7.48 [95% CI, 5.62-9.75] per million; P = .18) or females (3.38 [95% CI, 2.21-4.95] to 5.20 [95% CI, 3.84-6.90] per million; 
P = .07).

Jointpoint analysis revealed a significant increase in crude incidence for males (AAPC, 2.9; 95% CI, 2.3-3.6; P < .001) and females (AAPC, 3.5; 95% CI, 2.2-4.7; P < .001) overall. The crude incidence decreased after age adjustment but remained significant for both sexes (AAPC: males, 0.8 [95% CI, 0.1-1.5; P = .02]; females, 1.9 [95% CI, 0.6-3.2; P = .005]). Males aged 55 to 64 years were the only male age group with a significant increase, but females showed a significant increase in all age cohorts (Table).

Discussion | Our findings indicate the reported incidence of CJD has risen considerably, disproportionately affecting older and female individuals. These trends align with data from Japan and could be influenced by changing demographics. However, our findings may also reflect improved detection of CJD with new diagnostic tools, such as magnetic resonance imaging and real-time quaking-induced conversion testing.

This study is limited by a reliance on death certificate data for estimating CJD incidence. While research supports this approach, such data may be subject to miscoding or misdiagnosis. Results from both neuropathologic and genetic testing may complement death certificate data and enhance surveillance. The findings underscore the changing landscape of CJD and suggest a need for monitoring among the aging US population.

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

Amyloid-β (Aβ) accumulation is critical in Alzheimer disease (AD), and neprilysin is involved in physiologically clearing Aβ. 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. Patients needed to be cognitively capable of independently adhering to the protocol 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 Aβ42 and Aβ40, persisting at 52 weeks (Aβ42, 30.7% [95% CI, 23.7%-38.0%; P < .001]; Aβ40, 93.0% [95% CI, 81.3%-105.5%; P < .001]); plasma Aβ42/Aβ40 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 Aβ42/Aβ40.

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).

Plasma biomarker values were log10-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 Aβ42, 93% for Aβ, and 32% for the ratio of Aβ42 to Aβ40 (all \( P < .001 \)). LSM indicates least squares mean.
These treatment-related increases in plasma Aβ42 and Aβ40 likely reflect reduced peripheral neprilysin activity because sacubitril effectively inhibits neprilysin without substantially crossing the blood-brain barrier.2 This pattern of Aβ42/Aβ40 reduction (increases in both peptides) differs from AD, wherein Aβ42/Aβ40 is reduced, reflecting pathologic decreases of Aβ42 and unchanged Aβ40 levels.3 Our findings align with a pharmacokinetic study showing that sacubitril/valsartan did not alter cerebrospinal fluid Aβ42 or Aβ40 levels in healthy volunteers but consistently increased plasma Aβ40 levels with a less sensitive immunoassay.2

Plasma p-tau biomarkers, particularly p-tau217, are known to associate with Aβ and tau pathologies and predict cognitive decline, while plasma GFAP associates with Aβ 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-Aβ treatments3) is reassuring, treatment that substantially affected plasma Aβ did not affect other biomarkers.

Our study highlights sacubitril/valsartan's potential to confound plasma Aβ42/Aβ40 tests for AD. In AD, this ratio is only reduced by 8% to 14%,3 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 Aβ42/Aβ40 tests,5 results for patients receiving sacubitril/valsartan should be interpreted cautiously; treatment-related Aβ42/Aβ40 reductions may lead to false-positive results and misclassification of Aβ 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 p-tau and kidney disease,4 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.2 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 Aβ to be concerning given sacubitril/valsartan’s successful clinical implementation over almost a decade.
Clinical Trial Partners Ltd outside the submitted work. Prof Blennow reported having served as a consultant and on advisory boards for Acumen, ALZPath, BioArctic, Biogen, Eisai, Eli Lilly, Moleac Pte Ltd, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; having served on data monitoring committees for Julius Clinical and Novartis; lecture fees, production of educational materials, and participation in educational programs for AC Immune, Biogen, Celdara Medical, Eisai, and Roche Diagnostics; and cofounding Brain Biomarker Solutions in Gothenburg AB, which is a part of the GU Ventures Incubator Program, outside the work. No other disclosures were reported.

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CORRECTION

Addition of Nonauthor Collaborators and a Supplement: In the Original Investigation titled “Efficacy and Safety of XEN1101, a Novel Potassium Channel Opener, in Adults With Focal Epilepsy: A Phase 2b Randomized Clinical Trial,”1 published online October 9, 2023, and in the November 2023 issue, a group author name “for the X-TOLE Study Group” has been added to the byline and the Article Information, and a list of Nonauthor Collaborators has been added in a new Supplement. This article has been corrected.1


Change to Open Access Status: The Original Investigation titled “Thrombectomy With the pRESET vs Solitaire Stent Retrievers as First-Line Large Vessel Occlusion Stroke Treatment: A Randomized Clinical Trial,”1 published online January 2, 2024, was changed to open access status under a CC-BY-NC-ND license. This article was corrected online.