Medical Xpress

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

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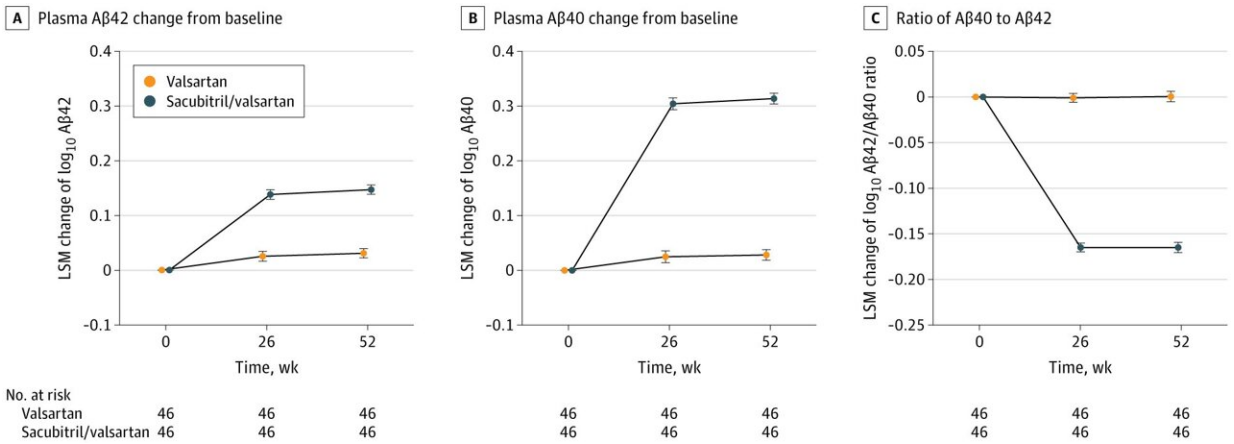

Changes in Aβ blood biomarkers following sacubitril/valsartan treatment. Credit: *JAMA Neurology* (2023). DOI: 10.1001/jamaneurol.2023.4719

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 (Aβ) 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 Aβ in the brain. The PERSPECTIVE trial (NCT02884206) showed that three-year neprilysin inhibition treatment was not associated with increased Aβ 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 Aβ 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 Aβ 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 Aβ 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 Aβ42 and Aβ40 markedly increased upon neprilysin inhibition. However, the increase was more pronounced for Aβ40 than for Aβ42 resulting in a 32-34% reduction in the plasma Aβ ratio, i.e., making sacubitril/valsartan-treated patients falsely positive on the plasma Aβ 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 Aβ ratio, a debated AD blood test. In fact, sacubitril/valsartan treatment impacted the plasma Aβ42/Aβ40 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 Aβ blood test.

Could lead to misclassification

Plasma Aβ42/Aβ40 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 Aβ plaque-positive (and thus having AD).

Further, from a scientific perspective, these findings call for a re-evaluation of published papers on plasma Aβ 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 Aβ 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

Provided by University of Gothenburg