EVALUATE-HF

Effect of Sacubitril-Valsartan Compared with Enalapril on Arterial Hemodynamics and Cardiac Remodeling in Heart Failure and Reduced Ejection Fraction

Primary Results of the EVALUATE-HF Trial

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ESC Congress Paris 2019 Together with World Congress of Cardiology

Disclosures

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- **Akshay Desai has received research grants from Alnylam, AstraZeneca, and Novartis and consulting fees from Abbott, Alnylam, AstraZeneca, Biofourmis, Boehringer-Ingelheim, Boston Scientific, Corvidia, DalCor Pharma, Novartis, Relypsa, and Regeneron.**

Background

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- In patients with HF and reduced ejection fraction (HFrEF), angiotensin receptor-neprilysin inhibition (ARNI) with sacubitril/valsartan reduces death and HF hospitalization compared to angiotensin converting enzyme (ACE) inhibition with enalapril[1]
- Guidelines now encourage substitution of ARNI for ACE inhibitors/ARBs in patients with symptomatic HFrEF[2,3]
- The pathophysiologic mechanisms responsible for the benefits of neprilysin inhibition in HFrEF are unclear

[1]McMurray, et al. NEJM 2014; [2]Yancy, et al. Circulation 2016; [3]Ponikowski, et al. Eur Heart J 2016

Study Rationale

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- Rapid reductions in natriuretic peptides and collagen turnover biomarkers with sacubitril/valsartan suggest early effects of neprilysin inhibition on hemodynamics and cardiac remodeling
- Central aortic stiffness is increased in HF and is a key determinant of ventricular load and cardiac performance
- In hypertensives, ACE/neprilysin inhibition with omapatrilat reduced central aortic stiffness and pulsatile load[1]
- Effects of sacubitril/valsartan in HFrEF might be related to favorable effects on central hemodynamics and cardiac structure and function

[1]Mitchell GF, et al. Circulation 2002 Jun 25;105(25):2955-61

Objective

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EVALUATE-HF was designed to determine whether treatment of HFrEF with sacubitril/valsartan improves central aortic stiffness and cardiac remodeling compared with enalapril

Study Design

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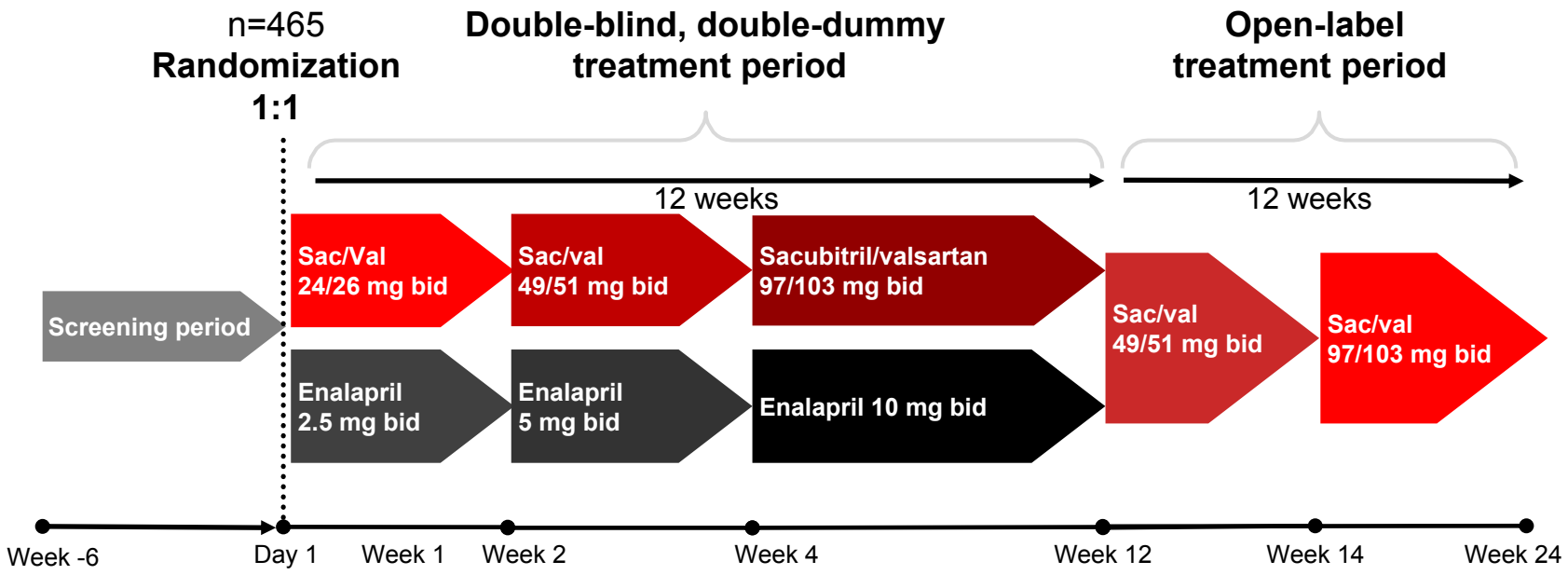

Hemodynamic Assessment	X		X	X
Echocardiography	X		X	X
Cardiac Biomarkers		X	X	X
KCCQ-12		X	X	X

Key Entry Criteria

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Included

- Age ≥ 50 yrs
- Chronic HF with EF≤40%
- NYHA I-III
- History of hypertension
- Stable doses of GDMT
- SBP > 105 mm Hg at randomization

Excluded

- Prior treatment with sacubitril/valsartan
- Persistent atrial fibrillation at screening or randomization
- Inadequate baseline hemodynamic study

Endpoints

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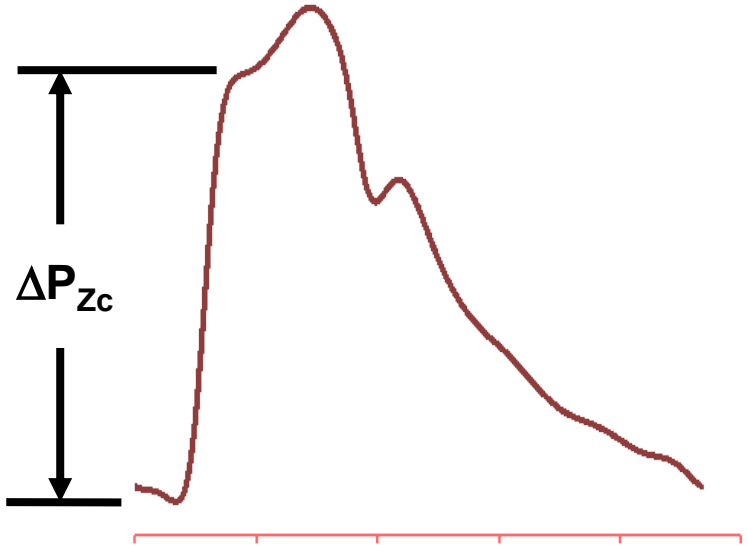
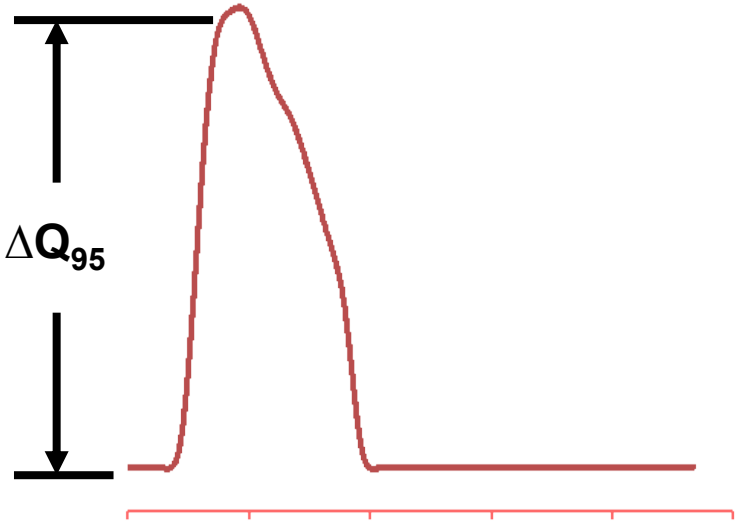
- **Primary Endpoint**
  - Change from baseline to week 12 in aortic characteristic impedance (Z_c), a measure of proximal aortic stiffness



Central Pressure Waveform (Carotid Tonometry)



Central Flow (LVOT Doppler)

$$Z_c = \Delta P_{Zc} / \Delta Q_{95}$$

Endpoints

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- Primary endpoint
  - Change from baseline to week 12 in aortic characteristic impedance (Z_c), a measure of proximal aortic stiffness
- **Secondary endpoints**
  - Change from baseline to week 12 in
    - Biomarkers: NTproBNP
    - Cardiac structure: LV end-diastolic and end-systolic volumes, left atrial volume index
    - Systolic function: ejection fraction, global longitudinal strain
    - Diastolic function: lateral mitral annular relaxation velocity (e'), mitral E/e'

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    - Diastolic function: lateral mitral annular relaxation velocity (e'), mitral E/e'
- **Exploratory endpoints**
  - Change from baseline to week 12 in
    - Other biomarkers: hsTnT, soluble ST2, urinary cGMP/Creatinine
    - Quality of life: KCCQ-12 Overall Summary Score

Patient Enrollment/Disposition

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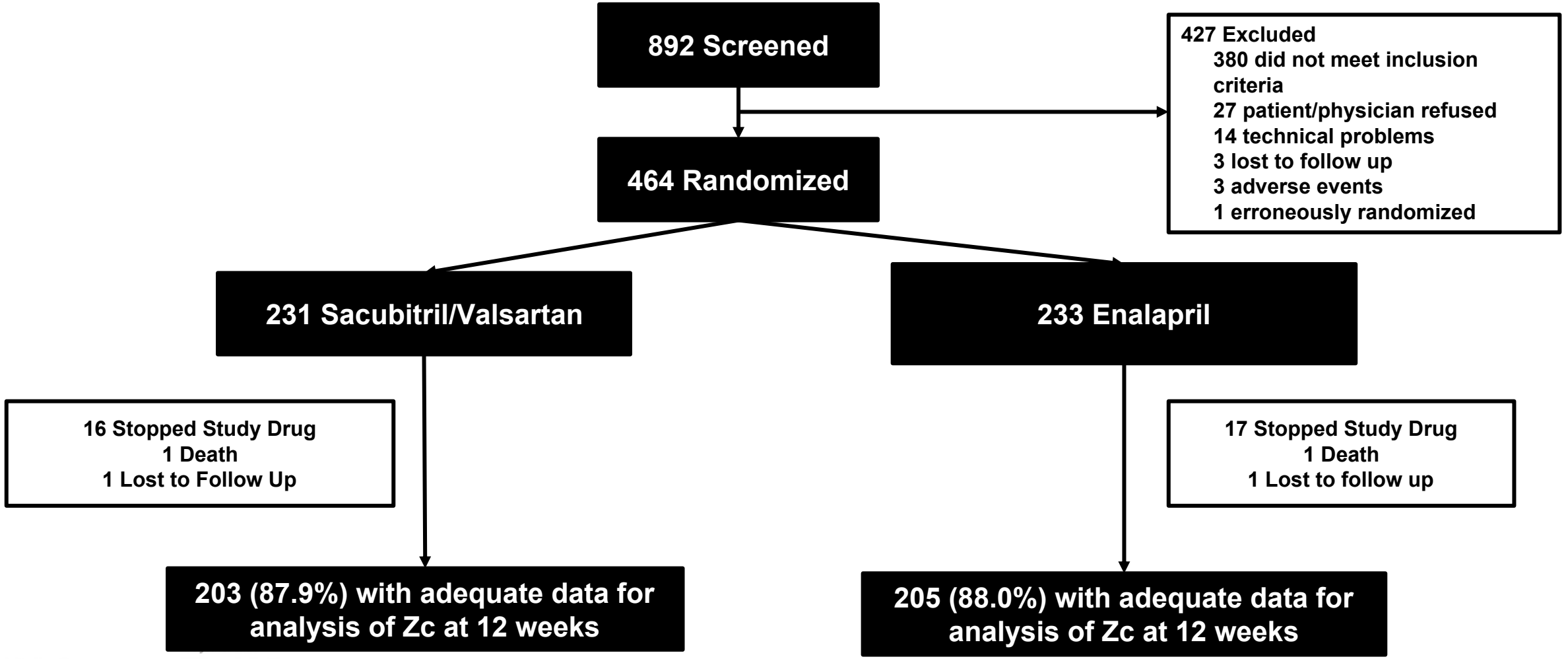

Baseline Characteristics

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	Sacubitril/Valsartan (N=231)	Enalapril (N=233)
Age, mean (SD), yr	68 (10)	67 (9)
Female Sex, %	26%	21%
Black Race, %	27%	23%
Systolic Blood Pressure, mean (SD), mm Hg	131 (15)	130 (13)
Diastolic Blood Pressure, mean (SD), mm Hg	77 (10)	78 (10)
Body Mass Index, mean (SD), kg/m^2	30.0 (5.7)	30.1 (5.8)
Estimated GFR, mean (SD), $mL/min/1.73\ m^2$	70 (22)	69 (20)
Left Ventricular Ejection Fraction, mean (SD), %	34 (10)	33 (10)
NTproBNP, median (IQR), pg/mL	595 (244, 1438)	560 (254,1498)
Prior HF Hospitalization, %	55%	49%
Functional Class, %		
NYHA Class I	14%	12%
NYHA Class 2	66%	69%
NYHA Class 3	20%	19%
On ACEi/ARB Prior To Randomization, %	81%	88%

Primary Endpoint: Change in Z_c from Baseline to Week 12

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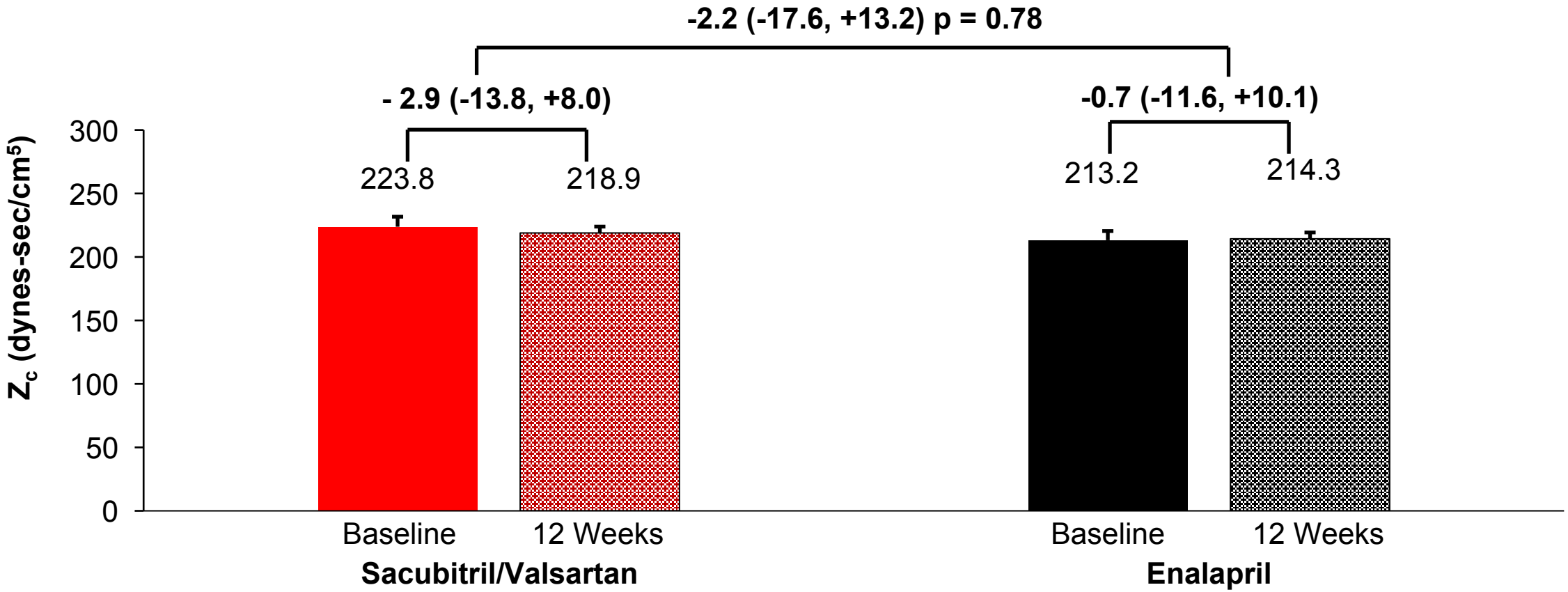

Secondary Endpoints: Change in Cardiac Structure from Baseline to 12 weeks, by Treatment

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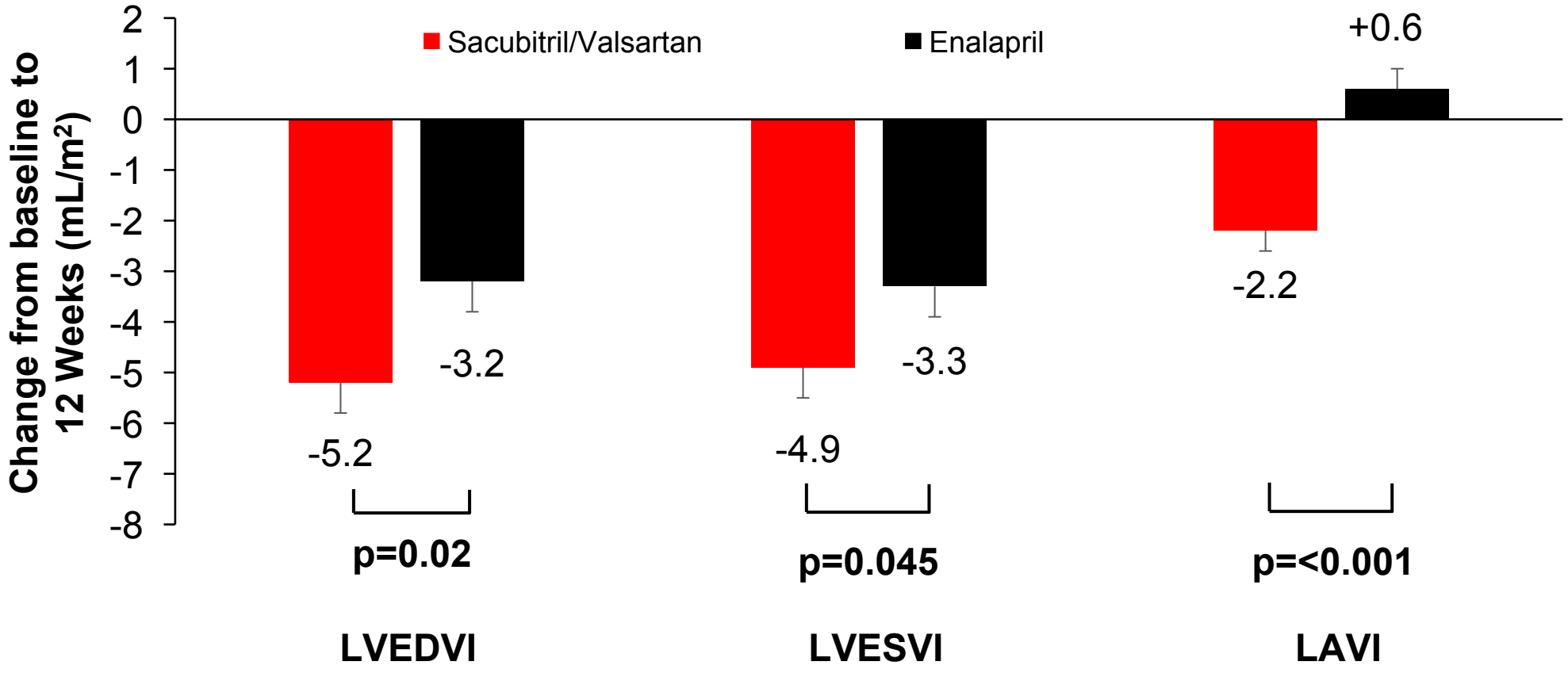

Secondary Endpoints: Change in Cardiac Function from Baseline to 12 weeks, by Treatment

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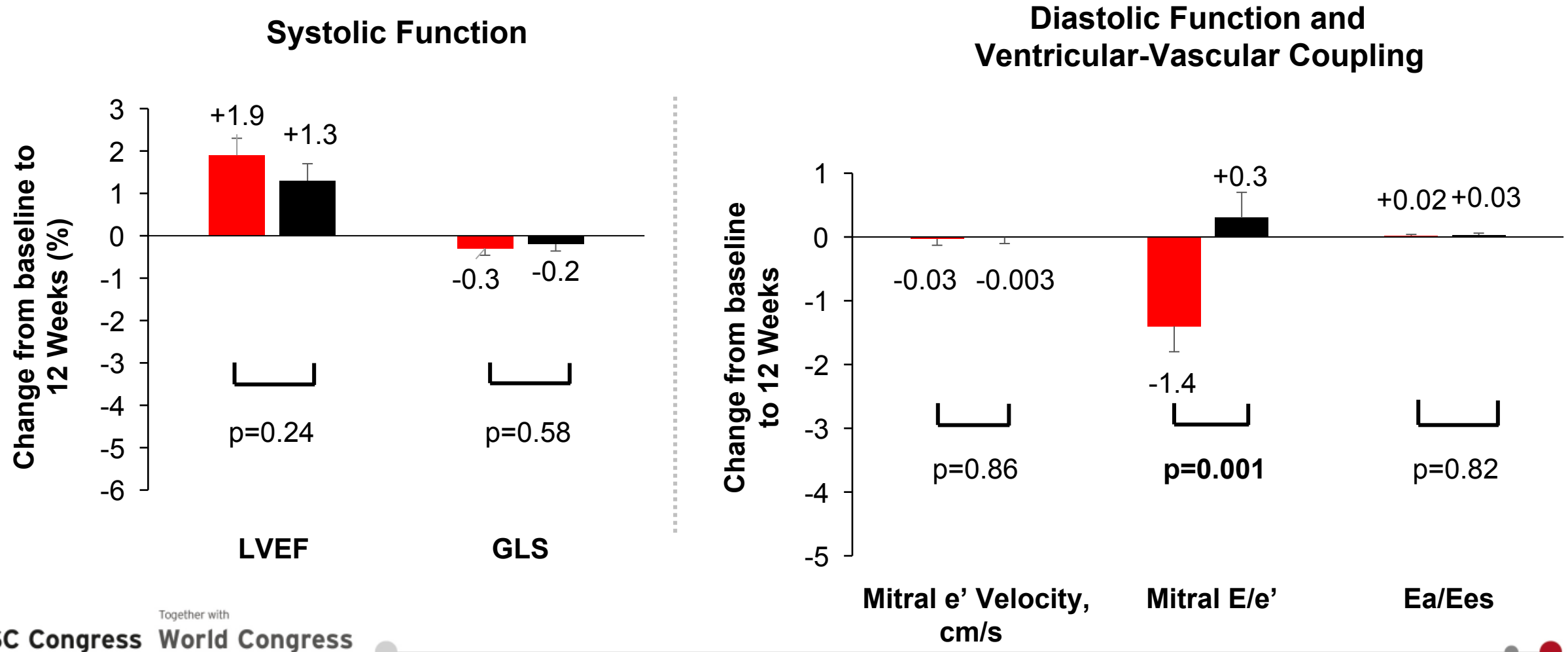

Change in Cardiac Biomarkers from Baseline to 12 weeks, by Treatment

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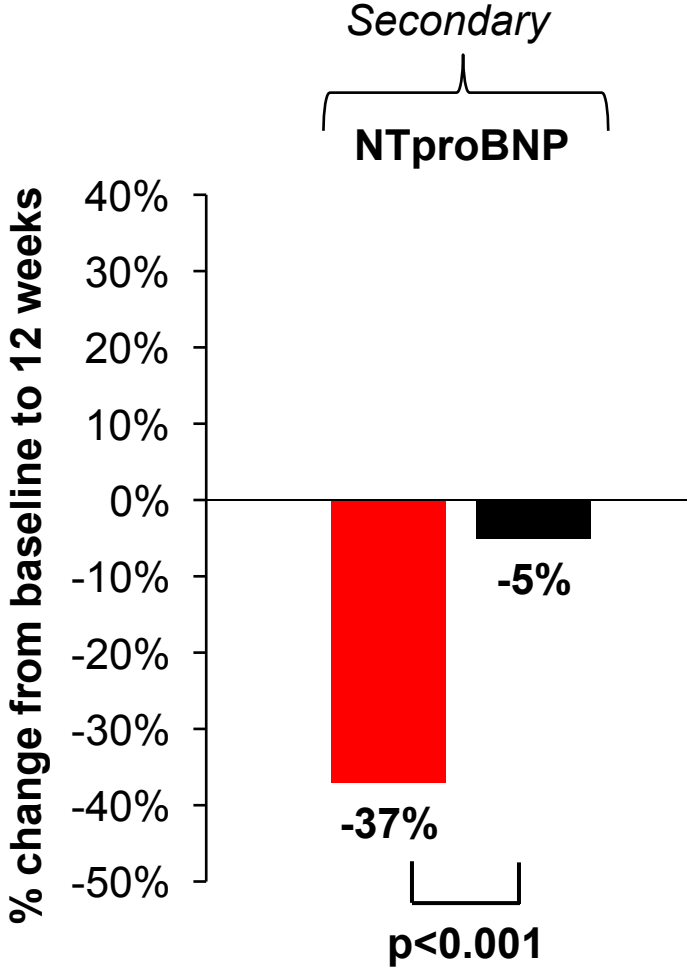
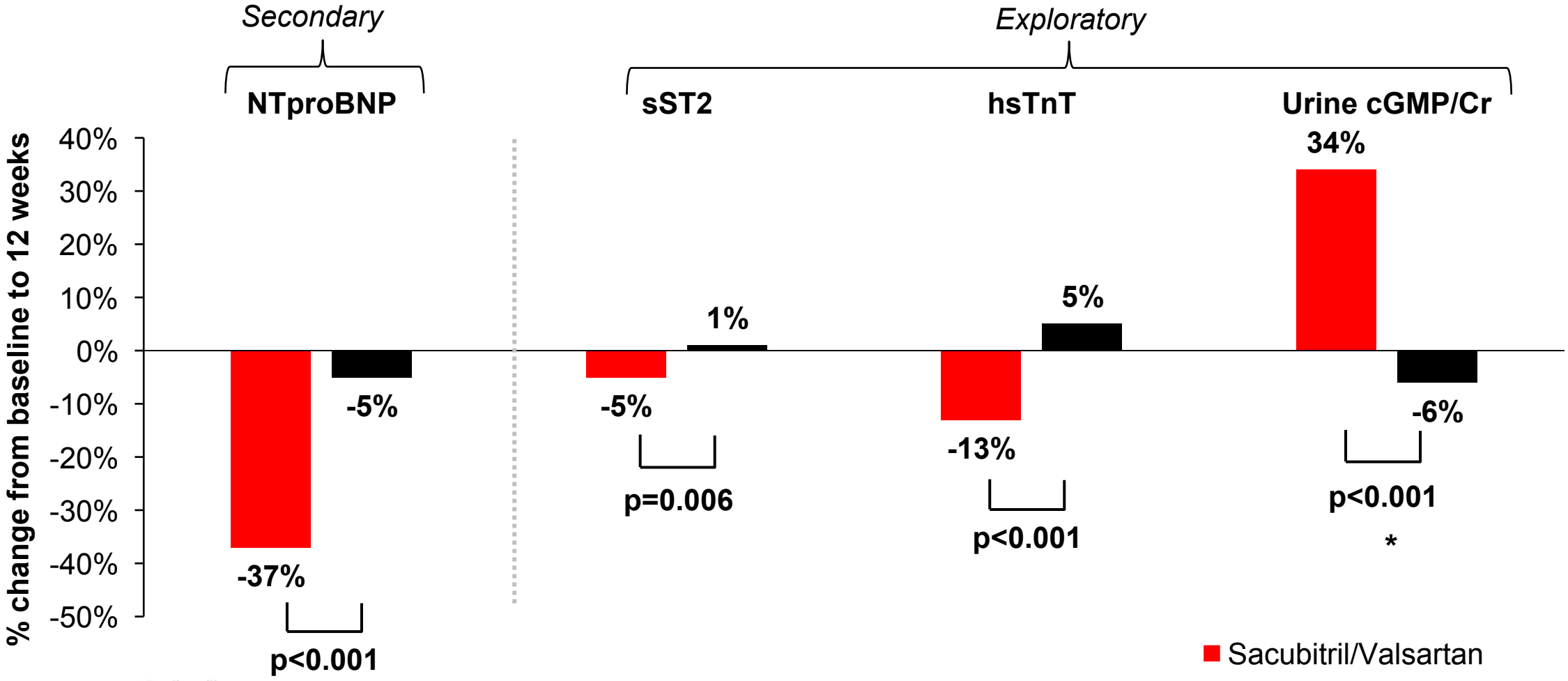


Change in Cardiac Biomarkers from Baseline to 12 weeks, by Treatment

EVALUATE-HF



Exploratory Endpoint: Change in KCCQ-12 Overall Summary Score at Week 12

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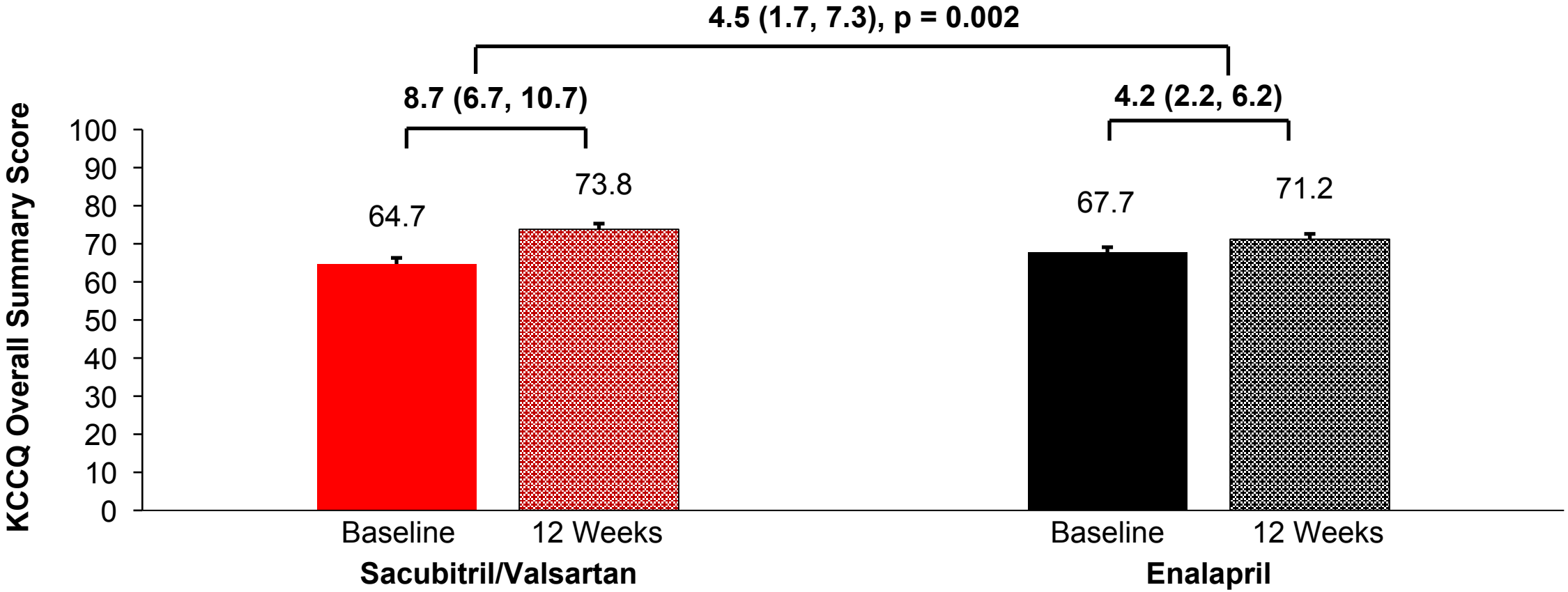

Correlation between changes from baseline to week 12 in LVEDVI, KCCQ, and NTproBNP

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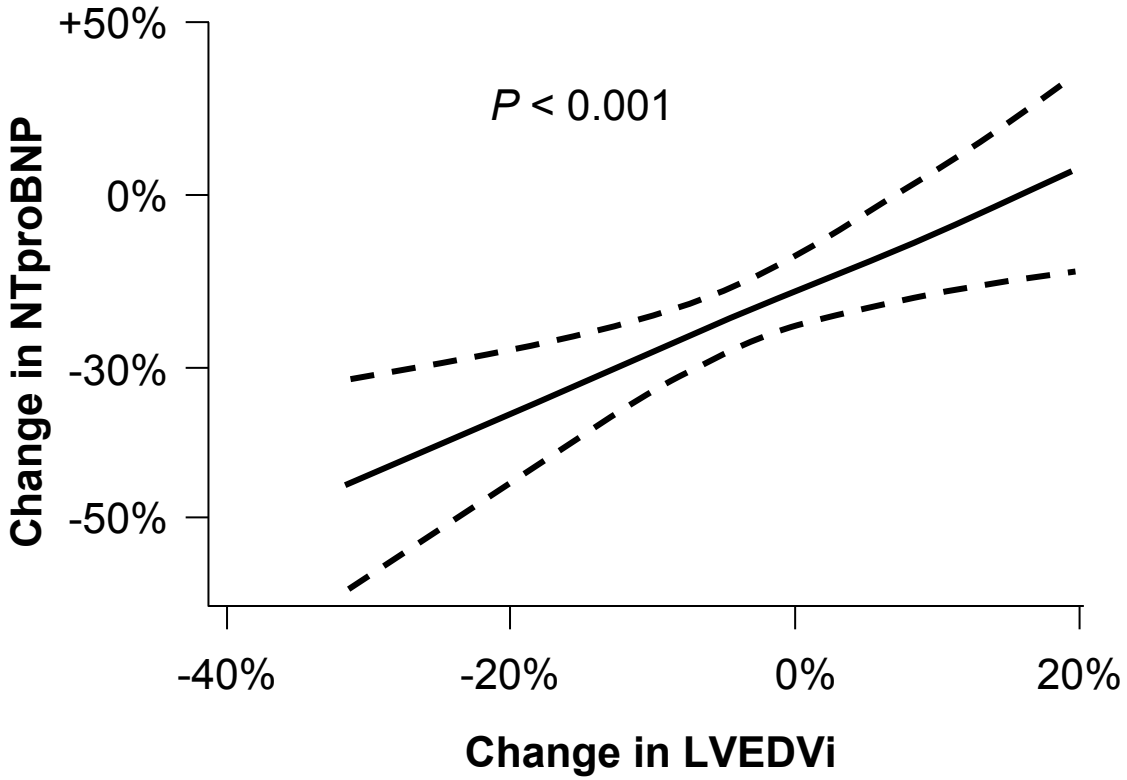

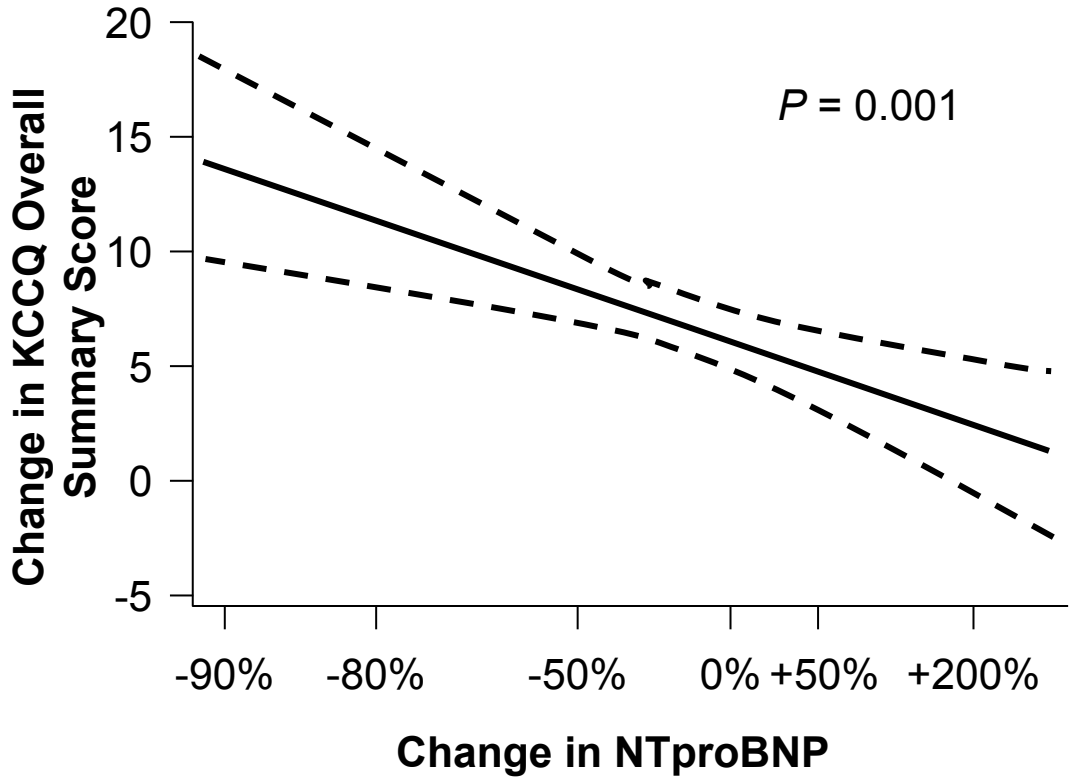

Adverse Events of Interest

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	Sacubitril/Valsartan (N=231)	Enalapril (N=233)	RR* [95% CI]
Hyperkalemia (K>5.3 meq/L), n (%)	37 (16)	30 (12.9)	1.24 (0.80,1.94)
Worsening renal function, n (%)**	12 (5.2)	14 (6.0)	0.86 (0.41, 1.83)
Hypotension (SBP< 90 mm Hg), n (%)	9 (3.9)	4 (1.7)	2.27 (0.71, 7.27)
Angioedema, n (%)	0 (0.0)	1 (0.4)	--

* sacubitril/valsartan vs. enalapril

**worsening renal function defined as decrease in eGFR of >=35% or increase in serum creatinine of >= 0.5 mg/dL from baseline AND decrease in eGFR of >=25% from baseline.

Limitations

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- No treatment effect on primary endpoint
  - Favorable changes in secondary endpoints should be interpreted in context of established clinical benefits of sacubitril-valsartan
- Randomized treatment exposure limited to 12 weeks
  - Longer duration felt to be unethical in light of PARADIGM-HF results
- Selected population with mild HF symptoms and no AF
- Not powered for clinical outcomes

Conclusions

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- Among patients with HFrEF, sacubitril/valsartan did not reduce Zc at 12 weeks compared with enalapril
- Significant reductions were seen with sacubitril/valsartan in left ventricular and left atrial volumes as well as mitral E/e' suggesting a favorable impact on ventricular remodeling and filling pressure
- Cardiac structural changes mirrored significant reductions in cardiac biomarkers and improvement in overall quality of life

Implications

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- **Clinical benefits of sacubitril/valsartan in HFrEF are likely unrelated to changes in central aortic stiffness or pulsatile load, but might be related to effects on myocardial remodeling and wall stress**

- **These data provide mechanistic support to the established clinical benefits of sacubitril/valsartan in HFrEF**

JAMA | Original Investigation

Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction

A Randomized Clinical Trial

Akshay S. Desai, MD, MPH; Scott D. Solomon, MD; Amil M. Shah, MD; Brian L. Claggett, PhD; James C. Fang, MD; Joseph Izzo, MD; Kevin McCague, MA; Cheryl A. Abbas, PharmD; Ricardo Rocha, MD; Gary F. Mitchell, MD; for the EVALUATE-HF Investigators

IMPORTANCE Compared with enalapril, sacubitril-valsartan reduces cardiovascular mortality and heart failure hospitalization in patients with heart failure and reduced ejection fraction (HFrEF). These benefits may be related to effects on hemodynamics and cardiac remodeling.

OBJECTIVE To determine whether treatment of HFrEF with sacubitril-valsartan improves central aortic stiffness and cardiac remodeling compared with enalapril.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind clinical trial of 464 participants with heart failure and ejection fraction of 40% or less enrolled across 85 US sites between August 17, 2016, and June 28, 2018. Follow-up was completed on January 26, 2019.

INTERVENTIONS Randomization (1:1) to sacubitril-valsartan (n = 231; target dosage, 97/103 mg twice daily) vs enalapril (n = 233; target dosage, 10 mg twice daily) for 12 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was change from baseline to week 12 in aortic characteristic impedance (Zc), a measure of central aortic stiffness. Prespecified secondary outcomes included change from baseline to week 12 in N-terminal pro-B-type natriuretic peptide, ejection fraction, global longitudinal strain, mitral annular relaxation velocity, mitral E/e' ratio, left ventricular end-systolic and end-diastolic volume indexes (LVESVI and LVEDVI), left atrial volume index, and ventricular-vascular coupling ratio.

RESULTS Of 464 validly randomized participants (mean age, 67.3 [SD, 9.1] years; 23.5% women), 427 completed the study. At 12 weeks, Zc decreased with sacubitril-valsartan and increased with enalapril; the between-group difference in change from baseline was not statistically significant. Of 9 prespecified secondary end points, no significant between-group difference in change from baseline was seen in 4, including LVEF. Greater reductions from baseline were seen with sacubitril-valsartan in all others, including left atrial volume index, LVEDVI, LVESVI, and mitral E/e' ratio. Rates of adverse events including hypotension (1.7% vs 3.9%) were similar in both groups.

Parameters	Sacubitril-Valsartan, Mean (SD)		Enalapril, Mean (SD)		Between-Group Difference (95% CI)
	Baseline	12 wk	Baseline	12 wk	
Primary End Point					
Aortic Zc, dyne × s/cm^5	223.8 (112.7)	218.9 (112.7)	213.2 (102.6)	214.3 (95.2)	−2.2 (−17.6 to 13.2)
Secondary End Points					
LVEF, %	34 (10)	36 (10)	33 (10)	35 (10)	0.6 (−0.4 to 1.7)
LVEDVI, mL/m^2	75.1 (26.1)	70.3 (23.5)	79.1 (25.9)	75.6 (23.7)	−2.0 (−3.7 to −0.3)
LVESVI, mL/m^2	50.8 (22.6)	46.3 (20.5)	54.1 (22.6)	50.6 (20.0)	−1.6 (−3.1 to −0.03)
Left atrial volume index, mL/m^2	30.4 (9.5)	28.2 (9.0)	29.8 (8.7)	30.5 (9.1)	−2.8 (−4.0 to −1.6)
Mitral E/e' ratio	13.8 (7.6)	12.3 (5.6)	13.4 (6.8)	13.8 (7.4)	−1.8 (−2.8 to −0.8)

CONCLUSIONS AND RELEVANCE Treatment of HFrEF with sacubitril-valsartan, compared with enalapril, did not significantly reduce central aortic stiffness. The study findings may provide insight into mechanisms underlying the effects of sacubitril-valsartan in HFrEF.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02874794

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Group Information: A list of the EVALUATE-HF Investigators appears at the end of this article.

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