# Safety and Efficacy of Sacubitril/Valsartan by Dose Level in Patients Hospitalized with Acute Heart Failure

## *Observations from PIONEER-HF*

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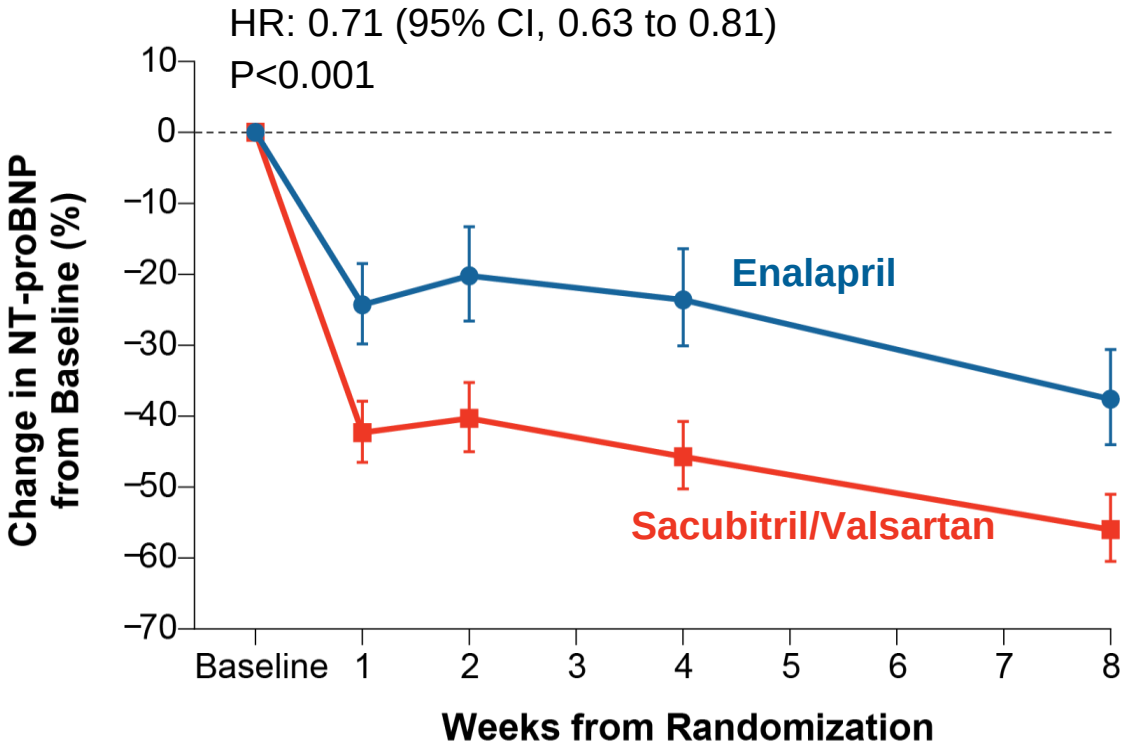
# Background

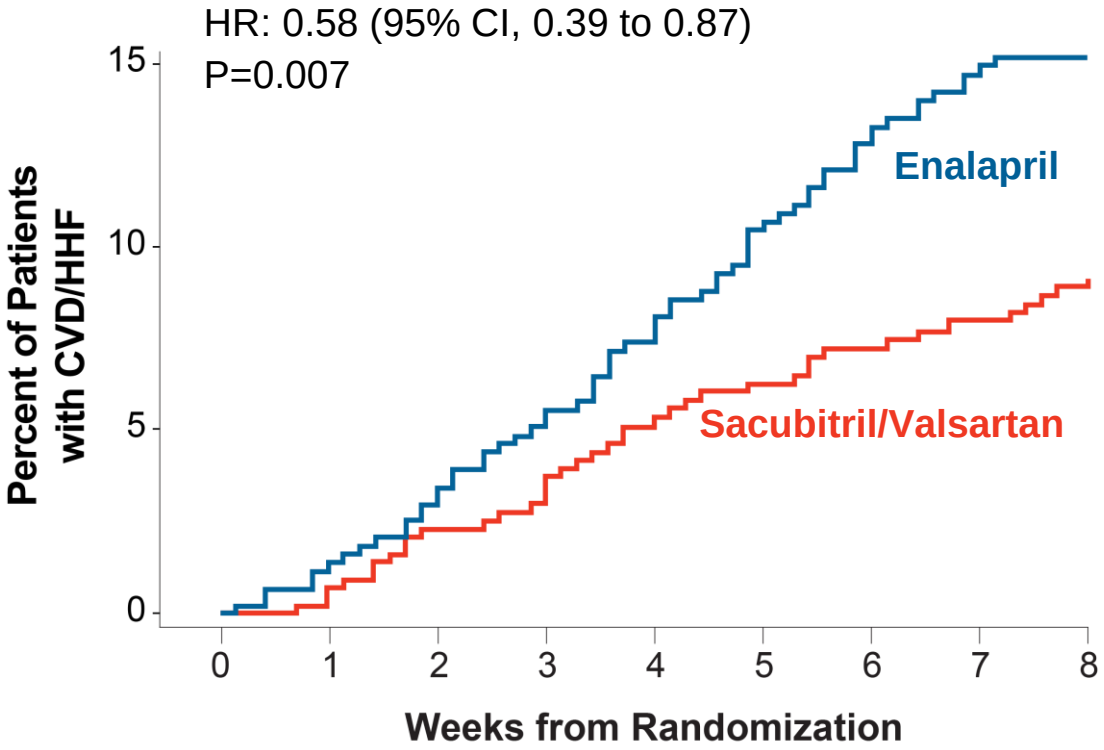
**Among pts w/ HFrEF hospitalized for ADHF, the in-hospital initiation of sacubitril/valsartan led to a greater ↓ in NT-proBNP and improved clinical outcomes compared w/ enalapril**

## *Change in NTproBNP*




Velazquez et al. N Engl J Med 2019;380:539-548

## *CV Death or Hospitalization for HF*




Morrow et al. Circulation 2019;139:2285–2288.

# Study Design

***N = 881***

## Hospitalized with ADHF (EF≤40%)

***Stabilized while still hospitalized***

- SBP ≥100 mmHg in prior 6h; no symptomatic ↓ BP
- No increase in IV diuretics in prior 6h
- No IV vasodilators in prior 6h
- No IV inotropes in prior 24h

**Sacubitril/valsartan**
**Target: 97/103 mg twice daily**

**vs**

**Enalapril**
**Target: 10 mg twice daily**

**In-hospital initiation**

**Blinded Study Rx for 8 weeks**

**Evaluate**

- NTproBNP
- Safety and tolerability
- Clinical outcomes



Velazquez et al. AHJ 2018;198:145-51
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# Study Design

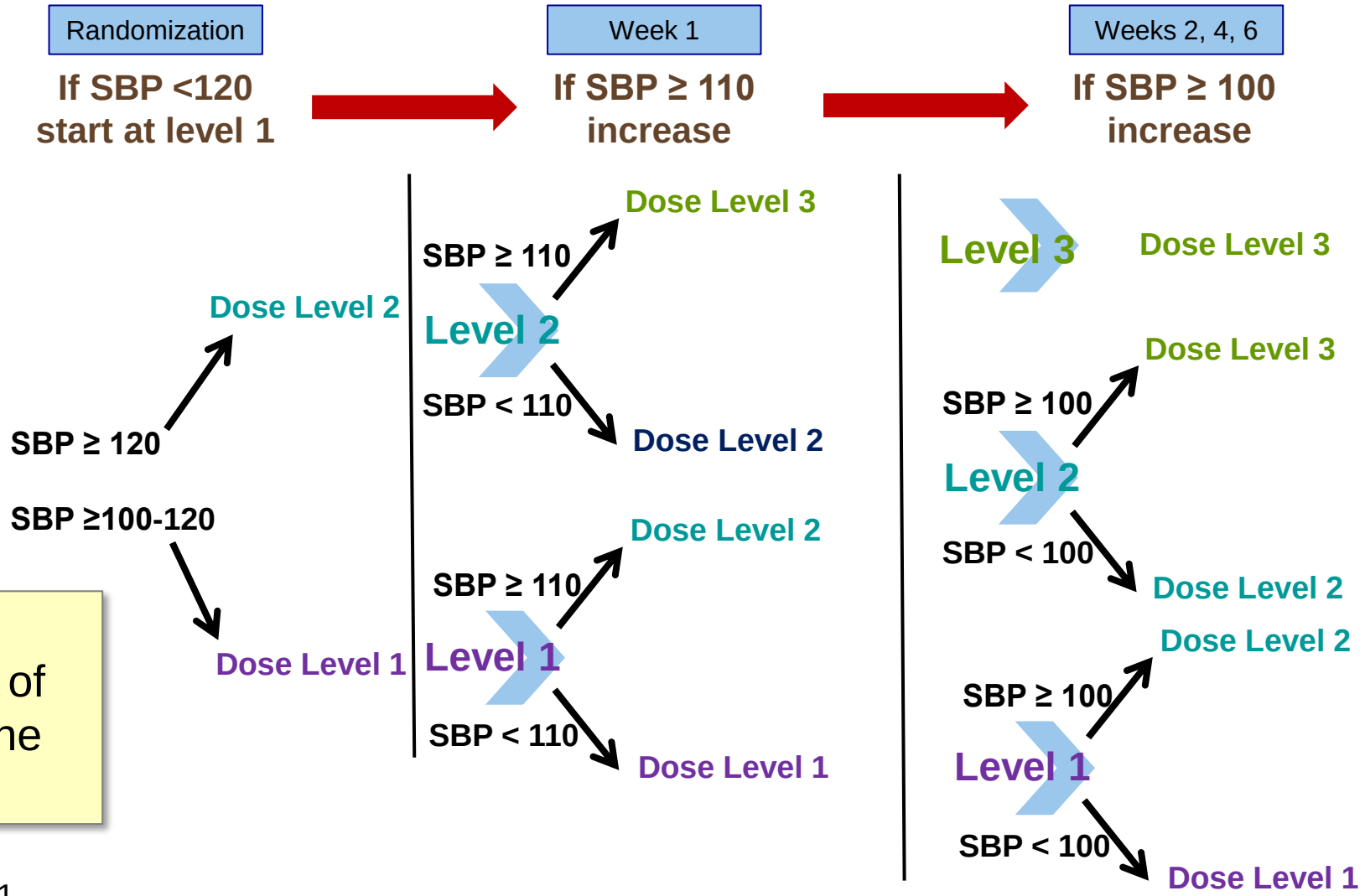
*Dose titration – Shifting BP thresholds with time*

**Unique low-dose option in PIONEER-HF**

1) LCZ696 24/26mg BID or Enalapril 2.5 mg BID
2) LCZ696 49/51mg BID or Enalapril 5 mg BID
3) LCZ696 97/103mg BID or Enalapril 10 mg BID

***Objective***

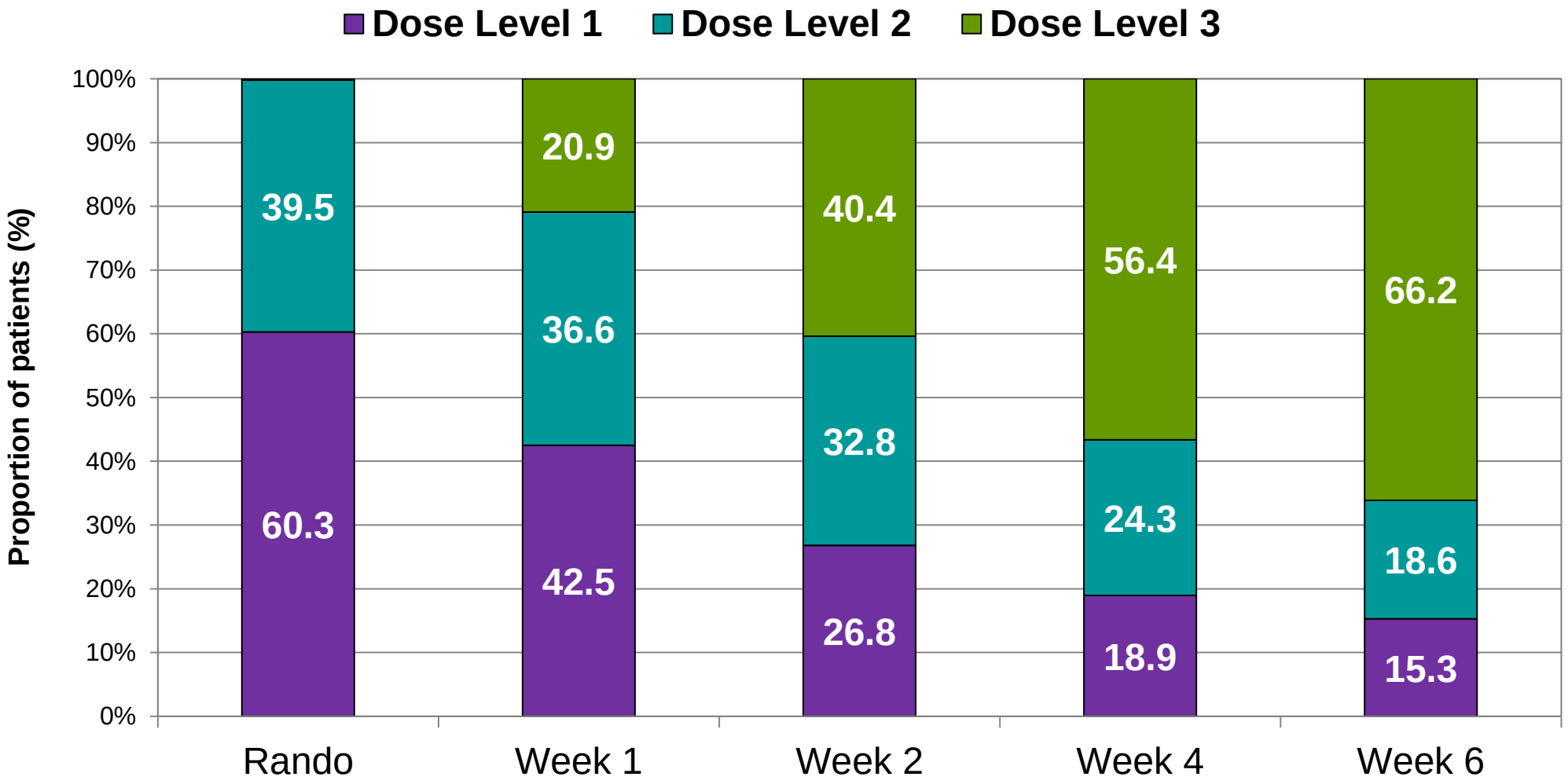
To assess the safety and efficacy of sacubitril/valsartan according to the dose level dispensed at Week 4






Velazquez et al. AHJ 2018;198:145-51

# Distribution of Dose Level Achieved



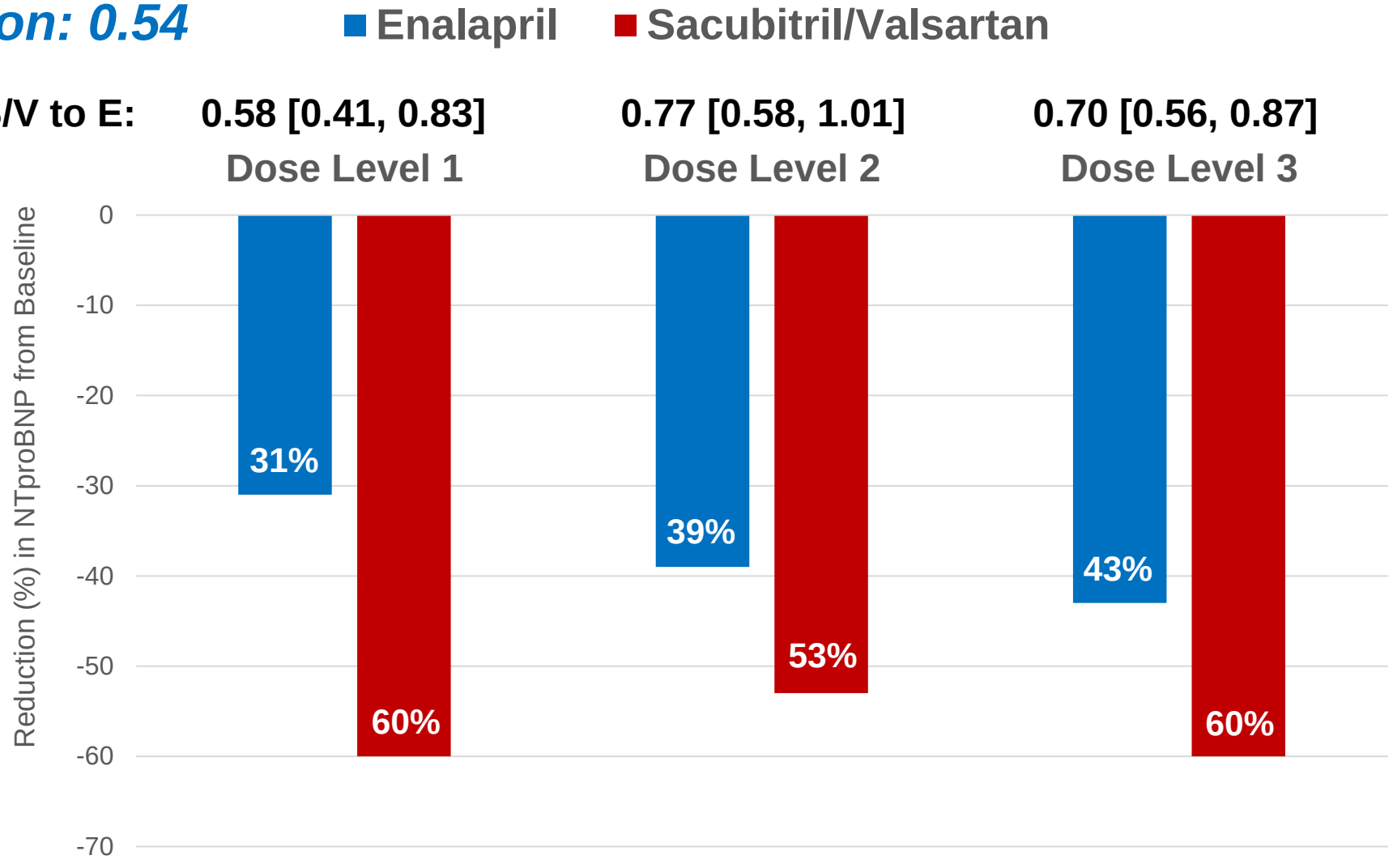

Among patients receiving study drug

# Baseline Characteristics

| *Dose level at Week 4* | Dose Level 1 (n = 137) | Dose Level 2 (n = 175) | Dose Level 3 (n = 412) |
|---|---|---|---|
| Age (years) | 67 [58, 73] | 64 [52, 71] | 59 [49, 68] |
| Women (%) | 27.0 | 26.3 | 27.4 |
| Black (%) | 19.7 | 28.0 | 43.4 |
| Prior HF diagnosis (%) | 63.5 | 62.3 | 61.7 |
| LVEF | 21 [15, 30] | 23 [18, 30] | 25 [20, 30] |
| Systolic pressure (mm Hg) | 111 [106, 117] | 115 [108, 126] | 125 [115, 138] |
| eGFR | 55 [46, 67] | 58 [47, 70] | 61 [50, 74] |
| NT-proBNP (pg/mL) | 3209 [1937, 6560] | 3004 [1482, 5215] | 2377 [1343, 4308] |
| ACEi/ARB therapy (%) | 43.8 | 45.7 | 48.8 |
| Beta-adrenergic blockers (%) | 56.9 | 58.3 | 58.3 |

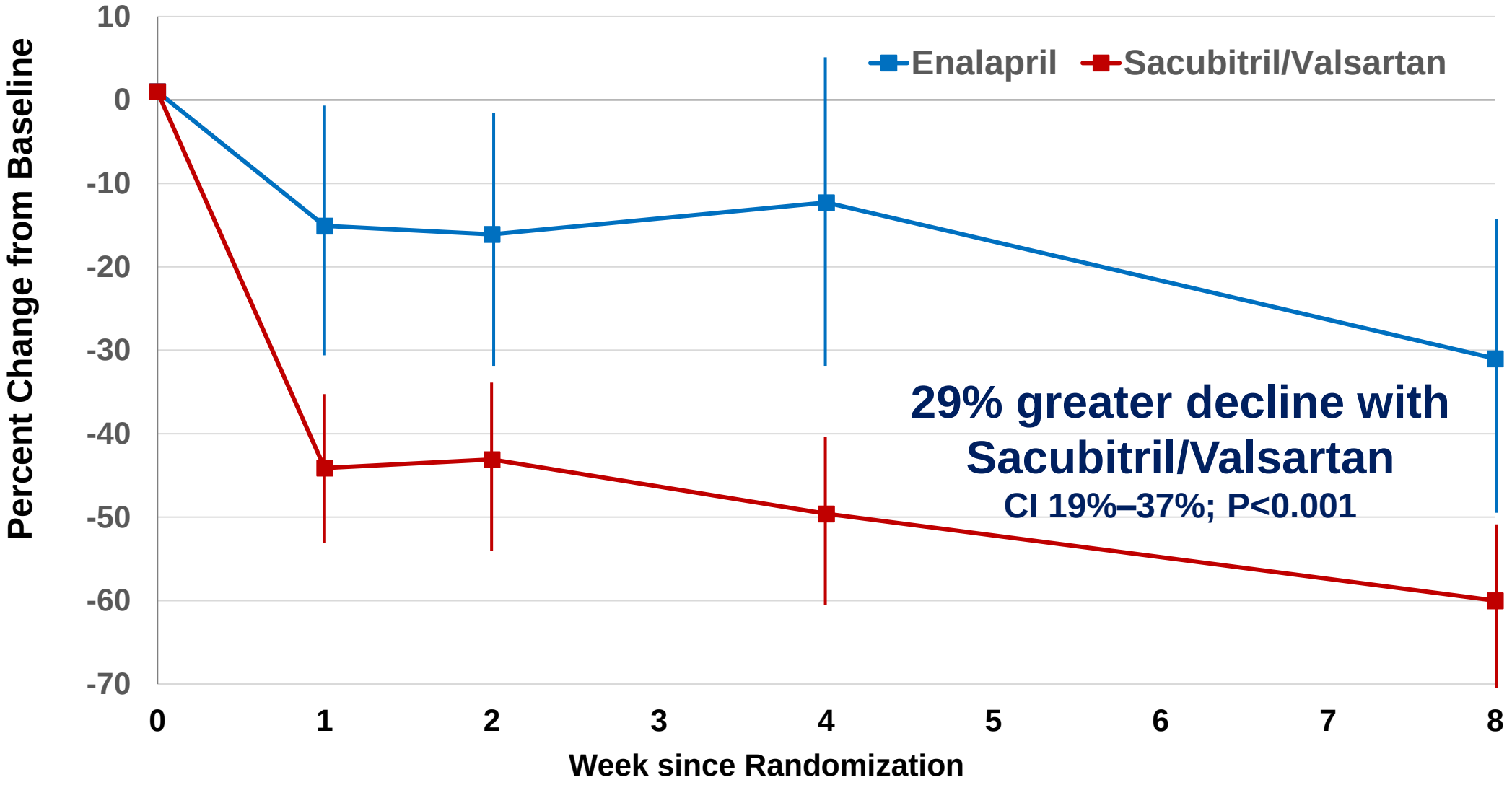
# Efficacy: NTproBNP at Week 8

***P-interaction: 0.54***



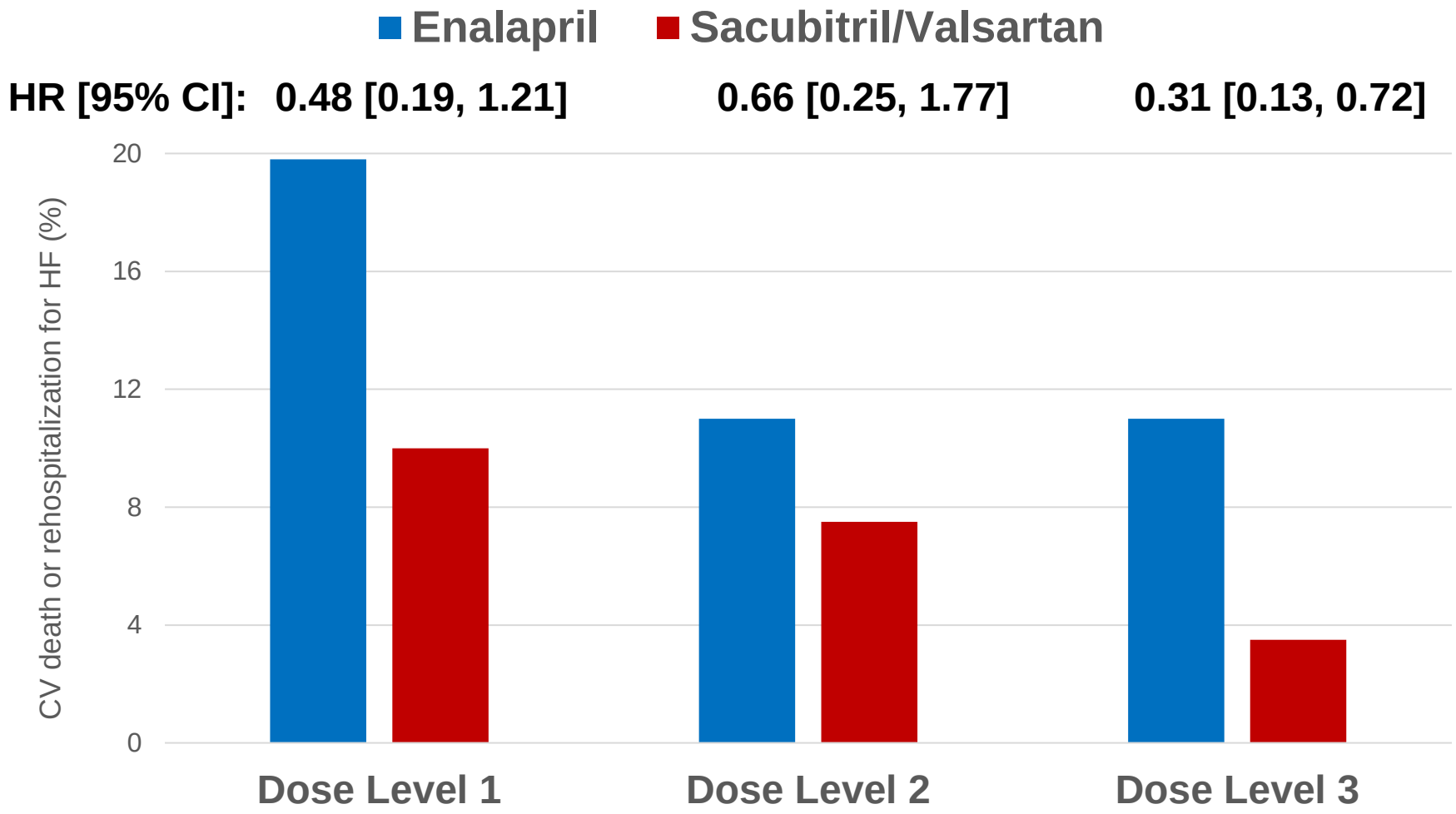
# NT-proBNP

## *% Change by Visit in Pts on Dose Level 1 at Week 4*



# CV Death or Rehosp for HF by Week 8

***P-interaction: 0.XX***



# Safety

| Safety Events (%) HR [95% CI] | Dose Level 1 | | Dose Level 2 | | Dose Level 3 | | |
|---|---|---|---|---|---|---|---|
| | Enalapril (n=66) | Sacubitril/ Valsartan (n=70) | Enalapril (n=82) | Sacubitril/ Valsartan (n=93) | Enalapril (n=210) | Sacubitril/ Valsartan (n=199) | P-interaction |
| Worsening renal function[a] | 33.3 | 24.3 | 22.0 | 14.0 | 11.9 | 12.6 | |
| | 0.73 [0.43, 1.25] | | 0.64 [0.33, 1.22] | | 1.06 [0.63, 1.77] | | |
| Hyperkalemia | 13.6 | 18.6 | 12.2 | 16.1 | 7.1 | 6.0 | |
| | 1.36 [0.62, 2.97] | | 1.32 [0.63, 2.78] | | 0.84 [0.41, 1.76] | | |
| Symptomatic hypotension | 27.3 | 20.0 | 19.5 | 15.1 | 5.2 | 10.1 | |
| | 0.73 [0.40, 1.35] | | 0.77 [0.40, 1.48] | | 1.92 [0.94, 3.90] | | |

[a]SCr ≥0.5 with simultaneous GFR reduction of ≥25%

**P = NS**

# Conclusions

**In hemodynamically stabilized patients with ADHF and reduced EF, the safety and efficacy of sacubitril/valsartan appears generally consistent among patients at various dose levels.**

- Similar greater decline in NTproBNP with sacubitril/valsartan
- Reduced HF rehospitalization
- Well tolerated w/ comparable rates of renal insufficiency, hyperkalemia, symptomatic hypotension

***Including consistency w/ sacubitril/valsartan 24/26mg BID***

# Clinical Implications

These results support the in-hospital initiation of sacubitril/valsartan for HFrEF, and titration toward the maximum tolerated dose up to 97/103 mg BID, and continuation of the maximum dose achieved.