Management of Heart Failure with Mid-range Ejection Fraction, HFmEF

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Definitions of heart failure

- HFrEF: LVEF ≤ 40% (Systolic HF)
- HFrEF: LVEF ≥ 50% (Diastolic HF)

Importance of Knowing Systolic Function

Systolic dysfunction
- Well studied
- Definite therapeutic recommendations

Diastolic dysfunction
- Poorly studied
- Generalizations:
  - Avoid tachycardia/arrhythmia
  - Treat ischemia
  - Control BP
  - Treat fluid

UPDATE: Evidence-Based Medical Therapy of HFrEF

Control Volume
- Reduce Mortality
  - Diuretics
  - Sodium restriction
  - Fluid restriction
  - Hydralazine/Isosorbide dinitrate
  - Can start inpatient
  - Digoxin
  - With/without ACE
  - Aldosterone* Antagonist
  - SGLT2i

With indicated patients

Definitions of heart failure

- HFrEF: LVEF ≤ 40%; (Systolic HF)
- HFmEF: LVEF 41-49%; (Mid-range HF)
- HFrEF: LVEF ≥ 50%; (Diastolic HF)
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**Should HFmEF Be Treated Differently?**

- Patients with HFmEF have reduced contractile function based on myocardial strain imaging.
- Randomized trials of RAAS inhibition in HF patients with LVEF >40-45% have failed to show clear overall benefit.
  - Post-hoc analyses have suggested potential benefit in HFmEF.
- Limitations in LVEF assessment
  - Inter-reader variability
  - Dependence of loading conditions
  - Valvular disease

**Spironolactone May Be Beneficial in HFmEF**

- Data from TOPCAT
  - LVEF ≥ 45%, HF hospitalization in prior year or elevated BNP or NTproBNP, signs/symptoms of HF
  - Spironolactone vs. placebo
  - Mean f/u 3.4 years
- Divided patients into LVEF groups:
  - 45-50%, 50-54.9%, >60%
- Primary outcome: composite of CV death, aborted cardiac arrest, or hospitalization for HF

**HFmEF Is Phenotypically Different From HFpEF**

- Those with lower LVEF were:
  - Younger
  - More likely to be male
  - More likely to have had a history of MI
  - Less likely to have a history of HTN, DM
  - Have slightly lower HR and BMI
  - Less likely to have been on ACE-I/ARB, diuretic

**Candesartan May Be Beneficial in HFmEF**

- Data from CHARMA
  - 7599 patients with symptomatic HF randomized to candesartan vs. placebo in:
    - CHARMA-Added (LVEF ≤40% treated with ACE-I, n = 2548)
    - CHARMA-Alternative (LVEF ≤40% intolerant to ACE-I, n=2028)
    - CHARMA-Preserved (LVEF >40%, 19% treated concomitantly with ACE-I)
- Divided patients into 3 groups:
  - 57% were HFrEF (LVEF <40%)
  - 17% were HFmEF (LVEF 40-49%)
  - 26% were HFpEF (LVEF ≥ 50%)
- Primary outcome: time to CV death or first HF hospitalization
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Characteristics of HFmEF Were Mixed

- HFmEF were similar to HFrEF with respect to:
  - Age, SBP, % women, previous MI, atrial fibrillation
- HFmEF was between HFpEF and HFrEF with respect to:
  - H/o HTN, distribution of NYHA class, BMI
- Rates of first HF hospitalization, CV death, all-cause death were similar in patients with HFmEF and HFpEF
  - And considerably lower than HFrEF

Primary Outcome: Time to CV Death or 1st HF Hospitalization

Candesartan Was Beneficial in HFrEF and HFmEF

What Do the Data from TOPCAT and CHARM Tell Us?

- Plausibility
  - HFmEF has different patient and outcome characteristics than HFpEF and HFrEF
  - Straddles either phenotype, sometimes one more than the other depending on clinical circumstances or patients studied
  - Usually have better outcomes than HFrEF

- Hypothesis generating
  - Treatments that are beneficial in HFrEF may be beneficial in HFmEF

Sacubitril/Valsartan in HF

- PARADIGM-HF
  - LVEF ≤40%, n=8399
  - Sacubitril/valsartan vs. enalapril in stable HFrEF

- PARAGON-HF
  - LVEF ≥ 45%, n=4796
  - Sacubitril/valsartan vs. losartan in stable HFpEF
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**PARADIGM-HF Study Design**
Randomization (n=8399, EF <35-40%, stable ACE/ARB/BB)
- Single-blind run-in period
- Double-blind period
  - (1:1 randomisation)
  - Enalapril 10 mg BID
  - LCZ696 200 mg BID
  - Enalapril 10 mg BID

*NNT = 21

**Effect of ARB vs placebo derived from CHARM-Alternative trial**

**Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial**

**Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial**

**Sacubitril/Valsartan and Effects on CV Death (Component of Primary Outcome)**

**PARAGON-HF Study Design**
Randomization (n=4822, EF ≥ 45%, structural heart disease)
- Single-blind run-in period
- Double-blind period
  - Sacubitril/valsartan 97/103 mg BID
  - Valsartan 160 mg BID

*Slide courtesy of Dr. Milton Packer*

P=0.06**
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Sacubitril/Valsartan in HFmEF?

Sacubitril/Valsartan Across the Spectrum of EF in HF

Divided into LVEF groups
- >22.5‐32.5%
- >32.5‐42.5%
- >42.5‐52.5%
- >52.5‐62.5%
- >52.5%

Outcomes
- First occurrence of CV death or HF hospitalisation
- CV death
- First occurrence of HF hospitalisation
- All-cause mortality

Benefit with Sacubitril/Valsartan for All Outcomes in the Pooled Cohort

Rates of primary outcome, HF hospitalisation, CV death, and all-cause mortality decrease with increasing LVEF.
- Rate of decline greatest in CV death
- Less apparent decline in HF hospitalisation
- Non-CV death was similar across LVEF, such that proportion of deaths that were non-CV increased with increasing LVEF.
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- **Women Derived Benefit With Sacubitril/Valsartan to a Higher LVEF**
  - Total HF Hospitalization and CV Death
  - Patients with LVEF less than “normal” (including HFmEF), may benefit from sacubitril/valsartan compared with RAS inhibition.
  - Women may have this benefit in a higher range of LVEF than men.
  - Because of the interrelationship between LVEF and sex, it is impossible to define a single LVEF cut-point which identifies both men and women likely to respond to sacubitril/valsartan.

- **Sacubitril/Valsartan Across the Spectrum of EF in HF**
  - Women Had Better Outcomes with Sacubitril/Valsartan
  - Characteristics of Women with Heart Failure
    - Among patients with HF, women are less likely to have LVEF ≤ 40%.
    - Women represent 25% of HFrEF, but >50% of HFpEF/HFmEF.
    - There is a greater HF therapeutic deficit for women compared with men.
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**Biologic Plausibility**
- LVEF range is higher in women than men
  - Reflects sex-related differences in cardiac remodeling
  - For a given LVEF, more women may have other evidence of contractile dysfunction
- Age-related arterial stiffening is more pronounced in women than in men, which may be a key pathophysiologic factor in HFpEF
- Natriuretic peptides are lower in women despite higher filling pressures
  - May be due to more visceral adiposity
  - May be due to cross-talk between sex hormones and natriuretic peptides, possibly leading to a decrease in natriuretic peptide levels after menopause
  - Thus, by augmenting natriuretic peptides, sacubitril-valsalan may have greater benefit in women

**Conclusions**
- HFmEF is likely a phenotype different from HFpEF and HFrEF.
  - Could be transitional
  - Patients with restrictive, infiltrative, hypertrophic CM have not been included in these studies.
- Treatment should be based on the patient as a whole with emphasis on the underlying etiology.
- Post-hoc analyses are inadequate to define thresholds and subsets of patients who may benefit from therapies.
- Future prospective randomized trials in women and HFmEF may help answer questions about treatment in these populations.