

Prospective comparison of ARNI with ARB Global Outcomes in heart failure with preserved ejection N fraction (PARAGON-HF)

Comparison of outcomes in women and men

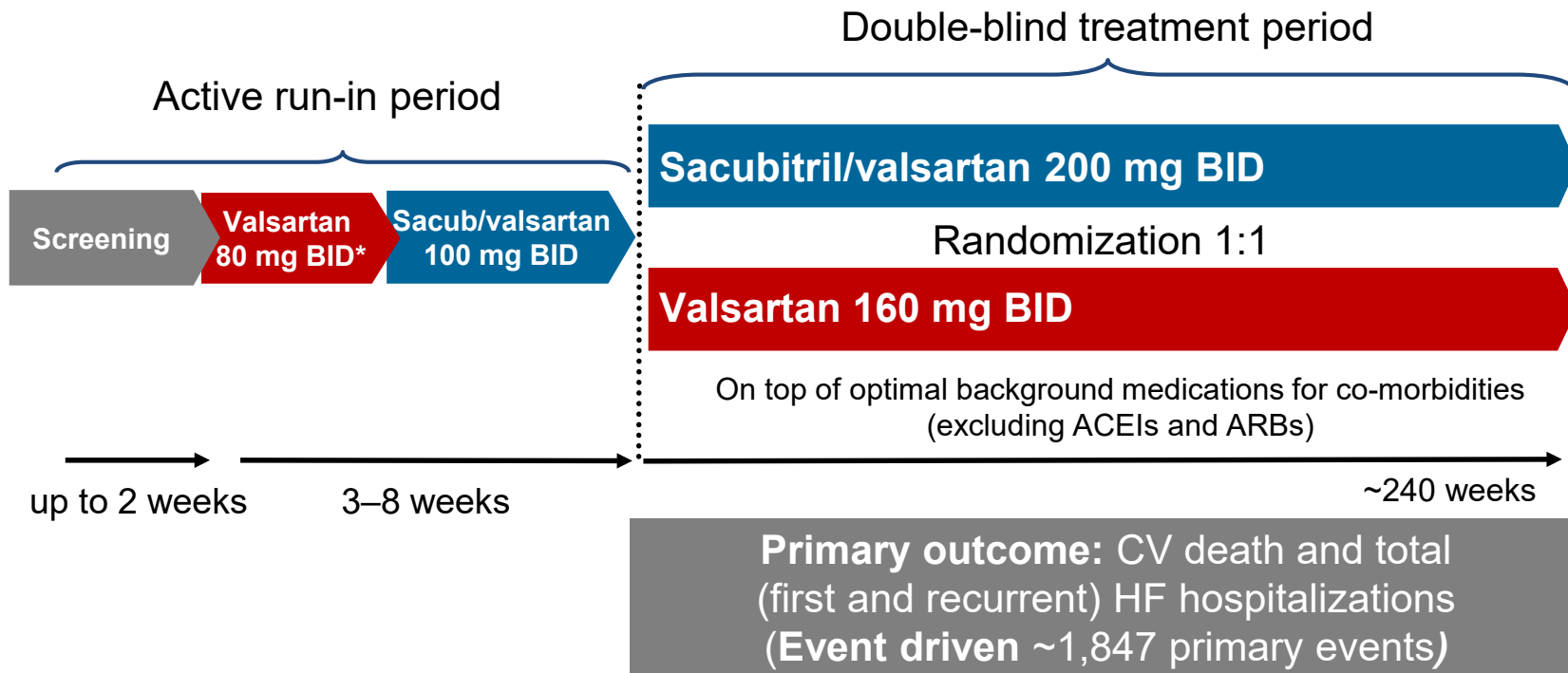
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Background

- Although there are multiple effective drug and device therapies for HFrEF, there are none approved for the treatment of HFpEF, the most common type of HF in women. Hence, there is a greater “therapeutic deficit” in women, compared with men, with heart failure.
- In PARAGON-HF, there were fewer primary endpoints in the sacubitril-valsartan group, compared with the valsartan group (894 vs. 1009), although the difference was of borderline statistical significance: rate ratio, 0.87 (95% CI 0.75 -1.01), $P=0.059$.
- Of the 12 pre-specified subgroup analyses in PARAGON-HF, only sex and LVEF appeared to modify the effect of sacubitril-valsartan, versus valsartan, on the primary outcome, with a more favorable treatment effect in women than in men (of the 4796 patients, analysed, 52% were women) .
- In view of the potential importance of this finding, we further investigated the interaction between sex and the effect of treatment with sacubitril/valsartan.

PARAGON-HF: Design

Target patient population: ~4,800 patients with symptomatic HF (NYHA Class II–IV), LVEF $\geq 45\%$, LVH/LAE & elevated NT-proBNP



Key baseline characteristics

Characteristic	Women (n=2479)	Men (n=2317)
Mean age (yr)	74	72
Age ≥70 yr (%)	72	61
NYHA class III/IV (%)	23	17
KCCQ-CSS (score out of 100)*	71	79
Mean LVEF (%)	59	56
Median NT-proBNP (pg/ml)	836	954
Mean systolic BP (mmHg)	131	130
Mean eGFR (ml/min/1.73m ²)	60	65
eGFR <60 ml/min/1.73m ² (%)	53	44
Atrial fibrillation/flutter on ECG (%)	29	36

*a lower score is worse

Baseline characteristics/treatments

Characteristic	Women (n=2479)	Men (n=2317)
History of hypertension (%)	97	95
History of myocardial infarction (%)	16	30
Diabetes (%)	40	46
Prior heart failure hospitalization (%)	46	49
Treatments		
Diuretic	95	96
ACE-inhibitor or ARB at screening	87	86
Beta-blocker	80	79
MRA	24	28
Calcium channel blocker	35	34
Digoxin	10	9

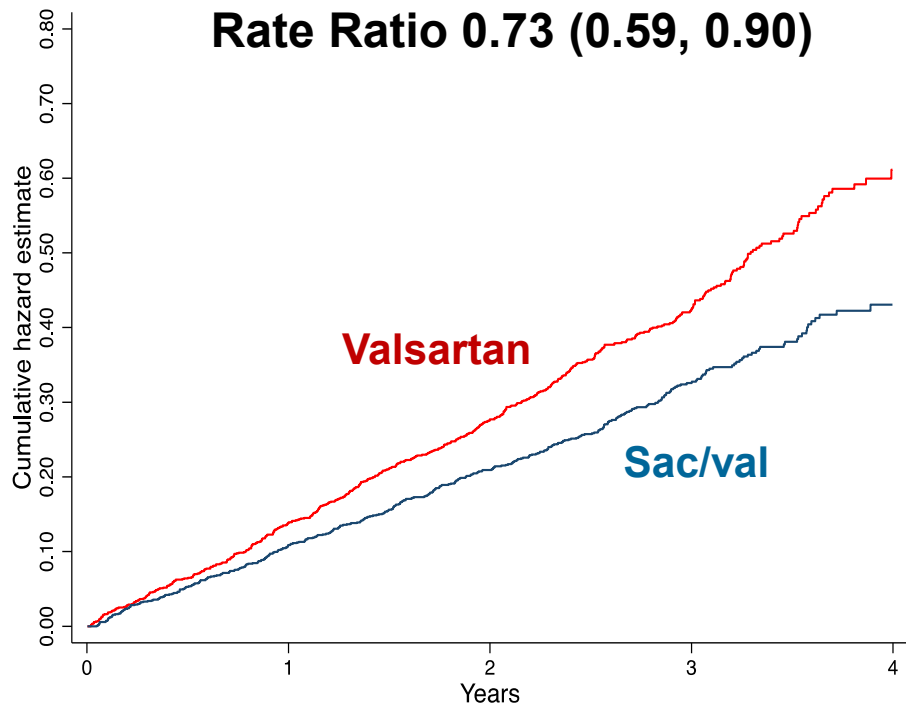
Primary outcome

Total HF hospitalizations and CV death

Including first and repeat hospitalizations

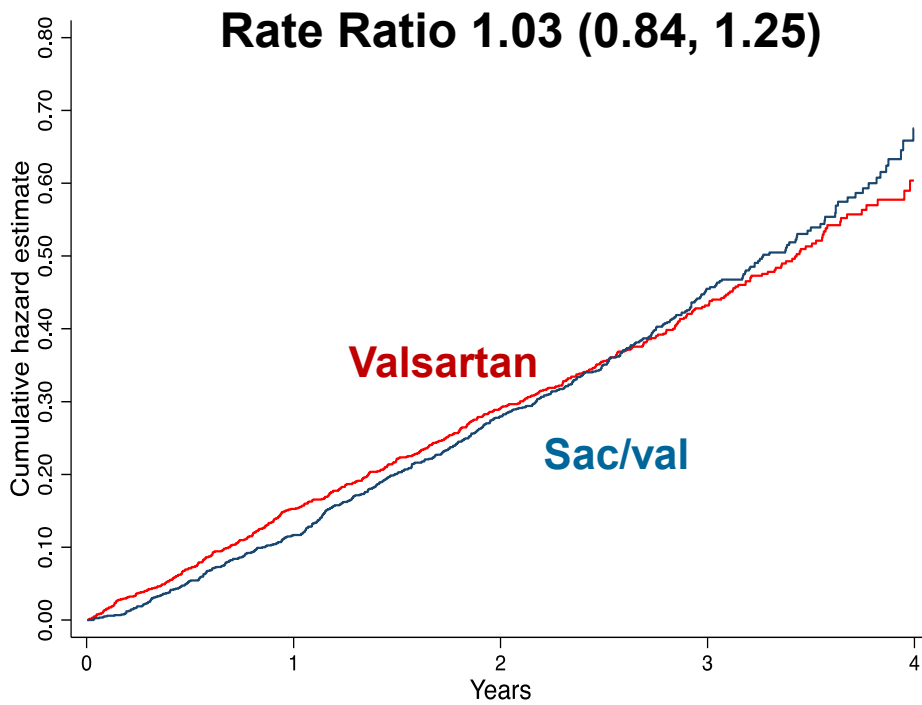
Women

Rate Ratio 0.73 (0.59, 0.90)



Men

Rate Ratio 1.03 (0.84, 1.25)

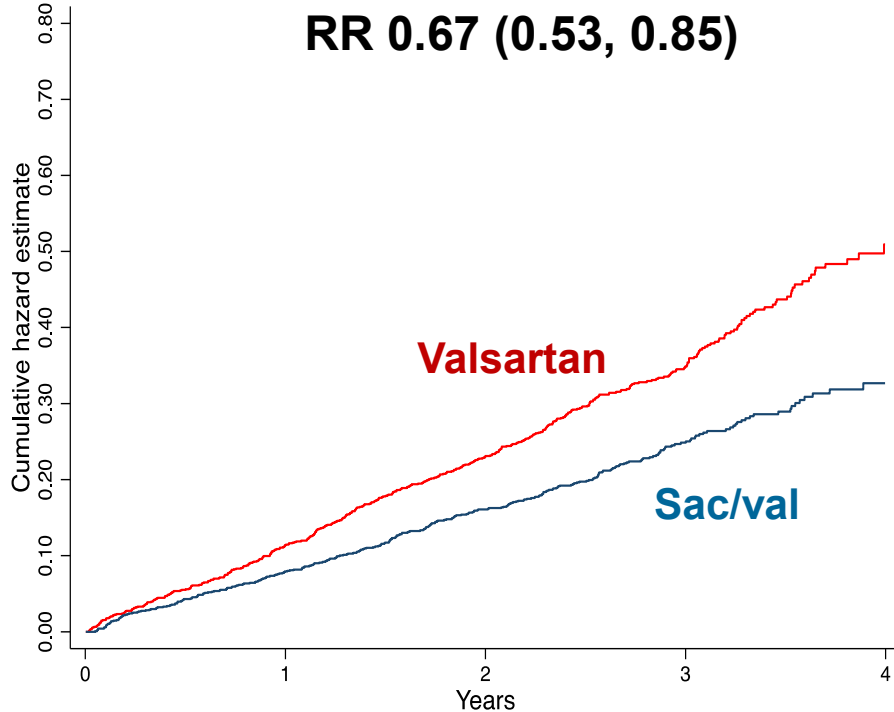


Components of primary outcome

Heart failure hospitalizations (first and repeat)

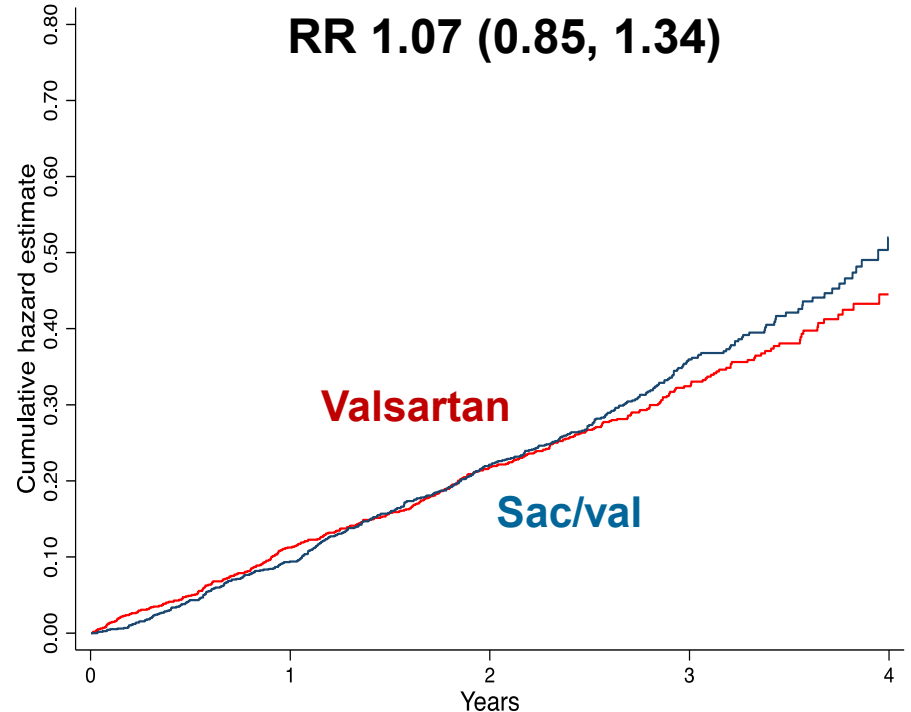
Women

RR 0.67 (0.53, 0.85)



Men

RR 1.07 (0.85, 1.34)

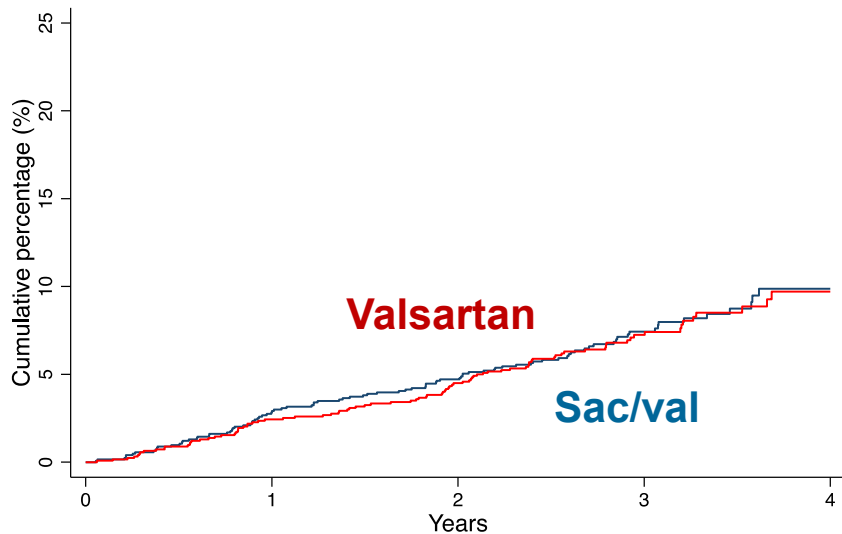


Components of primary outcome

Cardiovascular death

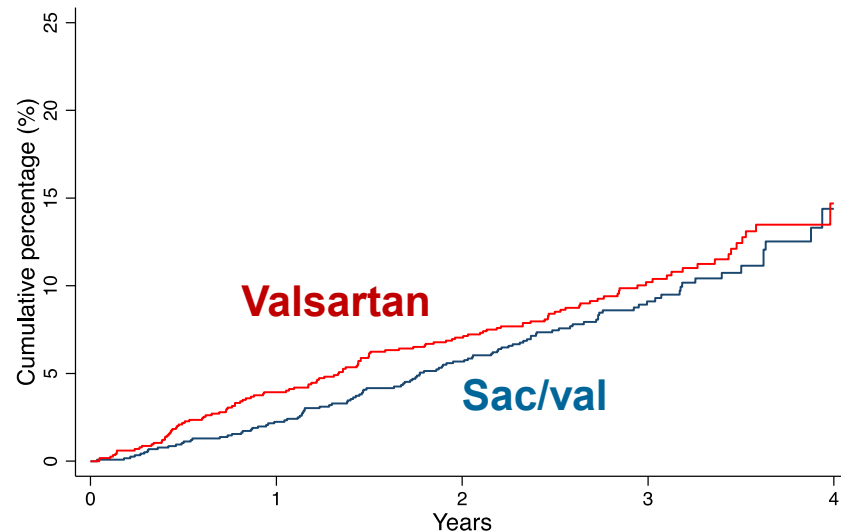
Women

HR 1.02 (0.76, 1.36)



Men

HR 0.90 (0.70, 1.17)



Number at risk

Sac/val	1241	1196	1154	556	75
Valsartan	1238	1194	1149	568	82

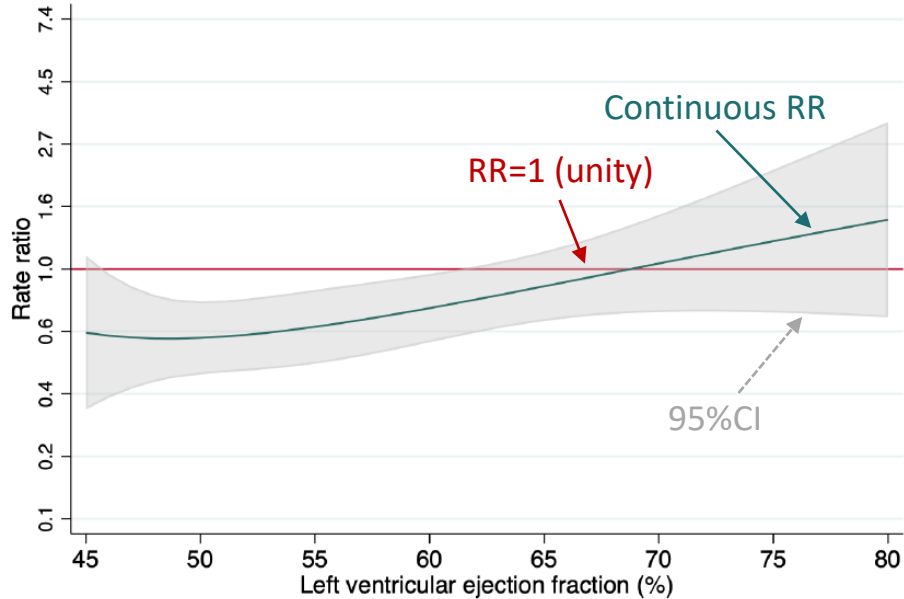
Number at risk

Sac/val	1166	1130	1055	506	60
Valsartan	1151	1092	1029	490	62

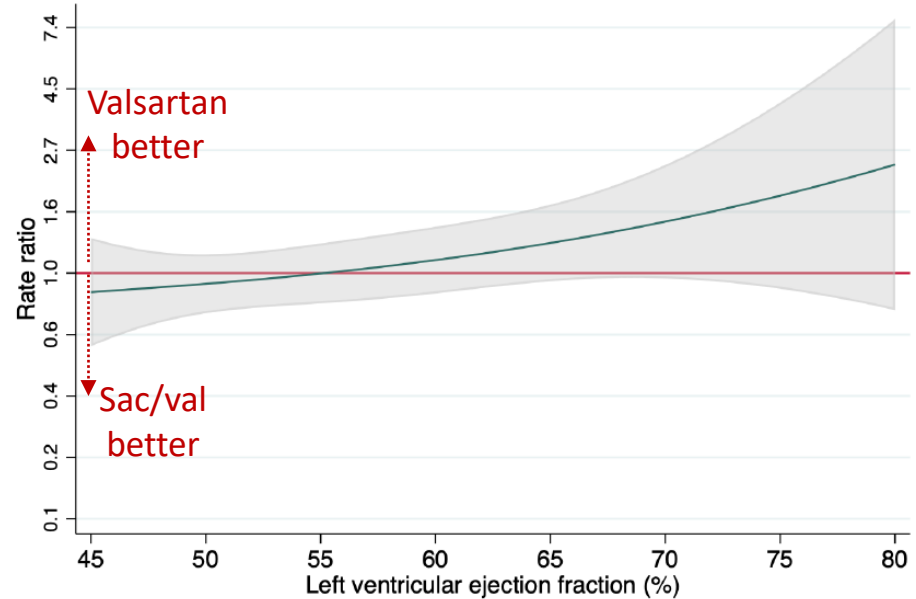
Treatment effect according to baseline LVEF

Primary composite outcome

Women



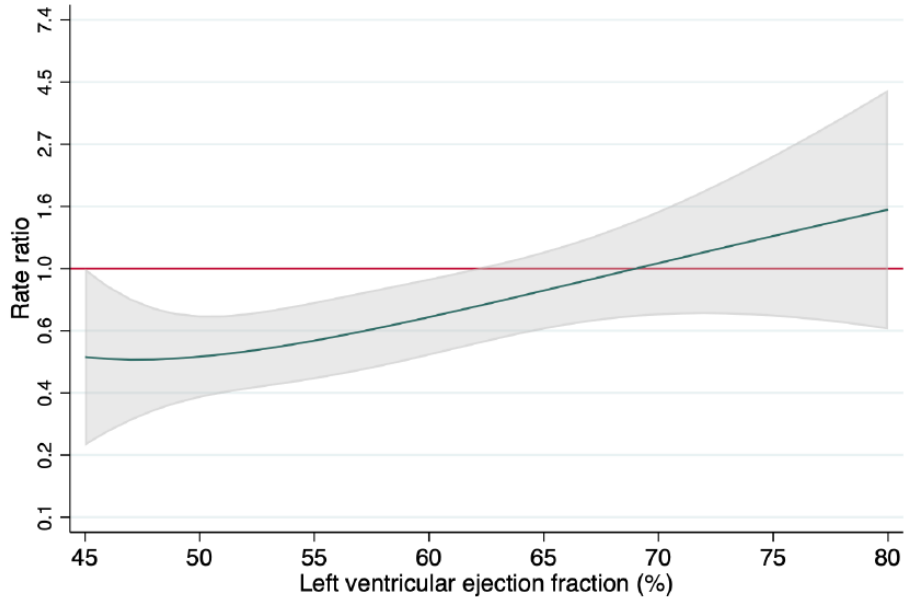
Men



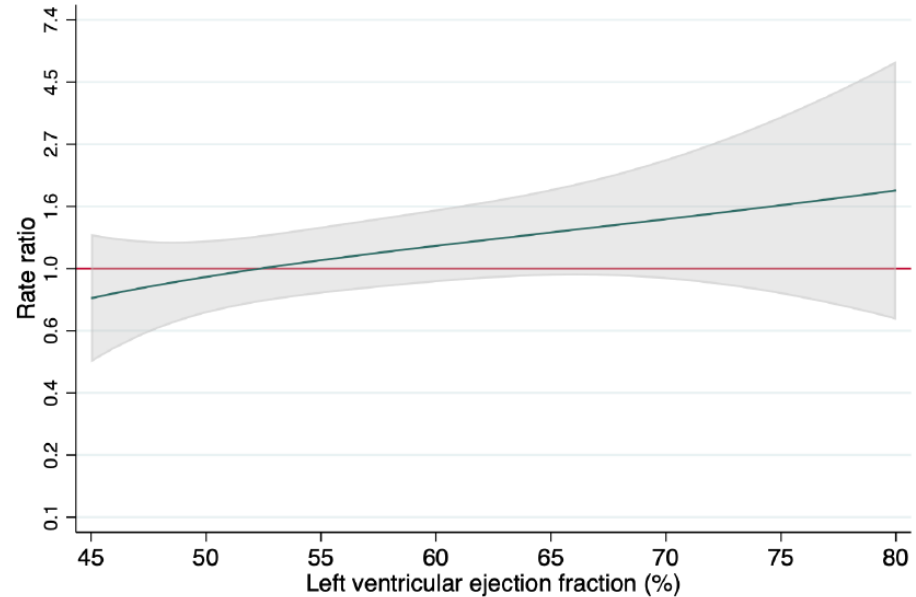
Treatment effect according to baseline LVEF

Heart failure hospitalizations (first and repeat)

Women



Men

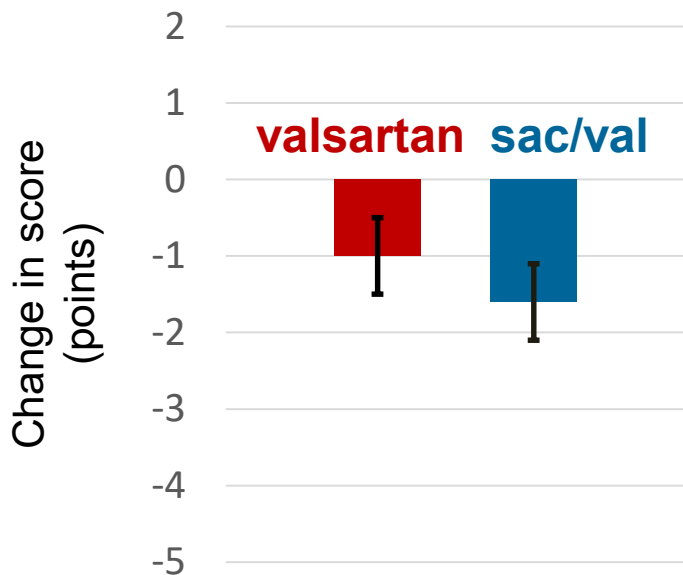


Secondary outcomes

In order of hierarchical testing

Mean change in KCCQ-CSS (baseline to 8 months)

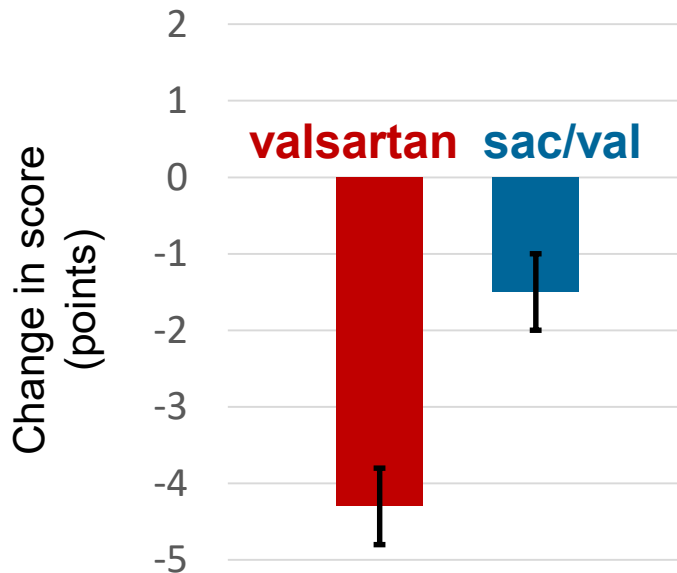
Women



**Difference at month 8:
-0.6 (-2.1, 0.8)**

P int. = 0.001

Men



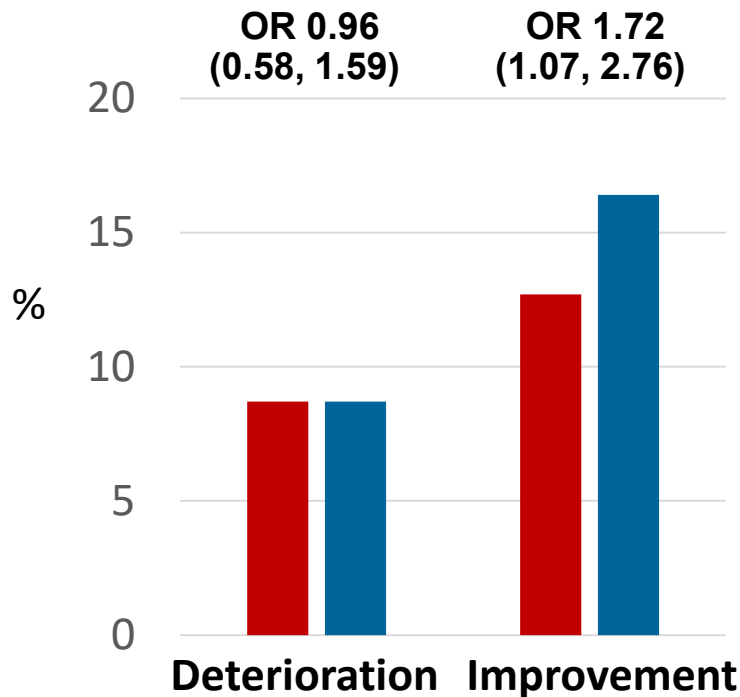
**Difference at month 8:
2.8 (1.3, 4.3)**

Change in NYHA class (baseline to 8 months)

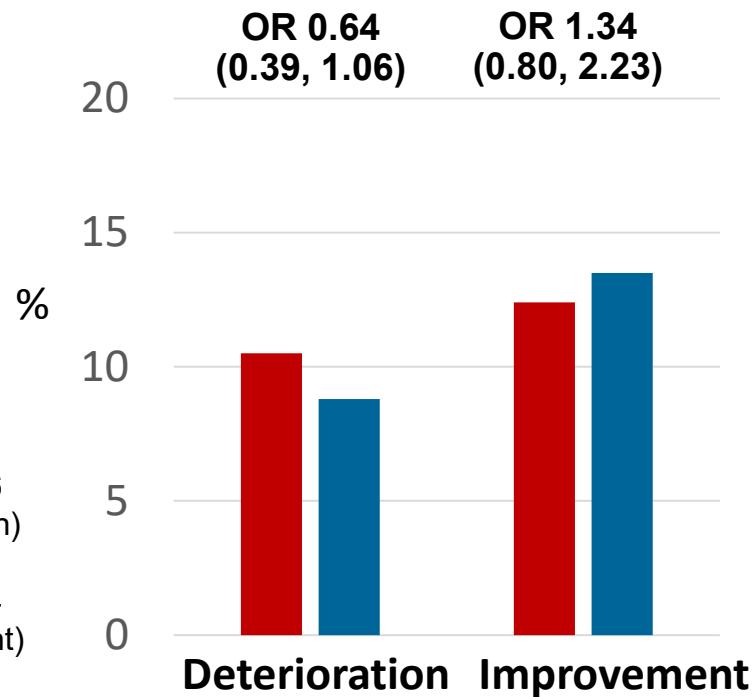
■ Valsartan

■ Sacubitril/valsartan

Women



Men



Worsening kidney function endpoint

Composite of: Sustained* $\geq 50\%$ reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

	Valsartan No. (%)	Sac/val No. (%)	Hazard ratio (95%CI)
Women (n=2479)	32 (2.6)	16 (1.3)	0.49 (0.27, 0.89)
Men (n=2317)	49 (2.8)	17 (1.5)	0.53 (0.29, 0.95)

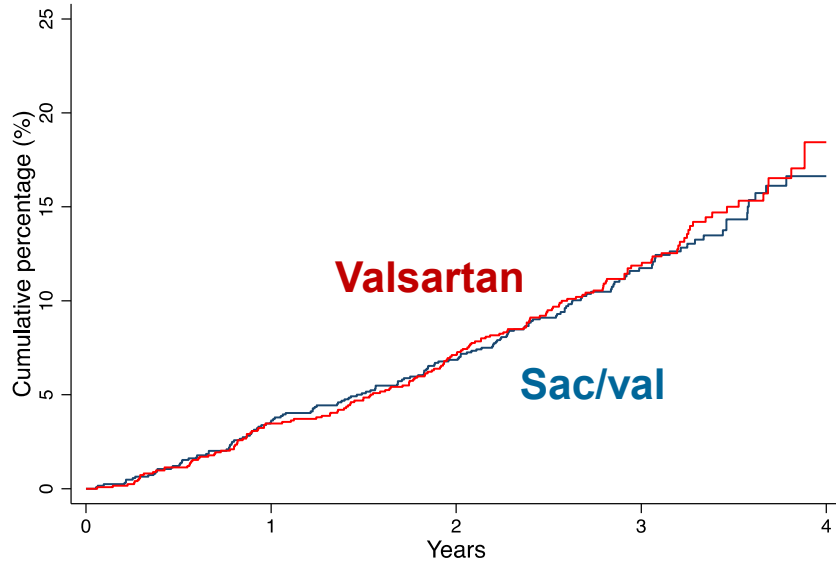
P int. = 0.90

ESRD consisted of sustained eGFR below 15 ml/min/1.73m², sustained dialysis or kidney transplantation *Sustained = 28 days or more

All-cause mortality

Women

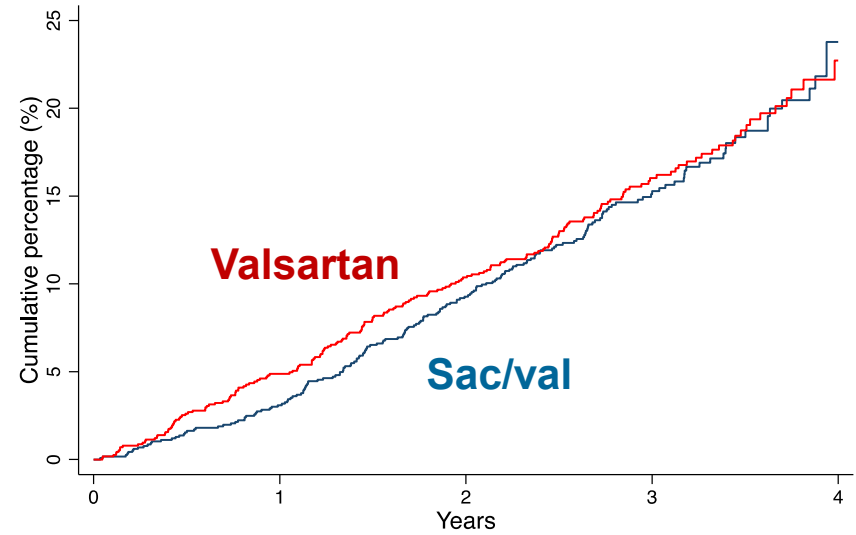
HR 0.96 (0.77, 1.20)



Number at risk					
Sac/val	1241	1196	1154	556	75
Valsartan	1238	1194	1149	568	82

Men

HR 0.97 (0.80-1.19)



Number at risk					
Sac/val	1166	1130	1055	506	60
Valsartan	1151	1092	1029	490	62

**Laboratory measures,
tolerability and safety**

Safety/adverse events (AEs)

	Women		Men		<i>P-value for inter.</i>
	Val.	Sac/val.	Val.	Sac/val.	
AE/abnormality of interest (%)					
Hypotension	9.9	15.7	11.7	15.9	0.38
Creatinine ≥2.5 mg/dl	2.4	2.3	6.9	5.9	0.81
Creatinine ≥3.0 mg/dl	0.8	1.0	2.6	2.2	0.51
Potassium ≥5.5 mmol/l	13.7	12.9	16.6	13.4	0.25
Potassium ≥6.0 mmol/l	4.1	2.8	4.3	3.4	0.65
Angioedema	0.2	0.9	0.1	0.3	0.88
Target dose of study drug (%)	84.5	80.6	85.7	83.3	-
Study drug discontinuation (%)*	27.7	27.1	25.6	23.5	-

*Discontinued for reasons other than death

Summary and conclusions

- As compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men, but the effects on KCCQ, NYHA class and worsening kidney function were not greater in women.
- Therefore, not clear whether this was a chance finding or a real difference.
- Several potential biological mechanisms may explain it e.g. a deficit in cGMP-PKG signalling in post-menopausal women and more systolic dysfunction in women than men in the EF range 40 to ~65%.
- Conversely, there may be more male “non-responders” because of alternative pathology (e.g. cardiac amyloidosis) and or the active comparator (valsartan) may have been more effective in men than women.
- The possible modification of the effect of sacubitril/valsartan by sex requires further investigation.

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EFFECTS OF SACUBITRIL-VALSARTAN, VERSUS VALSARTAN, IN WOMEN COMPARED TO MEN WITH HEART FAILURE AND PRESERVED EJECTION FRACTION: INSIGHTS FROM PARAGON-HF

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Back-up/extra slides

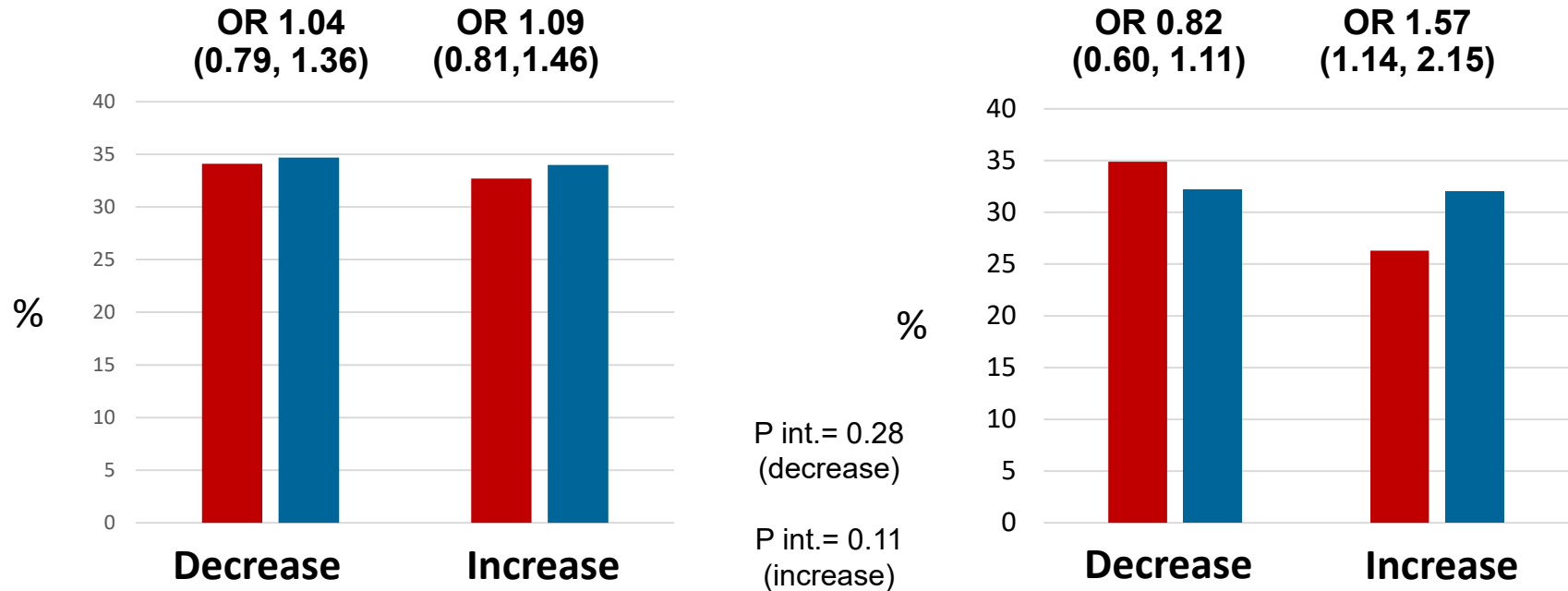
Clinically meaningful change (≥ 5 points) in KCCQ-CSS

■ Valsartan

■ Sacubitril/valsartan

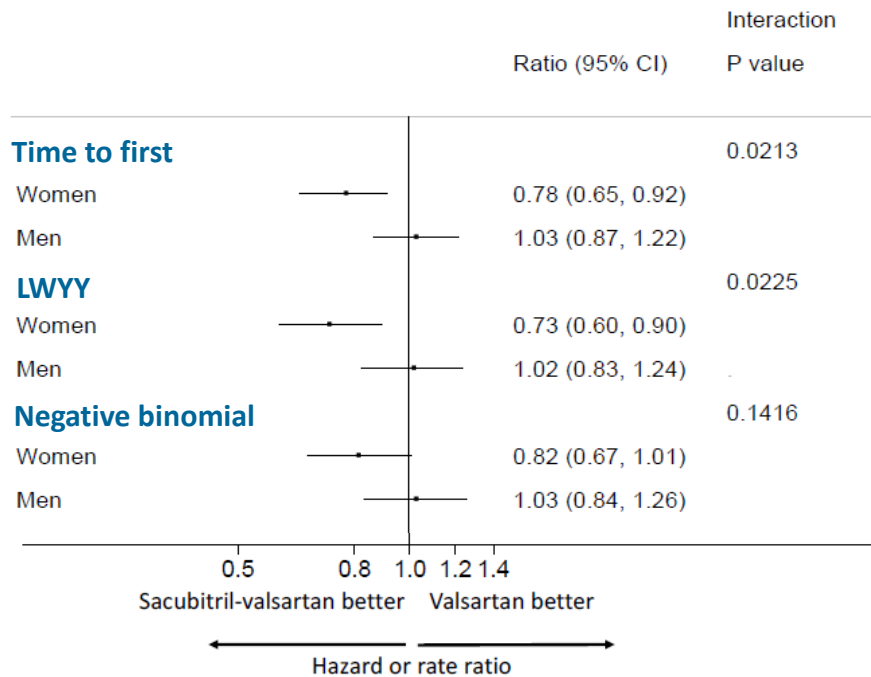
Women

Men



Time-to-first event and recurrent events analyses

Primary composite outcome



Hospital admissions (1st and repeat)

