Commentary on Sacubtril/Valsartan Across the Spectrum of Heart Failure

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Model of Sacubitril/Valsartan Across Low to Preserved EF By Gender

PARADIGM known benefits:
Reduction in mortality from 19.8 to 17 %
Absolute 2.8%, relative 14%

Reduction in HF hosp from 15.6 to 12.8 %
Absolute 2.8%, relative 18%

Benefit to Reduce Risk with Sacubitril/valsartan

PARADIGM --- PARAGON

RR = 1


AHA Late-Breaking Science 2019
Two Different Physiologies?  
Two Different Targets of Benefit?

**PARADIGM LVEF ≤ 0.40**

- Benefit not dependent on EF (.30 ± .06)
- Equivalent benefit across gender
- Benefit for mortality:
  \[ HR = 0.80 \text{ CV death, } 0.84 \text{ all death} \]
- Benefit more obvious in Class I-II
- Benefit apparent regardless of previous hospitalizations

**PARAGON LVEF ≥ 0.45**

- Benefit only if EF ≤ 0.57
- **Benefit only in women** (RR = 0.67) despite lower event rate than men
- No benefit for mortality even in women (RR = 1.05)
- Signal of benefit only in Class III-IV
- **Benefit only** in patients with prior hospitalization in the previous 6 months
Differential Impact of Prior HF Hospitalization On Benefit of Sacubitril/Valsartan Across EF

**PARADIGM Trial**
Equal Benefit Without Prior Hospitalization

**PARAGON Trial**
Only Benefit Is After Recent Hospitalization

Solomon, Claggett, Packer, Desai, Zile, Swedberg, Rouleau, Lefkowitz, McMurray
JACC Heart Failure 2016

Vaduganathan, Claggett, Desai, Anker, Perrone, Janssens, Milicic, Arango, Packer, Shi, Lefkowitz, McMurray, Solomon: AHA Sessions 2019
Targets for Therapy with Sacubitril/Valsartan

Heart failure with Low EF and LV dilation
- Decrease hospitalizations
- Decrease mortality

“Heart failure with Preserved EF”
- Decrease hospitalizations
- No impact on mortality

Prior HF hospitalization: Symptoms and signs of congestion treated with IV diuretics
- Decrease hospitalizations
- Decrease mortality

No prior congestion leading to hospitalization
- Fewer events, but still impact to
- Decrease hospitalizations
- Decrease mortality

Hospitalizations for congestion may be similar across EF

Disease progression and cardiac mortality may present better targets in low EF than in preserved EF.

NIH Heart Failure Network trials of HFpEF, Very few events in pts without prior HF hosp Reddy …Borlaug, Redfield et al AHA 2019
Shared Decision-Making For Patients Like You About Sacubitril/Valsartan for Low EF HF

If 100 patients like you add this medicine for 2 years, 17 will die
13 will be hospitalized for HF
78 will be alive without Hospitalization for HF

If 100 patients like you take the current meds for 2 years
20 will die
16 will be hospitalized for HF
73 will be alive without Hospitalization for HF

If the new medicine cost you an additional $5 / month, would you want it?
92% definitely or probably yes

If it cost you an additional $100/month?
43% definitely or probably yes

Smith, Shore, Allen, Markham, Mitchell, Moore, Morris, Speight, Dickert. J Am Heart Assoc 2019;8:e010635