Foundations of HFpEF

July 10, 2018

11:00am – 12:00pm Central

Presenters:

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GET WITH THE GUIDELINES. HEART FAILURE

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Foundations of HFpEF: Epidemiology and Pathophysiology

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Case Example

72 yo male with a recent diagnosis of acute heart failure here for follow-up

- Medical history: Hypertension, GERD, hernia repair
- Previously active but stopped exercising due to back pain
- Intermittent palpitations with tachycardia on his home BP machine since last Fall; recent diagnosis of atrial fibrillation treated with cardioversion and apixaban
- Hospitalized 3 weeks ago with orthopnea and edema and diagnosed with HF

Case Example

72 yo male with a recent diagnosis of acute heart failure here for follow-up

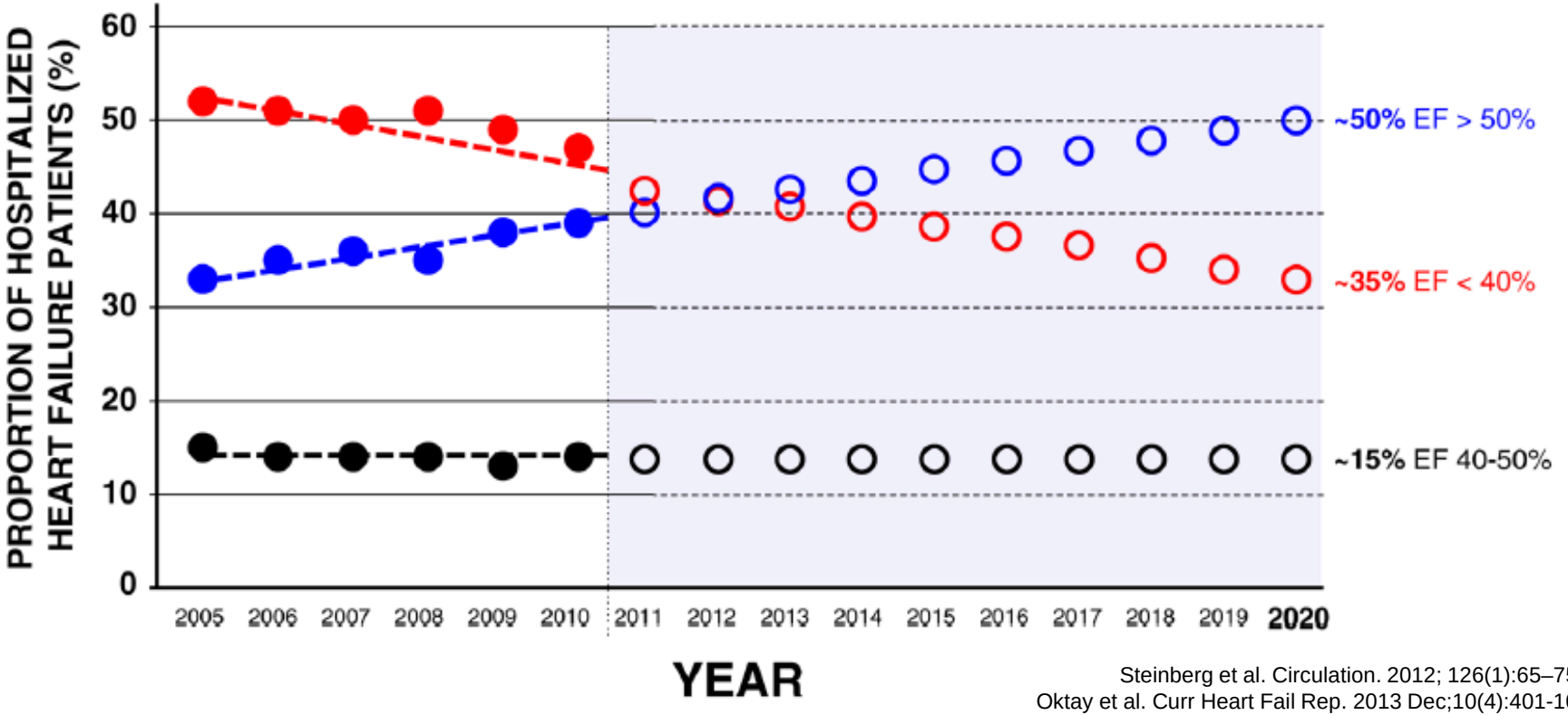
- NYHA Class II symptoms
- Amlodipine 5, apixaban 5mg twice daily, omega-3 fatty acids, metoprolol succinate 25mg daily
- Pulse 61 (sinus), BP 150/78, euvolemic, S4 on exam, warm extremities
- K 4.2, Cr 1.2
- Echocardiogram is shown

Case Example

72 yo male with a recent diagnosis of acute heart failure here for follow-up

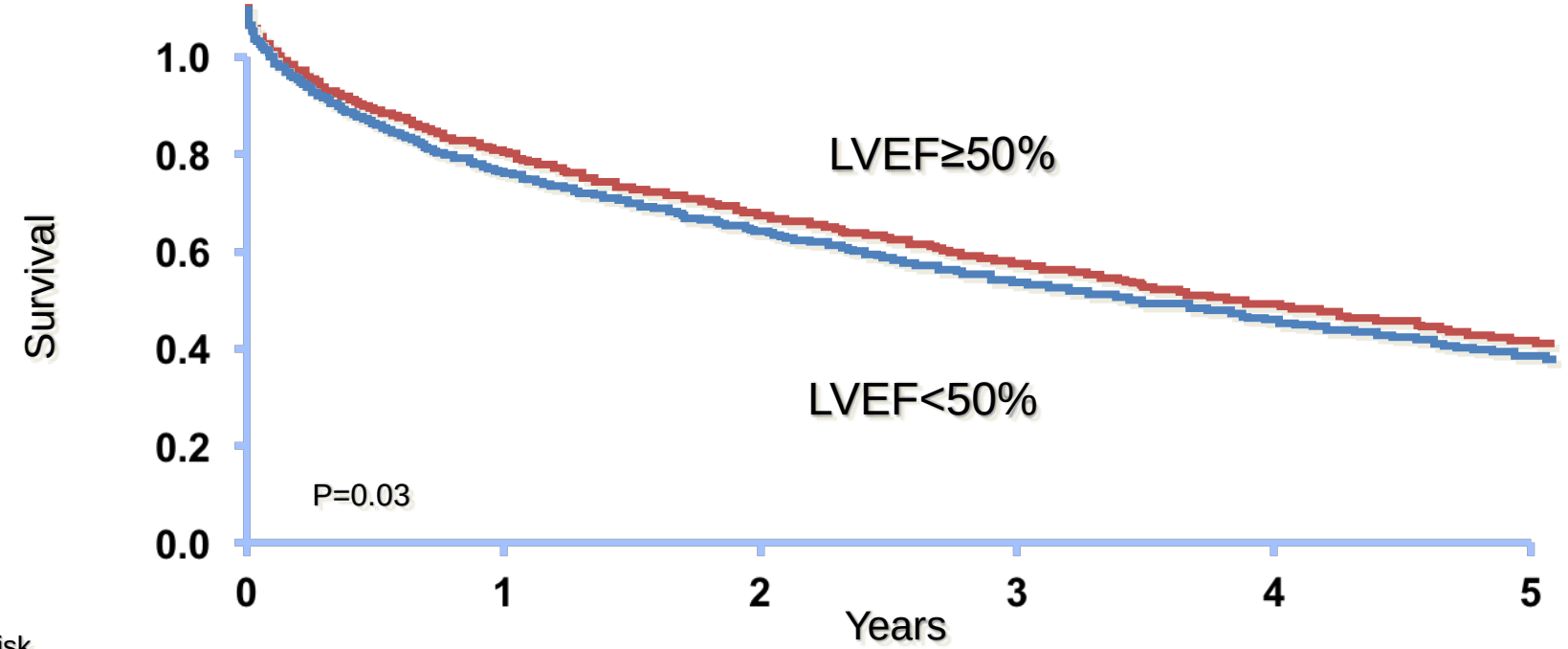
- Does he have HFpEF or a condition that mimics HFpEF?
- Have we considered and treated predisposing conditions?
- Are therapies for his cormorbid conditions optimized?
- Are his filling pressures optimized?
- Can we reduce his risk of future HF events with medical or non-pharmacologic interventions?

The Changing Epidemiology of Heart Failure



Steinberg et al. Circulation. 2012; 126(1):65–75
Oktay et al. Curr Heart Fail Rep. 2013 Dec;10(4):401-10

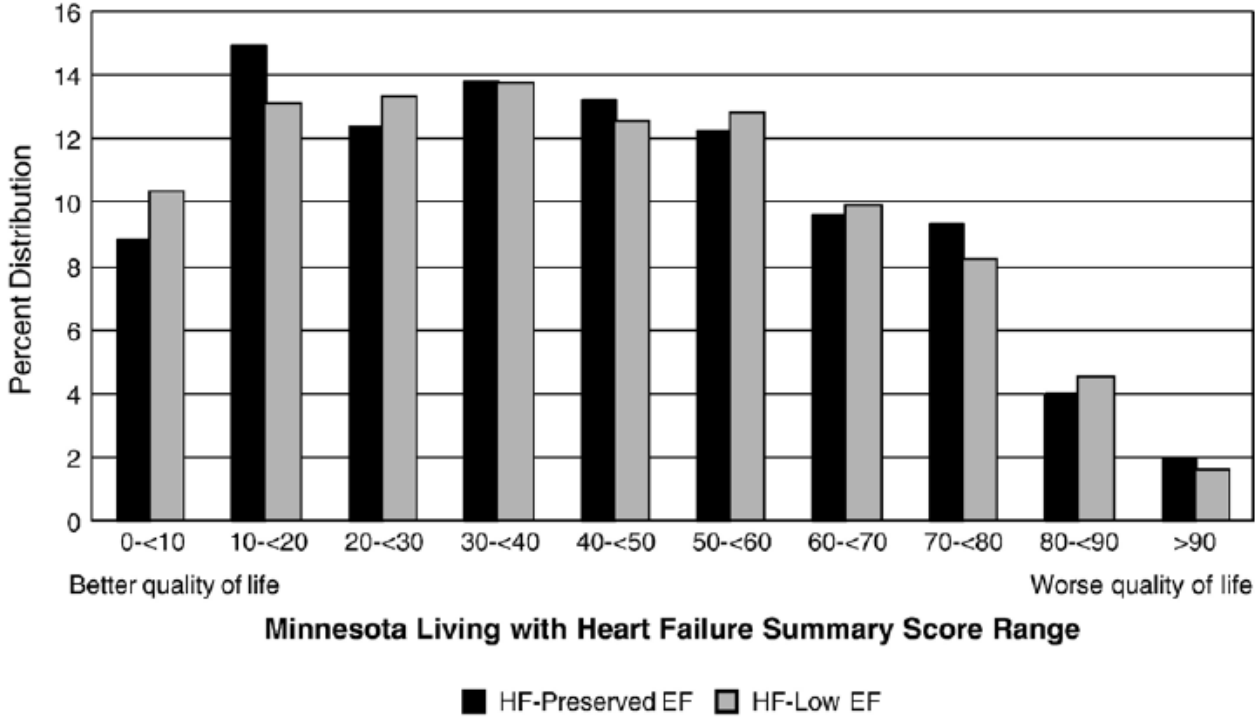
Mayo Data: Similar Survival for HFrEF and HFpEF



No. at risk						
EF<50%	2,424	1,637	1,350	1,049	813	604
EF≥50%	2,166	1,539	1,270	1,001	758	574

Owan T et al, NEJM, 2006

CHARM data: Health-related QOL in HFpEF vs HFrEF

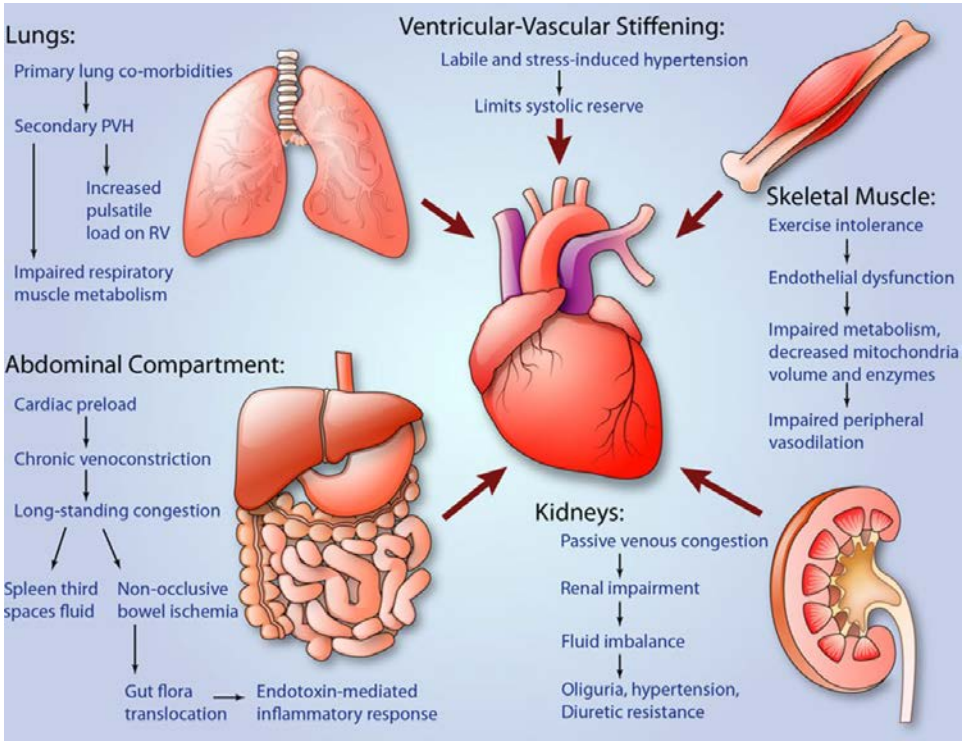


Lewis E et al. *Eur J Heart Fail*. 2007 Jan;9(1):83-91

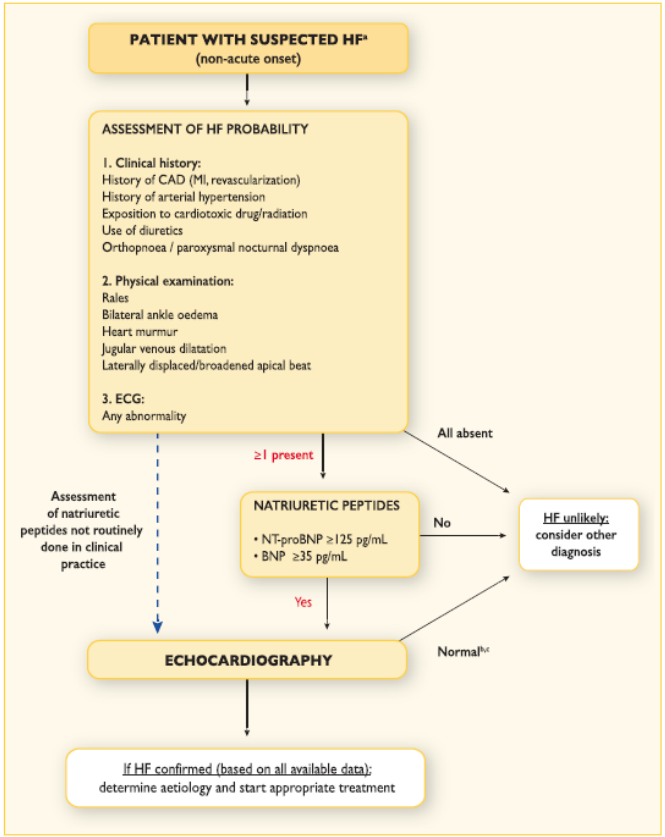
HFpEF Potential Cardiac Mechanisms

- Left ventricular hypertrophy and fibrosis (reduced chamber compliance)
- Impaired diastolic relaxation and elevated left-sided filling pressures
- Systolic dysfunction (sometimes subclinical)
- Abnormal ventricular-vascular coupling
- Chronotropic incompetence and cardiovascular reserve
- Increased oxidative stress and depressed NO signaling (i.e., inflammation) leading to endothelial dysfunction
- Comorbidity-induced systemic inflammation

Extracardiac Mechanisms of HFpEF



Sharma K and Kass DA. *Circulation Research*. 2014;115:79-96



HFpEF: Making the Diagnosis

Table 1 Diagnosis of heart failure

The diagnosis of HF-REF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Reduced LVEF
The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)

2016 ESC Heart Failure Guidelines

The Search for “Other” Causes of HFpEF

- Hypertrophic cardiomyopathy
- Infiltrative or restrictive cardiomyopathy
- Pulmonary arterial hypertension
- Constrictive pericarditis
- High output heart failure
- Valvular disease
- Coronary artery disease
- Pulmonary embolism
- Right ventricular myopathies

Phenoytpic-specific Management

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation Phenotypes					
		Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
	Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion + Rate Control **+Anticoagulation**
	+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion + Rate Control **+Anticoagulation**
	+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion + Rate Control **+Anticoagulation**
	+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion + Rate Control **+Anticoagulation**

Shah et al. *Circulation*. 2016;134:73-90

Important Comorbidites in Heart Failure


Renal dysfunction


COPD


Diabetes


Sleep apnea


Fe Deficiency +/- anemia


Depression


Frailty

Medical Therapy for HFpEF: Trials and Guideline Recommendations

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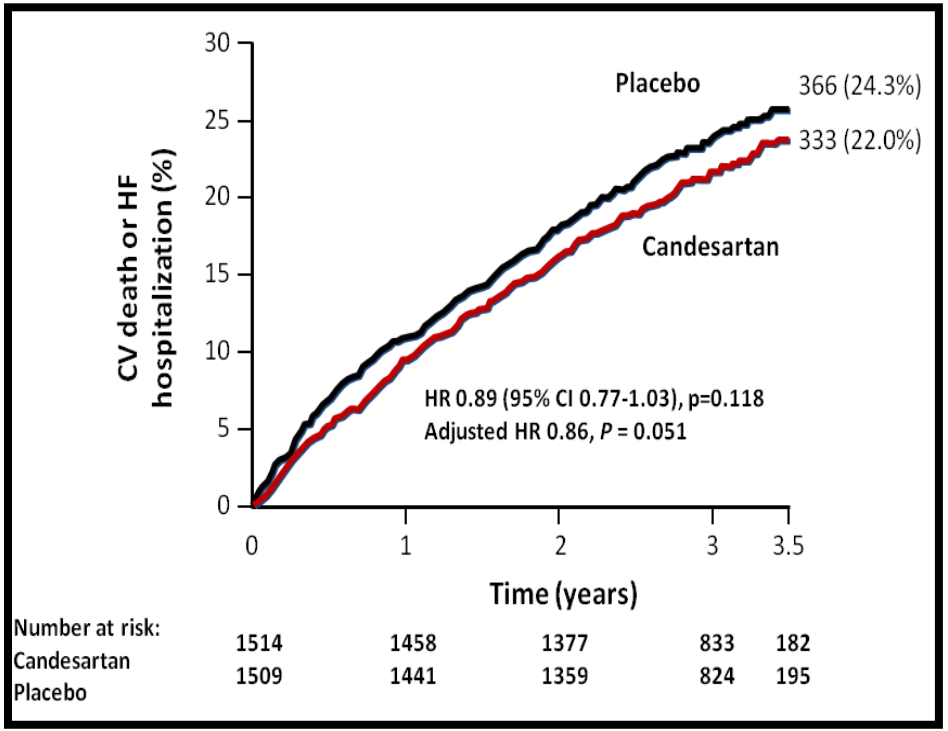
Therapies demonstrated to Improve Survival in HFpEF

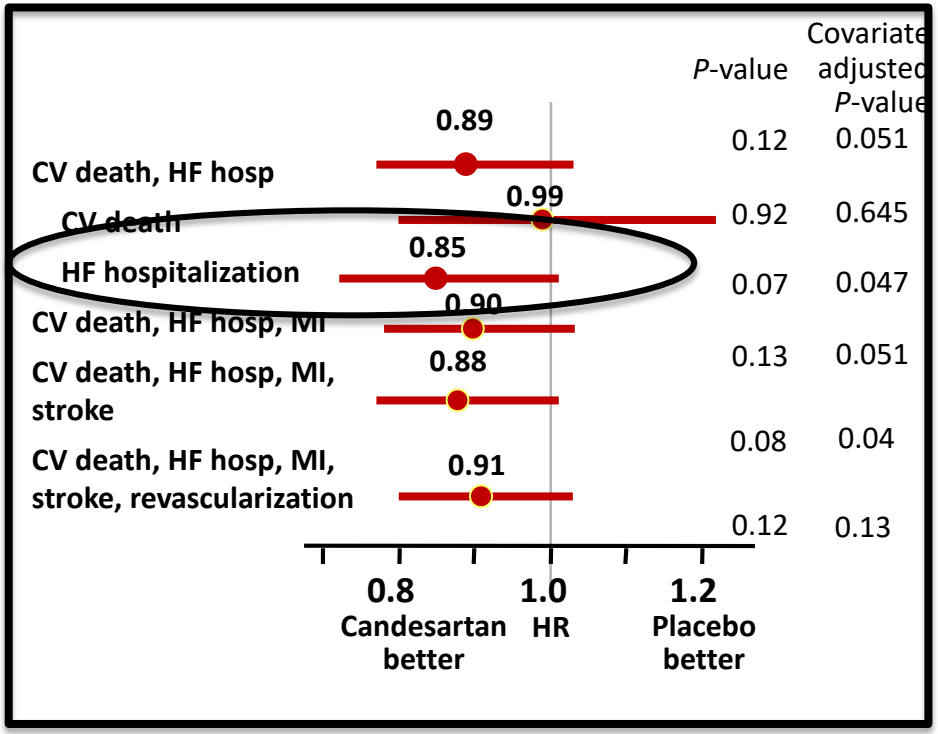
HFrEF

- ACE Inhibitors
- Angiotensin Receptor Blockers (ARBs)
- Angiotensin Receptor Neprilysin Inhibitors (ARNI)
- Beta Blockers
- Aldosterone Receptor Blockers
- Hydralazine/Nitrates
- ICDs; CRT Cardiac Resynchronization Therapy

HFpEF

ARBs in HFpEF: CHARM-PRESERVED

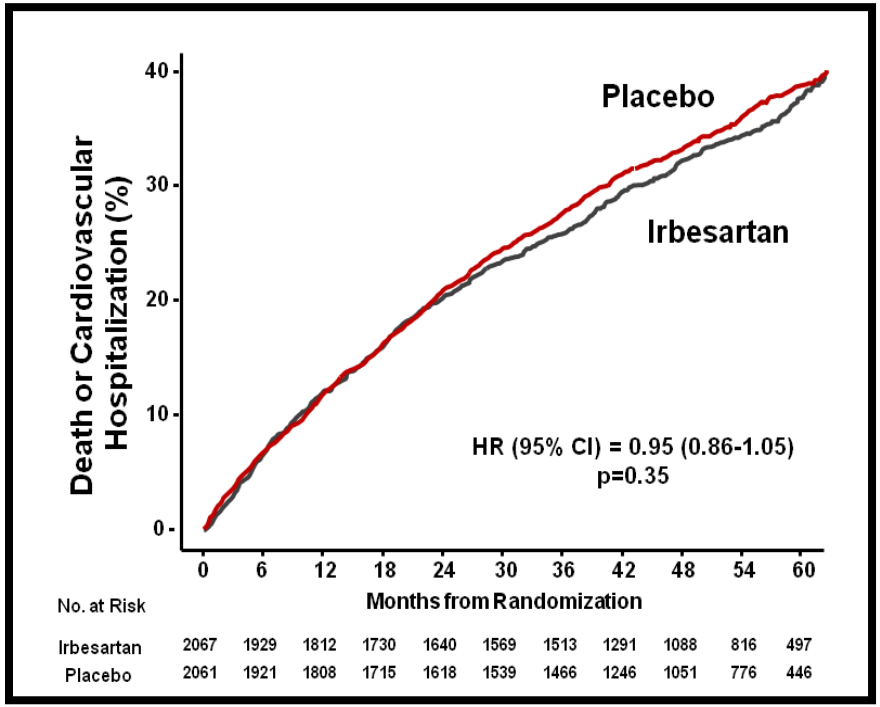




Yusuf S, et al. Lancet 2003; 362:777-781

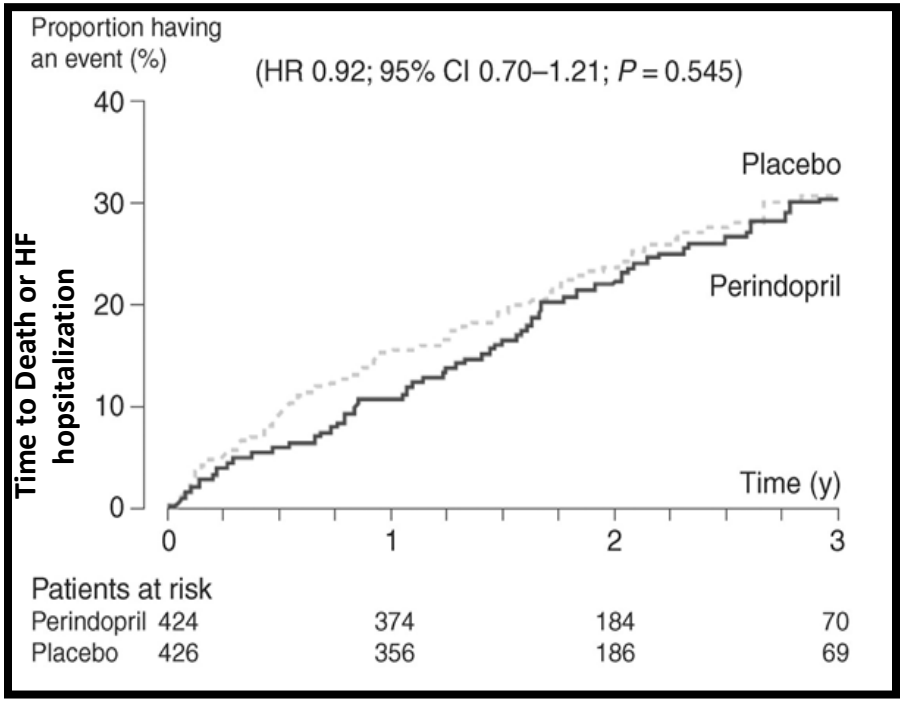
ARBs & ACE-I in HFpEF

I-PRESERVE



Massie B, et al. N Engl J Med 2008; 359:2456-2467

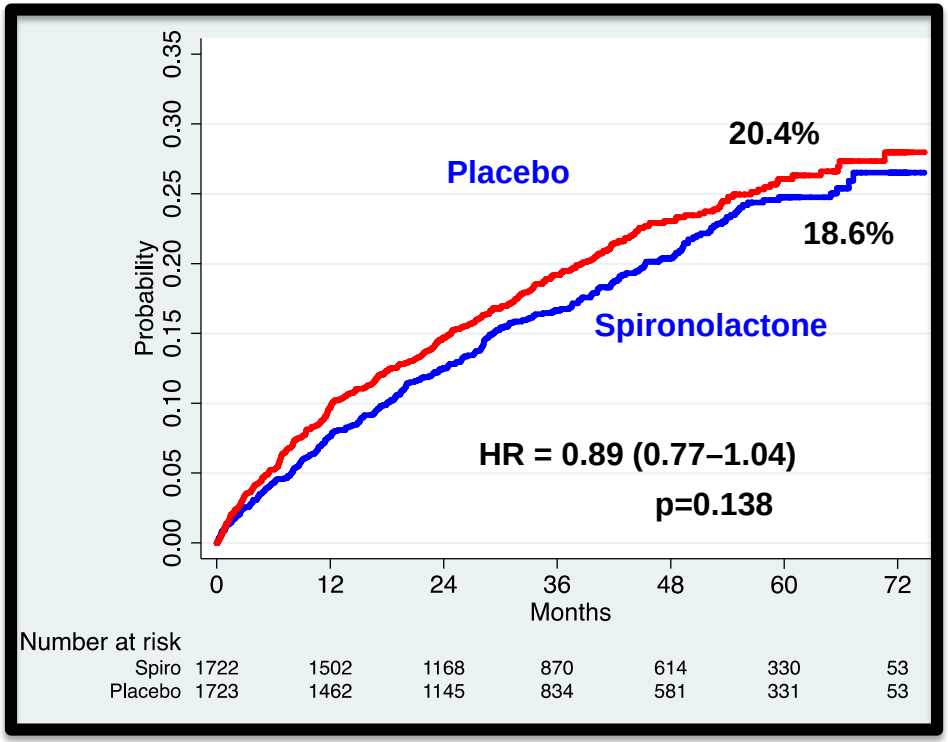
PEP-CHF



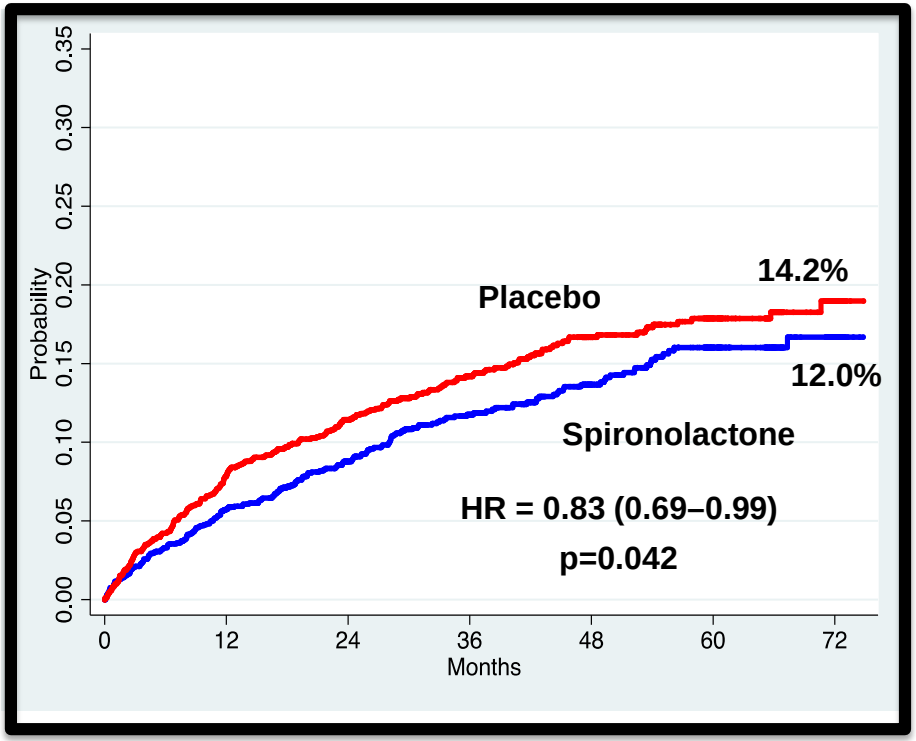
Cleland JGF, et al. Eur Heart J 2006; 27:2338-2445

Aldosterone Receptor Blockers in HFpEF: TOPCAT

CV Death, HF Hosp, or Resuscitated Cardiac Arrest



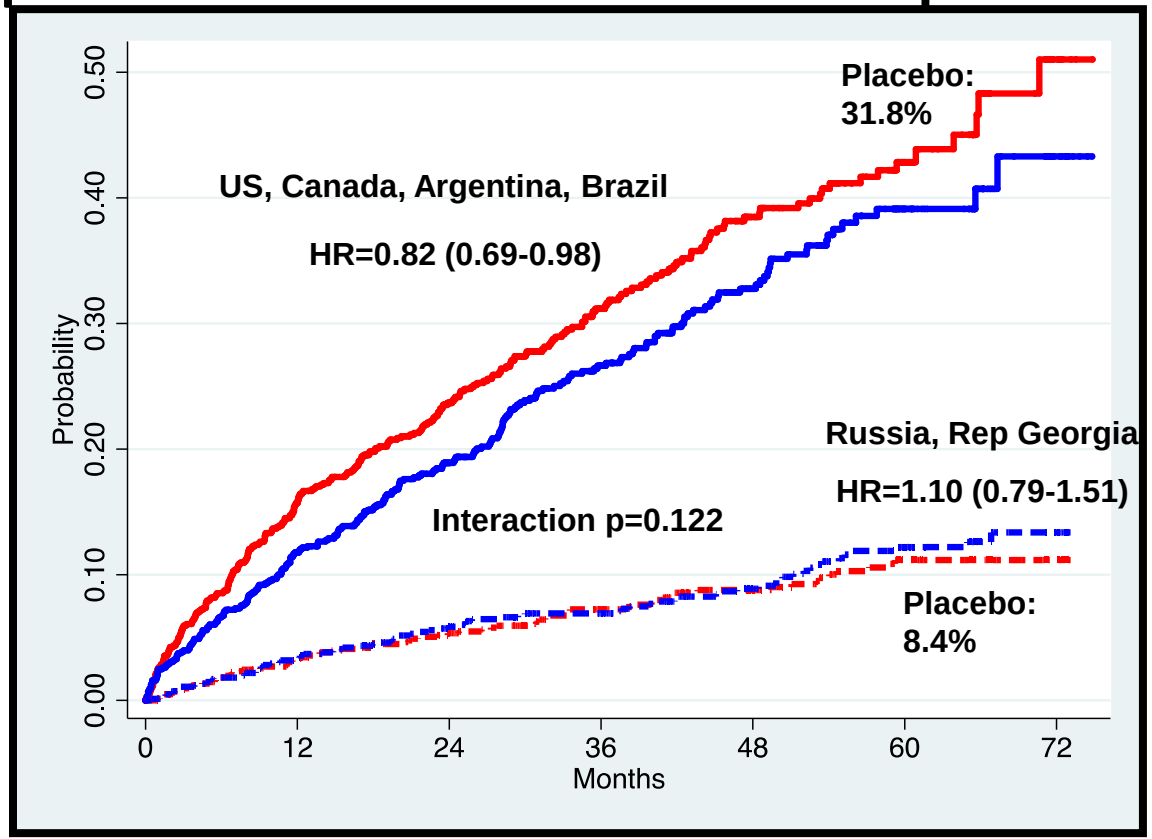
HF Hospitalizations



Pitt B, et al. N Engl J Med 2014; 370:1383-1392

Post Hoc Analysis: TOPCAT

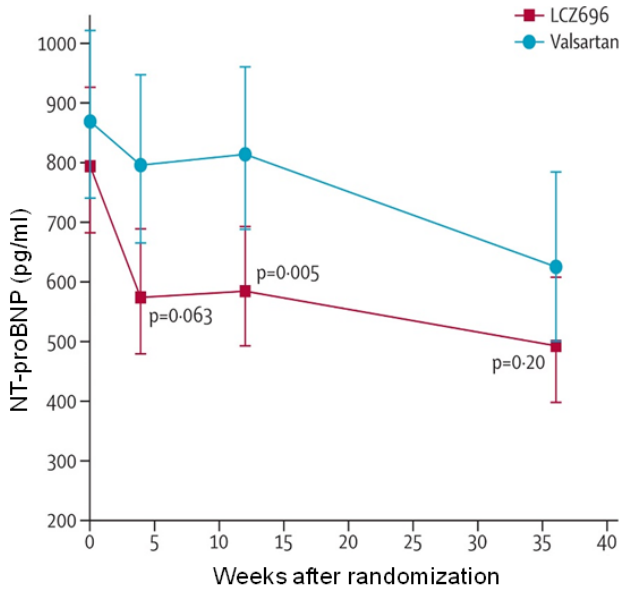
Geographic Differences in Event Rates & Spironolactone Effect



Pfeffer MA, et al. Circulation 131(1):34-42, 2015.

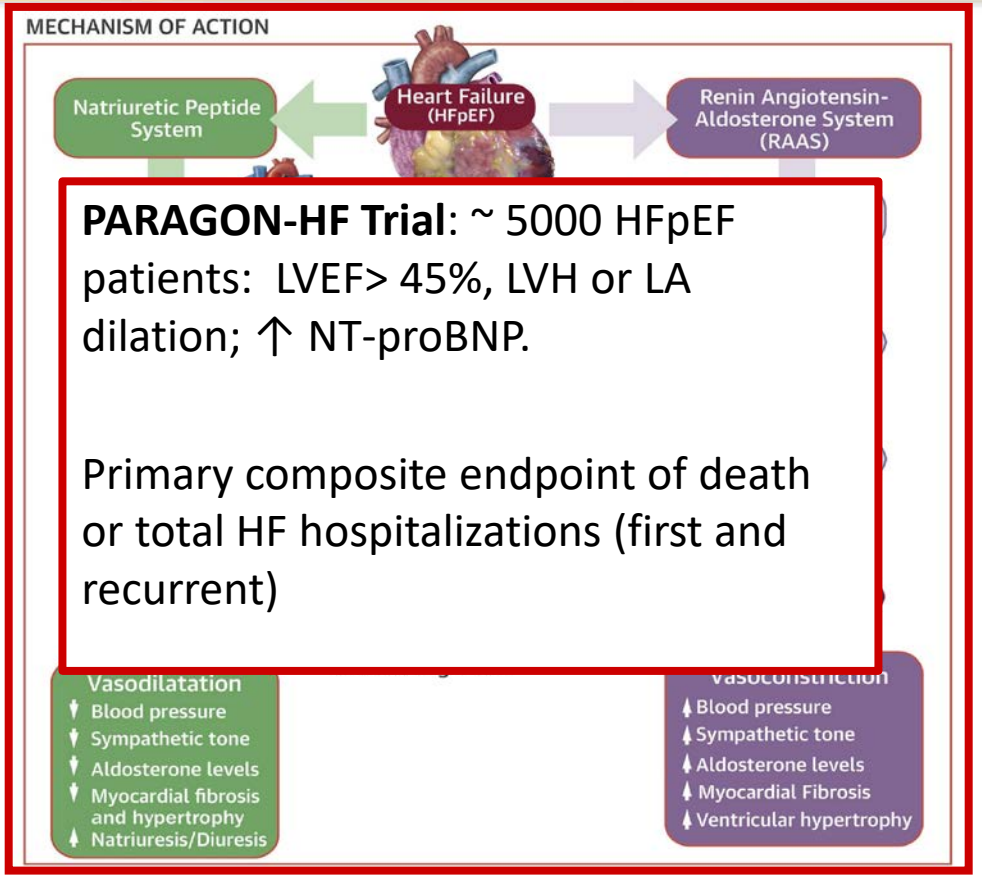
ARNI (Sacubitril/Valsartan) in HFpEF

PARAMOUNT Trial



Secondary: LA volume significantly ↓, NYHA class improved

Solomon SD, et al. Lancet 2012; 380:1387-1395



PARAGON-HF Trial: ~ 5000 HFpEF patients: LVEF> 45%, LVH or LA dilation; ↑ NT-proBNP.

Primary composite endpoint of death or total HF hospitalizations (first and recurrent)

Solomon SD, et al. JACC Heart failure 5(7):471-482, 2017

Other Endpoints and Trials in HFpEF

- Digoxin (post hoc in HFpEF group) : Mortality↔, HF Hospitalizations↓, all Hospitalizations ↔
- SENIORS (BB – nebivolol): ↓ time to death/HF hospitalization, but few with LVEF>50%
- RELAX (sildenafil): no change in peak VO2
- NEAT (isosorbide mononitrate): decreased daily activity levels and did not improve submaximal exercise capacity, quality-of-life scores or NT-proBNP levels
- INDIE (inorganic nitrite): no change in peak VO2

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

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Guidelines: Medical Therapy for HFpEF -I

COR	LOE	
IIa	C	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF.
IIb	B-R	In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83,166,167).
IIb	B	The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF (169).

COR: Class of Recommendation: I-III
I: Strong; benefit >>> risk
IIa: Moderate; benefit >> risk
IIb: Weak; benefit ≥ risk
III: No benefit (moderate); benefit=risk
III: Harm (strong); risk > benefit

LOE: Level (quality) of Evidence: A-C
A: Best quality of evidence (often high quality RCTs)
B, C

Circulation; 2017

Guideline: Medical Therapy for HFpEF -II

COR	LOE	
III: No Benefit	B-R	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective (171,172). See Online Data Supplement C.
III: No Benefit	C	Routine use of nutritional supplements is not recommended for patients with HF*p*EF.
I	C	Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF.

2017 AHA/ACC/HFSA focused update of the 2013 AHA/ACCF Guideline for the Management of heart Failure. Circulation; 2017

Guideline: Treatment of Hypertension in HFpEF

COR	LOE	RECOMMENDATIONS
I	B	Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity (164,165).
I	C-LD	Patients with HF*p*EF and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (9,167,169,170,195–199).

2017 AHA/ACC/HFSA focused update of the 2013 AHA/ACCF Guideline for the Management of heart Failure. Circulation; 2017

Guideline: Treatment of Comorbidities in HFpEF

IIa	C	Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT.
IIa	C	Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF. (AF=Atrial fibrillation)
IIa	C-LD	In patients with NYHA class II-IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable
IIb	B-R	In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204).

2017 AHA/ACC/HFSA focused update of the 2013 AHA/ACCF Guideline for the Management of heart Failure. Circulation; 2017

Prevention of Heart Failure (incl. HFpEF)

COR	LOE	RECOMMENDATIONS
I	B-R	In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg (189-193).

2017 AHA/ACC/HFSA focused update of the 2013 AHA/ACCF Guideline for the Management of heart Failure. Circulation; 2017

Summary: Current Treatment of HFpEF

1. Treat symptoms of volume overload with diuretics

2. Treat hypertension: Goal in most patients < 130/80 mm Hg

3. In patients at high risk for HF hospitalization: may consider ARBs or aldosterone receptor antagonists (if no contraindications)

4. Treat comorbidities, e.g. atrial fibrillation, CAD

Non-Pharmacological Care, Transitions of Care and Future Possibilities in HFpEF

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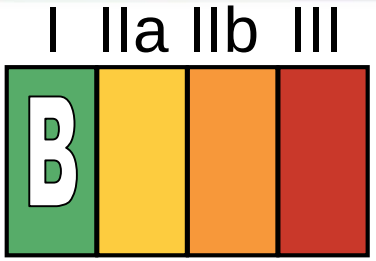
HFpEF Recap

- ↑ prevalence
- High morbidity/ mortality
- No proven therapies
- Treat comorbidities
- Ensure disease management and transition care to reduce morbidity and mortality

Transitions of Care in HF



Before discharge & at EACH post discharge visit:

- **Manage comorbid conditions:**
  - **Cardiac related (CAD, AF, HTN)**
  - **Mimics of HF symptoms: anemia, COPD, CRI…**
- **Address HF cause, barriers to care & limitations in support - Complex!**
- **Ensure HF education, self-care, emergency plans, and adherence; discuss “how”, not just “what”**
- **Discuss palliative or hospice care**

Yancy CW, et al. *Circulation.* 2013;128:e240–e327.

H2H Strategies- Reduce HF Hospitalization

Quality Improvement (QI) resources and performance monitoring:

1. **≥ 1 QI team for reducing readmission for HF**
2. **Monitor proportion of discharged patients with follow-up appointment within 7 days**
3. **Monitor 30-day readmission rates**

http://cvquality.acc.org/en/Initiatives/H2H/About-H2H.aspx

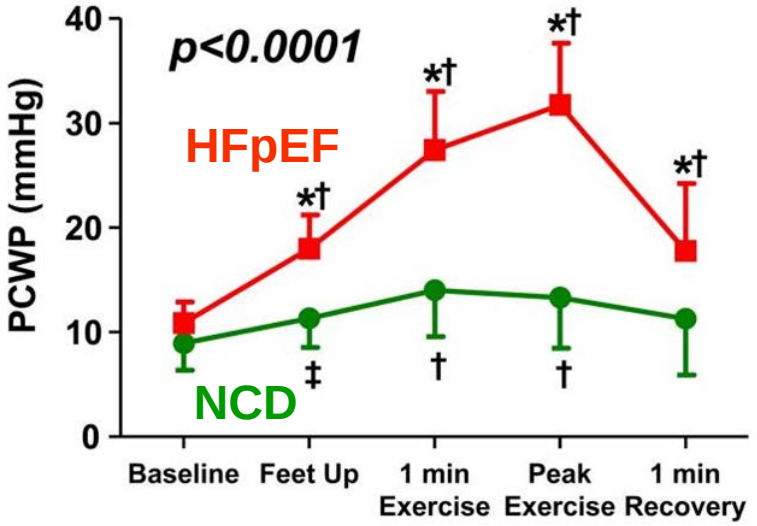
HFpEF Recap

- ↑ prevalence
- High morbidity/ mortality
- No proven therapies
- Treat comorbidities

Common pathophysiologic thread:

- ⇧LA pressure at rest or with exertion

Exercise Hemodynamics in HFpEF



N = 55; HFpEF, n = 32
NCD, noncardiac dyspnea, n=23

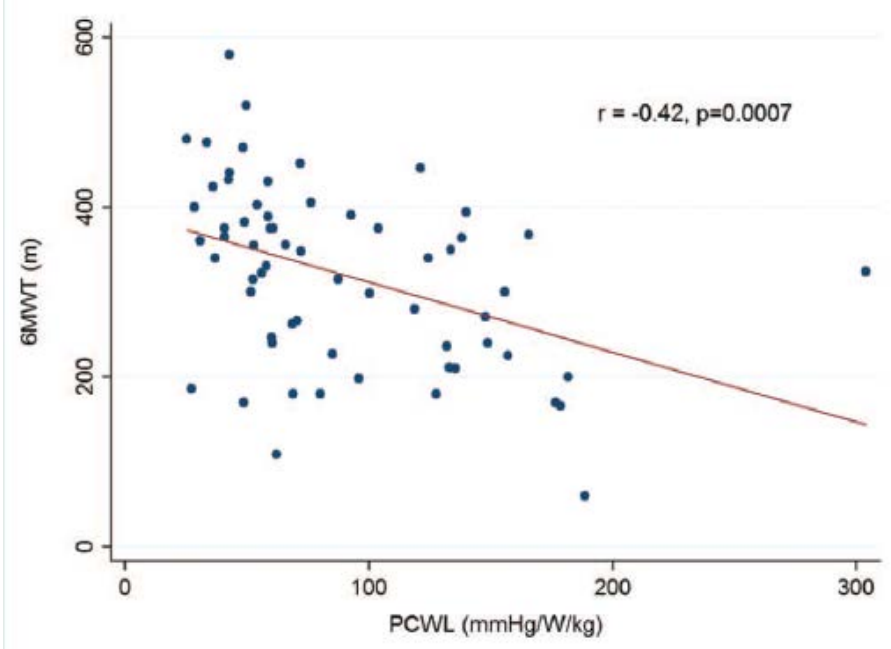
*, *p*<0.0001 for change PCWP
†, p< 0.001 vs baseline (within gp)
‡, p<0.01 vs baseline (within gp)

Conclusion:

- Euvolemic patients with exertional dyspnea, normal BNP, and normal cardiac filling pressures at rest may have markedly abnormal hemodynamic responses during exercise
- Chronic symptoms are related to HF
- Earlier /more accurate Dx using exercise hemodynamics may allow better targeting of interventions to treat / prevent HFpEF progression

Borlaug BA, et al. *Circ Heart Fail* 2010;3(5):588-595.

Hemodynamics & 6 Minute Walk Test



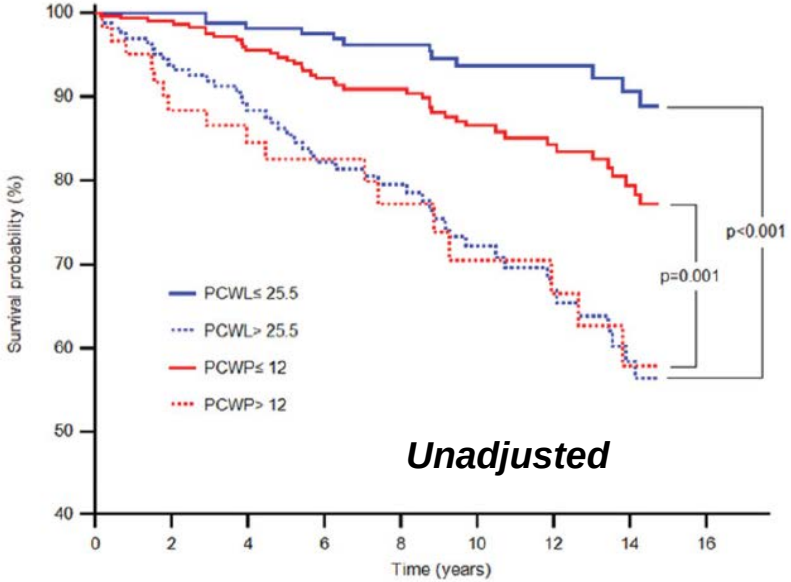
64 patients; mean age 70±8 yrs; mean 6MWT distance was 318±108 m

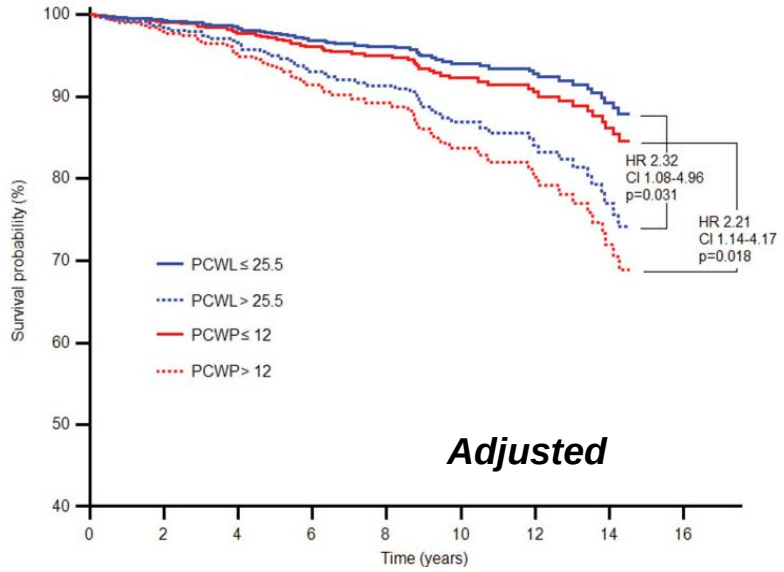
- At *rest*, only PCWP was associated with 6MWT
  - -5.4 (95% CI: -10.4, -0.5) *p*=0.033
- With *light/moderate exercise*, mean PAP was associated with 6MWT
  - -3.5 (95% CI: -6.8, 0.3) *p*=0.033
- During *peak exercise*, workload corrected PCWP was the only variable associated with 6MWT
  - -0.8 (95% CI: -1.3, -0.4) *p*<0.001

Wolsk E, et al. *Eur J Heart Fail*. 2018; 20:715-722

PCWP during Exercise -Long Term Mortality

- **N = 355; 12 month follow-up**





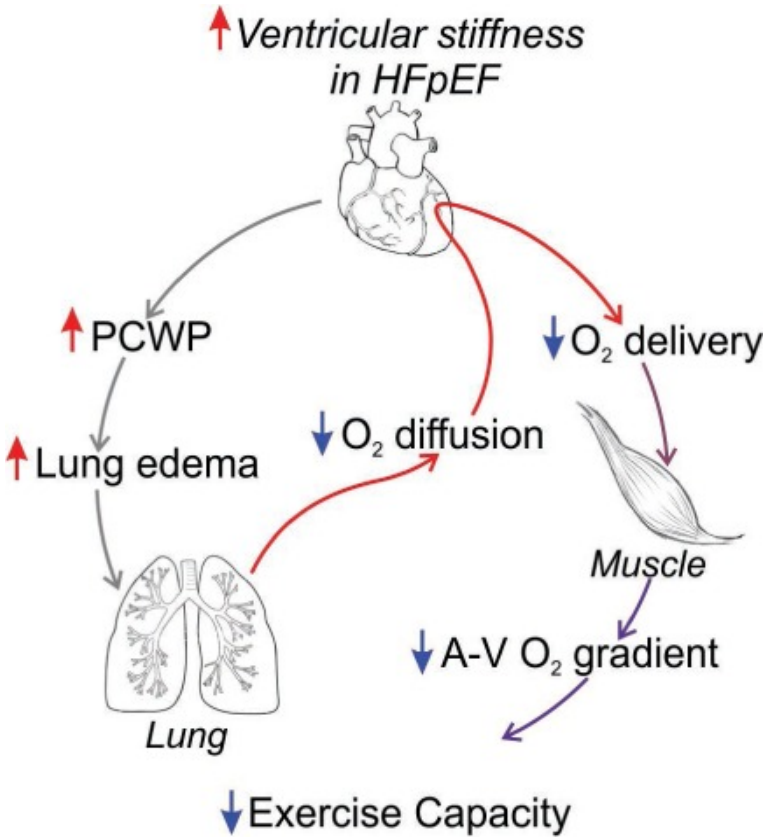
Numbers at risk

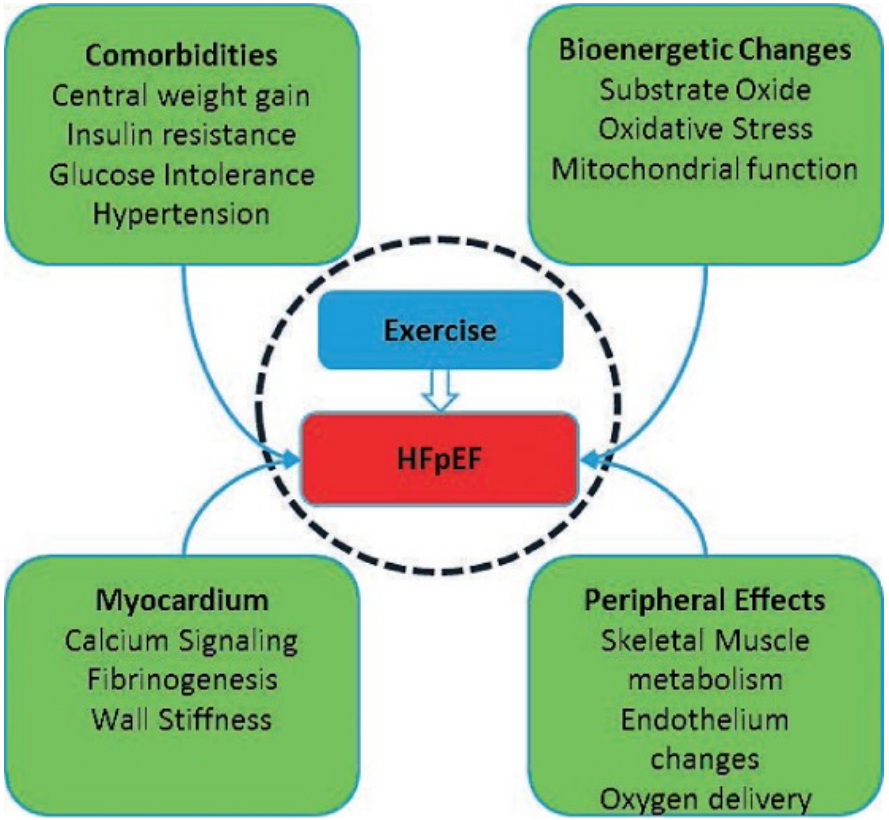
Low PCWL	192	182	160	149	122	95	74	55	10
High PCWL	163	150	124	100	81	61	47	31	6
Low PCWP	295	279	241	214	176	137	104	74	16
High PCWP	60	53	43	35	27	19	17	12	0

PCWP at peak exercise to workload normalized to bodyweight [PCWL (mmHg/W/kg)]

Dorfs S, et al. *Eur Heart J*. 2014; 35:3103-3112.

Mechanisms for Reduced O2 Uptake & Delivery





Gupte AA, et al. *Methodist DeBakery Cardiovasc J* 2016; 12(2):105-109.

Aerobic Exercise/Caloric Restriction (Weight Loss)

Obese (BMI ≥ 30), clinical stable HFpEF patients aged 60+ years

- **Mean age 67 [5] yrs; EF ~ 61%; NYHA FC II/III**

Intervention: 20 weeks + telephone calls q 2 weeks from staff

- **1-hr supervised exercise (walking) 3x/week**
- **Hypocaloric diet; meals prepared in a metabolic kitchen (at Wake Forest Univ, Gen Clin Res Ctr)**

2x2 Factorial Groups: 100 pts enrolled (92 analyzed)

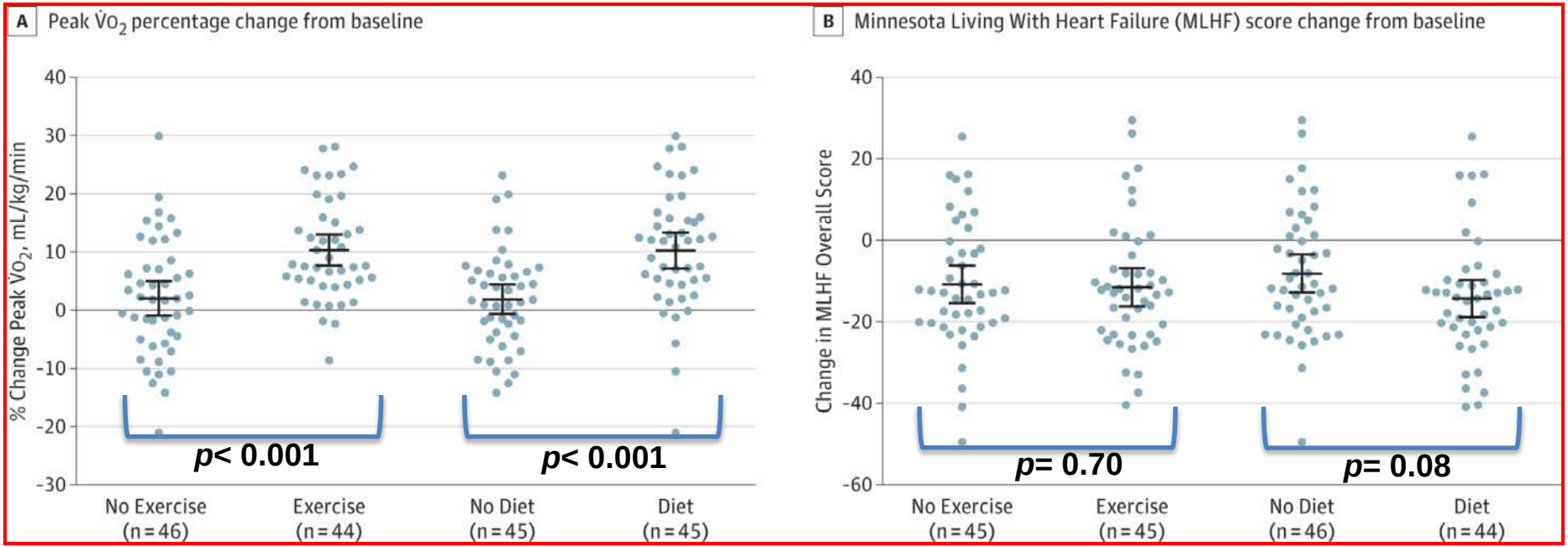
- **25 (22) attention control**
- **26 (24) exercise only**
- **24 (24) diet only**
- **25 (22) exercise + diet**

Baseline Medications:

ACEi/ARB: 37%/28%	Ca antagonists: 35%
Diuretics: 76%	Nitrates: 9%
B-Blockers: 40%	

Kitzman DW, et al. *JAMA.* 2016;315(1):36-46.

Aerobic Exercise/Caloric Restriction (Weight Loss)

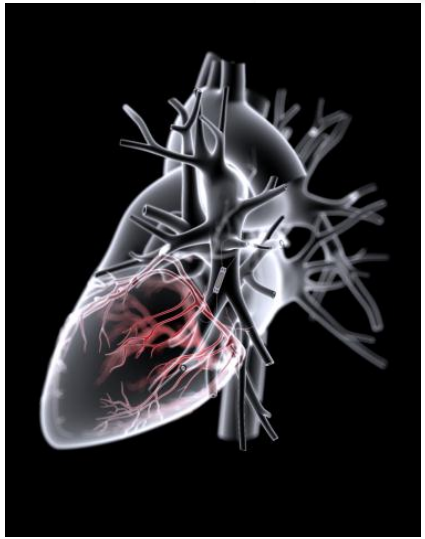


- **Combo of exercise + diet was additive: change in peak VO2 was 2.5 ml/kg/min**
- **Change in peak VO2 was associated w change in lean body mass: *r*=0.32, *p* =0.003**

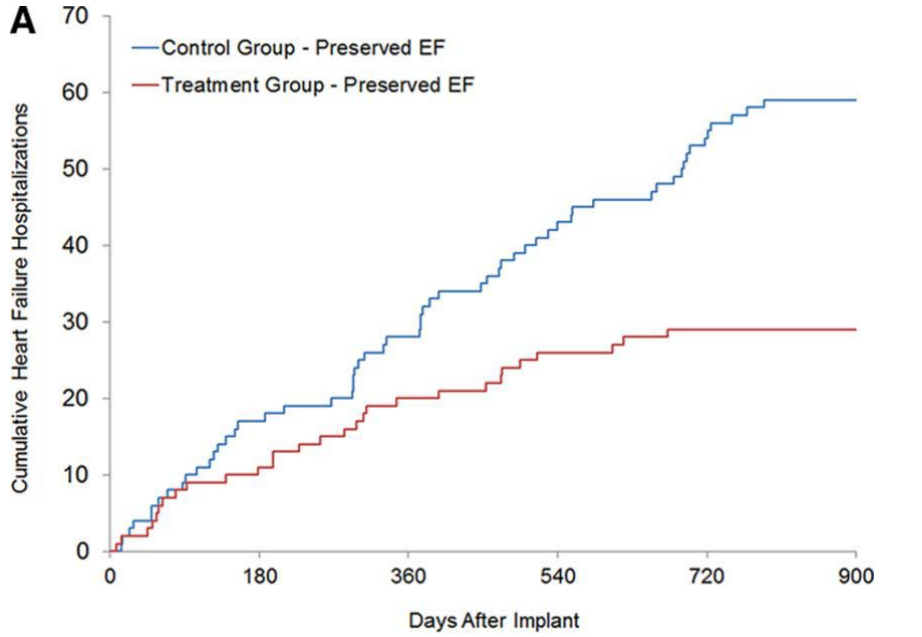
Kitzman DW, et al. *JAMA.* 2016;315(1):36-46.

Wireless PA Pressure Monitoring in HFpEF

Pulmonary artery pressure sensor is implanted via a RHC



Adamson et al.
Circ Heart Fail.
2014;7:935-944.



> 6 month HF Hospitalization IRR:
- **0.54; 95% CI, 0.38–0.70; *P*<0.0001**

~ 17.6 month blinded FU HF Hospitalization IRR:
- **0.50; 95% CI, 0.35–0.70; *P*<0.0001**

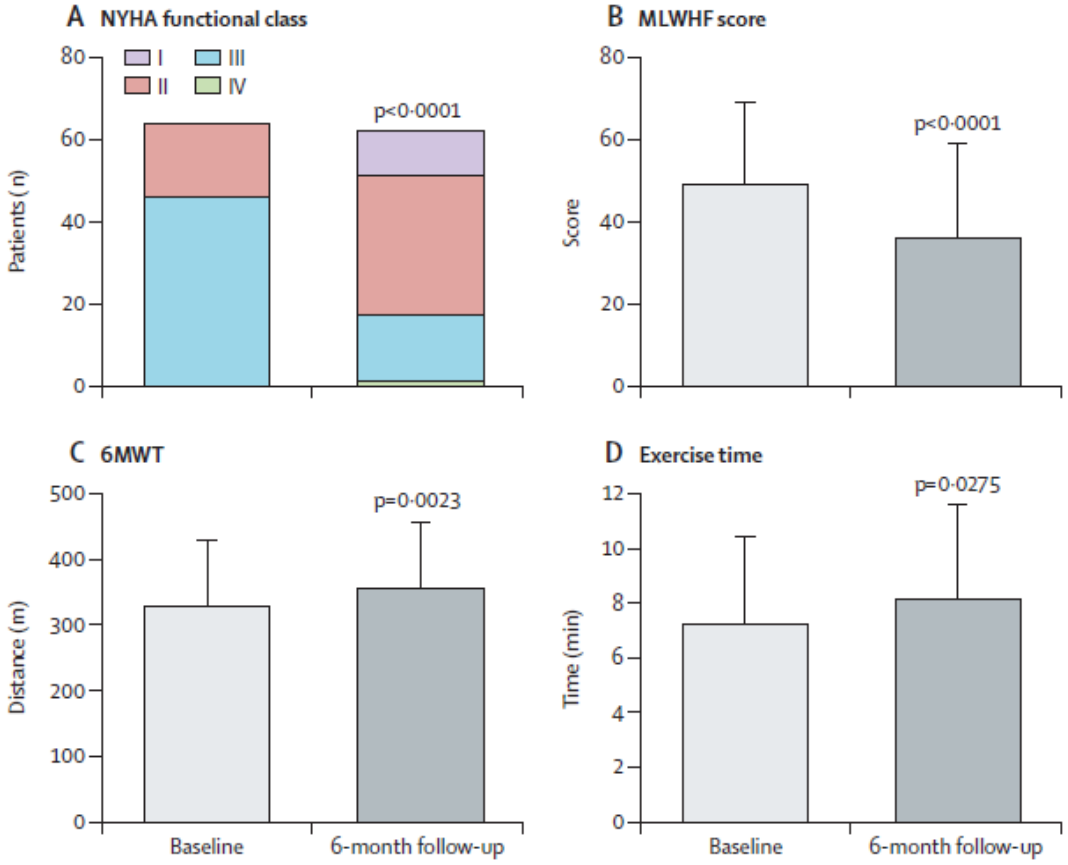
Future Direction?

InterAtrial Shunt Device

Mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA → RA

Feldman T, et al. *Circ Heart Fail.* 2017; 9:e003025.

REDUCE LAP -HF

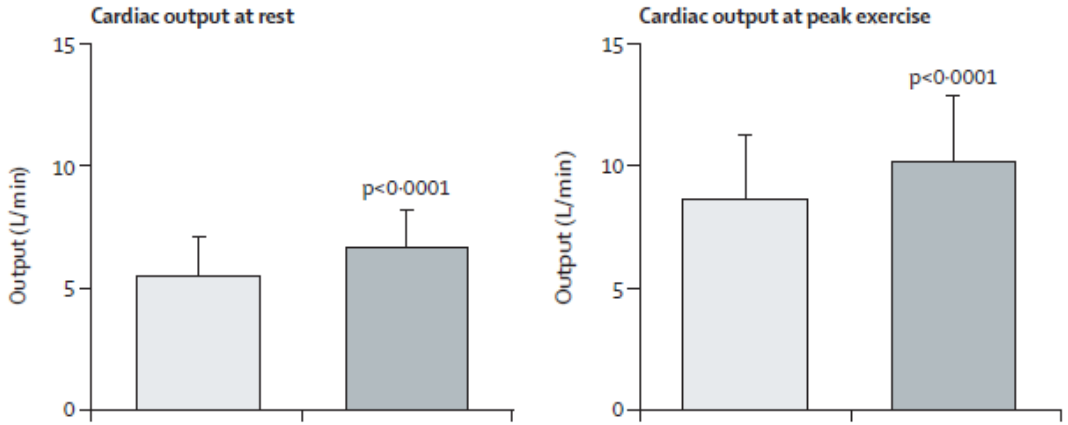


Open-label, single-arm, phase 1 study of a transcatheter interatrial shunt device (IASD, Corvia Medical, Tewkesbury, MA, USA)

- **Designed to assess performance and safety**
- **N=64**

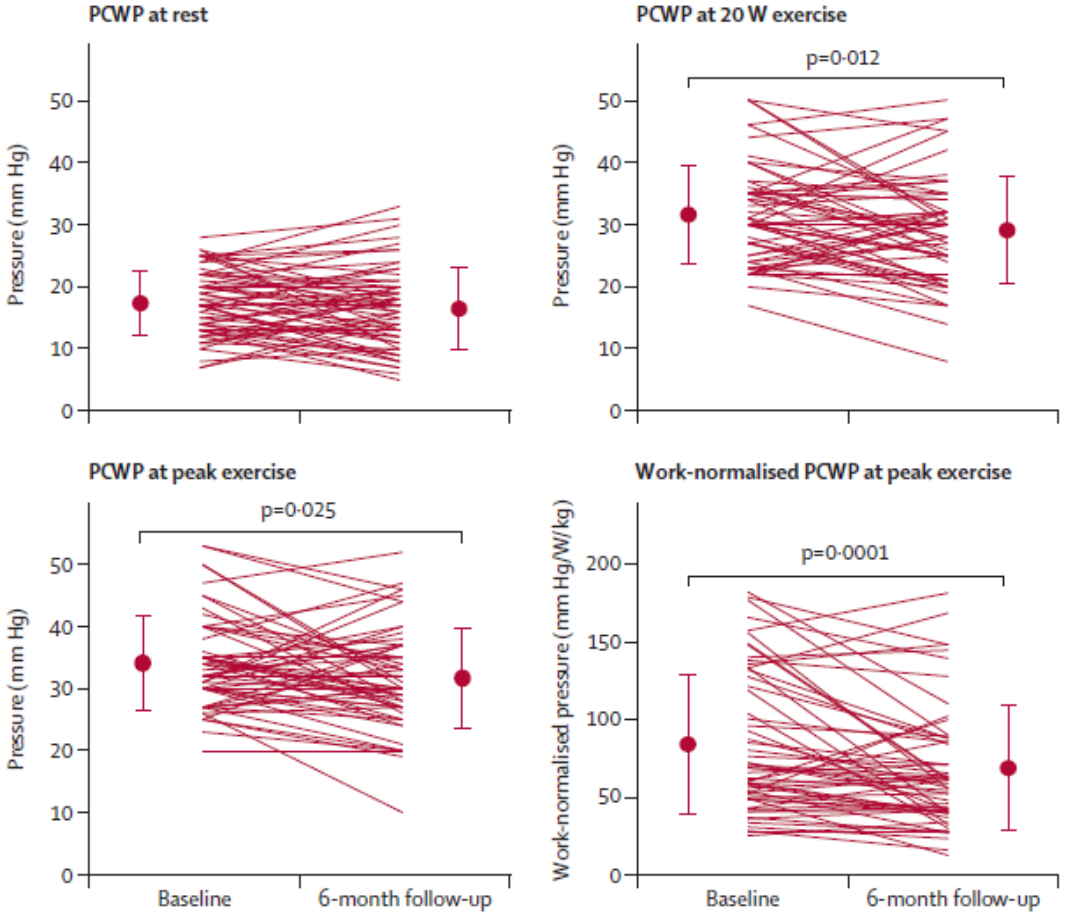
Hasenfub G, et al. *Lancet*. 2016; 387:1298-304.

REDUCE LAP -HF



Hasenfub G, et al. *Lancet*. 2016; 387:1298-304.

REDUCE LAP -HF



Conclusion:

- **Is feasible**
- **Might be associated with improvements in exercise hemodynamics, functional capacity and quality of life**
- **Need to replicate findings in a randomized controlled blinded trial**

Hasenfub G, et al. *Lancet*. 2016; 387:1298-304.

Discussion - Questions and Answers

Contact Us to Learn More

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Thank you for your active participation and contributions to GWTG-Heart Failure!