PIONEER Commentary

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The Need for PIONEER
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1. Contrast of evidence for acute versus chronic HFrEF Rx

Ambulatory
- Enalapril (SOLVD)
- Carvedilol (COPERNICUS)
- Spironolactone (RALES)

Hospitalized
- Nesiritide (ASCEND)
- Tolvaptan (EVEREST)
- Serelaxin (RELAX)
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1. Contrast of evidence for acute versus chronic HFrEF Rx

- Ambulatory
- Hospitalized
  - 70% of care
  - Captive audience
  - Transitions fragile

Data  Action
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1. Contrast of evidence for acute versus chronic HFrEF Rx

2. Limitations of PARADIGM-HF
   - Stable ambulatory patients
   - Run-in phase
   - <2% NYHA IV
   - Concerns about hypotension

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

McMurray et al. NEJM 2014
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1. Contrast of evidence for acute versus chronic HFrEF Rx
2. Limitations of PARADIGM-HF
3. Sacubitril/valsartan use low:

<15% eligible patients in CHAMP
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1. Contrast of evidence for acute versus chronic HFrEF Rx
2. Limitations of PARADIGM-HF
3. Sacubitril/valsartan use low:

WHY?
- Not trust a single trial?
- Switching complicated?
- Background Rx complicated?
- Cost?
- Clinical inertia?!
PIONEERING Success

1. Safe:
   • Renal parameters (similar)
   • Blood pressure (14% hypotension, <2% difference)
PIONEERing Success

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2. Effective
   - NT-proBNP ↓ 29%
   - Serious event composite: ↓ 46% at 8 weeks
     - HF Readmission: 13.8% to 8.0% = 5.8% ARR (p=0.005)
     - Death: 3.4% to 2.3% = 1.1% ARR (NS)
PIONEER Questions

• Trial population
  Young: 62 years
  Reasonably diverse: ~30% women, 36% Black
  Few Stage D: excluded if SBP <100 mmHg, cardiorenal
  New onset HFrEF in a third
**PIioneer Questions**

- **Trial population**
  - Young: 62 years
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  - Few Stage D: excluded if SBP <100 mmHg, cardiorenal
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- **Surrogate as the primary outcome**
  - NT-proBNP changes backed by impressive secondary endpoints
  - Consistent with PARADIGM
The Post-PIONEER World

• Simple (simpler) algorithm for inpatient and subsequent outpatient HFrEF management
  Better for clinicians
  Better for patients

KEEP IT SIMPLE
The Post-PIONEER World

• Simple (simpler) algorithm for inpatient and subsequent outpatient HFrEF management
  Better for clinicians
  Better for patients

• Reinforces the importance and safety of aggressive GDMT in most patients
THANK YOU!