

# Neprilysin inhibition does not affect cognitive function in patients with heart failure

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Sacubitril/valsartan does not change cognitive function, compared with valsartan, in patients with heart failure and mildly reduced or preserved ejection fraction, according to late breaking research presented in a Hot Line session today at ESC Congress 2022.

It is estimated that 30–80% of patients with heart failure exhibit some degree of cognitive impairment. Patients with heart failure are at increased risk of developing dementia compared to the general population. Sacubitril/[valsartan](#) combines the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan. Neprilysin is one of multiple enzymes involved in the proteolytic degradation of amyloid  $\beta$  peptides associated with Alzheimer's type dementia and concern had been raised that their accumulation in the brain during sustained neprilysin inhibition could cause or worsen cognitive impairment. When the US Food and Drug Administration (FDA) approved sacubitril/valsartan, it and other health authorities required a randomized trial evaluating its effects, compared to valsartan, on cognitive function assessed by a comprehensive neurocognitive battery and [positron emission tomography](#) (PET) imaging in patients with [chronic heart failure](#).

PERSPECTIVE was the first randomized trial to prospectively evaluate the effect of long-term treatment with sacubitril/valsartan, compared with valsartan, on cognitive function in patients with heart failure and mildly reduced and preserved ejection fraction (HFmrEF and HFpEF), meaning a left ventricular [ejection fraction](#) over 40%. The trial enrolled adults aged 60 years and above with chronic symptomatic heart failure plus [heart failure](#) hospitalization in the prior 12 months and/or NT-proBNP above 200 pg/mL. Patients with known or suspected cognitive impairment were ineligible. A total of 592 patients from 137 centers in 20 countries were randomized 1:1 to either sacubitril/valsartan (target dose 97/103 mg twice daily) or valsartan (target dose 160 mg twice daily). The average age of participants was 72.4 years and 46.8% were women.

The primary endpoint was the change in cognitive function from baseline to three-year follow up. Cognitive function was evaluated using the CogState global cognition composite score (GCCS), which includes

seven tasks assessing attention, episodic memory, and executive function. The change in GCCS from baseline to three years did not differ between patients treated with sacubitril/valsartan compared to those treated with valsartan. The difference in least-squares mean change in GCCS was -0.0180 (95% confidence interval [CI] -0.1230 to 0.0870;  $p=0.74$ ). The Cohen's  $d$  effect size was -0.0277 (95% CI -0.1101 to 0.0778), indicating non-inferiority.

The principal secondary outcome was the change from baseline to three years in amyloid  $\beta$  deposition in the brain measured using PET in 491 patients. The difference in least-squares mean change in the standardized uptake value ratio was -0.0292 (95% CI -0.0593 to 0.0010;  $p=0.058$ ), indicating that amyloid  $\beta$  deposition in the brain tended to be less in patients treated with sacubitril/valsartan compared with valsartan.

Sacubitril/valsartan was well tolerated compared with valsartan, with fewer deaths (28 [9.5%] versus 39 [13.1%]) and adverse events leading to treatment discontinuation (47 [16.0%] versus 61 [20.5%]).

Study author Professor John McMurray of the University of Glasgow, UK says that "there was no evidence that neprilysin inhibition increased the risk of [cognitive impairment](#) due to accumulation of amyloid  $\beta$  in the brain in patients with HFmrEF and HFpEF. The concern about increased cerebral amyloid  $\beta$  deposition with sacubitril/valsartan was always hypothetical and multiple enzymatic and other amyloid  $\beta$  clearance pathways exist in the brain that would likely compensate for any decreased clearance related to neprilysin inhibition. The trend towards decreased amyloid deposition on PET scanning is a surprise and may just reflect the play of chance. The absence of any negative effect on cognitive function is very important in removing a concern some doctors had about long-term treatment with sacubitril/valsartan."

**More information:** Conference presentation: [digital-](#)

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