Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction

Primary results of the PARAGON-HF trial

Scott D. Solomon, MD, and John J.V. McMurray, MD

for the PARAGON-HF Committees, National Leaders and Investigators

Declaration of interest

- Research contracts (Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (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)

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

Background and rationale

Heart failure with preserved ejection fraction (HFpEF) accounts for half of heart failure, is rising in prevalence, and is associated with substantial morbidity and mortality[1]

While evidence-based therapies exist for heart failure with reduced ejection fraction (HFrEF; LVEF ≤40%), no therapies have been proven beneficial in those with LVEF >40%

In PARADIGM-HF, the angiotensin receptor neprilysin inhibitor sacubitril/valsartan reduced HF hospitalization and CV death, compared with enalapril, in patients with HFrEF (LVEF ≤40%)[2]

In a phase II trial in HFpEF, sacubitril/valsartan reduced NT-proBNP, improved left atrial size and NYHA functional class, when compared with valsartan[3]

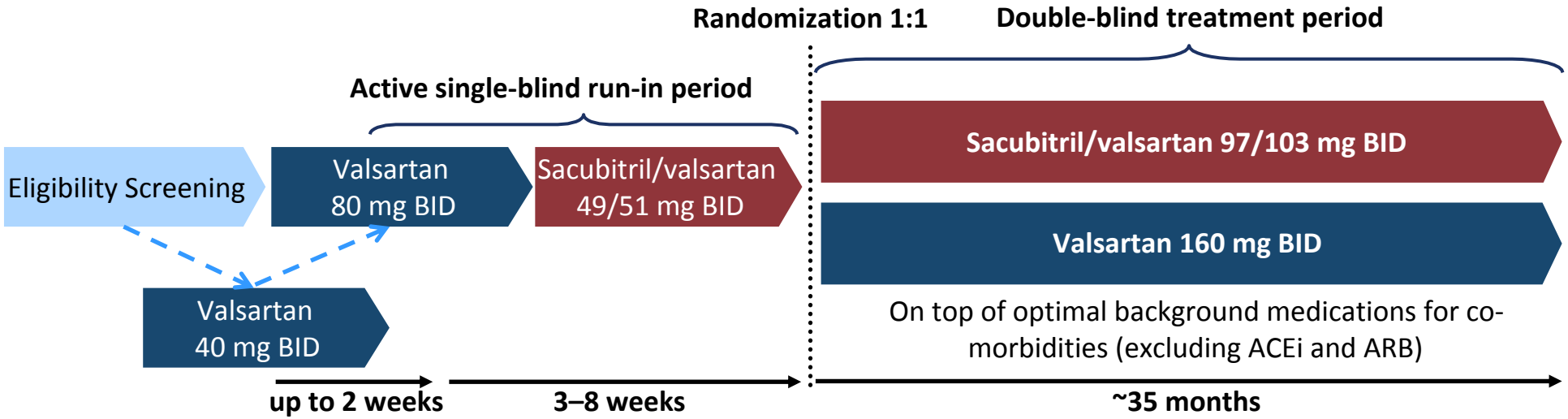
1. Redfield MM, *et al. N Engl J Med* 2017;376:89.

2. McMurray JJ, *et al. N Engl J Med* 2014;371:993–1004.

3. Solomon SD, *et al. Lancet* 2012;380:1387–95.

PARAGON-HF study design

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death



Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

Solomon SD, *et al. JACC-Heart Fail* 2017; 5(7):471-482.

Key inclusion & exclusion criteria

Key inclusion criteria	Key exclusion criteria
• ≥ 50 years of age and LVEF ≥ 45% • Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s) for at least 30 days prior to enrollment • Structural heart disease (LAE or LVH by echocardiography) • Elevation in natriuretic peptides • NT-proBNP 200 pg/ml if hospitalized for HF within 9 months, and 300 pg/ml if not hospitalized; 3-fold increase for patients in AF at enrollment	• Any prior measurement of LVEF < 40% • Current acute decompensated heart failure • Alternative reason for signs and symptoms • SBP < 110 or > 180mm Hg (or > 150mm Hg if patient not taking 3 or more antihypertensive medications)

Solomon SD, *et al. JACC-Heart Fail* 2017

Statistical considerations

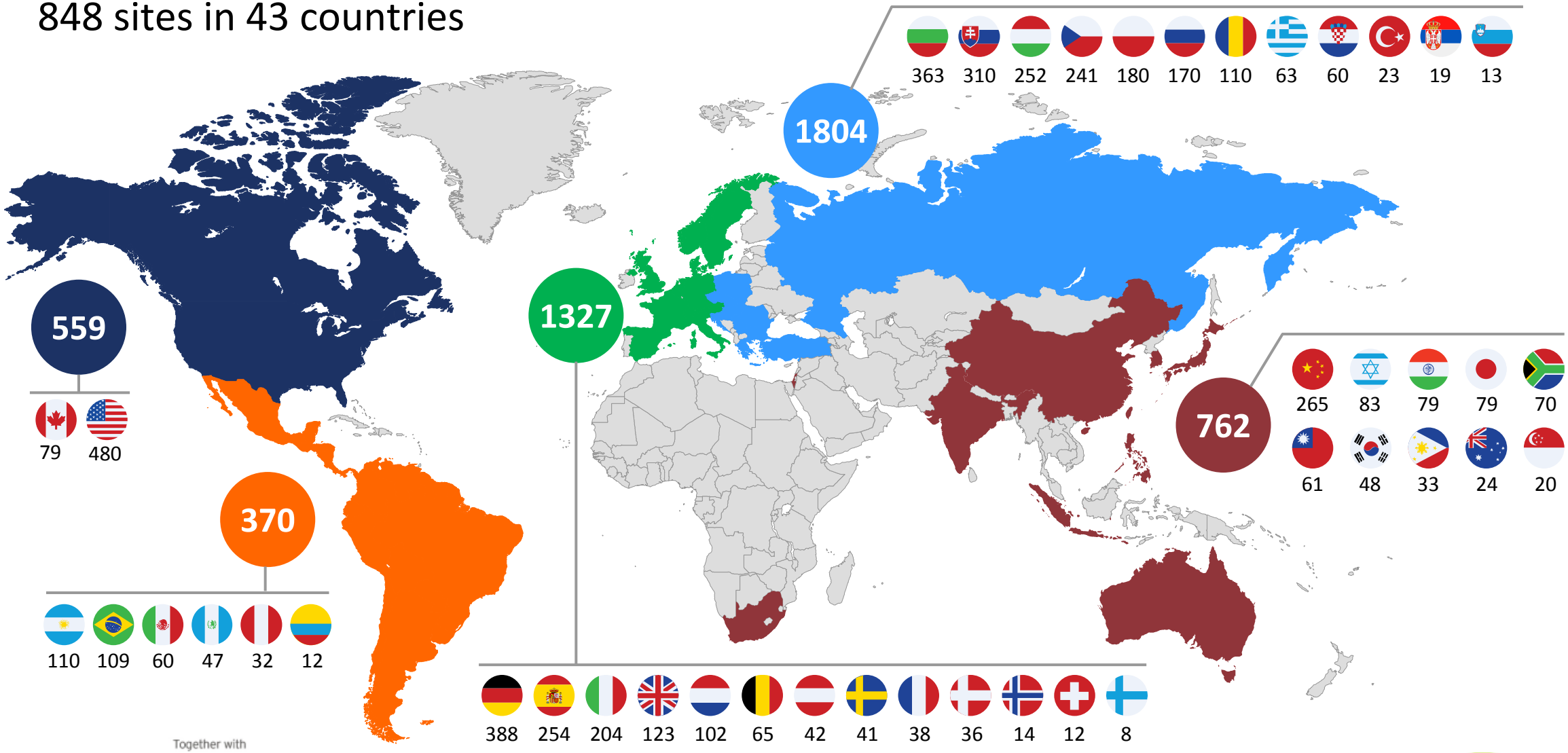
To fully capture the total burden of disease in this population, the primary analysis incorporated total (first and recurrent) HF hospitalizations and CV death, utilizing the semi-parametric proportional rates model of Lin, Wei, Yang, Ying[1] (LWYY), a modified Anderson-Gill model with a robust variance estimator to account for the correlation between events. This method considers the time from randomization to each of the total HF hospital admissions and CV death

We calculated that accrual of 1847 primary events would provide greater than 80% power with a two -sided alpha level of 0.05 to show a 19% relative rate reduction

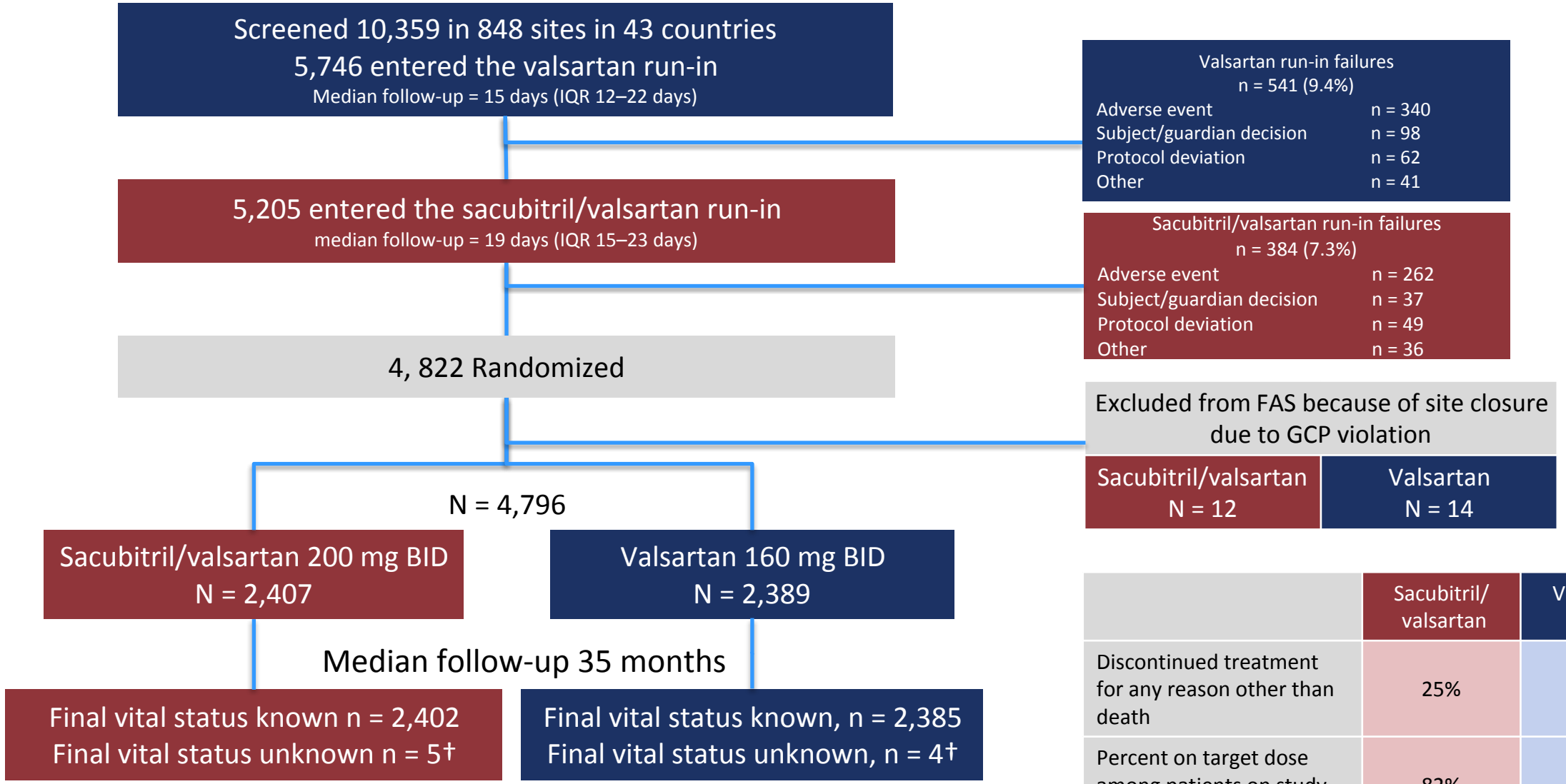
1. Lin DW, *et al. J R Statist Soc B* 2000;62:711–30.

PARAGON-HF was a global trial

848 sites in 43 countries



Patient disposition



	Sacubitril/ valsartan	Valsartan
Discontinued treatment for any reason other than death	25%	27%
Percent on target dose among patients on study medication at final visit	82%	85%

†7 withdrew consent, 2 lost to follow-up.

Baseline demographics

		Sacubitril/valsartan N=2,407	Valsartan N=2,389
Age (years) – mean (SD)		72.7 (8.3)	72.8 (8.5)
Sex – n (%)	Male	1166 (48.4)	1151 (48.2)
	Female	1241 (51.6)	1238 (51.8)
Race – n (%)	Caucasian	82%	81%
	Black	2.2%	2.1%
	Asian	12%	13%
Region – n (%)	North America*	12%	11%
	Latin America	7.9%	7.5%
	Western Europe	29%	29%
	Central Europe	36%	36%
	Asia/Pacific/other**	16%	16%
Baseline LVEF – median [IQR]		57 [51,62]	57 [50,63]
Baseline NT-proBNP (pg/mL) – median (IQR) – Sinus rhythm		583 [370, 1046]	611 [389, 1072]
Baseline NT-proBNP (pg/mL) – median (IQR) – Atrial fibrillation		1633 [1191, 2368]	1536 [1153, 2212]

*North America = US and Canada. **Asia/Pacific/Other includes Israel, South Africa, Australia, China, India, Japan, Rep of Korea, Philippines, Singapore, Taiwan.

Baseline demographics

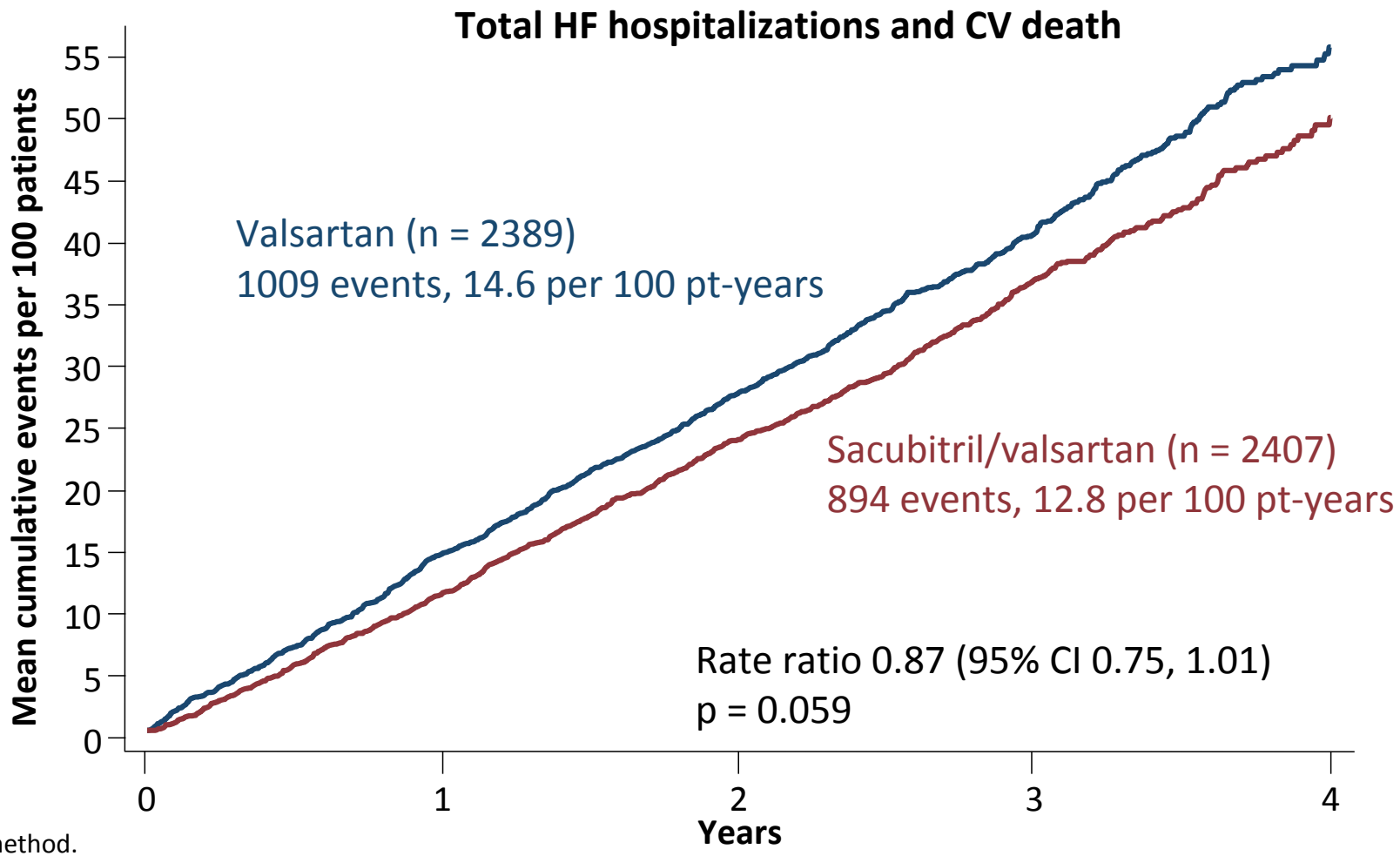
			Sacubitril/valsartan N=2,407	Valsartan N=2,389
NYHA class at randomization – n (%)		Class I	3.0%	2.7%
		Class II	78%	77%
		Class III	19%	20%
		Class IV	0.3%	0.5%
BMI – mean (SD)			30.2 (4.9)	30.3 (5.1)
Baseline systolic/diastolic blood pressure at randomization – mean (SD)/mean(SD)			130.5 (15.6)/74.3 (10.6)	130.6 (15.3)/74.3 (10.4)
Medical history – n (%)		Hypertension, n (%)	96%	95%
		Diabetes mellitus, n (%)	44%	43%
		Atrial fibrillation at screening ECG, n (%)	32%	33%
		Hospitalization for HF within 9 months	38%	39%
Medications	*Prior to randomization*	ACEi or ARBs	87%	87%
	At randomization	Diuretics	94%	95%
		MRA	24%	27%*
		Beta blockers	79%	79%
		Calcium channel blockers	34%	34%

Baseline characteristics balanced if not noted by *p<0.05.

Solomon SD, *et al. Circ Heart Fail.* 2018

PARAGON-HF primary results

Recurrent event analysis of total HF hospitalizations and CV death*



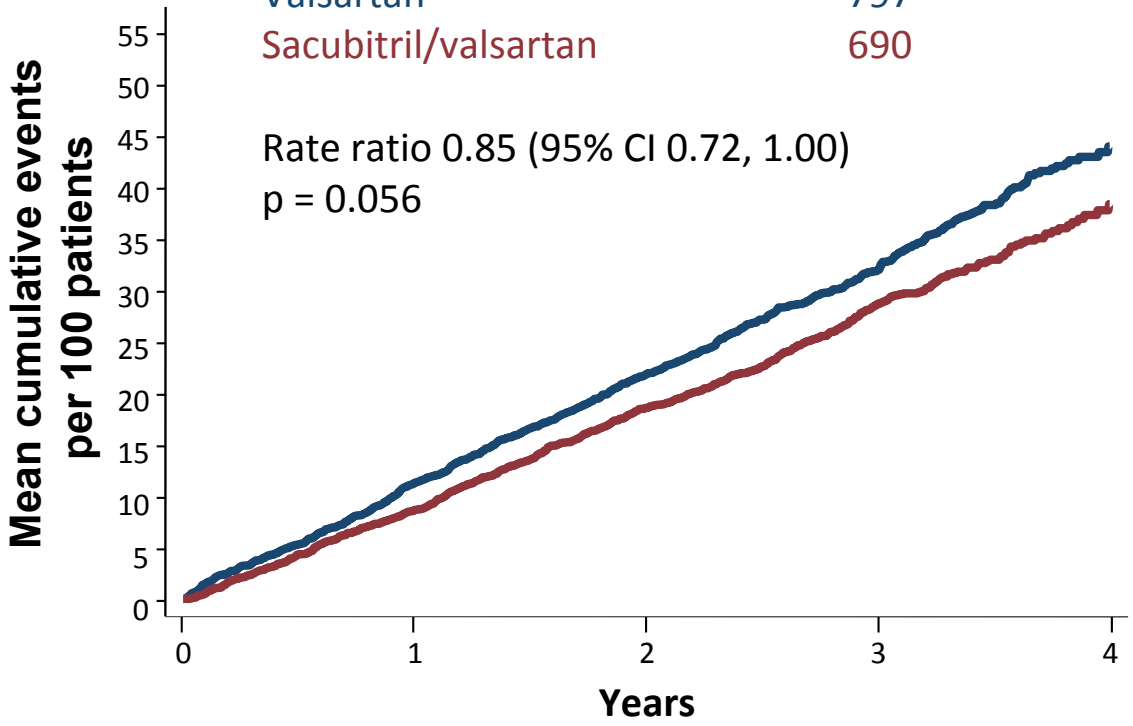
*Semiparametric LWYY method.

HF hospitalizations and CV death

HF hospitalizations*

	Events
Valsartan	797
Sacubitril/valsartan	690

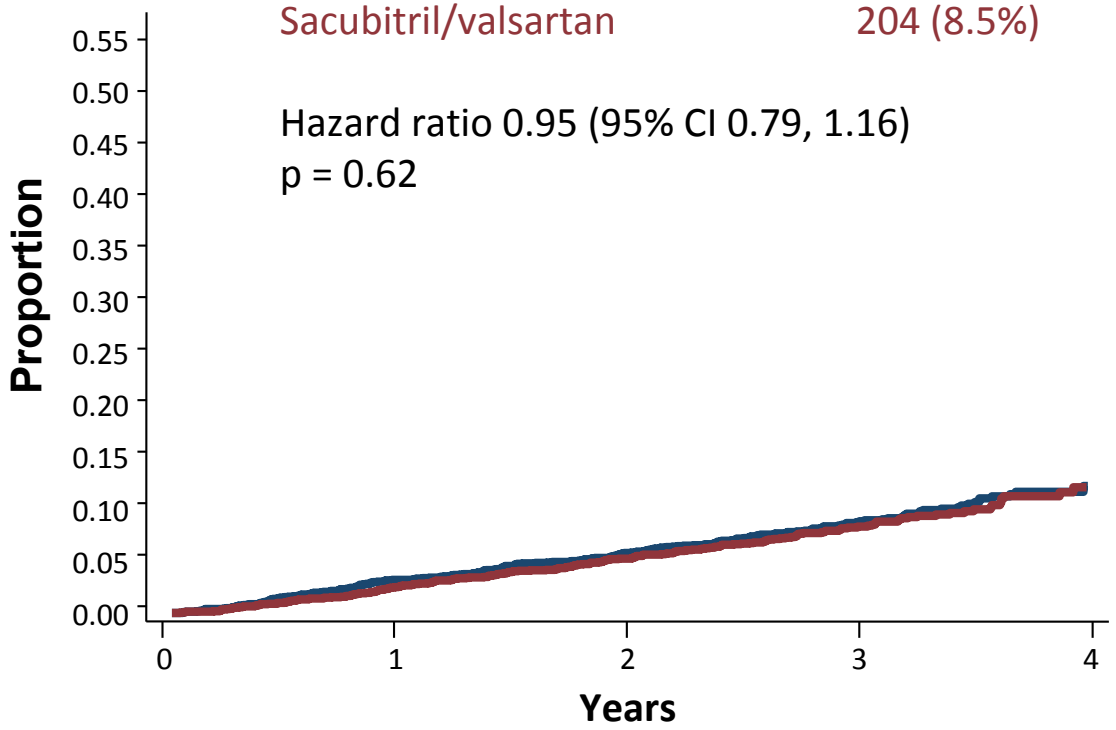
Rate ratio 0.85 (95% CI 0.72, 1.00)
p = 0.056



CV death*

	Patients
Valsartan	212 (8.9%)
Sacubitril/valsartan	204 (8.5%)

Hazard ratio 0.95 (95% CI 0.79, 1.16)
p = 0.62



*Semiparametric LWYY method

Sensitivity and supportive analyses for primary endpoint

Consistent with primary endpoint

Sensitivity analysis	Estimate (RR or HR)	Nominal P-value
Primary analysis LWYY (stratified by region) – adjudicated	**RR = 0.87 (0.75, 1.01)**	**0.059**
Primary analysis (LWYY) including adjudicated urgent HF visits in composite	RR = 0.86 (0.75, 0.99)	0.040
Investigator reported events (LWYY)	RR = 0.84 (0.74, 0.97)	0.014
Negative binomial method	RR = 0.87 (0.74, 1.01)	0.066
Primary analysis LWYY (stratified by country)*	RR = 0.86 (0.75, 0.997)	0.045
Time to first composite event (CV death or HF hospitalization)	HR = 0.92 (0.81, 1.03)	0.15

*Post-hoc analysis; LWYY, Lin, Wei, Yang, Ying; RR, rate ratio.

Secondary endpoints

	Sacubitril/valsartan N = 2316	Valsartan N = 2302	Effect size (95% CI)	Nominal P-value
NYHA functional classification at 8 months – Change from baseline (%) Improved Unchanged Worsened	 15.0% 76.3% 8.7%	 12.6% 77.9% 9.6%	OR for improvement 1.45 (1.13, 1.86)	0.004
KCCQ clinical summary score at 8 months – Change from baseline (SE)	-1.6 (0.4)	-2.6 (0.4)	LSM of difference = 1.03 (0.00, 2.1)	0.051
KCCQ responder (> than 5-point improvement)	33.0%	29.6%	OR = 1.30 (1.04, 1.61)	0.019
Worsening Renal Function Composite of renal death, reaching ESRD, or ≥50% decline in eGFR relative to baseline.	1.4%	2.7%	HR = 0.50 (0.33, 0.77)	0.002
All-cause mortality (%)	14.2%	14.6%	HR = 0.97 (0.84, 1.13)	0.68

Safety endpoints

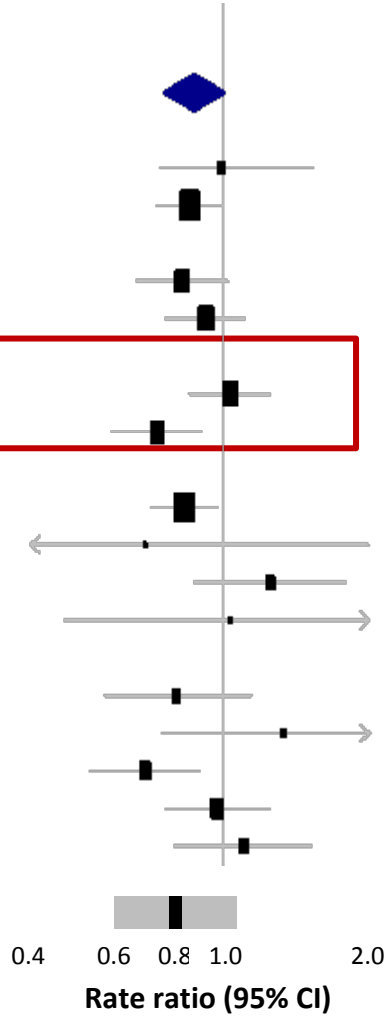
Adverse event		Sacubitril/valsartan (N = 2407)	Valsartan (N = 2389)	P-value
Hypotension with SBP < 100 mm Hg		15.8%	10.8%	<0.0001
Elevated serum creatinine	≥ 2.0 mg/dl	10.8%	13.7%	0.002
	≥ 2.5 mg/dl	4%	4.6%	0.36
	≥ 3.0 mg/dl	1.6%	1.7%	0.79
Elevated serum potassium	> 5.5 mmol/liter	13.2%	15.3%	0.05
	> 6.0 mmol/liter	3.1%	4.3%	0.04
Angioedema*		0.6%	0.2%	0.02

*Adjudicated

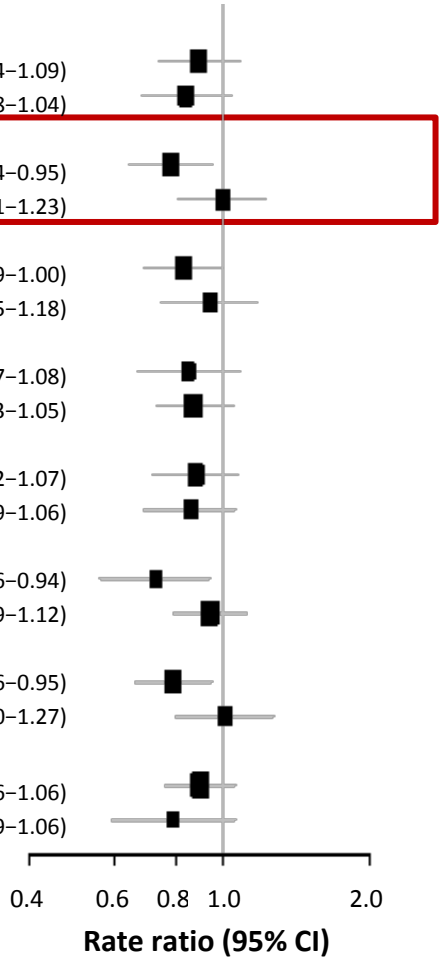
Pre-specified subgroups for primary endpoint

Evidence for overall heterogeneity

Subgroup	No. of events /patients	Rate ratio (95% CI)
Overall	**1903/4796**	**0.87 (0.75–1.01)**
Age (years)		
Less than 65 years	276/825	0.99 (0.64–1.53)
65 years or older	1627/3971	0.85 (0.73–0.99)
Age (years)		
Less than 75 years	938/2597	0.82 (0.66–1.02)
75 years or older	965/2199	0.92 (0.76–1.11)
Sex*		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race		
Caucasian	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia/Pacific	332/762	1.10 (0.79–1.52)



Subgroup	No. of events /patients	Rate ratio (95% CI)
Diabetic		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
LVEF*		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)
History of AF		
Yes	1140/2521	0.83 (0.69–1.00)
No	763/2275	0.94 (0.75–1.18)
Screening NT–proBNP		
at or below median (911 pg/mL)	708/2379	0.85 (0.67–1.08)
above median (911 pg/mL)	1183/2378	0.87 (0.73–1.05)
Screening SBP		
at or below median (137 mmHg)	984/2450	0.88 (0.72–1.07)
above median (137 mmHg)	919/2344	0.86 (0.69–1.06)
MRA use		
Yes	543/1238	0.73 (0.56–0.94)
No	1360/3558	0.94 (0.79–1.12)
Baseline eGFR		
<60 mL/min/1.73m^2	1115/2341	0.79 (0.66–0.95)
>=60 mL/min/1.73m^2	787/2454	1.01 (0.80–1.27)
NYHA class		
I/II	1402/3843	0.90 (0.76–1.06)
III/IV	499/951	0.79 (0.59–1.06)

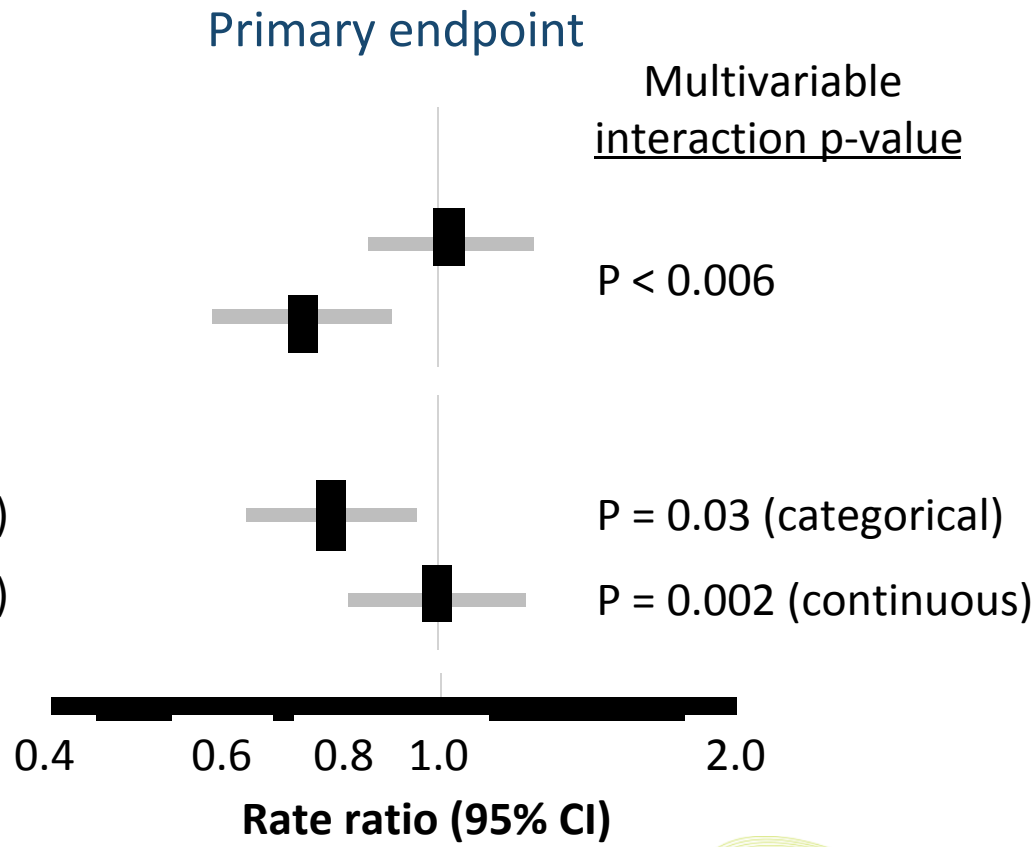


Multivariate interaction p < 0.05.

Significant Heterogeneity in Multivariate Analysis by Ejection Fraction and Sex

Only interactions for sex and ejection fraction remained nominally significant

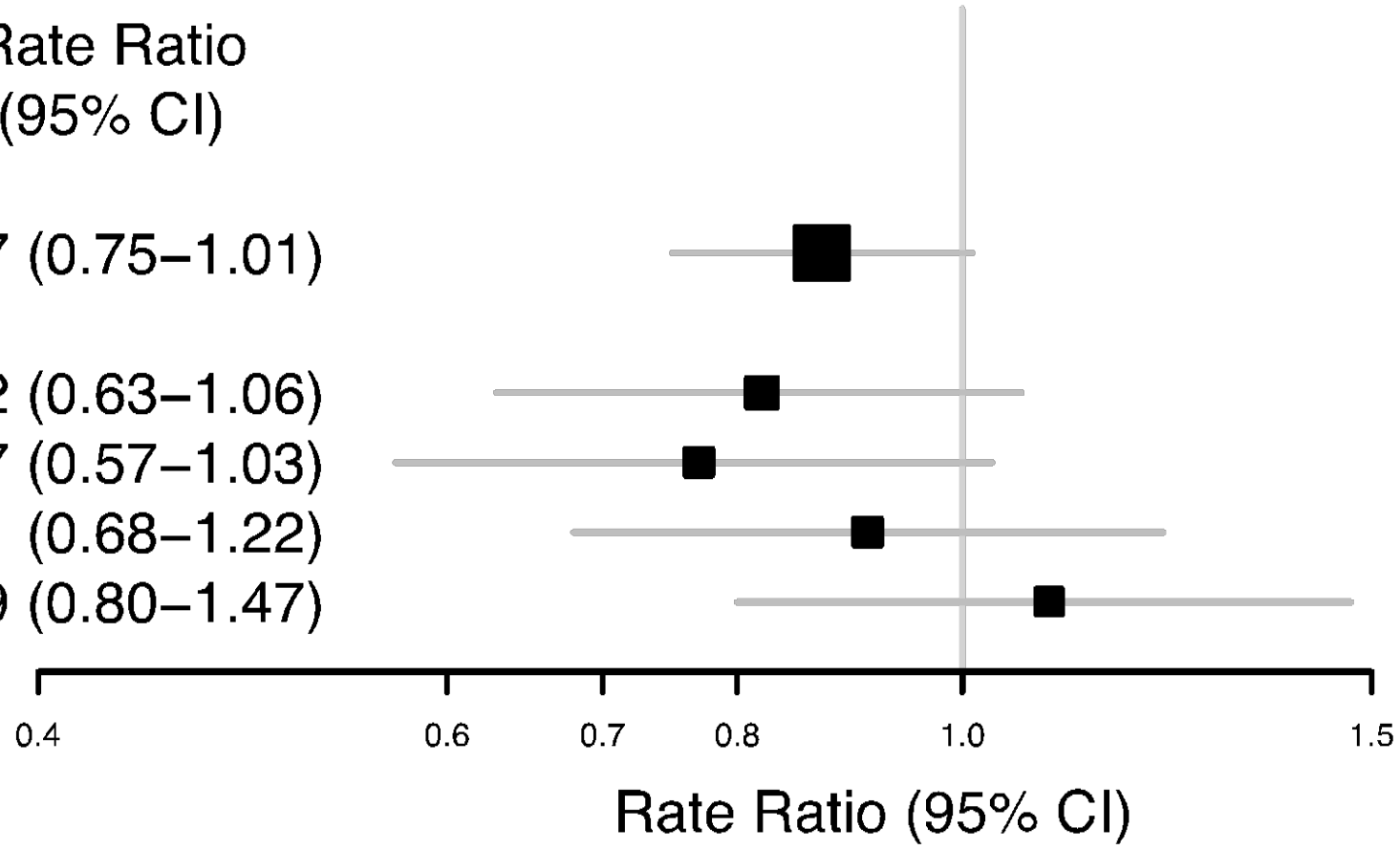
Subgroup	No. of events/ patients	Rate ratio (95% CI)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
LVEF		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)



Treatment effect by ejection fraction quartiles

Primary composite total HF hospitalizations and CV death

Subgroup	No. of Events/Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
EF		
<=50	512/1208	0.82 (0.63–1.06)
>50–57	536/1287	0.77 (0.57–1.03)
>57–63	467/1202	0.91 (0.68–1.22)
>63	388/1099	1.09 (0.80–1.47)



Conclusions

In patients with HFpEF, when comparing sacubitril/valsartan to valsartan, we observed a modest non-significant ~13% reduction in the primary outcome overall, which was driven mainly by a reduction in first and recurrent HF hospitalizations

Several sensitivity analyses and secondary analyses, including improvement in various measures of symptoms, quality of life, and renal function, suggested benefits with sacubitril/valsartan compared with valsartan

The use of an angiotensin receptor blocker as an active comparator, which we felt necessary not because this is standard of care in this population, but because of the large number of patients with HFpEF already on RAS inhibitors, may have attenuated our overall treatment effect

Our data suggest heterogeneity in the treatment response, with suggestion of greater benefit in women and in individuals with lower LVEF

Interpretation

Although subgroups need to be interpreted with caution, these data should be considered in the context of PARADIGM-HF, with nearly identical enrollment criteria with the exception of ejection fraction, in which sacubitril/valsartan reduced CV death and HF Hospitalization in patients with LVEF ≤ 40%

These data suggest that sacubitril/valsartan may be beneficial in some patients with HFpEF, particularly in those with ejection fraction that is not frankly reduced, but less than normal, with potentially clinically important relative and absolute risk reduction in these patients

More broadly, these data support the concept that HFpEF may be both phenotypically heterogeneous, and heterogeneous with respect to treatment. Further investigation should explore which patients will benefit most from sacubitril/valsartan as well as other therapies that may modify disease in this heterogeneous syndrome

These findings have implications for our understanding and treatment of heart failure with preserved ejection fraction.

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We thank the participants!!

PARAGONHF

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ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees