Circulating Amyloid-Beta (1-40) Predicts Clinical Outcomes in Patients With Heart Failure

El amiloide beta (1-40) circulaute predice eventos en pacientes con insuficiencia cardiaca

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Amyloid-\(\beta\) peptides are cleavage products of the amyloid-precursor protein (APP)\textsuperscript{,1}. Amyloid-beta 1-42 peptides form oligomeric aggregates in the brain and their levels have been associated with the development of Alzheimer disease\textsuperscript{,1}. In addition, amyloid-beta 1-40 (A\(\beta\)40) has been described to accumulate mainly in cerebrovascular vessels, inducing cerebral amyloid angiopathy\textsuperscript{,1}. Recent evidence suggests that A\(\beta\)40 is also present in atherosclerotic plaques\textsuperscript{,2,3} and in myocardial tissues from patients with Alzheimer disease and heart failure (HF)\textsuperscript{.3,5}. Experimental evidence suggests that APP and its cleavage product, A\(\beta\)40, exert their detrimental effects on the cardiovascular system by promoting vascular inflammation and atherosclerosis\textsuperscript{.2,3}. Along this line, we have recently reported that circulating A\(\beta\)40 is associated with the presence and extent of atherosclerosis and with cardiovascular mortality in patients with stable coronary artery disease\textsuperscript{.5}. However, whether circulating A\(\beta\)40 is associated with mortality in patients with HF is unknown.

In a recent article published in Revista Española de Cardiología, Bayes-Genis et al\textsuperscript{.7} investigated whether circulating A\(\beta\)40 predicts mortality and cognitive decline in patients with HF. In this carefully designed study using a thorough and contemporary statistical analysis, they found that circulating A\(\beta\)40 was a predictor of all-cause, cardiovascular, and HF-related mortality in a relatively large real-life HF cohort of 939 ambulatory patients after 5.1 \(\pm\) 2.9 years of follow-up. In contrast, A\(\beta\)40 was not associated with cognitive impairment at baseline or cognitive decline at follow-up, which is consistent with a previous report showing no association with the rate of cognitive decline in patients with Alzheimer disease\textsuperscript{.8}. Importantly, adding A\(\beta\)40 to the best prognostic models improved calibration and reclassification metrics (continuous net reclassification improvement ranging between 28.8\% and 34.3\%) for all outcomes of the study. The reclassification incremental value of A\(\beta\)40 supports a clinically meaningful contribution of this peptide to risk stratification in HF patients. The findings of the present study corroborate previous reports showing an association between A\(\beta\)40 and risk factors for HF. For instance, circulating A\(\beta\)40 levels have been shown to positively correlate with renal dysfunction, diabetes, and coronary artery disease\textsuperscript{.6,9}, which are all well-accepted predisposing risk factors for incident HF\textsuperscript{.6,9}. Further, a recent study reported that plasma A\(\beta\)40 levels are increased in patients with HF compared with control participants\textsuperscript{.4}. Interestingly, Alzheimer disease is associated with left ventricular diastolic dysfunction, while A\(\beta\)40 has been detected in oligomeric aggregates in the hearts of patients with Alzheimer disease\textsuperscript{.5}. In myocardial biopsies of patients with ischemic HF, messenger RNA levels of \(\beta\)-secretase (BACE1) and of the APP were also found to be increased compared with those in controls\textsuperscript{.4}. Taken together, converging data suggest that A\(\beta\)40 may be a factor predisposing to the development of HF and its outcome.

The findings of the present study by Bayes-Genis et al\textsuperscript{.7} justify the need for further research on the impact of HF therapy on A\(\beta\)40 levels. As expected, in the present study, most of the patients were receiving left ventricular anti-remodeling therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB), as well as beta-blockers, diuretics, and statins. These drugs may effectively alter tissue and circulating levels of A\(\beta\)40\textsuperscript{.11}. Interestingly, Bayes-Genis et al. observed that a history of treatment with these drugs was associated with plasma A\(\beta\)40 levels, while the significance of the association between HF-related events and A\(\beta\)40 was lost in a multivariate model including ACEI/ARBs and beta-blockers\textsuperscript{.7}. Thus, it should be further explored whether A\(\beta\)40 levels and their change in response to treatment, at the time of first diagnosis of HF, confer stronger prognostic value than a single A\(\beta\)40 measurement taken at a random time point post-treatment during the course of the disease. Along this line, the authors stress the significance of the A\(\beta\)40-neprilysin interaction in light of its emerging clinical usefulness\textsuperscript{.12} and new recommendations for HF therapy with neprilysin inhibition by sacubitril/valsartan\textsuperscript{.13,14}. A\(\beta\)40 is degraded by neprilysin and therefore its inhibition may increase A\(\beta\)40 plasma levels\textsuperscript{.13}. In the study by Bayes-Genis et al., none of the patients were receiving sacubitril/valsartan, while circulating soluble neprilysin levels did not correlate with A\(\beta\)40 levels\textsuperscript{.14}. However, the observed associations of A\(\beta\)40 with adverse outcome in HF highlight the hypothesis that some beneficial effects of sacubitril/valsartan may be partly offset.
Given the expected widening of the indications of sacubitril/valsartan in HF, randomized trials should assess the net survival benefit of HF patients who would respond to treatment with increasing plasma Aβ40 levels.

Bayes-Genis et al. report that circulating Aβ40 levels are associated with aging, renal insufficiency, atrial fibrillation, and a history of diabetes and hypertension, which are all factors leading to or accelerating the progression of preclinical left ventricular diastolic dysfunction. Interestingly, patients with HF with preserved ejection fraction (HFpEF) in the present study had increased circulating Aβ40 levels. Diastolic dysfunction and subsequent HFpEF are considered prominent manifestations of myocardial aging. Given that Aβ40 levels are associated with arterial aging (progression in arterial stiffness), it is tempting to hypothesize that Aβ40 levels may demonstrate the extent of cardiovascular aging, determined as arterial and myocardial stiffening. In turn, arterial and left ventricular stiffening may invoke deregulation in arterioventricular coupling, leading to labile blood pressure fluctuations, decreased left ventricular diastolic reserve, and increased left ventricular filling pressures, which all together could affect prognosis in HFpEF. However, whether Aβ40 has a causal relationship with the development of HFpEF is a question that can only be definitively answered by murine or other animal studies. Nevertheless, given that the currently recommended strategies for the treatment of HFpEF are directed at symptoms due to the disappointing results to date from etiological treatments, further research in Aβ40 as a possible biomarker and therapeutic target in this type of HF is of particular clinical importance. Additionally, the response of circulating Aβ40 to acute exacerbations of decompensated HF and its clinical significance is unknown and should be also prospectively examined.

In conclusion, the present study by Bayes-Genis et al. published in Revista Española de Cardiología provides important novel evidence that circulating Aβ40 is associated with adverse outcomes in a mixed population of ambulatory HF patients. From a mechanistic point of view, the findings are supported by the literature and should stimulate further research to better clarify the role of this peptide as a biomarker in different types of HF and particularly in HFpEF. Finally, assessment of the clinical significance of the response of this peptide for treatment to HF and specifically to the newly introduced nepriylin inhibitors on circulating Aβ40 may be of great importance in future.

CONFLICTS OF INTEREST

None declared.

REFERENCES