

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

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Disclosures

- None

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Definitions of heart failure

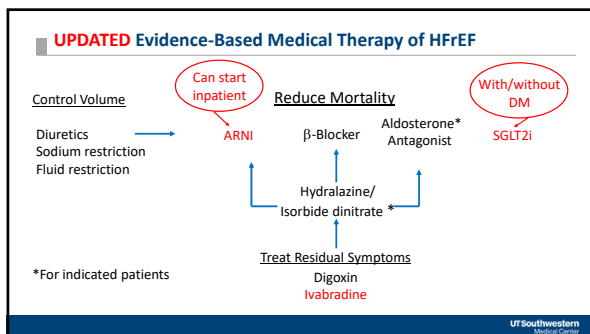
- HFrEF: LVEF \leq 40% (Systolic HF)
- HFpEF: LVEF \geq 50% (Diastolic HF)

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Importance of Knowing Systolic Function

<p>Systolic dysfunction</p> <ul style="list-style-type: none"> • Well studied • Definite therapeutic recommendations 	<p>Diastolic dysfunction</p> <ul style="list-style-type: none"> • Poorly studied • Generalizations <ul style="list-style-type: none"> – Avoid tachycardia/arrhythmia – Treat ischemia – Control BP – Treat fluid
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Definitions of heart failure

- HFrEF: LVEF \leq 40%; (Systolic HF)
- HFmEF: LVEF 41-49% (Mid-range HF)
- HFpEF: LVEF \geq 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

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Spirolactone May Be Beneficial in HFmEF

- Data from TOPCAT
 - LVEF \geq 45%, HF hospitalization in prior year or elevated BNP or NTproBNP, signs/symptoms of HF
 - Spirolactone 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

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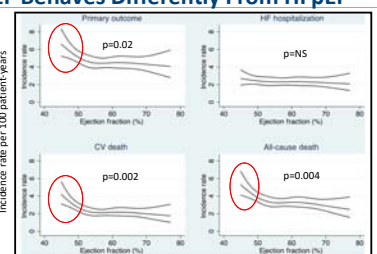
HFmEF Is Phenotypically Different From HFpEF

- 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

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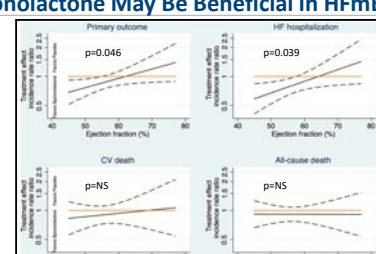
HFmEF Behaves Differently From HFpEF



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Spirolactone May Be Beneficial in HFmEF



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Candesartan May Be Beneficial in HFmEF

- Data from CHARM
 - 7599 patients with symptomatic HF randomized to candesartan vs. placebo in:
 - CHARM-Added (LVEF \leq 40% treated with ACE-I, n = 2548)
 - CHARM-Alternative (LVEF \leq 40% intolerant to ACE-I, n=2028)
 - CHARM-Preserved (LVEF >40%, 19% treated concomitantly with ACE-I)
- Divided patients into 3 groups:
 - 57% were HFpEF (LVEF <40%)
 - 17% were HFmEF (LVEF 40-49%)
 - 26% were HFpEF (LVEF \geq 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

Lund LH et al. Eur J Heart Fail. 2018;20:1230-39

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

Lund LH et al. Eur J Heart Fail. 2018;20:1230-39

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

HFmEF: HR 0.76 (0.61-0.96) P=0.02

Number at risk	0	1	2	3
Placebo	655	568	522	320
Candesartan	667	608	559	349

Lund LH et al. Eur J Heart Fail. 2018;20:1230-39

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Candesartan Was Beneficial in HFrEF and HFmEF

Lund LH et al. Eur J Heart Fail. 2018;20:1230-39

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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

Drazner et al. Circ Heart Fail. 2008;1:170-7

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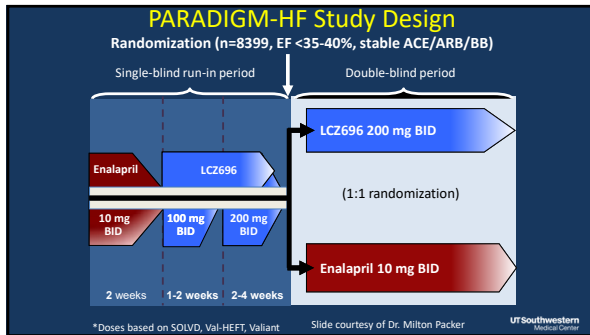
Sacubitril/Valsartan in HF

- 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

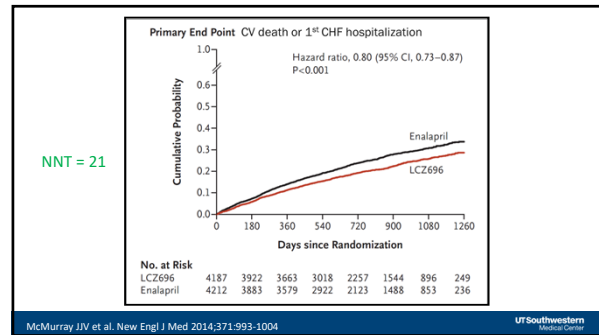
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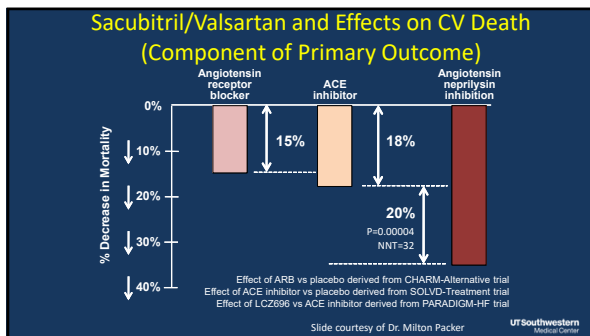
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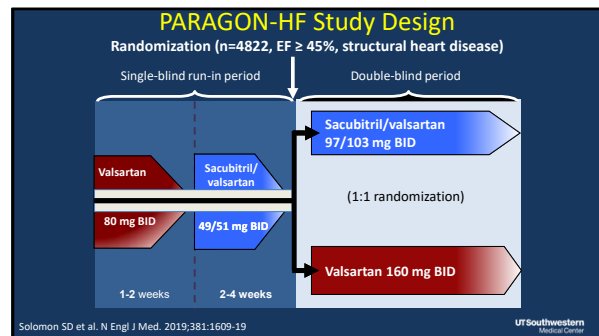
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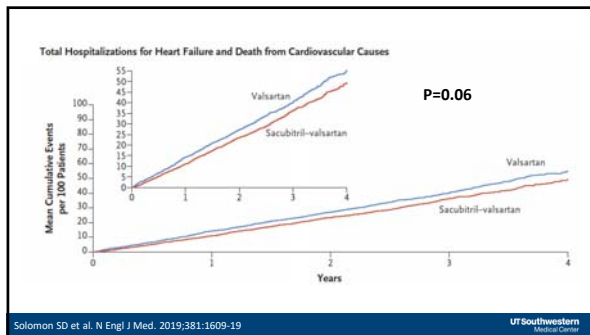
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Sacubitril/Valsartan in HFmEF?



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Circulation

ORIGINAL RESEARCH ARTICLE

Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure

Editorial, see p 362

BACKGROUND: While disease-modifying therapies exist for heart failure (HF) with reduced left ventricular ejection fraction (LVEF), few options are available for patients in the higher range of LVEF (>40%). Sacubitril/valsartan has been compared with a renin-angiotensin-aldosterone-system inhibitor alone in 2 similarly designed clinical trials of patients with reduced and preserved LVEF, permitting examination of its effects across the full spectrum of LVEF.

METHODS: We combined data from PARADIGM-HF (LVEF eligibility <40%, n=8399) and PARADIGM-PHF (LVEF eligibility >45%, n=4790) in a prespecified pooled analysis. We divided randomized patients into LVEF categories: <22.5% (n=1268); >22.5% to <32.5% (n=3987); >32.5% to <42.5% (n=3143); >42.5% to <52.5% (n=1423); >52.5% to <62.5% (n=3766); and >62.5% (n=3222). We assessed...

Scott O. Solomon, MD | Muthiah Vaduganathan, MD, MPH | Brian L. Claggett, PhD | Milton Packer, MD | Michael Sliwa, MD | Karl Swedberg, MD | Jean Rouleau, MD | Marc A. Pfeffer, MD, PhD | Akhlay Desai, MD | Lars H. Lund, MD, PhD | Lars Køber, MD | Indar Anand, MD | Nancy Sweitzer, MD | Gerard Limans, MD | Bala Mervin, MD

Solomon SD et al. Circulation. 2020;141:352-361

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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%
- >62.5%

Outcomes

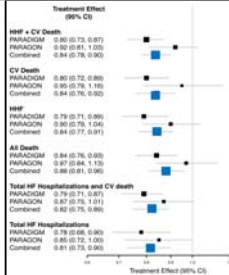
- First occurrence of CV death or HF hospitalization
- CV death
- First occurrence of HF hospitalization
- All-cause mortality

Solomon SD et al. Circulation. 2020;141:352-361

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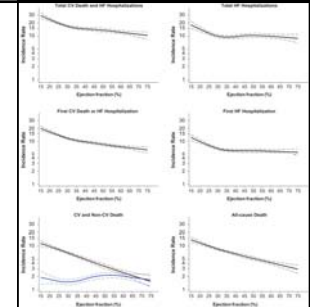
Benefit with Sacubitril/Valsartan for All Outcomes in the Pooled Cohort



Solomon SD et al. Circulation. 2020;141:352-361

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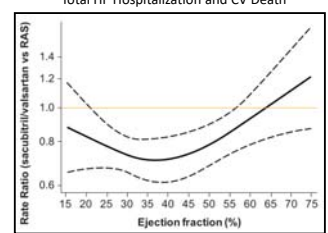
- Rates of primary outcome, HF hospitalizations, CV death, and all-cause mortality decrease with increasing LVEF.
- Rate of decline greatest in CV death
- Less apparent decline in HF hospitalization
- Non-CV death was similar across LVEF, such that proportion of deaths that were non-CV increased with increasing LVEF.

Solomon SD et al. Circulation. 2020;141:352-361

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Treatment Effect of Sacubitril/Valsartan vs RAS Inhibition Across LVEF

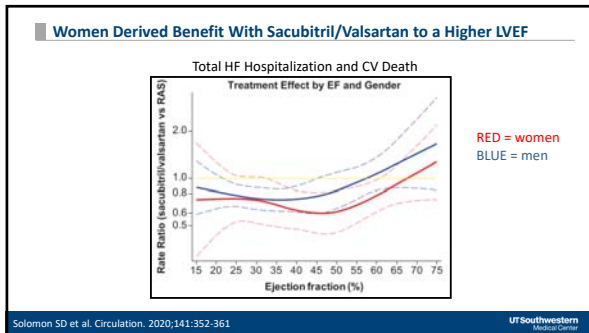


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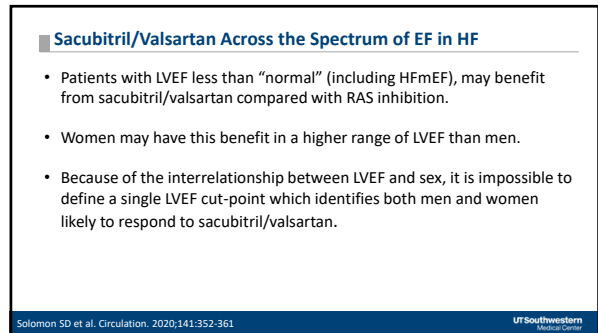
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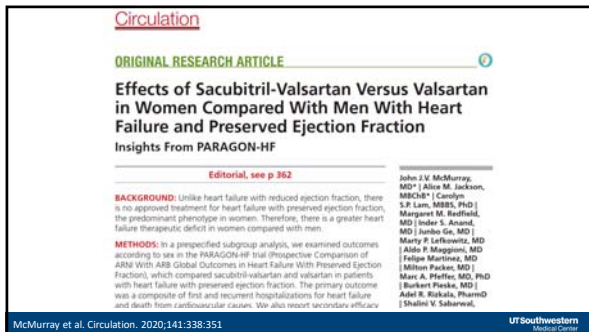
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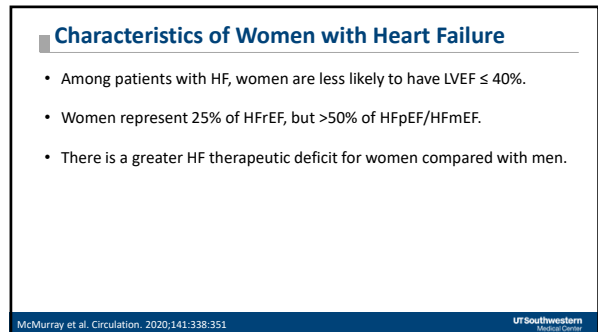
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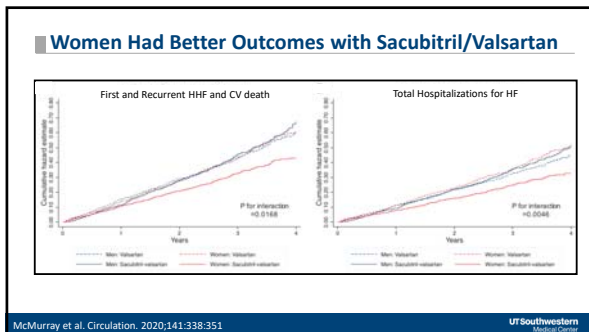
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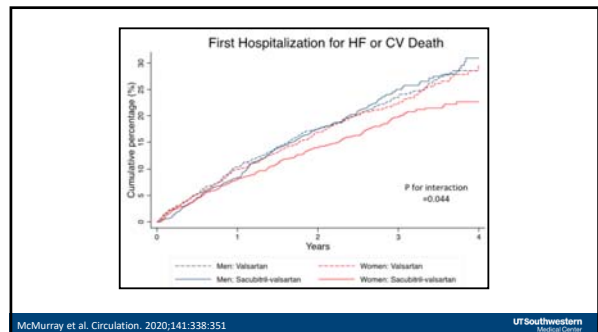
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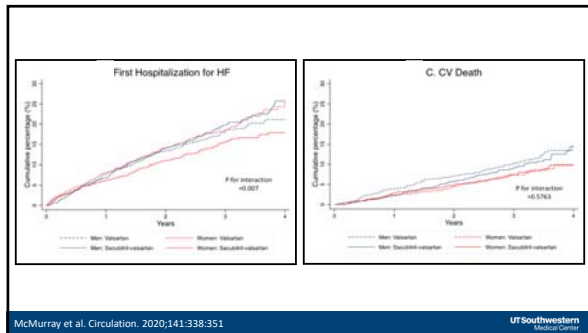


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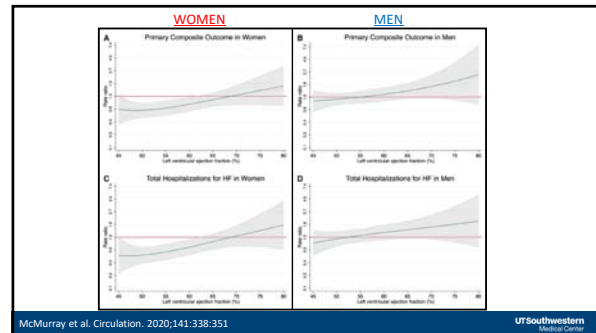


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Biologic Plausibility

- 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-valsartan may have greater benefit in women

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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.

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