Diastolic Heart Failure or Heart Failure with Preserved Ejection Fraction

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Diastolic Heart Failure Risk Factors

Common Risk Factors
- Aging
- Female gender
- Obesity
- Hypertension
- Diabetes mellitus
- Coronary artery disease
- Chronic kidney disease
- Aortic stenosis

Uncommon Risk Factors
- Myocardial disorders
- Amyloidosis
- Sarcoidosis
- Fatty infiltration
- Idiopathic cardiomyopathy
- Hypertrophic cardiomyopathy
- Hyperesinophilic syndrome
- Hemosiderosis
- Glycogen storage disease
- Pericardial disorders
- Constrictive pericarditis
- Effusive-constrictive pericarditis
- Pericardial effusion

Ejection Fraction in Patients With Chronic Heart Failure

Cardiovascular Health Study (CHS), n=4842

<table>
<thead>
<tr>
<th></th>
<th>Normal (≥ 55%)</th>
<th>Mildly Reduced (45% - 54%)</th>
<th>Moderately (30-44%) or Severe reduced (&lt; 30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>18%</td>
<td>42%</td>
<td>47%</td>
</tr>
<tr>
<td>Men</td>
<td>31%</td>
<td>27%</td>
<td>42%</td>
</tr>
</tbody>
</table>
Overall Survival by EF Following HF Hospitalization

2802 pts with CHF, EF assessment Ontario Province 1999-2001
Mortality: EF<40% vs. EF>50%
30 days 7% vs. 5% (p=0.08)
1 year 26% vs. 22% (p=0.07)
HR 1.13 (0.94-1.36) p=0.18

Heart Failure with preserved Ejection Fraction (HFpEF)

Four main points:
Why HFpEF? What happened to DHF
Diagnosis
Prevention: The best option
Management:
Pharmacology
Monitoring/Surveillance
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Mechanisms of HFpEF

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Heart Failure with preserved Ejection Fraction (HFpEF)

**Diagnosis**

Three Obligatory Conditions for HFpEF:

1. Signs or Symptoms of congestive heart failure
2. Normal or mildly abnormal systolic left ventricular function (LVEF >50%)
3. Evidence of diastolic LV dysfunction

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How to diagnose HFpEF:

- Presence of signs or symptoms
- Normal or mildly abnormal systolic function (LVEF >50%)
- Evidence of diastolic LV dysfunction

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**Heart Failure with preserved Ejection Fraction (HFpEF)**

**Prevention**

- Blood pressure control
  - HTN is a major RF for both HFrEF and HFpEF
  - BP treatment reduces risk of incident HF by approximately 50%
  - NNT 52 to 125 (SPRINT) trial to prevent one HF event
    - 150 doctors with patient panels of 2,000 to 3,000
      - (Conservatively 200 patients each (30% prevalence of HTN) at high risk of developing CHF?)
    - 30,000 patients at risk
    - Could collectively prevent:
      - 240 new cases of HF (NNT 125)
      - 577 new cases of HF (NNT 52)
    - And that’s just treatment of HTN!

**HOPE - Secondary and Other Endpoint Results**

![Graph showing HOPE results](image-url)

- 16% Risk Reduction (p<0.05)
- 12% Risk Reduction (p<0.05)
- 11.7% Risk Reduction (p<0.05)
- 7.4% Risk Reduction (p<0.05)
- 6.2% Risk Reduction (p<0.05)
- 3.3% Risk Reduction (p<0.05)
- 2.1% Risk Reduction (p<0.05)
- 3.7% Risk Reduction (p<0.05)
- 5.3% Risk Reduction (p<0.05)

- Complications
- Hospitalization
- New diagnosis of diabetes mellitus
- HF hospitalization
Role of Diuretics in the Prevention of Heart Failure

- ALLHAT study of 33,357 high-risk hypertensive patients >55 years
- Excluded patients with history of HF
- HF occurred in 1773 patients over 4.9 years of follow-up
- Over the first year, chlorthalidone was significantly more effective at prevention of HF than amlodipine and lisinopril
- After the first year, chlorthalidone was more effective at prevention of HF than amlodipine but not different than lisinopril

Davis, et al., Circulation. 2006;113:2201-2210.

SPRINT trial: Intensive BP control associated with a 38% reduction in HF incidence

Heart Failure with preserved Ejection Fraction (HFpEF) Prevention

- Treatment of dyslipidemia and vascular risk
- Obesity and diabetes mellitus
Cardiovascular and noncardiac risk factors to the development and progression of PDD and HFpEF. Both cardiovascular and noncardiovascular risk factors contribute to the development of preclinical diastolic dysfunction (PDD, Stage 0). Both cardiovascular and noncardiovascular risk factors contribute to the progression from PDD to symptomatic heart failure with preserved ejection fraction (HFpEF, Stage 1). Beneath these stages, disease severity increases, and treatment becomes necessary in a timely manner.
Heart Failure with preserved Ejection Fraction (HFpEF)

Four main points:
- Why HFpEF? What happened to DHF Diagnosis
- Prevention: The best option
- Management:
  - Pharmacologic Monitoring/Surveillance

HFpEF Therapies with little efficacy in HFpEF

Aldosterone Antagonists
TOPCAT trial
Heart Failure with preserved EF
Guideline Directed Medical Therapy

2013 ACCF/AHA Guidelines for Management of Heart Failure

HFpEF Therapy

No approved pharmacologic therapies to reduce hospitalization or mortality for HFpEF
Guideline-directed management is limited to diuretics and treatment of comorbidities
ACE-Is and ARBs not effective in reducing mortality
Beta-blockers have not shown benefits
Spironolactone improves DD and LVH, but not clinical outcomes
Exercise training in HFpEF improves symptoms and QOL
CardioMEMS PA pressure monitoring reduces hospitalization

HFpEF Therapy

"Considering its prevalence and outcomes, future projections, and lack of effective therapies, HFpEF represents the single largest unmet need in cardiovascular medicine."

--Developing Therapies for Heart Failure with Preserved Ejection Fraction: Current State and Future Directions
J Am CollCardiolHF 2014;1:197–112
New Management Strategies for HFpEF

I.) Drug Therapy
   A. PARAGON-HF – Entresto

II.) Surveillance
   A. CardioMEMS
   B. SMILE – lung fluid status monitoring
   C. Cardiospire

LCZ696 Angiotensin Receptor Neprilysin Inhibitor (ARNI)

LCZ696 is a new compound with a complex molecular structure.

1. LCZ696 is the first in a new class of compounds called angiotensin receptor neprilysin inhibitors (ARNIs).

Molecular structure of LCZ696:

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LCZ696 Enhances the Beneficial Effects of the Endogenous NP System while Simultaneously Blocking the RAAS
Restoring the Neurohormonal Balance in HF

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LCZ696 vs Enalapril (High dose) for Heart Failure (EF=35) Endpoint - Death or HF Hospitalization

N = 8458
PARAMOUNT-HF

LCZ696 Entresto vs Valsartan
For Diastolic Heart Failure

PARAMOUNT Trial

NT-ProBNP at 4, 12 and 36 weeks

Week 4  Week 12  Week 36

Weeks post randomization

P = 0.003  LCZ696 vs. valsartan

Paramount Trial

Long-term evaluation of left atrial size and over 36 weeks

12 weeks  36 weeks

P = 0.18  P = 0.003
**PARAMOUNT Trial**

**Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=89)</th>
<th>valsartan (n=87)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Any adverse event</td>
<td>52 (58)</td>
<td>50 (57)</td>
<td>0.52</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>91 (64)</td>
<td>111 (73)</td>
<td>0.14</td>
</tr>
<tr>
<td>Adverse events of interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (3)</td>
<td>5 (5)</td>
<td>0.54</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2 (2)</td>
<td>9 (9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>12 (13)</td>
<td>9 (9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>15 (10)</td>
<td>17 (11)</td>
<td>0.90</td>
</tr>
<tr>
<td>Abnormal laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decrease &gt; 10 g/dL</td>
<td>3 (3)</td>
<td>4 (4)</td>
<td>0.97</td>
</tr>
<tr>
<td>SBP decrease &gt; 10 mmHg</td>
<td>3 (3)</td>
<td>4 (4)</td>
<td>0.98</td>
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LCZ696 was well tolerated – the number of patients with hypotension, renal dysfunction or hyperkalemia did not differ between groups.

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**PARAGON-HF**

- Large outcomes trial of LCZ696 (Entresto) in HFpEF
- Enroll 4,300 patients
- LVEF ≥ 45%
- History of HF hospitalization within 9 months or elevated NPs
- Evidence of structural heart disease (LVH or LA enlargement)
- Primary endpoint: composite of CV death or total HF hospitalizations

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**CardioMEMS**

About 22% of patients in CHAMPIONS had EF>40%
A Novel Approach to Monitoring Pulmonary Congestion in Heart Failure: Initial Animal and Clinical Experiences Using Remote Dielectric Sensing Technology

- Remote Dielectric Sensing (ReDS) technology measures the dielectric properties of tissues.
- Low power electromagnetic signals are emitted into the body, and the intercepted signals reflect the dielectric properties of tissues, which reflect fluid content of the lungs.
- Transmitter/Sensors are attached to anterior and posterior chest.
- Dielectric coefficients used to determine water content of the lungs.
- Received FDA 510K clearance.

Remote Dielectric Sensing Technology: Sensible Medical Innovations

- SMILE study
  - Prospective, randomized, controlled, multicenter trial
  - Patients enrolled during an index hospitalization for ADHF
  - Patients selected to PEO5 values
  - Diagnosis of HF, with preserved or reduced LVEF
  - Hospitalized for ADHF
  - Primary outcome: rate of recurrent HF admissions (3-9 months)

Cardiospire Device (Respirx)

- Non-invasive device
- Detects minor, cyclic waveforms caused by cardiac pulses, or cardiogenic oscillations (COS) during the measurements of inspiration and expiration.
- Amplitude of COS is directly affected by pulmonary blood flow, and correlated to the pulmonary artery compliance (PAC).
- PAC amplitude are directly proportional to CO and inversely proportional to pulmonary artery pressure.
- Preclinical testing demonstrated that the PAC had an excellent inverse correlation to PA pressures.
- Current study purpose is to assess correlation between noninvasive PA compliance and PA pressure measured by the cardioMEMS device.
- Available to patients who have a cardioMEMS device currently.