Angiotensin-neprilysin inhibition in heart failure across the spectrum of ejection fraction

A prespecified pooled analysis of the PARADIGM-HF and PARAGON-HF trials

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for the PARADIGM-HF and PARAGON-HF Investigators

PARADIGMHF

PARAGONHF

Disclosures

- Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos, and has consulted for Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya

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Background and Rationale

- Although heart failure with reduced ejection fraction (HFrEF) has multiple etiologies, virtually all patients with this disorder respond to several classes of pharmacologic therapies that have, in clinical trials, been shown to contribute to step-wise reductions in morbidity and mortality.
- Nevertheless, few options have been available for patients with ejection fraction above the “reduced” range, generally considered 40% or less.
- Sacubitril/valsartan has now been compared with a renin-angiotensin-system (RAS) inhibitor alone in two similarly designed large outcomes trials of patients with reduced and preserved LVEF, permitting examination of its effects across the full spectrum of LVEF.

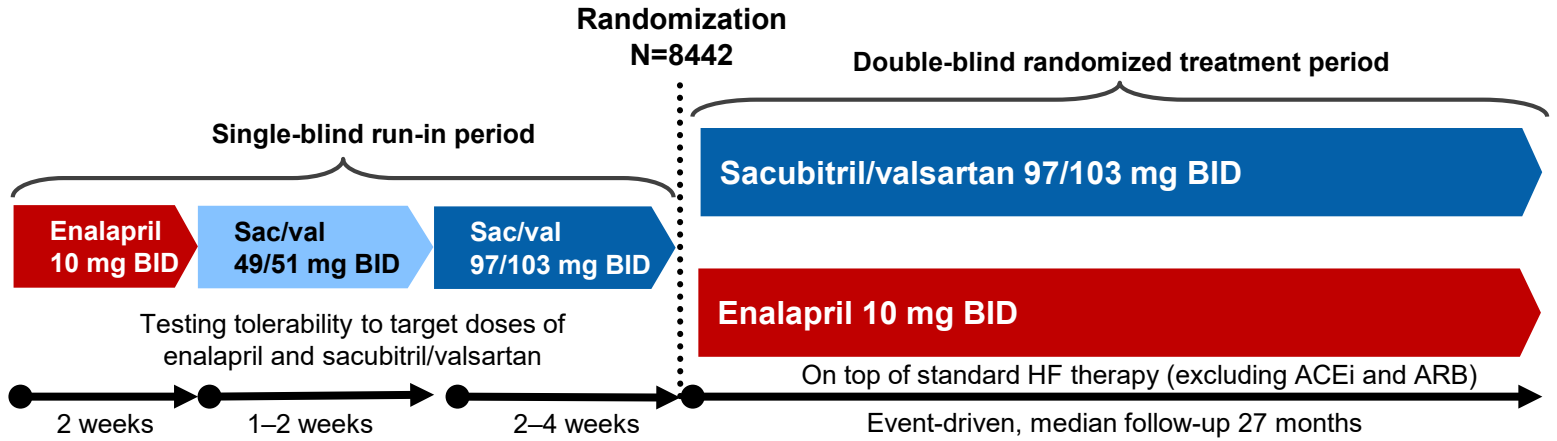
1. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. Lancet. 2019;393:1034-1044;
2. McMurray JJ, et al. N Engl J Med 2014;371:993–1004;
3. Solomon SD, et al. Lancet 2012;380:1387–95.

Entry criteria

PARADIGM-HF

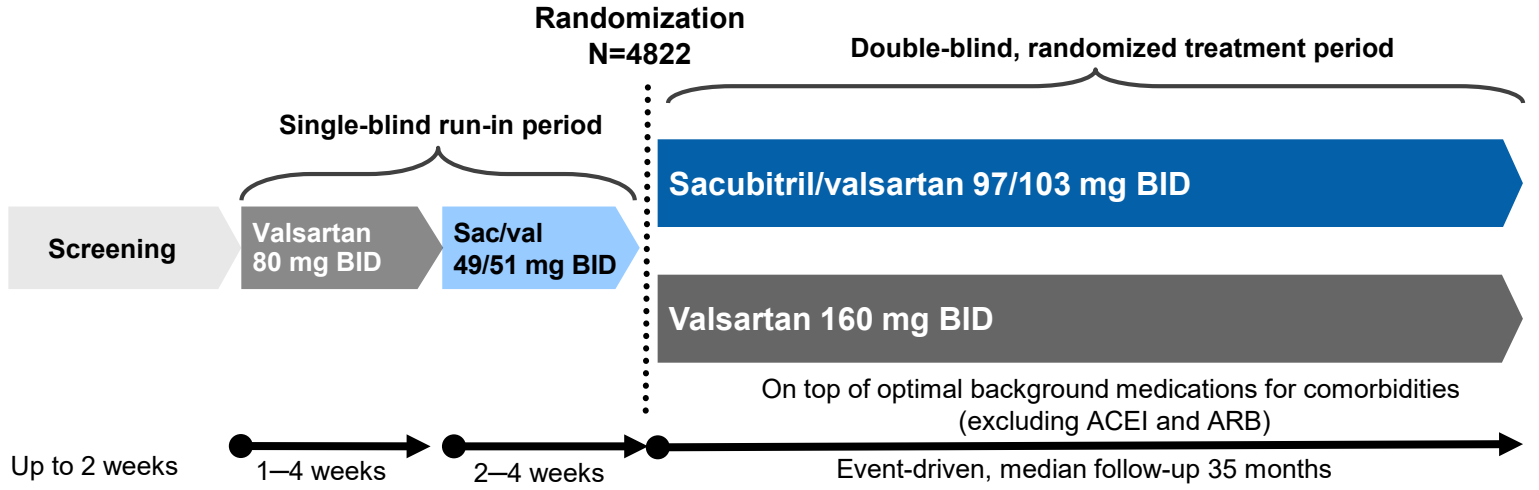
- Age ≥18 years
- Signs/symptoms of heart failure (NYHA II-IV)
- LVEF ≤40%
- Elevation in NT-proBNP (400/600 or BNP 100/150 depending on prior HF hospitalization)

Study design



PARAGON-HF

- Age ≥50 years
- Signs/symptoms of heart failure (NYHA II-IV)
- LVEF ≥45%
- Elevation in NT-proBNP (200/600 or 300/900 depending on prior HF hospitalization and AF)
- Structural heart disease (LVH or LAE)
- No prior LVEF <40%

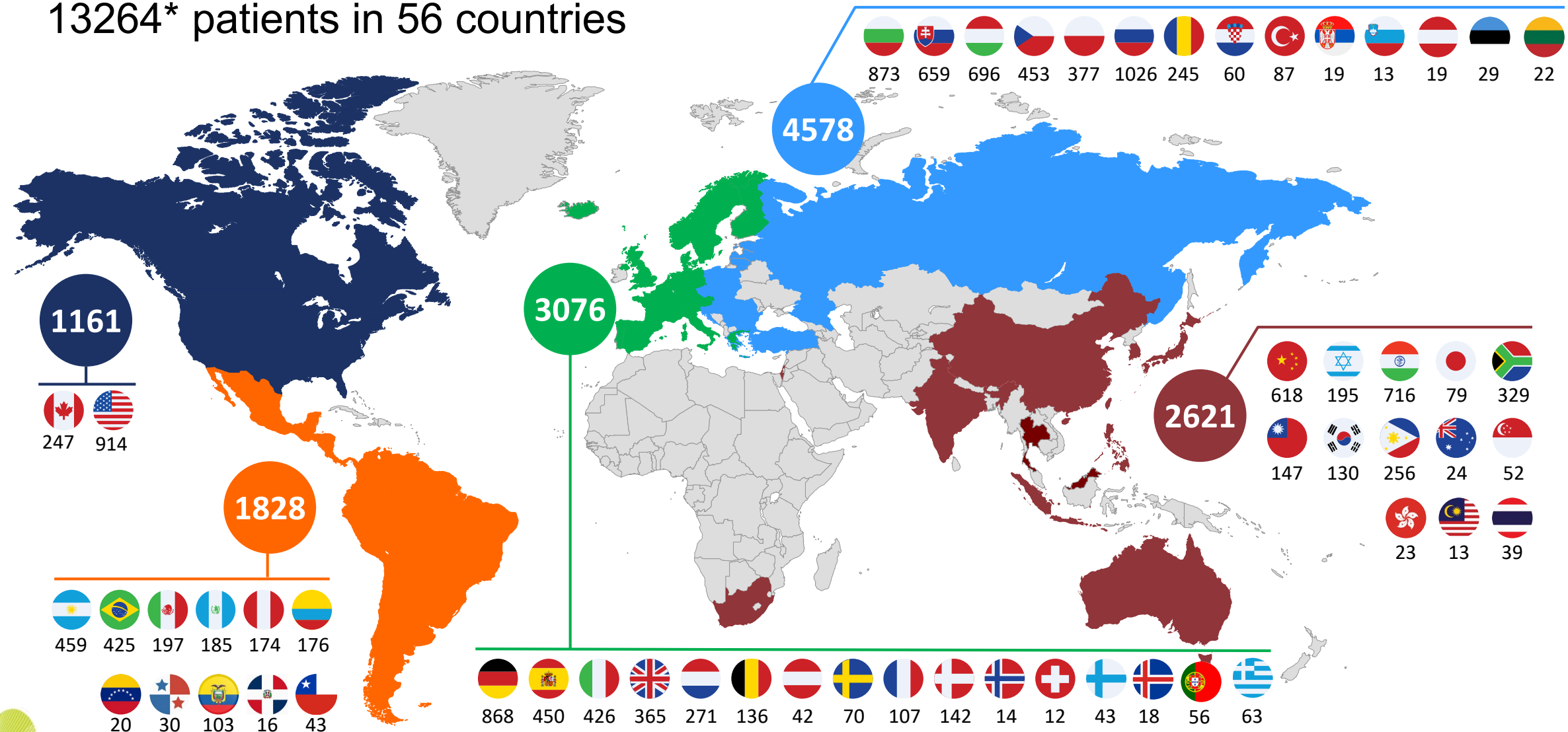


PARADIGMHF

PARAGONHF

PARAGON-HF and PARADIGM-HF combined

13264* patients in 56 countries



PARADIGMHF

*46 patients from PARADIGM-HF and 26 from PARAGON-HF excluded from final analysis

PARAGONHF

Methodologic Considerations

- 13,195 patients from two trials
- Ejection fractions measured at sites (exact numbers required)
- Pooling results from PARADIGM-HF and PARAGON-HF was prespecified prior to unblinding
- We divided patients into 10 point EF groups (≤22.5%, >22.5 to 32.5%, >32.5% to 42.5%, >42.5% to 52.5%, >52.5% to 62.5%, >62.5) avoiding cut-offs on multiples of 5 because of substantial digit preference
- We compared treatment effects for those randomized to sacubitril/valsartan compared with RAS inhibitor (enalapril or valsartan) overall (stratifying by study) and within each EF group, and using continuous analyses
- We assessed both time to first composite of CV death or heart failure hospitalization (PARADIGM primary endpoint) and the composite of total heart failure hospitalizations and cardiovascular death (PARAGON primary endpoint) across the spectrum of LVEF

1. Lin DW, et al. J R Statist Soc B 2000;62:711–30;
2. Solomon S et al. JACC-HF. 2017;5(7):471–482.

Baseline Characteristics (1/2)

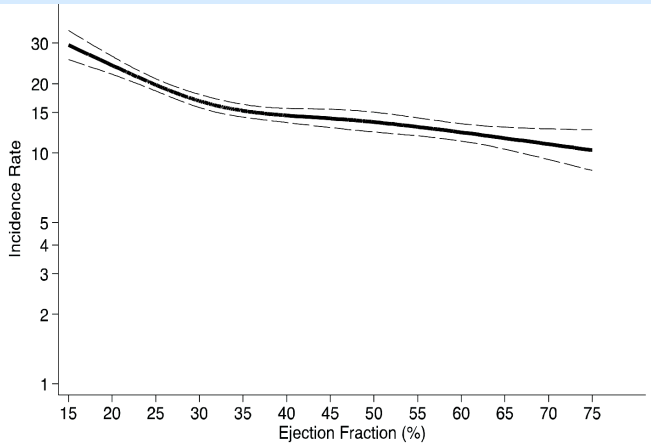
	Categories of left ventricular ejection fraction (%)						
	≤22.5 n=1269	>22.5 to 32.5 n=3987	>32.5 to 42.5 n=3143	>42.5 to 52.5 n=1427	>52.5 to 62.5 n=2166	>62.5 n=1202	P-trend
LVEF (%)	18.6±3.0	28.2±2.7	35.5±2.1	48.6±2.2	57.6±2.7	68.1±4.6	--
Age (years)	61±12	63±11	66±11	71±9	73±8	74±8	<0.001
Female sex (%)	19	21	24	40	54	63	<0.001
White race (%)	55	62	76	82	84	76	
NYHA I/II (%)	79	76	72	79	79	84	
NYHA III/IV (%)	21	24	28	22	21	16	
Prior HF hospitalization (%)	64	63	62	51	48	45	<0.001
Hypertension (%)	61	68	79	94	96	97	<0.001
Diabetes mellitus (%)	34	34	35	44	44	41	<0.001
History of MI (%)	39	44	45	32	20	16	<0.001
AF at baseline (%)	28	33	45	34	34	29	0.49

Baseline Characteristics (2/2)

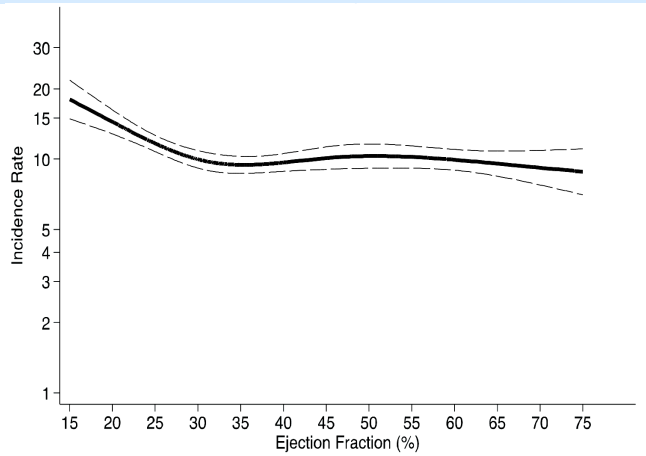
	Categories of left ventricular ejection fraction (%)						
	≤22.5 n=1269	>22.5 to 32.5 n=3987	>32.5 to 42.5 n=3143	>42.5 to 52.5 n=1427	>52.5 to 62.5 n=2166	>62.5 n=1202	P-trend
SBP (mmHg)	117±15	121±15	124±15	131±15	131±16	130±16	<0.001
NT-proBNP at baseline	2183 [1135−4700]	1645 [897−3422]	1406 [805−2577]	1070 [556−1875]	894 [457−1563]	714 [419−1412]	<0.001
Estimated GFR (mL/min/1.73 m²)	68±21	68±20	67±20	65±20	62±19	61±18	<0.001
Medications (%)							
ACE inhibitors	79	78	77	47	39	36	<0.001
ARBs	22	23	23	41	47	49	<0.001
ACE inhibitors or ARBs	>99	>99	>99	88	86	85	< 0.001
β-blockers	93	94	93	82	80	76	<0.001
MRAs	62	58	50	30	23	24	<0.001
Diuretics	83	81	78	95	95	93	<0.001

Event Rates by Baseline Ejection Fraction

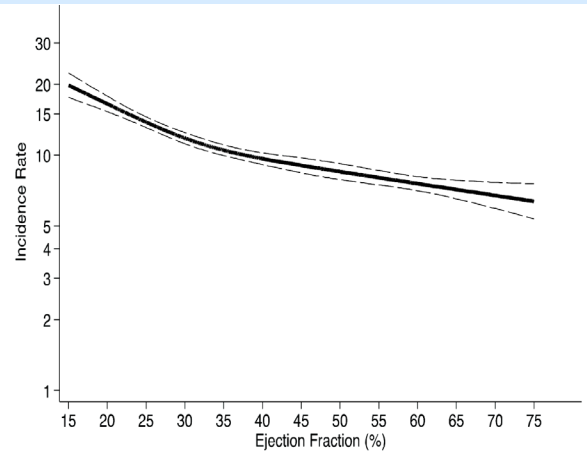
Total CV death and HF hospitalizations



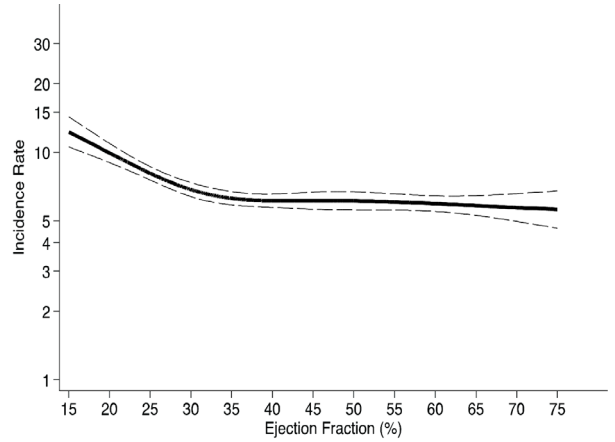
Total HF hospitalizations



First CV death and HF hospitalizations



First HF hospitalizations



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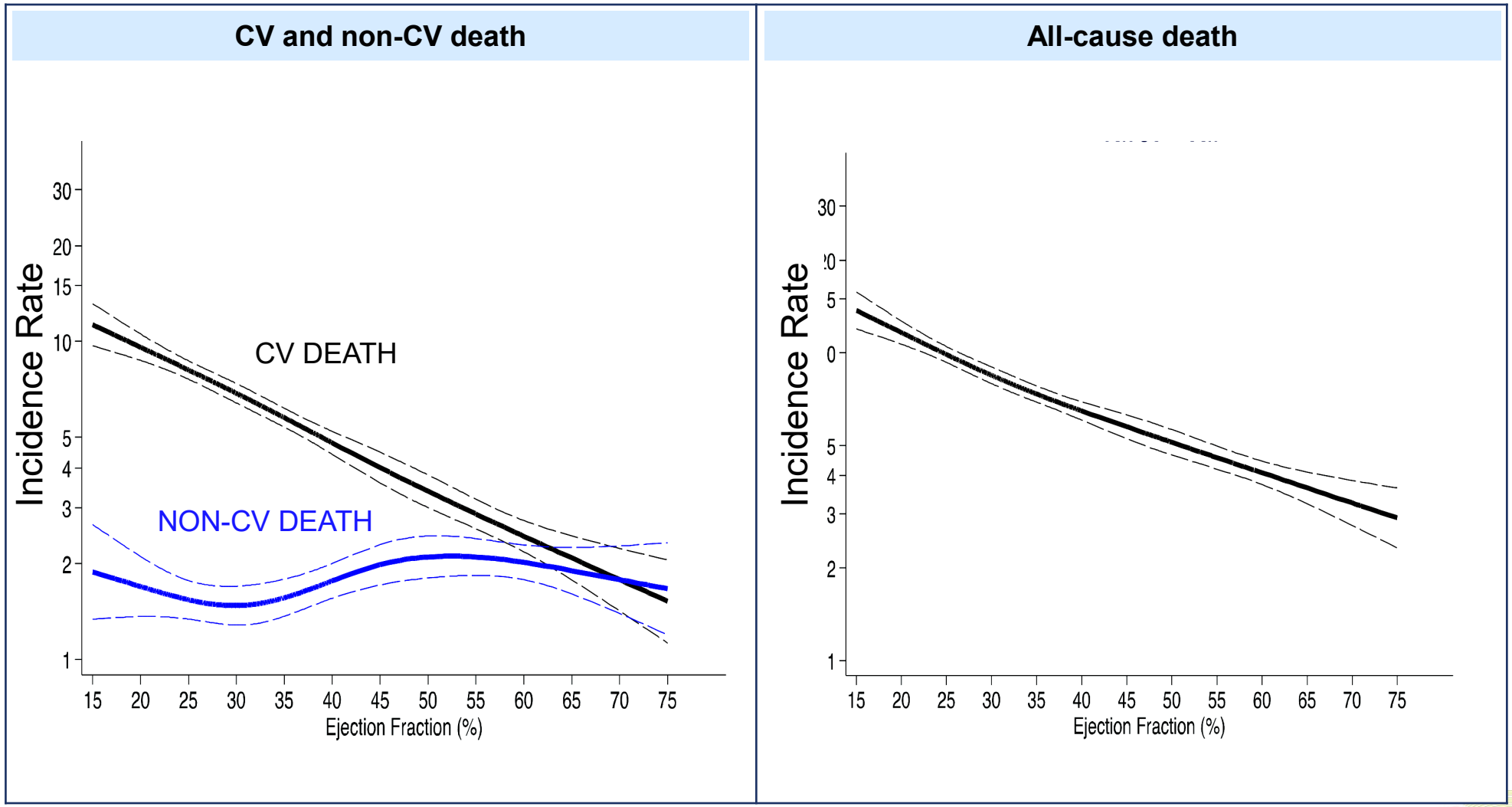
Influence of Ejection Fraction on CV, non-CV and All-cause Mortality



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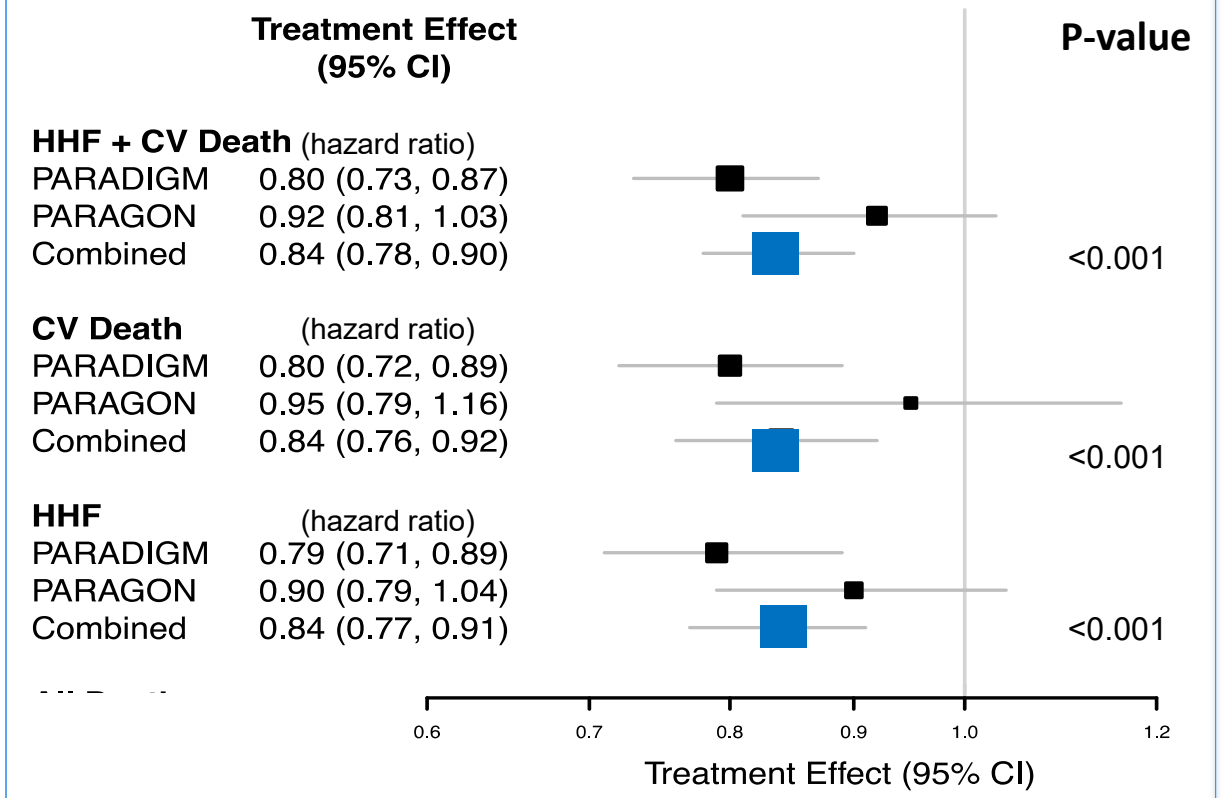
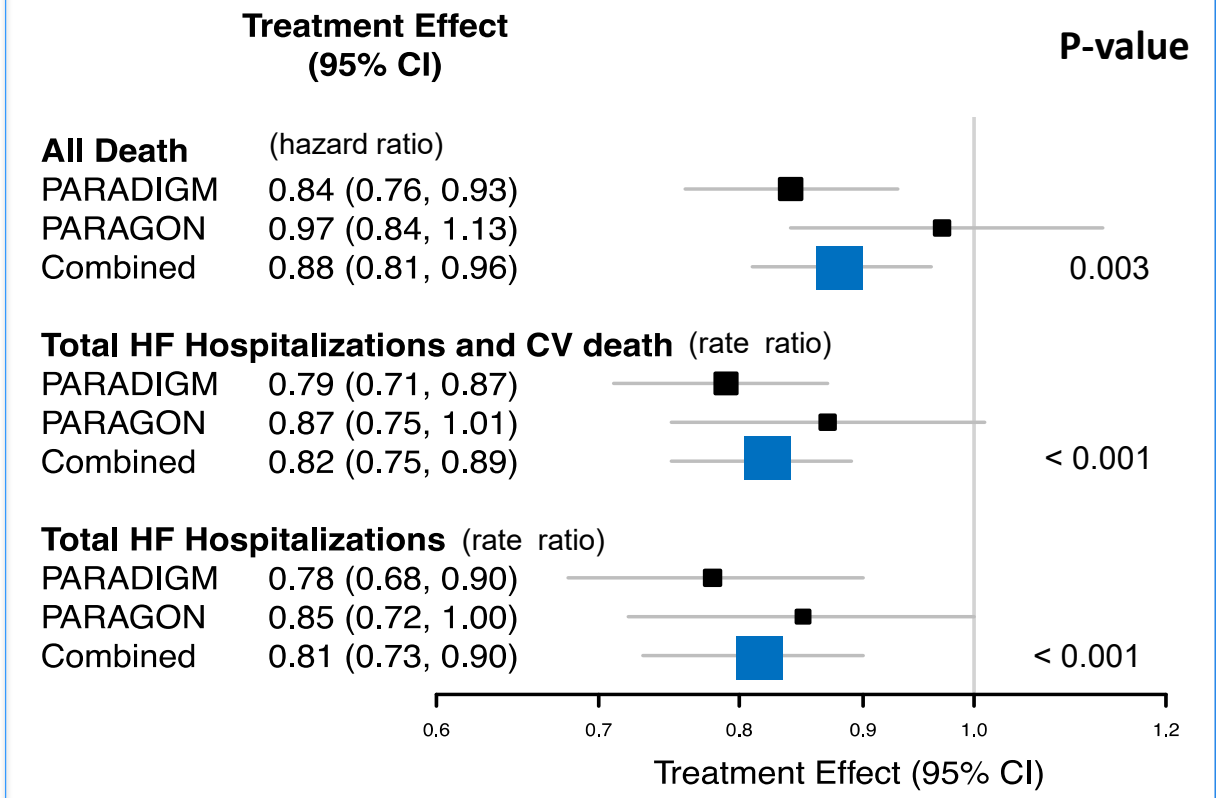
Sacubitril/Valsartan vs. RAS inhibitor in Pooled Analysis (N=13,195)





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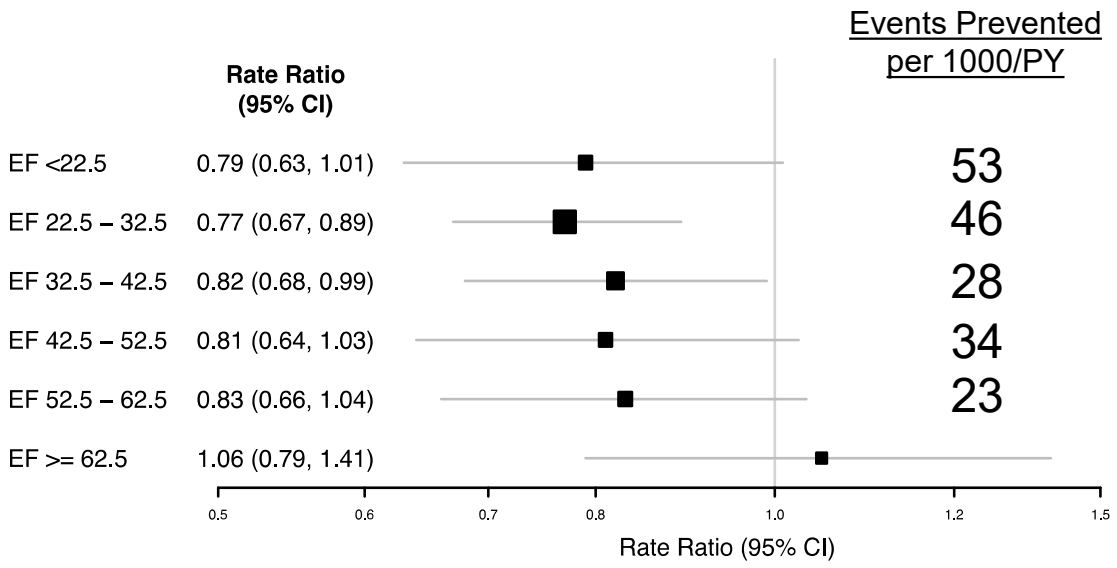
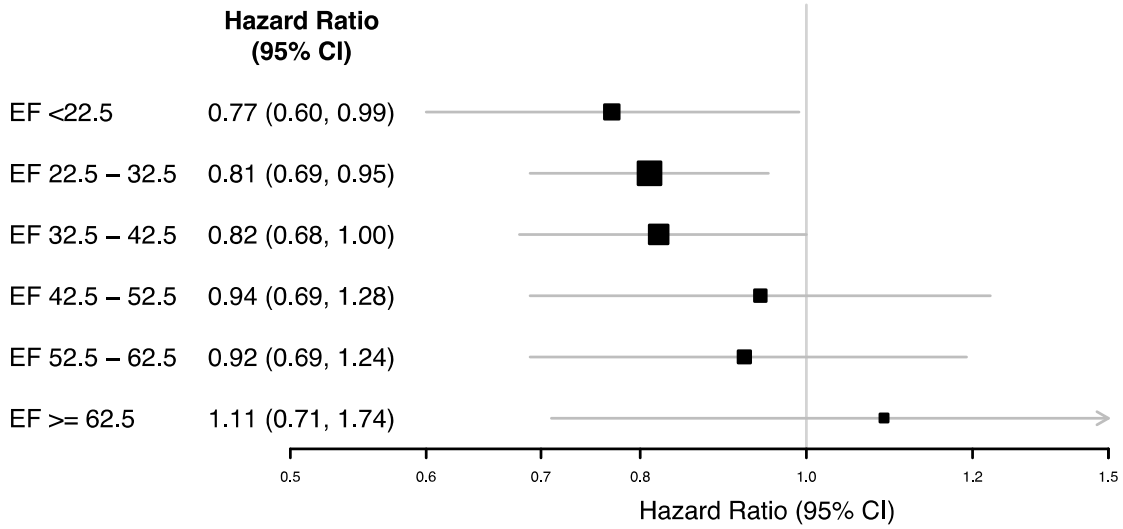
Treatment Efficacy across the Spectrum of Ejection Fraction

CV death and total HF hospitalizations



CV death



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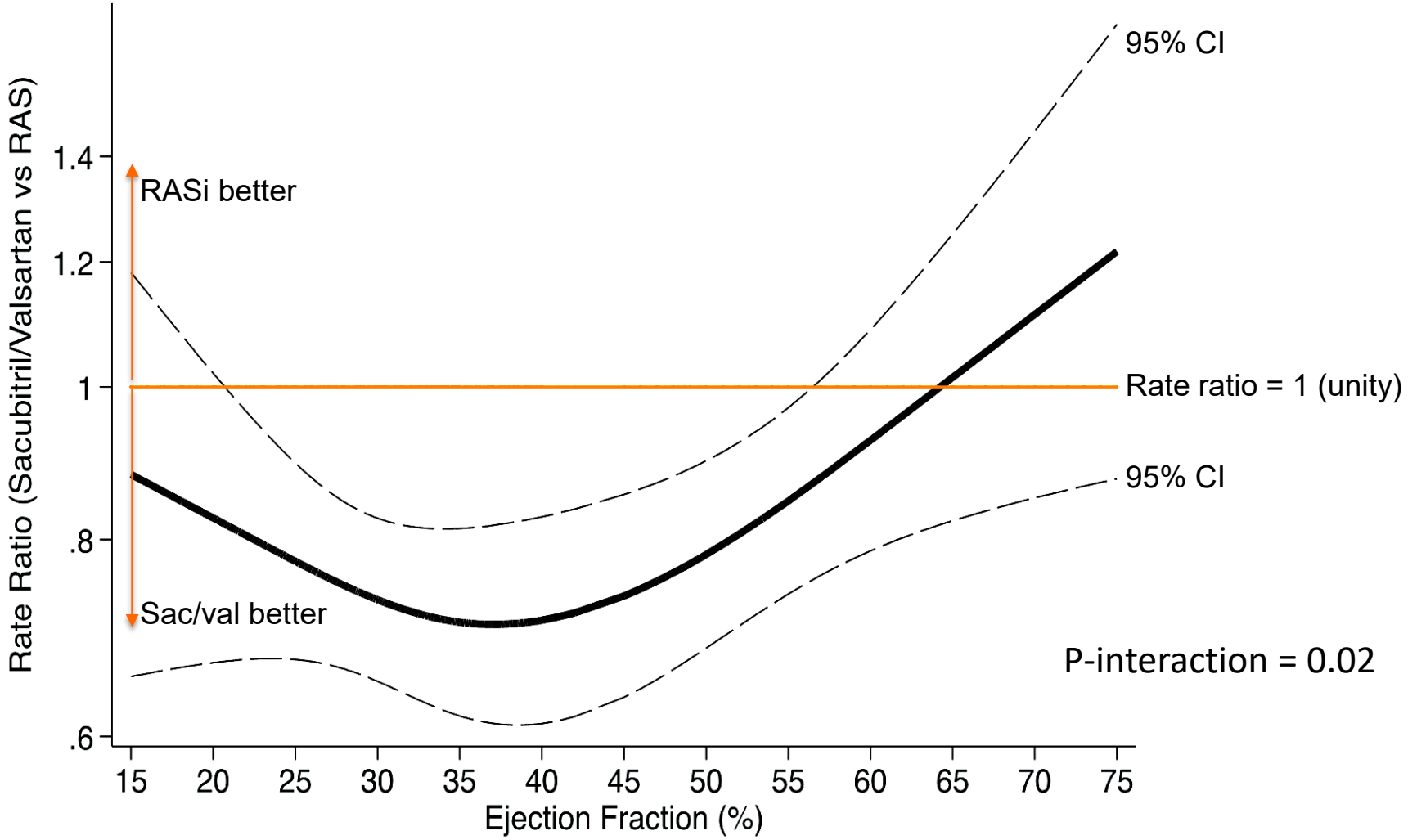
Treatment Effect by Continuous Ejection Fraction

Total HF Hospitalizations and CV Death (PARAGON-HF Primary Endpoint)



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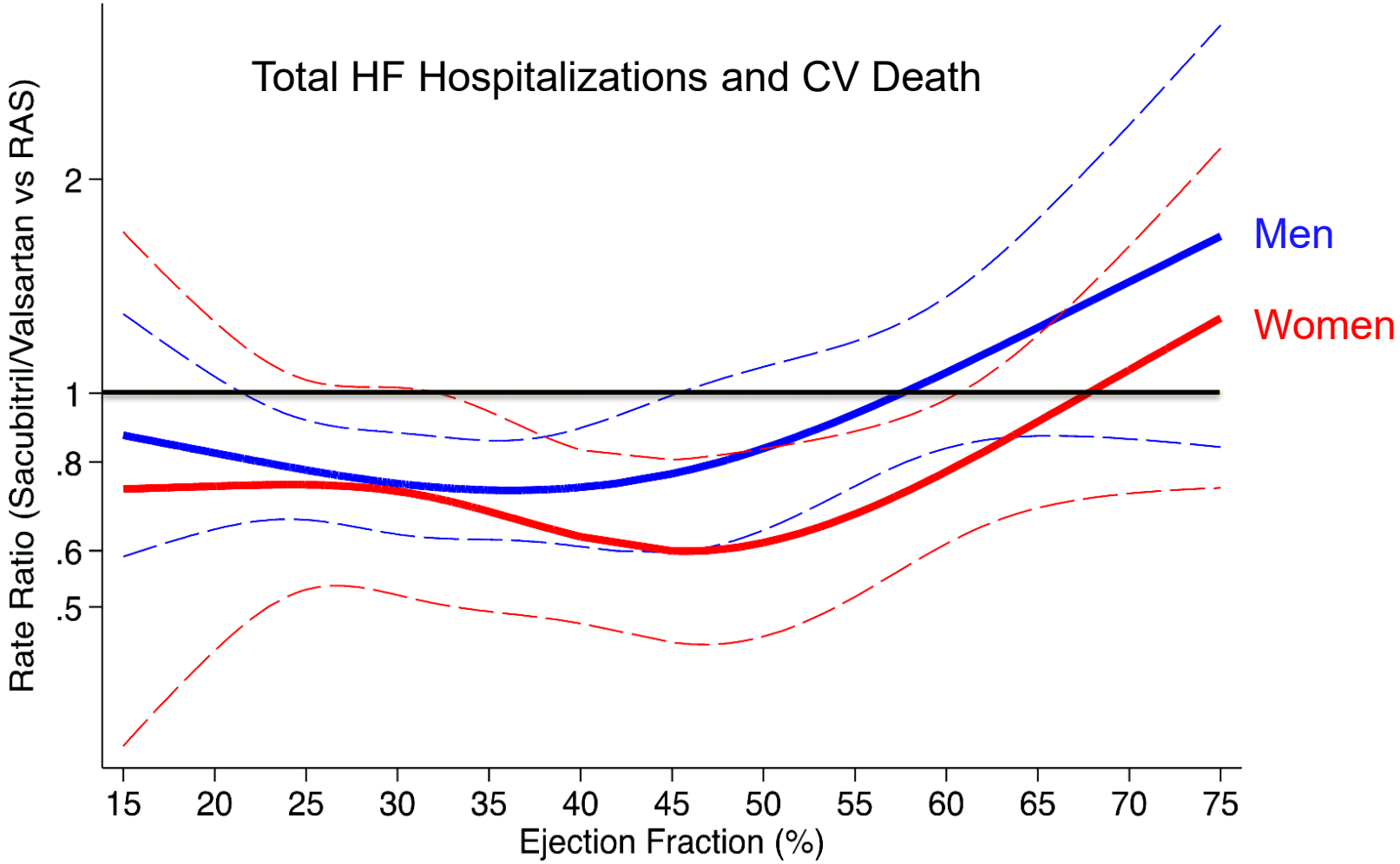
Treatment Effect by LVEF and Sex

Benefit extends to higher LVEF in Women



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Safety by Ejection Fraction

Left Ventricular Ejection Fraction (%)													
	≤22.5 n=1269		>22.5 to 32.5 n=3987		>32.5 to 42.5 n=3143		>42.5 to 52.5 n=1427		>52.5 to 62.5 n=2166		>62.5 n=1202		Interaction with treatment P-value
	RAS	S/V	RAS	S/V	RAS	S/V	RAS	S/V	RAS	S/V	RAS	S/V	
Hypotension (SBP<100) (%)	31	38	20	27	15	15	9	13	12	15	11	20	0.15
Creatinine ≥2.5 mg/dl (%)	6	3	4	3	4	4	5	5	6	4	3	3	0.31
Potassium >5.5 mmol/l (%)	17	15	16	16	19	19	17	13	15	14	13	12	0.58

Conclusions

- In this large, patient-level analysis of two pivotal trials we observed overall benefit comparing sacubitril/valsartan to RAS inhibition alone.
- These findings were driven by an observed benefit in patients with chronic HF and LVEF below the “normal” range, with women deriving benefit to a higher LVEF than men.
- These data suggest that the therapeutic response to sacubitril/valsartan may be heterogeneous with respect to ejection fraction, and that the benefits of sacubitril/valsartan, compared with a RAS inhibitor alone, appear to extend to patients with heart failure and mildly reduced ejection fraction, with women perhaps benefiting to higher ejection fractions than men.

Circulation

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Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure

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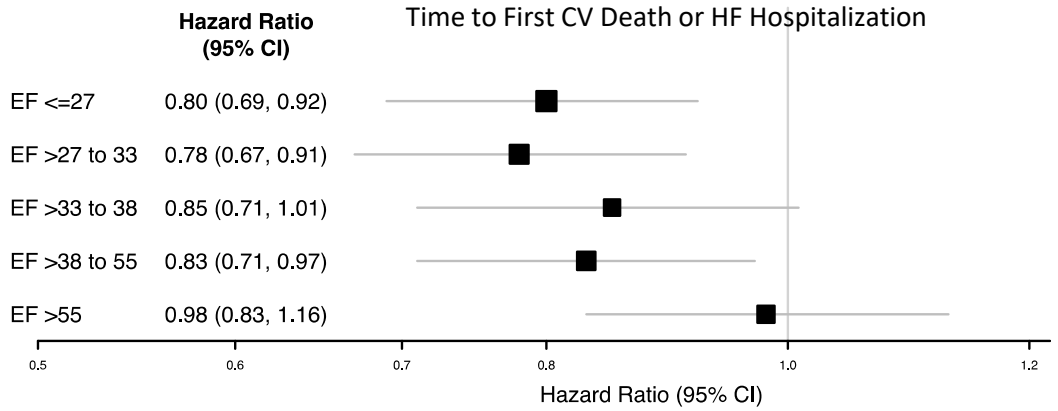
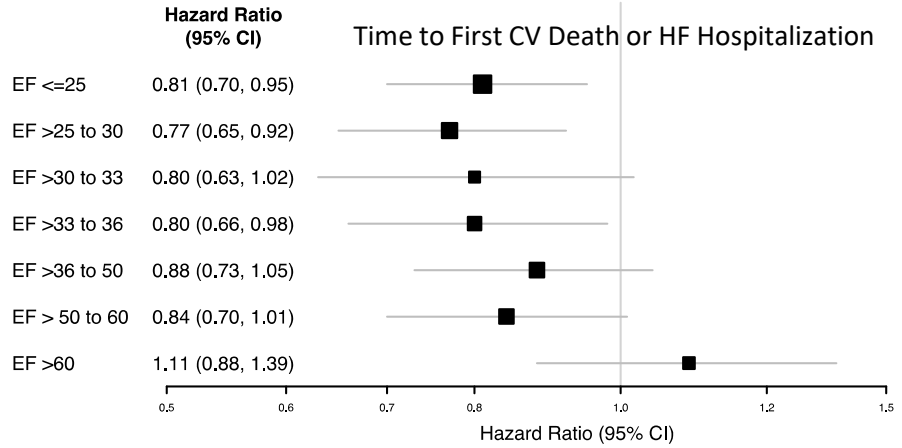
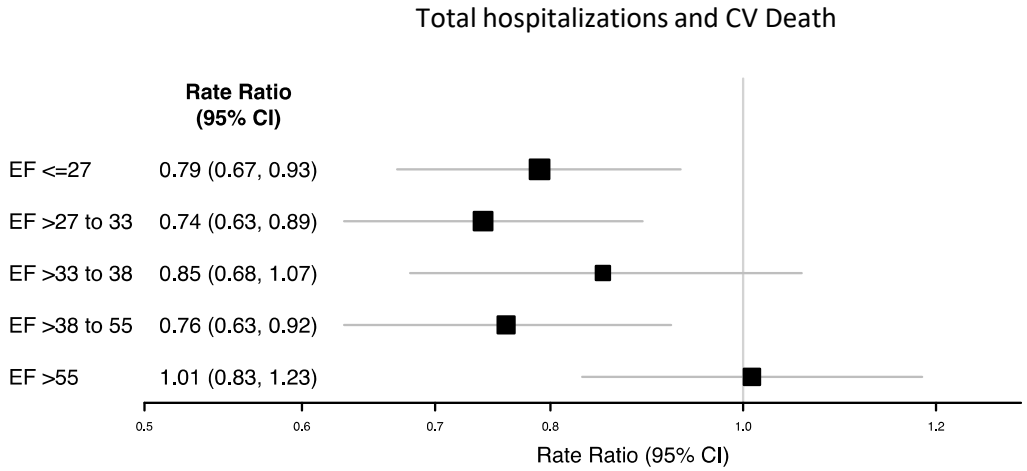
Benefit of sacubitril/valsartan across Quantiles of Ejection Fraction

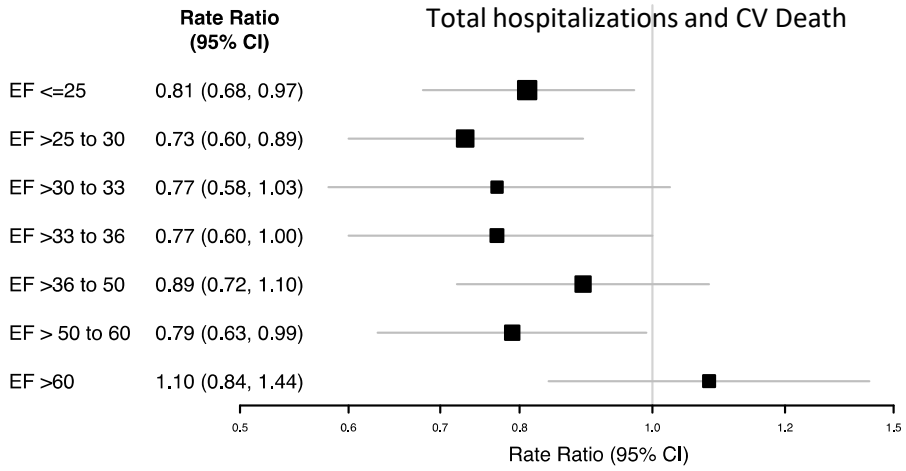
Quintiles



Septiles







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