

# Letters

## RESEARCH LETTER

### Effect of Neprilysin Inhibition on Alzheimer Disease Plasma Biomarkers: A Secondary Analysis of a Randomized Clinical Trial

Amyloid- $\beta$  (A $\beta$ ) accumulation is critical in Alzheimer disease (AD), and neprilysin is involved in physiologically clearing A $\beta$ . Concerns exist regarding long-term use of sacubitril/valsartan, a neprilysin inhibitor and angiotensin receptor blocker used for heart failure, and its potential to increase AD risk. We evaluated neprilysin inhibition's effect on AD blood biomarkers in patients with coronary heart disease.

**Methods** | In a post hoc exploratory analysis of a 52-week randomized clinical trial (NCT03552575), we examined the effect of sacubitril/valsartan vs valsartan (ie, neprilysin inhibition) on AD blood biomarkers in patients with asymptomatic left ventricular systolic dysfunction late after myocardial infarction (eFigure and eMethods in Supplement 2). The primary analysis showed no significant results.<sup>1</sup> Patients needed to be cognitively capable of independently adhering to the protocol (Supplement 1) throughout the study. The protocol was approved by the East of Scotland Research Ethics Committee. Patients provided informed consent. This study followed the CONSORT reporting guideline.

A 2-sided  $P < .05$  was considered significant. Analyses were exploratory and not corrected for multiple testing. Participants were recruited between July 2018 and June 2019, with follow-up until June 2020. This data analysis was performed

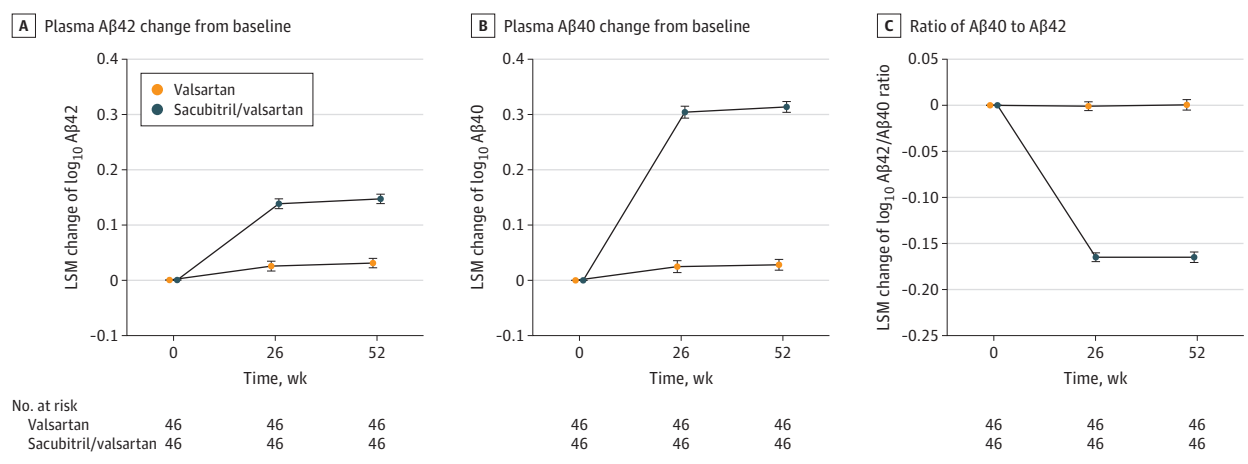
from November to December 2022 using R, version 4.1.1 (R Foundation for Statistical Computing).

**Results** | Ninety-two patients (46 per group; mean [SD] age, 61.0 [10.3] years; 84 men [91.3%]; 8 women [8.7%]; 2 [2.8%] self-reporting as South Asian and 90 [97.8%] as White) were examined. At 26 weeks, the sacubitril/valsartan vs valsartan group showed significant increases from baseline in plasma A $\beta$ 42 and A $\beta$ 40, persisting at 52 weeks (A $\beta$ 42, 30.7% [95% CI, 23.7%-38.0%;  $P < .001$ ]; A $\beta$ 40, 93.0% [95% CI, 81.3%-105.5%;  $P < .001$ ]); plasma A $\beta$ 42/A $\beta$ 40 ratio significantly decreased at 26 weeks, persisting at 52 weeks (-31.7%; 95% CI, -34.1% to -29.1%;  $P < .001$ ) (Figure 1). Notably, 3 female participants randomized to sacubitril/valsartan also experienced reductions in plasma A $\beta$ 42/A $\beta$ 40. No significant differences were observed for biomarkers of phosphorylated tau at threonine 217 (p-tau217) and 181, glial fibrillary acidic protein (GFAP), or neurofilament light (Figure 2).

**Discussion** | These treatment-related increases in plasma A $\beta$ 42 and A $\beta$ 40 likely reflect reduced peripheral neprilysin activity because sacubitril effectively inhibits neprilysin without substantially crossing the blood-brain barrier.<sup>2</sup> This pattern of A $\beta$ 42/A $\beta$ 40 reduction (increases in both peptides) differs from AD, wherein A $\beta$ 42/A $\beta$ 40 is reduced, reflecting pathologic decreases of A $\beta$ 42 and unchanged A $\beta$ 40 levels.<sup>3</sup> Our findings align with a pharmacokinetic study showing that sacubitril/valsartan did not alter cerebrospinal fluid A $\beta$ 42 or A $\beta$ 40 levels in healthy volunteers but consistently increased plasma A $\beta$ 40 levels with a less sensitive immunoassay.<sup>2</sup>

Plasma p-tau biomarkers, particularly p-tau217, are known to associate with A $\beta$  and tau pathologies and predict cog-

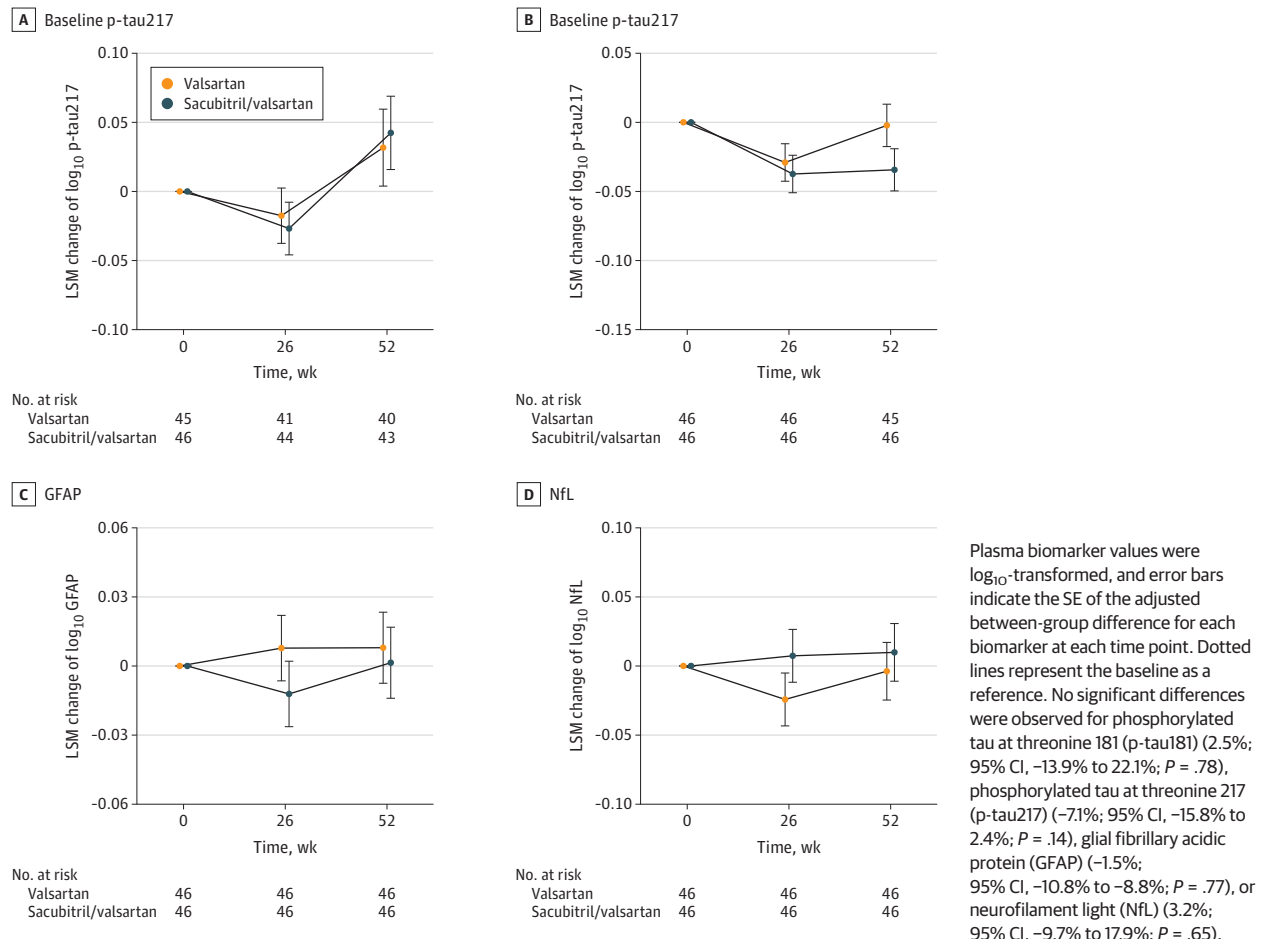
Figure 1. Changes in Amyloid- $\beta$  (A $\beta$ ) Blood Biomarkers Following Sacubitril/Valsartan Treatment



Plasma biomarker values were log<sub>10</sub>-transformed, with error bars indicating the SE of the adjusted between-group difference for each biomarker at each time point. Dotted lines represent the baseline as a reference. Relative differences in

the sacubitril/valsartan group compared with the valsartan group was 31% for A $\beta$ 42, 93% for A $\beta$ , and 32% for the ratio of A $\beta$ 42 to A $\beta$ 40 (all  $P < .001$ ). LSM indicates least squares mean.

Figure 2. Changes in Other Blood Biomarkers Following Sacubitril/Valsartan Treatment



tive decline, while plasma GFAP associates with A $\beta$  pathology, and neurofilament light with neuronal injury. While the absence of changes in these biomarkers (observed within a time frame in which p-tau217 and GFAP were already changed by anti-A $\beta$  treatments<sup>4</sup>) is reassuring, treatment that substantially affected plasma A $\beta$  did not affect other biomarkers.

Our study highlights sacubitril/valsartan's potential to confound plasma A $\beta$ 42/A $\beta$ 40 tests for AD. In AD, this ratio is only reduced by 8% to 14%,<sup>3</sup> while sacubitril/valsartan reduces it by approximately 30%. Given the frequent co-occurrence of heart disease and cognitive impairment and increasing clinical availability of plasma A $\beta$ 42/A $\beta$ 40 tests,<sup>5</sup> results for patients receiving sacubitril/valsartan should be interpreted cautiously; treatment-related A $\beta$ 42/A $\beta$ 40 reductions may lead to false-positive results and misclassification of A $\beta$  positivity as being AD. This drug interaction contraindication for an AD blood test underscores the importance of considering potential confounders, especially in patients with comorbidities, such as for p-tau and kidney disease,<sup>6</sup> and suggests that a multibiomarker assessment may better control for factors affecting individual biomarker classes.

Limitations include the absence of cerebrospinal fluid and positron emission tomography biomarkers, which have been previously explored.<sup>2</sup> Further studies with racial and ethnic diversity and between-sex balance are warranted. While not directly

tested here, we do not consider sacubitril/valsartan-related increases in plasma A $\beta$  to be concerning given sacubitril/valsartan's successful clinical implementation over almost a decade.

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**Author Contributions:** Mr Brum and Prof Blennow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mr Brum and Dr Docherty contributed equally as co-first authors. Dr McMurray and Prof Blennow contributed equally as co-senior authors.

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**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Brum, Docherty, Ashton, Blennow.

**Critical review of the manuscript for important intellectual content:** Brum, Zetterberg, Hansson, McMurray, Blennow.

**Statistical analysis:** Brum, Docherty.

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**Data Sharing Statement:** See the [Supplement 3](#).

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