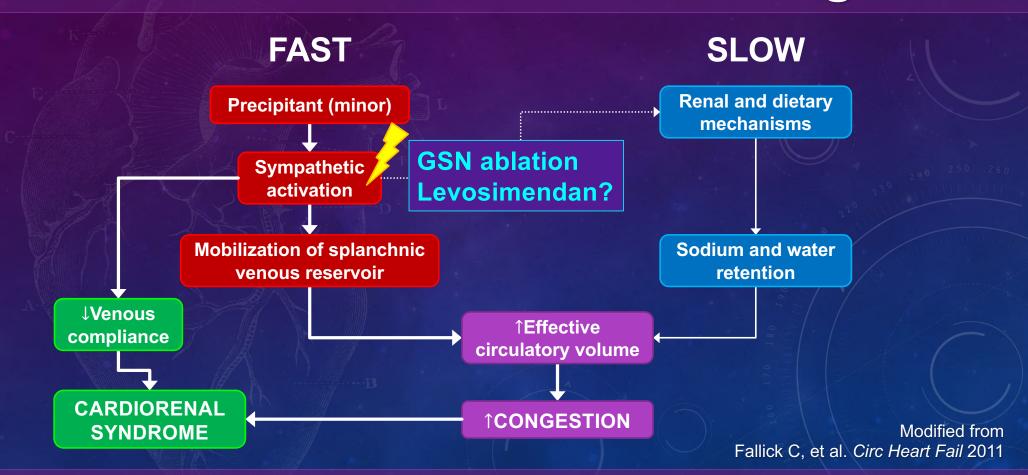
Improving PA compliance

Aria CV device

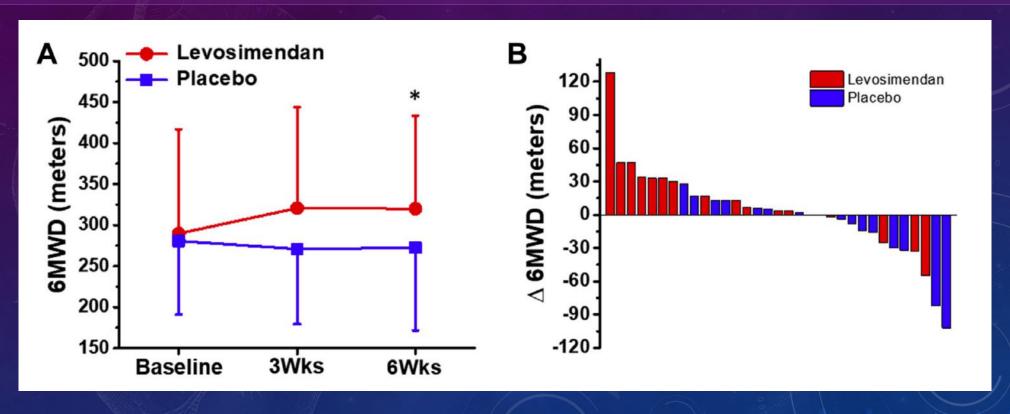
**Increasing unstressed blood volume** 

Levosimendan Greater splanchnic nerve (GSN) ablation SGLT2i

# Fast vs. slow mechanisms of congestion

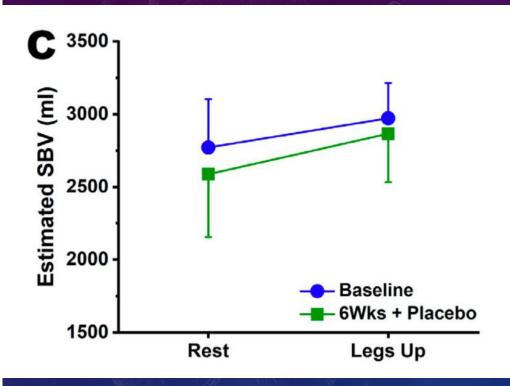


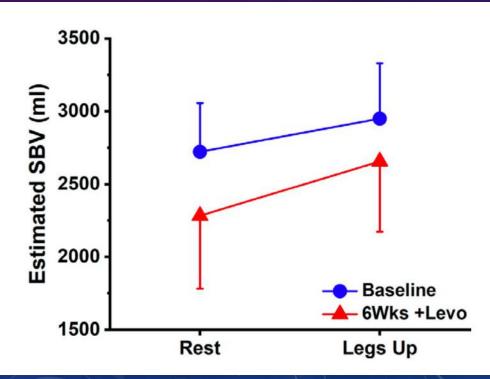
# HELP-PH-HFpEF phase 2 RCT



Burkhoff D, et al. *JACC Heart Fail* 2021 Brenner MI, et al. *J Card Fail* 2021

# HELP-PH-HFpEF phase 2 RCT

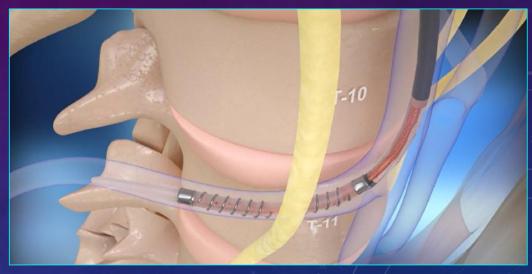




Burkhoff D, et al. JACC Heart Fail 2021 Brenner MI, et al. J Card Fail 2021

# First-in-human GSN ablation in HFpEF





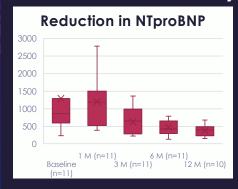
- Procedure completed successfully in all 11 patients based on ability to deploy ablation catheter and delivery of RF energy as intended
- All patients discharged from the hospital day after procedure

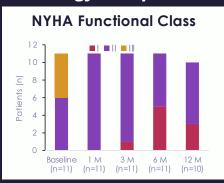
# FIH Endovascular GSN ablation in HFpEF

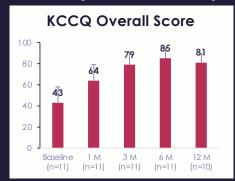
- Transvenous GSN ablation with Satera Ablation System
- ▶ 11 HFpEF patients
- No device-related serious adverse events
- Durable through 12-month Follow-up

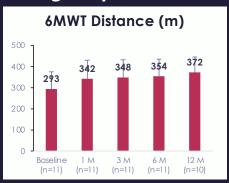


#### Demonstrated clinically meaningful improvements in key clinical and physiological parameters









Shah SJ, et al. Presented at THT 2022 (Clinicaltrials.gov: NCT04287946)