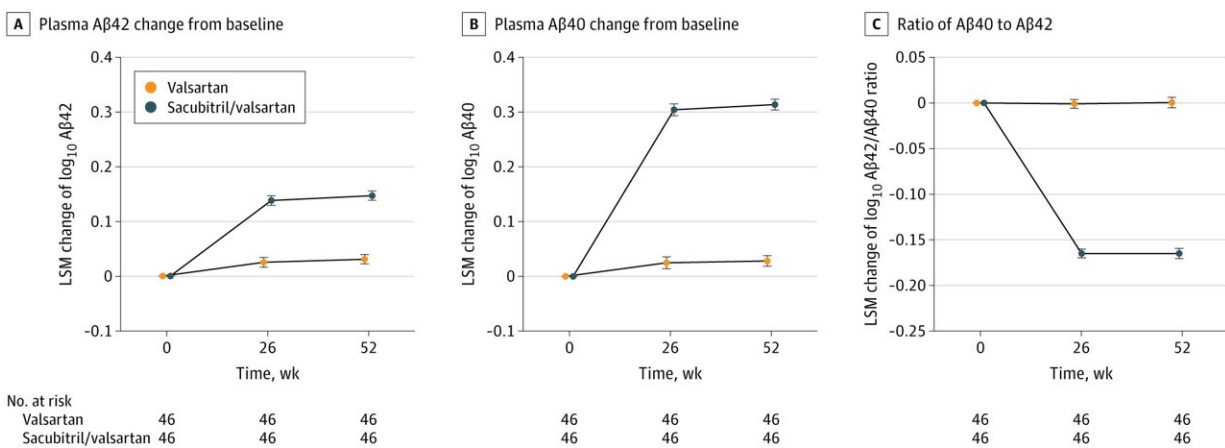


Common drug for cardiac failure may interfere with debated blood test for Alzheimer's disease

December 19 2023



Changes in Aβ blood biomarkers following sacubitril/valsartan treatment. Credit: *JAMA Neurology* (2023). DOI: 10.1001/jamaneurol.2023.4719

Researchers from the University of Gothenburg, in collaboration with colleagues from University of Glasgow, present data that the drug Entresto (sacubitril/valsartan) which is commonly used for the treatment of cardiac failure leads to a marked reduction in plasma Aβ ratio, a candidate blood test for Alzheimer's disease (AD). This interaction may have clinical consequences with risk of misdiagnosis and puts this debated test into further question.

Alzheimer's disease (AD) is associated with damaging protein aggregates in the brain, with β -amyloid ($A\beta$) aggregates called plaques being the key pathology. Entresto (sacubitril/valsartan) is a combined neprilysin inhibitor and angiotensin receptor blocker, approved for the treatment of heart failure.

Concerns were raised by the FDA that this neprilysin inhibition treatment may increase the risk of AD, since neprilysin is one of the main enzymes responsible for degrading $A\beta$ in the brain. The PERSPECTIVE trial (NCT02884206) showed that three-year neprilysin inhibition treatment was not associated with increased $A\beta$ accumulation, determined by PET, or with cognitive deterioration, which was reassuring.

Less invasive and debated test

The initiation of disease-modifying treatments (anti-amyloid immunotherapies) warrants exact [diagnostic tests](#) to verify the presence of brain amyloidosis. While FDA-approved [cerebrospinal fluid](#) (CSF) and PET methods are available, less invasive and more accessible screening tests would simplify the diagnostic work-up and patient management.

A [blood test](#) called [plasma](#) $A\beta$ ratio has, in research studies, been found to have a high performance in detecting brain amyloidosis, and this test is today offered for clinical use in patients with cognitive impairment in the US. However, the "fold change" (difference in plasma $A\beta$ values between AD patients and healthy elderly) is very minor, with only around 10–12% reduction in AD. This is likely due to the fact that $A\beta$ in blood largely comes from peripheral tissues, which blurs the brain signal.

The small fold change indicates poor clinical robustness of this test, which has led to a debate on whether it is suitable for [clinical use](#) or not.

Marked change in all patients on Entresto

This study assessed the effect of 52 weeks of treatment with a combination of the neprilysin inhibitor sacubitril and the [angiotensin receptor blocker](#) valsartan (sacubitril/valsartan, Entresto) vs. valsartan alone on AD blood biomarkers in a clinical trial (NCT035525575) on 92 patients with cardiac failure.

At week 26, and persisting at week 52, both plasma A β 42 and A β 40 markedly increased upon neprilysin inhibition. However, the increase was more pronounced for A β 40 than for A β 42 resulting in a 32-34% reduction in the plasma A β ratio, i.e., making sacubitril/valsartan-treated patients falsely positive on the plasma A β test.

This marked change was found in all patients on Entresto. No changes were found in other AD blood biomarkers (pTau217, pTau181, GFAP or NFL).

Importantly, this study highlights that a commonly used treatment in the elderly confounds the plasma A β ratio, a debated AD blood test. In fact, sacubitril/valsartan treatment impacted the plasma A β 42/A β 40 ratio more than 3-fold (>30% reduction) more than the mean change seen in AD patients (~10% reduction). The study is [published](#) in the journal *JAMA Neurology*.

There are more than 5 million people in the US with AD and around the same number with heart failure. Importantly, about 40% of patients with heart failure also present cognitive impairment, making them potentially eligible for taking the A β blood test.

Could lead to misclassification

Plasma A β 42/A β 40 tests are available clinically in the US. We therefore recommend caution when interpreting the results in patients receiving sacubitril/valsartan, as the observed reduction in the ratio could lead to misclassification of patients as A β plaque-positive (and thus having AD).

Further, from a scientific perspective, these findings call for a re-evaluation of published papers on plasma A β tests, to adjust results after removal of potential false positives (patients on Entresto).

From a clinical perspective and for ethical reasons, these findings also suggest that patients who have had a plasma A β test should be contacted to clarify whether they were on Entresto treatment at the time of blood sampling and thus may have had a false positive test result.

More information: Wagner S. Brum et al, Effect of Neprilysin Inhibition on Alzheimer Disease Plasma Biomarkers, *JAMA Neurology* (2023). [DOI: 10.1001/jamaneurol.2023.4719](https://doi.org/10.1001/jamaneurol.2023.4719)

Provided by University of Gothenburg

Citation: Common drug for cardiac failure may interfere with debated blood test for Alzheimer's disease (2023, December 19) retrieved 27 April 2024 from <https://medicalxpress.com/news/2023-12-common-drug-cardiac-failure-debated.html>

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