PHARMACOTHERAPY IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Incidence: 600,000-700,000 new HF cases annually in US
  - HFpEF occurs in 40-60% of newly diagnosed HF cases
Healthcare expenditure: $40 billion on HF in 2010
  - Center for Medicare and Medicaid Services reimbursement
Annual mortality: 5-30%

- Circulation 2011;123:e18-209.
## Types of Heart failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction (EF)</th>
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<tbody>
<tr>
<td>Heart failure with reduced ejection fraction (HFrEF)</td>
<td>≤ 40%</td>
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<tr>
<td>• Formerly referred to as systolic heart failure</td>
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<tr>
<td>Heart failure with preserved ejection fraction (HFpEF)</td>
<td>≥ 50%</td>
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<td>• Formerly referred to as diastolic heart failure</td>
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<td>HFpEF borderline</td>
<td>41-49%</td>
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<td>HFpEF improved (patients with a history of HFrEF)</td>
<td>&gt; 40%</td>
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*Source: Circulation 2013;128:e240-327.*
HFpEF pathophysiology

Ventricular hypertrophy

Inflammation

Impaired cardiac relaxation

LV

Neurohormones
HFpEF Treatment options

- **Non-pharmacologic**
  - Sodium and fluid restriction
  - Regular exercise
  - Weight loss

- **Pharmacologic**
  - Diuretics
  - ACE inhibitors/ARBs
  - Aldosterone antagonists
  - β-blockers
  - Calcium channel blockers
  - Digoxin
  - Statins
Loop Diuretics

- Benefit in HFpEF
  - Inhibition of sodium/fluid reabsorption results in a reduction in total fluid volume lessening volume overload symptoms

- Useful in prevention and management of acute volume overload

- Use only in small doses with caution

- Avoid large volume depletion.

HFpEF patients (EF > 45%) were randomized to diuretic alone or in combination with an ACE inhibitor or ARB.

Slight reduction in LV filling pressures with ACE inhibitor/ARB.

QOL scores improved by nearly 50% in each treatment group.

Conclusion: No clinical benefit of adding an ACE inhibitor or ARB to diuretic therapy in patients with HFpEF.

Heart 2008;94:573-80.
Thiazide Diuretics

- Proposed benefits in HFpEF
  - Inhibition of sodium/fluid reabsorption results in a reduction of blood pressure and left ventricular pressure
  - Prevention of HFpEF in hypertensive patients
- Thiazide diuretics have minimal benefit for the management of volume overload symptoms
Thiazide Diuretics

- Thiazide diuretics are a viable first line therapy for hypertension management to reduce the risk of HFpEF
- (ALLHAT subanalysis)
Diuretics in HFpEF

- No mortality benefit of diuretics
- Loop diuretics useful in relieving HF symptoms
- Thiazide diuretics may reduce the risk of HFpEF
- Heart failure guidelines
  - Management of volume overload symptoms
  - Therapeutic option for control of hypertension

Eur Heart J 2012;33:1787-1847.
ACE Inhibitors AND ARBs

- Inhibition of AngII reduces vascular resistance decreasing blood pressure
- Prevent cardiac remodeling and myocardial hypertrophy
- Manage co-morbidities in HFrEF (diabetes, CAD, CKD)

- Efficacy data in HFrEF
  - Conflicting data with variability in study design
  - Few large prospective randomized controlled trials

Eur Heart J 2006;27:2338-45.
MAJOR TRIALS

- CHARM PRESERVE
- PEP-CHF
- I-PRESERVE
PEP-CHF trial

- Perindopril compared to placebo in 850 symptomatic HFpEF patients (EF > 40%)
- Non-significant difference in mortality or HF hospitalizations with perindopril (23.6% vs 25.1%)
- Perindopril significantly improved symptoms and exercise capacity
- Conclusion: ACE inhibitor improved HFpEF symptoms but had no reduction in mortality or HF hospitalizations

Eur Heart J 2006;27:2338-45.
CHARM-preserved

- Candesartan compared to placebo in 3,023 symptomatic HFpEF patients (EF > 40%)

- Significant decrease in HF hospitalizations with ARB (15% vs. 18%)

- No difference in mortality (11% for each treatment)

- Conclusion: No mortality benefit with use of an ARB in HFpEF but mild impact in preventing HF hospitalization
Symptomatic HFpEF patients (EF > 45%) who were > 60 years were randomized to irbesartan or placebo (N = 4,128)

No difference in composite primary endpoint of death or cardiovascular hospitalization between groups (36% vs. 37%)

Conclusion: No benefit of an ARB in HFpEF

ACE inhibitors/ARBs in HFpEF

- No mortality benefit in HFpEF from prospective trials
- Utility in HFpEF driven by co-morbidities (diabetes, CAD, CKD)
- Heart failure guidelines
  - First line medication for hypertension management in HFpEF
  - ARBs may be considered to decrease hospitalization
  - Use if compelling co-morbidities

- Manage co-morbidities in HFpEF (diabetes, CAD, CKD)

Eur Heart J 2012;33:1787-1847.
Aldosterone antagonists

- Proposed benefits in HFpEF
  - Inhibit sodium/fluid reabsorption
  - Prevent cardiac remodeling and myocardial hypertrophy
  - Affect myocardial fibrosis

- Efficacy data in HFpEF
  - Small trials have illustrated improvement in HF symptoms and exercise capacity along with improved left ventricular function

J Am Coll Cardiol 2009;54:1674-82.
Symptomatic HFpEF patients (EF > 45%) were randomized to spironolactone or placebo (N = 3,445)

No difference in composite outcome of CV death, aborted cardiac arrest, or HF hospitalization (8.6% vs. 20.4%)

- Spironolactone did significantly reduce hospitalizations (12% vs. 14%)

Conclusion: Mild benefit of spironolactone in HFpEF
**β-Blockers**

- Proposed benefits in HFP EF
  - Decrease chronotropy
    - Decrease myocardial oxygen demand
    - Increase left ventricular filling time
  - Efficacy data in HFP EF
    - Small trials have demonstrated improvement of HF symptoms and left ventricular function with one study demonstrating mortality benefit

Compared nebivolol to placebo in patients > 70 years with an EF > 35% (N = 752)

No significant difference for the composite primary endpoint of mortality and HF hospitalization (29% vs. 33%)

Conclusion: No benefit of β-blockers in HFpEF

Authors stated benefit undetermined in HFpEF as the study was not designed to detect a difference

β-Blockers in HFpEF

- Mortality benefit?
- Useful for patients with atrial fibrillation or a history of coronary artery disease
- Heart failure guidelines
  - First line medication for hypertension management in HFpEF
  - Management of atrial fibrillation

Eur Heart J 2012;33:1787-1847.
Calcium channel blockers

- Non-DHPs: diltiazem, verapamil

- Proposed benefits in HFpEF
  - Decrease chronotropy
  - Decrease inotropy

- Efficacy data in HFpEF
  - Two studies showed enhanced ventricular relaxation and filling

Digoxin

- Proposed benefits in HFpEF
  - Decrease chronotropy

- Efficacy data in HFpEF
  - Conflicting results from post-hoc analyses of DIG study

- Heart failure guidelines
  - No specific recommendations for digoxin in HFpEF, but could be used in patients atrial fibrillation

Eur Heart J 2006;27(2):178-86.
Am J Cardiol 2008;102:1681-6.
Eur Heart J 2012;33:1787-1847.
Statins

- Proposed benefits in HFpEF
  - Prevent cardiac remodeling and myocardial hypertrophy
  - Pleiotropic effects including benefits for endothelial function and inflammation
- Efficacy data in HFpEF
  - Retrospective claims data studies support mortality benefit of statins
  - Limited prospective trials support potential benefit in HFpEF

Circulation 2005;112:357-63.
Am J Cardiol 2014;113:1198-1204.
Investigational therapies in HFpEF

Sildenafil
- Inhibits of cardiac remodeling

Ranolazine
- Improves myocardial relaxation

Alegabrium
- Prevents excessive myocardial cross-linking

# Treatment of HFpEF

<table>
<thead>
<tr>
<th>HFpEF Characteristic</th>
<th>Treatment Recommendations</th>
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<tr>
<td>Volume overload symptoms</td>
<td>Diuretic</td>
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<tr>
<td>Hypertension</td>
<td>ACE inhibitor, ARB, β-blocker</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>β-blocker, non-DHP CCB, digoxin, amiodarone</td>
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<tr>
<td>Diabetes/CKD</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>ACE inhibitor or ARB + β-blocker</td>
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Newer therapeutic options

- CRT
- Non Invasive ventilation in OSA
- ICDs
- Inter Atrial shunt devices
From: Developing Therapies for Heart Failure With Preserved Ejection Fraction: Current State and Future Directions


Potential Therapeutic Targets in HFpEF
HFpEF = heart failure with preserved ejection fraction.

Figure Legend:
SUMMARY

- Patho physiology of HFpEF still not understood clearly
- No drug has shown to reduce mortality compared to HFrEF
- Treatment of Coexisting comorbid conditions extremely important
- Currently used drugs are the ones used in HFrEF also.
- Newer approaches needed to reduce mortality in HFpEF in view of the large patient population at risk.