Effect of sacubitril/valsartan on cognitive function in patients with HFpEF: a prespecified analysis of PARAGON-HF

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Background: A theoretical concern has been raised about detrimental effects of sacubitril/valsartan (sac/val) on cognitive function as neprilysin is one of many pathways involved in clearance of amyloid beta peptides from brain tissue.

Purpose: To examine effect of sac/val, compared with valsartan, on cognitive function in patients with heart failure (HF) and preserved ejection fraction (HFpEF).

Methods: In the PARAGON-HF trial, cognitive function was tested in a subgroup of patients at baseline and follow-up, using Mini-Mental State Examination [MMSE] having a maximum score of 30 (higher scores reflect better cognitive function). Change in MMSE score from baseline to 96 wks was a prespecified exploratory endpoint. Other post hoc analyses included "cognitive decline" (fall in MMSE $\geq$3 pts) and assessment of cognition-related adverse events (AEs).

Results: Among 2895 patients (60% of total) in PARAGON-HF with baseline MMSE measurement, mean (SD) score was 27.4 (3.0) in patients receiving sac/val (1453) and 27.4 (2.9) in patients receiving valsartan (1442). There was no difference between sac/val and valsartan in MMSE score change from baseline to wk 96: sac/val –0.02 (SE 0.07) and valsartan 0.00 (0.07); between-treatment difference –0.02 (95% CI: –0.22 to 0.18); p-value = 0.83. Cognitive decline at 96 weeks occurred in 115 of 1071 evaluable patients (10.7%) in sac/val group and 121 of 1053 patients (11.5%) in valsartan group; risk ratio 0.97 (0.75–1.26), p-value = 0.82. Cognition-related AEs were more frequent, than in PARADIGM-HF (likely as patients in PARAGON-HF were older) but, as in PARADIGM-HF, did not differ between sac/val and comparator treatment (Table).

Conclusions: Cognitive change, measured by MMSE, did not differ between treatment with sac/val & valsartan in patients with HFpEF.

AE	PARAGON-HF		PARADIGM-HF	
	Sac/Val (2407)	Valsartan (2389)	Sac/Val (4187)	Enalapril (4212)
Cognitive impairment (Narrow SMQ)				
No. (%)	31 (1.29)	44 (1.84)	12 (0.29)	15 (0.36)
Event rate/100 pt. yrs (95% CI)	0.45 (0.31–0.64)	0.64 (0.48–0.87)	0.12 (0.07–0.21)	0.16 (0.10–0.27)
Cognitive impairment (Broad SMQ)				
No. (%)	127 (5.28)	140 (5.86)	104 (2.48)	97 (2.30)
Event rate/100 pt. yrs (95% CI)	1.88 (1.58–2.23)	2.09 (1.77–2.47)	0.92 (0.75–1.14)	0.91 (0.73–1.12)

AEs coded using 17.0 version of Medical Dictionary for Regulatory Activities (MedDRA) using Standardized MedDRA Queries (SMQs) with "broad" & "narrow" preferred terms related to cognition-related AEs.