

TREATMENT OF DIASTOLIC  
HEART FAILURE -  
**Aldosterone Blockade**

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# DEFINITION

- Heart failure with preserved ejection fraction (HF-PEF), historically known as Diastolic HF (DHF) is characterized by
  - 1. A normal LVEF
  - 2. Normal LV end-diastolic volume
  - 3. Abnormal diastolic function, usually with concentric remodeling or hypertrophy.
- The dominant abnormality resides in diastole.
- However, in clinical practice, the diagnosis of DHF is often one of exclusion based on the finding of a normal or near normal (or “preserved”) LVEF.
- Its prevalence has been increasing during the past 2 decades and accounts for approximately half the cases of HF.

# HFpEF versus diastolic HF

- Diagnosis of diastolic HF requires the presence of diastolic dysfunction since there are causes of HF other than diastolic dysfunction in patients with preserved LVEF.
- Diastolic dysfunction and DHF are not synonymous terms .
- Diastolic dysfunction indicates
  - 1. A functional abnormality of diastolic relaxation, filling, or distensibility of the LV
  - 2. Regardless of whether the LVEF is normal or abnormal
  - 3. Whether the patient is symptomatic or not.

# Incidence

- Various studies estimate that as many as 40 to 60 percent of patients with HF have diastolic dysfunction as defined by a normal LVEF.
- However, there has been a marked variability in the reported prevalence of HF with a preserved EF (ranging from 13 to 74 percent) due to the use of heterogeneous criteria and hospital-based data.

# HFpEF – age

- The prevalence of HF with a preserved EF (HFpEF) increases with age.

Age	HFpEF incidence
< 50 yrs	15%
50 to 70 yrs	33%
>70 yrs	70%

# ETIOLOGY

- Systolic hypertension both with and without left ventricular hypertrophy (LVH)
- Aging
- Coronary heart disease
- Diabetes mellitus
- Breathing disorders during Sleep
- Obesity
- Kidney disease

# According to ADHERE database

- HFpEF had the following clinical characteristics compared with those with reduced EF :
  - More likely to be older, female, and hypertensive, obese.
  - Less likely to have had a prior myocardial infarction
  - Lower in-hospital mortality (3 versus 4 %) but similar intensive care unit and hospital length of stay.

HFpEF	HFrEF
Female sex	Male
Atrial fibrillation	Smoking
Increased urinary albumin excretion	hs-TnT, and prior MI
Increased cystatin-C	

# Mortality differences between HFpEF and HFrEF

- HFpEF appears to be associated with a better prognosis than HF due to systolic dysfunction (annual mortality 8 to 9 vs 19%) in some reports.
- A meta-analysis of nearly 42,000 patients with HF in 31 studies suggested that mortality of HF with a preserved EF is about 30 percent lower than that of HF with a reduced EF.
- More recent data suggest that mortality rates and rates of rehospitalization are not significantly different between the 2 groups.
- However, in contrast to the improvements in survival with systolic HF, mortality from HF-pEF has remained the same.
- This dissociation may in large part be due to the clinical and pathophysiologic heterogeneity of HF-pEF and the consequent varied and noncardiovascular causes of death in patients with this syndrome.

# PATHOPHYSIOLOGY

- Heterogeneous disorder with multiple pathophysiologic processes.
- Primary cardiac disorder of myocardial stiffening from hypertrophy and fibrosis, abnormal calcium handling, and even venous turgor.
- The renin-angiotensin-aldosterone system (RAAS) contributes to the fibrosis of hypertensive heart disease, and the stiff heart then requires increased pressure to fill the left ventricle to a normal end-diastolic volume.
- Abnormal ventricular-vascular coupling
- Sex-related differences in vascular function and LV remodeling
- Indirect evidence suggests that nitric oxide bioavailability may be important in modulating peripheral and pulmonary vascular tone and LV compliance, paving the way for phosphodiesterase-5 inhibition as a therapeutic target.

- Surprisingly, in contrast to the well-established role of neurohormonal activation in systolic HF, evidence supporting such a mechanism in HF-PEF is scarce.
- However, most clinicians think that neurohormonal antagonism, eg, RAAS and adrenergic blockers, is effective in HF-PEF despite a lack of evidence to support this paradigm.
- Importantly, the primary stimulus for salt and water retention in this condition is unclear.
- A unifying hypothesis for HF-PEF remains elusive and represents the primary challenge to finding effective therapies for HF-PEF.

# CLINICAL MANIFESTATIONS

- Clinical manifestations of heart failure with preserved ejection fraction (HFpEF) are the same as those for HF with reduced EF (HFrEF).
- Symptoms and signs include dyspnea (including dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea), fatigue, elevated jugular venous pressure, pulmonary rales, and lower extremity edema.

# Triggers for decompensated DHF

- Uncontrolled hypertension
- Increased salt and water intake and/or retention
- Tachyarrhythmias
- Ischemia
- Chronic kidney disease
- Anemia
- Chronic lung disease
- Infection

# TREATMENT

- The 2009 focused American College of Cardiology/American Heart Association HF update :
- (1) Aggressive control of systolic and diastolic HTN
- (2) Coronary revascularization in patient with CAD
- (3) Control of ventricular rate especially in the setting of atrial arrhythmias
- (4) Control of fluid overload with diuretics while being cautious with the dose because patients with HF-PEF may be sensitive to preload reduction, which could lead to hypotension.
- However, these recommendations were based primarily on consensus opinion.

# 2013 ACC/AHA HF guidelines for treatment of patients with HFpEF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B (28,247)
Diuretics should be used for relief of symptoms due to volume overload	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B (248)
Nutritional supplementation is not recommended in HFpEF	III: No Benefit	C

# Treatment trails

- Clinical trials evaluating the treatment of HFpEF have not yielded significant improvements in clinical outcomes.
- The PEP-CHF, CHARM-Preserved, and I-PRESERVE trials evaluated ACE inhibitors and ARBs in the management of HFpEF and identified no mortality reduction but fewer hospital admissions.
- In the OPTIMIZE-HF registry, beta-blockers were ineffective in reducing mortality or hospitalization in patients with HFpEF.
- Therefore, current guidelines offer no specific recommendations for treating patients with HFpEF, apart from the managing their symptoms, medical comorbidities, and cardiovascular risk.

# Aldosterone Antagonism

- Activation of the mineralocorticoid receptor system by aldosterone promotes hypertension, endothelial dysfunction, left ventricular hypertrophy, and myocardial fibrosis.
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers inhibit angiotensin II-mediated aldosterone release, but despite optimized therapy, a large proportion of patients with heart failure have elevated aldosterone plasma levels (aldosterone escape).
- Spironolactone has been shown to decrease extracellular matrix turnover and myocardial collagen content, mechanisms known to influence the progression of heart failure.

# Mottram study

- Mottram et al randomized 30 patients with treated HTN, EF greater than 50%, exertional dyspnea, and diastolic dysfunction to spironolactone or placebo for 6 months.
- Spironolactone treatment resulted in reduction in posterior wall thickness, long-axis strain rate, peak systolic strain, and cyclic variation of integrated back-scatter.
- The increase in strain was independent of changes in blood pressure in the spironolactone group.

# Improvement of exercise capacity

- Aldosterone plays an important role in the pathogenesis of vascular stiffening and endothelial dysfunction.
- A preliminary open label, non-placebo controlled study documented improvements in exercise capacity and the E/E' ratio in HFpEF patients treated with spironolactone, and aldosterone antagonists are currently being actively investigated for HFpEF in the USA and Europe.

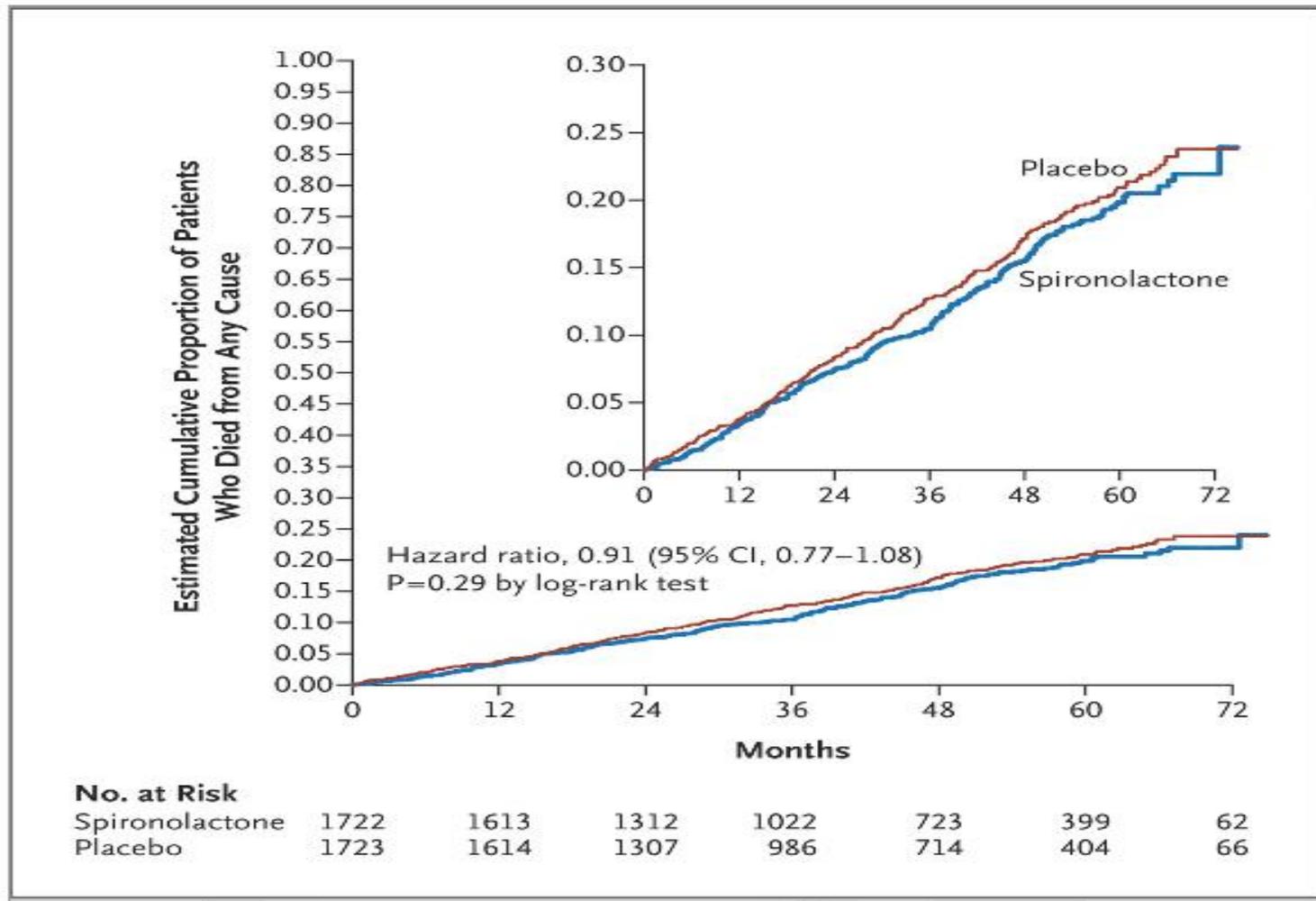
# Studies that are evaluate the role of aldosterone antagonism in HFpEF

- **TOPCAT.** Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist (TOPCAT) is an ongoing National Institutes of Health-sponsored, double-blind, randomized, placebo-controlled, multicenter, international trial.
- The trial randomly assigned 3445 patients with symptomatic HF and LVEF  $\geq 45$  percent to receive either spironolactone or placebo.
- The composite primary outcome consisted of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF.
- The mean follow-up was 3.3 years.

**Table 2.** Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.\*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI) <sup>†</sup>	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

# Kaplan–Meier Plot of Time to Death from Any Cause



- Subgroup analysis showed a significant reduction in the primary outcome with spironolactone among patients who were enrolled according to natriuretic peptide criteria but not among those enrolled on the basis of hospitalization for HF in the past year.
- Thus, for patients with clear evidence of HFpEF (including increased BNP) who can be carefully monitored for changes in serum potassium and renal function, better to add spironolactone therapy to their medical regimens.
- The serum potassium should be  $<5.0$  meq/L and estimated glomerular filtration rate should be  $\geq 30$  mL/min per  $1.73$  m<sup>2</sup>.

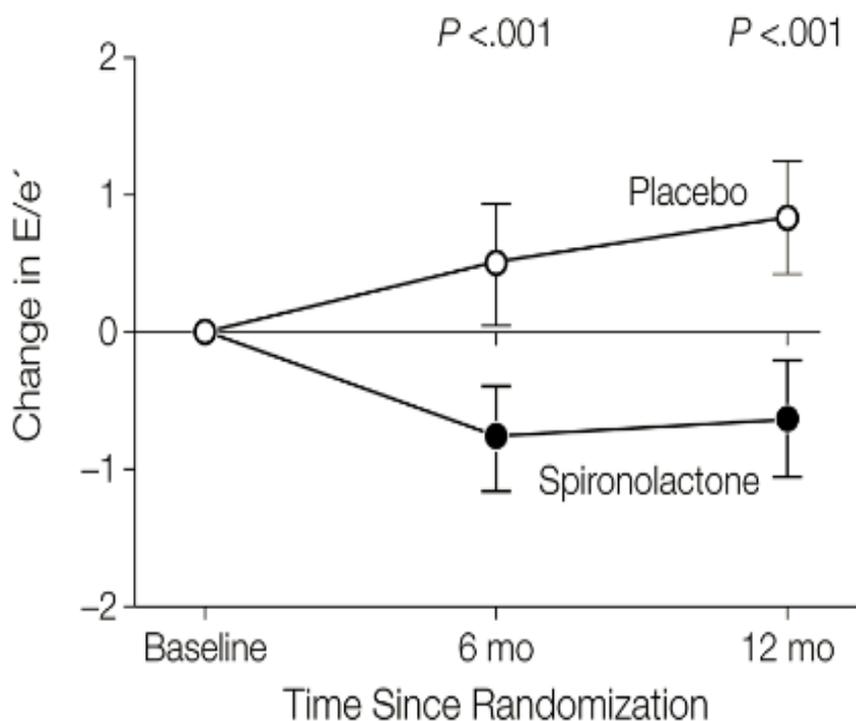
- Although the trial did not reach statistical significance for the primary endpoint, there were several interesting findings that point toward efficacy of MRA in HFPEF.
- First, there was a significant reduction in the secondary outcome of HF hospitalization among patients treated with MRAs.
- Second, participants enrolled in the trial based on elevated NT-ProBNP levels seemed to benefit significantly with use of MRAs.
- Finally, the recently published regional post-hoc analyses demonstrated significant clinical improvements among patients from the Americas.

# Aldo-DHF

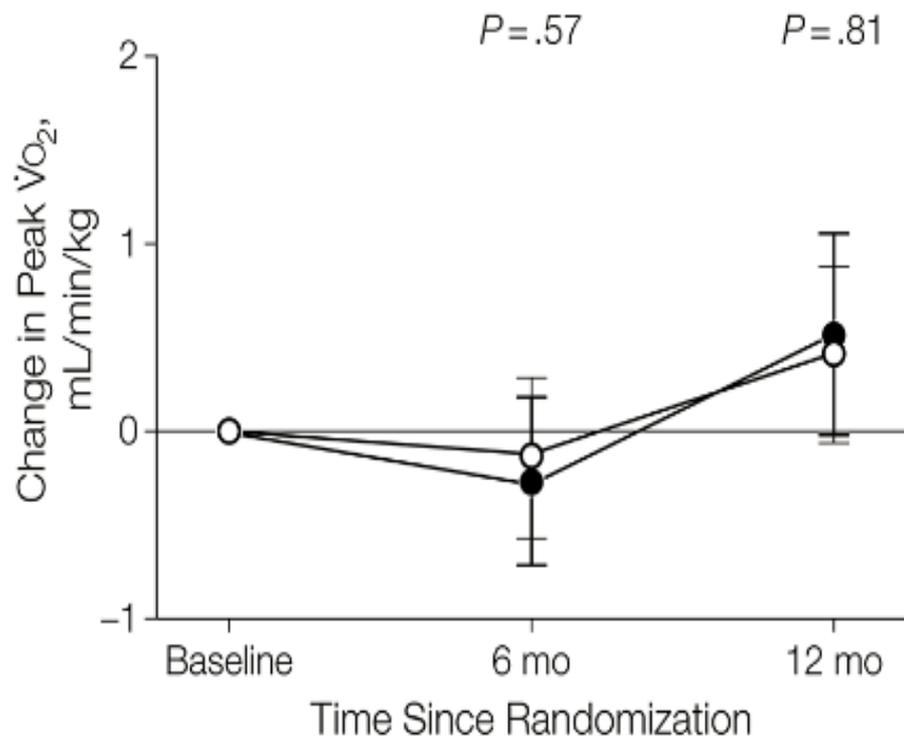
- A multicenter, prospective, randomised, double-blind, placebo-controlled trial conducted between March 2007 and April 2012.
- 422 ambulatory patients (mean age 67 years; 52% female) with **chronic NYHA class II or III HF**, a preserved **ejection fraction of 50% or greater**, and evidence of diastolic dysfunction, were random assigned to 25mg of spironolactone once daily or matching placebo.
- The primary endpoints were changes in diastolic function (E/e') on echocardiography and maximal exercise capacity (peak VO<sub>2</sub>) on cardiopulmonary exercise testing, both measured at 12 months.
- This study will look at secondary end points of quality of life and morbidity.

# Results

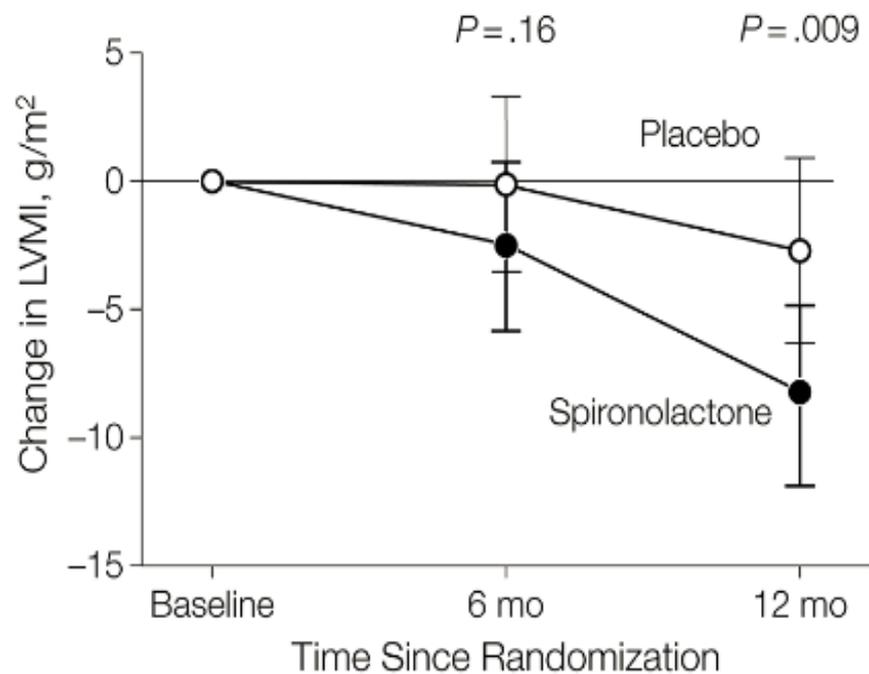
**A** E/e' medial velocity ratio



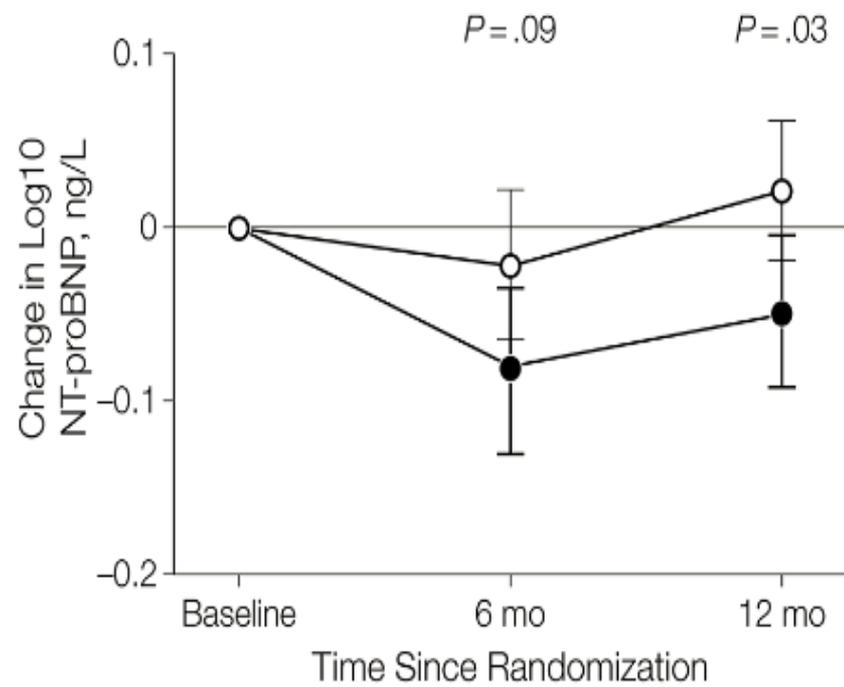
**B** Peak  $\dot{V}O_2$



**A** Left ventricular mass index



**B** Log<sub>10</sub> NT-proBNP



# CONCLUSIONS AND RELEVANCE

- In this randomized controlled trial, long-term aldosterone receptor blockade improved left ventricular end-diastolic filling, left ventricular remodeling, and neurohumoral activation, whereas maximal exercise capacity and quality-of-life measures remained unchanged.
- Whether the improved left ventricular function observed in the Aldo-DHF trial is of clinical significance requires further investigation in larger populations.

# Commentary on this study

- The beneficial effects of spironolactone on diastolic function were not associated with any clinical improvement.
- Study population in this study may have been too young or too healthy, or the treatment period may have been too short, for observing a translation of improved diastolic function into a clinical benefit.
- The low event rate in the Aldo-DHF trial may indicate that the study population likely represented early-stage HF with preserved EF, and longer follow-up may have been needed to fully evaluate the potential effects of spironolactone on symptomatic or clinical outcome end points.
- The neutral effect of spironolactone on peak  $\text{VO}_2$  and the small negative effect on 6-minute walking distance could possibly also be explained by a reduction in filling pressures.
- However, the known antiandrogenic action of spironolactone, with adverse effects on skeletal muscle function and strength independent of myocardial function and left ventricular remodeling, might also have contributed to the lack of symptomatic improvement in these patients.

# STRUCTURE trial

- The authors sought to identify improvement in exercise capacity with spironolactone in the subset of patients with HFpEF with exercise-induced increase in ratio between early mitral inflow velocity and mitral annular early diastolic velocity ( $E/e'$ ) reflecting elevation of left ventricular (LV) filling pressure.
- At follow-up, 131 patients completed therapy—64 taking spironolactone and 67 placebo.
- There was a significant interaction of spironolactone and change in  $E/e'$  on  $VO_2$  ( $p = 0.039$ ).
- The spironolactone arm also showed favorable changes in metabolic equivalents, exercise time, and respiratory exchange ratio at follow-up. There was no improvement in GLS.

# Clinical implications of this study

- The advantage of this study over previous trials was that the assessment of LV function was performed both at rest and immediately post-exercise.
- Selection of patients on the basis of exercise-induced increase in  $E/e'$  (suggesting the elevation of LVFP), might have helped to select the HFpEF subgroup that is most responsive to MRA.
- The clinical profile of the study population, with lower circulating BNP and lower incidence of emergency hospitalizations for HF, suggests a less severe stage of disease.

# Information from all spironolactone studies

- Therefore, in certain patients with poor diastolic function, symptom burden, and frequent hospitalizations, one could consider using spironolactone to reduce hospitalizations, with possible benefits of cardiac remodeling, and reducing cardiovascular death and cardiac arrest.
- Adverse events were prevalent across both trials including hyperkalemia and worsening renal function, but not dialysis, highlighting the importance of routine follow-up and regular bloodwork after initiating spironolactone.
- Eplerenone may be considered in patients developing significant gynecomastia after the initiation of spironolactone.

Effect of Mineralocorticoid Receptor Antagonists on Cardiac Structure and Function in Patients With Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: A Meta-Analysis and Systematic Review- [J Am Heart Assoc](#). 2015 Oct

- MRA therapy in patients with asymptomatic diastolic dysfunction or HFPEF is associated with significant improvement in diastolic function and markers of cardiac fibrosis without a significant change in LV mass or dimensions.

# STUDIES with EPLERENONE

- In one study of 44 patients with HF-PEF, therapy with eplerenone, an aldosterone antagonist, was associated with attenuation of myocardial fibrosis and improvement of diastolic function at 12 months but had no effect on clinical variables or brain natriuretic peptide.
- In another study of 44 HF-PEF patients, eplerenone similarly improved myocardial fibrosis and diastolic function but had no effect on exercise capacity

# Future directions

- Additional trials with rigorous enrollment criteria and follow-up will be needed to further evaluate if MRAs can reduce mortality in patients with heart failure with preserved ejection fraction.
- Future studies on heart failure with a preserved ejection fraction should include markers of ventricular fibrosis and remodeling such as galectin-3 and growth differentiation factor 15 to identify patients who may benefit from spironolactone treatment.

# Take home message

- The pathophysiology of HFpEF is not completely understood
- The terms 'diastolic dysfunction' and 'HFpEF' are not synonymous.
- Further work is required to define patients with HFpEF more precisely, and it may well be that there are several different groups of patients in this group, who require different treatment strategies.
- The data from the Aldo-DHF trial including fall in BNP, and improvement in echocardiographic parameters provide some support for the continued use of spironolactone in HFpEF patients
- Beyond this, it is difficult to recommend more widespread use of spironolactone in HFpEF, but further studies could certainly be justified.