Angiotensin Receptor-Neprilysin Inhibition in Patients Hospitalized With Acute Decompensated Heart Failure

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Background

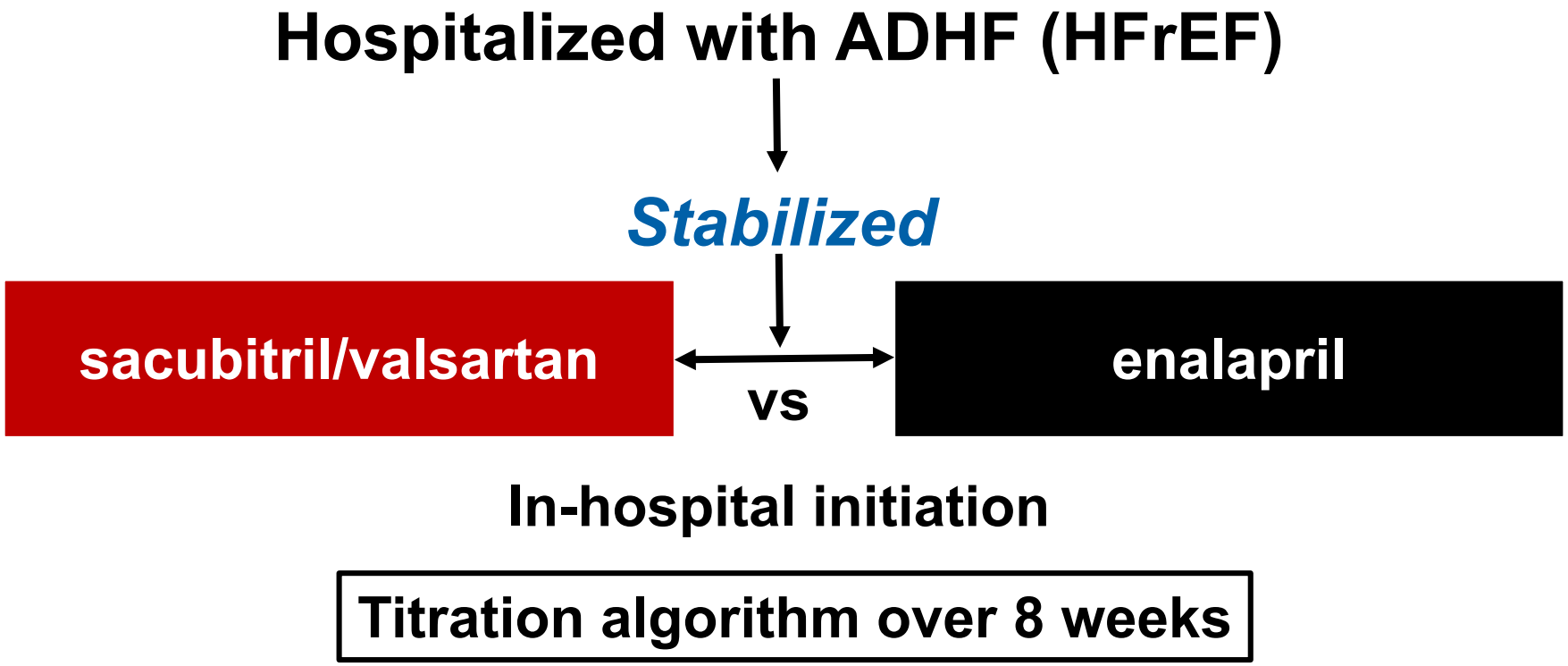
- **Acute decompensated heart failure (ADHF) accounts for over 1M hospitalizations in the US annually**
- **Guideline-directed therapy for ADHF is limited**
  - **Decongestion with diuretics and hemodynamic support with vasodilators remain the standards of care**

Rationale

- **PARADIGM-HF trial in chronic HFrEF: sacubitril/valsartan → ↓ CV death or HF hospitalization compared to enalapril**
  - **Patients with ADHF requiring IV therapy were excluded**
  - **Stable HF therapy with adequate doses for >4 weeks**
  - **Required sequential run-in with high dose enalapril and sacubitril/valsartan before randomization**
- **It is unknown if in-hospital initiation of sacubitril/valsartan compared to enalapril is safe and effective in ADHF**

McMurray JJ. *NEJM*. 2014;371:993-1004.

Study Design



In-hospital initiation

Titration algorithm over 8 weeks

- **Evaluate biomarker surrogates of efficacy**
- **Evaluate safety and tolerability**
- **Explore clinical outcomes**

Key Entry Criteria

- Hospitalized for ADHF (signs and symptoms of fluid overload)
- LVEF ≤40% within the last 6 months
- NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (screening)
- Stabilized while still hospitalized
  - In the prior 6 hours:
    - SBP ≥100 mmHg, no symptomatic hypotension
    - No increase in IV diuretics
    - No IV vasodilators
  - In the prior 24 hours: no IV inotropes

Key Endpoints

- **Primary endpoint:** Proportional change in NT-proBNP from baseline to the mean of weeks 4 and 8
- **Safety**
  - Worsening renal function
  - Hyperkalemia
  - Symptomatic hypotension
  - Angioedema
- **Exploratory Clinical Outcomes**
  - Serious clinical composite: death, re-hospitalization for HF, LVAD, or listing for cardiac transplant
  - Expanded composite: Serious composite + addition of HF med, unplanned outpatient IV diuretics or >50% increase in dose

SBP Dose Titration Algorithm

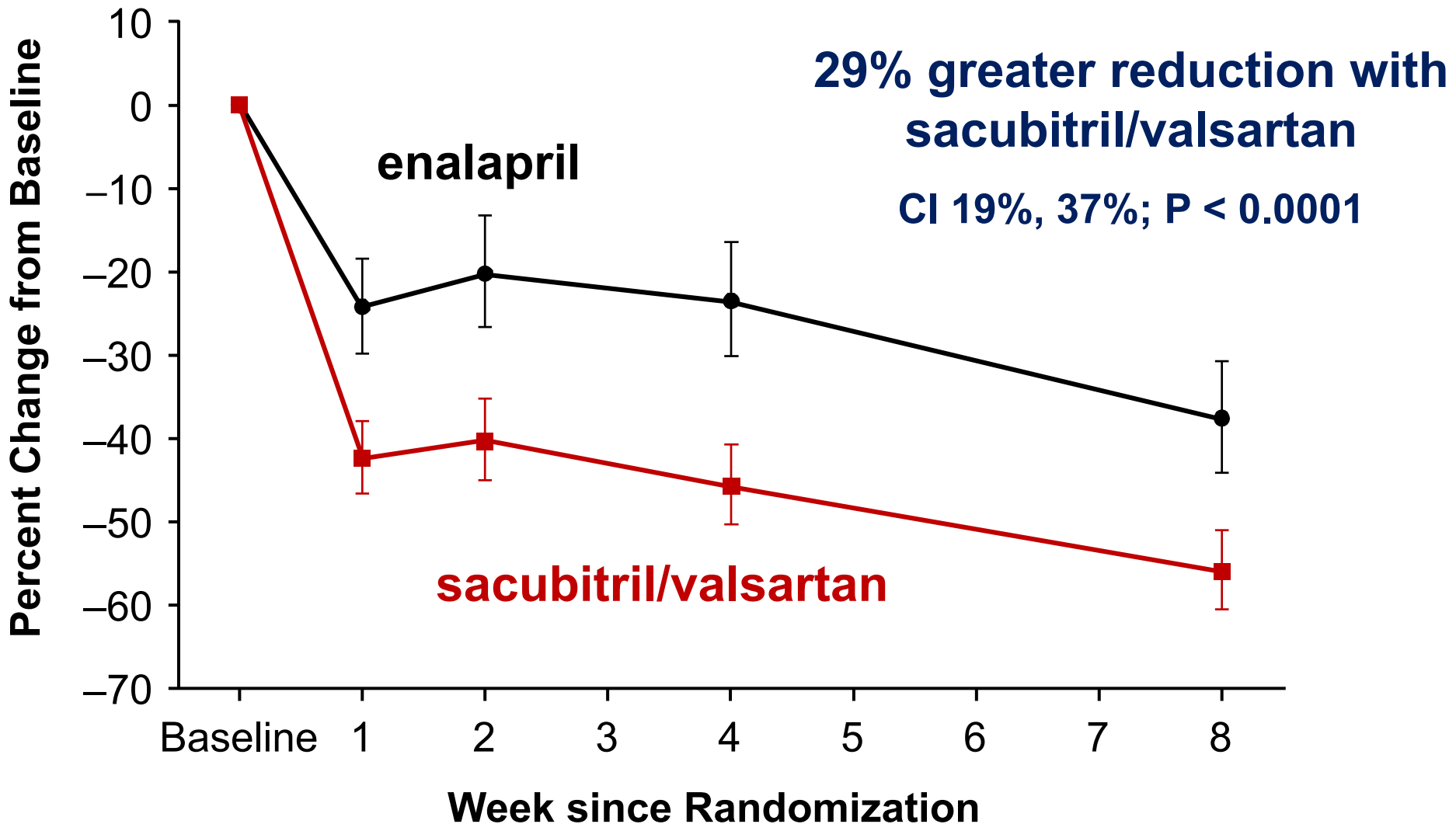
- **Starting dose level based on SBP**
  - **If 100 to <120 mm Hg, sacubitril/valsartan 24/26 mg or enalapril 2.5 mg twice daily**
  - **If ≥120 mm Hg, sacubitril/valsartan 49/51 mg or enalapril 5 mg twice daily**
- **Up-titration based on SBP (clinical judgement permitted)**
- **Target doses**
  - **sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily**

Baseline Characteristics

	sacubitril/valsartan (n=440)	enalapril (n=441)
Age* (years)	61 (51, 71)	63 (54, 72)
Women (%)	25.7	30.2
Black (%)	35.9	35.8
No prior HF diagnosis (%)	32.3	37.0
No ACEi/ARB therapy (%)	52.7	51.5
LVEF*	0.24 (0.18, 0.30)	0.25 (0.20, 0.30)
SBP (mm Hg)*	118 (110, 133)	118 (109, 132)
NT-proBNP (pg/mL)*	2883 (1610, 5403)	2536 (1363, 4917)

*Median (interquartile range) .

Primary Endpoint: % Change in NT-proBNP



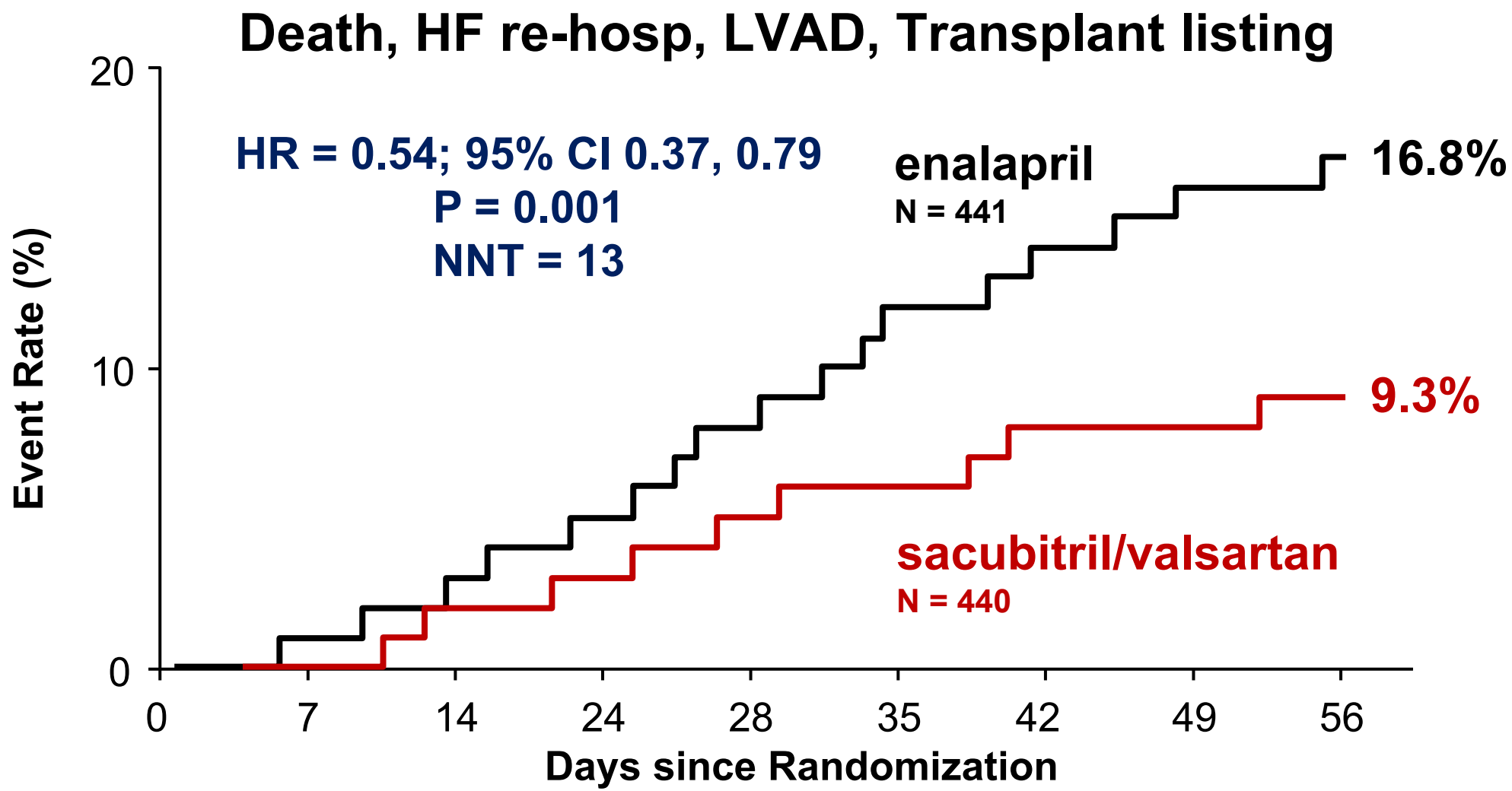
Safety

Safety Events (%)	sacubitril/ valsartan (n=440)	enalapril (n=441)	RR (95% CI)
Worsening renal function*	13.6	14.7	0.93 (0.67-1.28)
Hyperkalemia†	11.6	9.3	1.25 (0.84-1.84)
Symptomatic hypotension	15.0	12.7	1.18 (0.85-1.64)
Angioedema event	1 (0.2%)	6 (1.4%)	0.17 (0.02-1.38)

P = NS for all safety events

*Cr ≥0.5 with simultaneous reduction in eGFR of ≥25%
†K+ >5.5 mg/dl

Serious Composite Clinical Endpoint



Exploratory Clinical Endpoints

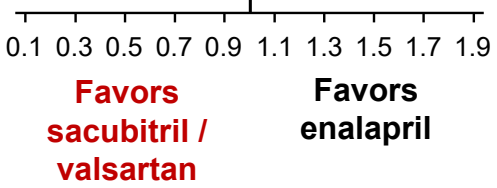
	sacubitril/ valsartan (n=440)	enalapril (n=441)	HR	P-value
Serious Composite, %	**9.3**	**16.8**	**0.54**	**0.001**
Death, %	2.3	3.4	0.66	0.311
Re-hosp for HF, %	8.0	13.8	0.56	0.005
LVAD, %	0.2	0.2	0.99	0.999
Cardiac Transplant, %	0	0	-	-
Expanded Composite*, %	**56.6**	**59.9**	**0.93**	**0.369**
Unplanned IV diuretics, %	0.5	0.5	0.99	0.997
Addition of HF med, %	17.7	19.1	0.92	0.58
>50% diuretic increase, %	49.6	50.3	0.98	0.812

*Serious composite + addition of HF med, no unplanned outpatient IV diuretics or >50% increase in dose

Key Subgroup Analyses

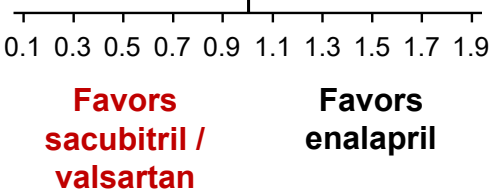
Change in NT-proBNP

Subgroup	sacubitril/valsartan vs. enalapril mean [95% CI]
All Patients	0.71 [0.63, 0.81]
Prior HF	
No	0.65 [0.53, 0.81]
Yes	0.72 [0.63, 0.83]
Prior ACEi/ARB	
No	0.72 [0.60, 0.86]
Yes	0.72 [0.61, 0.85]



Serious Composite Endpoint

Subgroup	Hazard Ratio [95% CI]
All Patients	0.54 [0.37, 0.79]
Prior HF	
No	0.37 [0.12, 1.15]
Yes	0.53 [0.35, 0.80]
Prior ACEi/ARB	
No	0.52 [0.29, 0.95]
Yes	0.56 [0.34, 0.92]



P value (interaction) = NS

Conclusions

Among hemodynamically stabilized acute heart failure patients with reduced EF, compared with enalapril, sacubitril/valsartan administered over 8 weeks …

- Led to greater reduction in NT-proBNP
- Reduced re-hospitalization for heart failure
- Was well tolerated with comparable rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema

Clinical Implications

These results support the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure and reduced EF, irrespective of prior ACEi/ARB use, or prior HF diagnosis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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