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INVITED EDITORIAL

Insulin-like growth factor binding protein-7 in heart failure: The challenge of moving from risk prediction to a biomarker-guided management

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This article refers to 'Insulin-like growth factor binding protein-7 concentrations in chronic heart failure: Results from the EMPEROR programme' by J.P. Ferreira *et al.*, published in this issue on pages xxx.

Despite significant advances in treatment over the last decades, heart failure (HF) still represents an important cause of morbidity and mortality, with a similar or even worse prognosis than many cancers.[1] Natriuretic peptides has fuelled the dream of unveiling circulating signals that could help predict future HF development, aid diagnosis, risk prediction, therapy monitoring and follow-up, and even serve as surrogate endpoints for clinical trials.[2] Many other biomarkers have shown prognostic value, including high-sensitivity cardiac troponins (hs-cTn),[3] soluble suppression of tumorigenesis-2 (sST2),[4] and growth differentiation factor-15 (GDF-15),[5] but they have not entered clinical practice so far.[2] One of the proposed HF biomarkers with prognostic significance is insulin-like growth factor binding protein-7 (IGFBP7), a biomarker associated with cellular senescence, tissue aging, and obesity[2] that is secreted by cardiomyocytes in the failing heart.[6]

In this issue of the Journal, Ferreira *et al.*[7] assess the association between IGFBP7 and outcomes in 1125 study participants from the EMPEROR-Reduced ($n = 594$) and EMPEROR-Preserved trials ($n = 531$), which tested empagliflozin in HF outpatients with left ventricular ejection fraction (LVEF) ≤40% and LVEF >40%, respectively. In a prognostic model including age, sex, LVEF, estimated glomerular filtration rate (eGFR), baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hs-cTnT, among other variables, patients in the highest tertile of IGFBP7 had the greatest risk for the primary endpoint (cardiovascular death or HF hospitalization) as well as other cardiovascular and renal events including cardiovascular death, sustained eGFR reduction ≥40% or end-stage renal disease. No significant interaction was observed between the prognostic value of IGFBP7 tertiles and LVEF ≤40% versus >40% categories. Interestingly, changes in IGFBP7 during the first 3 months of the study yielded prognostic significance on top of the same prognostic model plus baseline IGFBP7. As for the relationship between the prognostic value of IGFBP7 and treatment assignment, higher IGFBP7 levels were associated with higher event rates regardless of the randomization group, and the prognostic benefit from empagliflozin was unaffected by baseline IGFBP7. Proteomic analysis revealed only modest associations between baseline IGFBP7 levels and other proteins, such as bone morphogenic protein-10, fatty acid binding protein-3, and GDF-15.[7]

Ferreira and co-workers should be congratulated for this comprehensive analysis of IGFBP7 and outcome in the EMPEROR cohort, which adds to the body of literature about the prognostic value of IGFBP7 in HF. Most notably, the association between IGFBP7 and worse clinical status and risk of cardiac and renal outcomes was previously reported from the PARAMOUNT and DAPA-HF trials,[8,9] enrolling patients with stable HF, and in a real-world cohort of patients with new-onset or worsening HF (BIOSTAT-CHF).[10] In the present study, Ferreira *et al.* report an association between high IGFPB7 and outcome in patients with stable HF and LVEF either ≤40% or >40%.[7] Additionally, they report that baseline IGFPB7 has additive prognostic value to NT-proBNP and hs-cTn, as well as to GDF-15, and that changes in IGFBP7 hold prognostic significance.[7] Notably, empagliflozin treatment did not have any meaningful effect on IGFBP7 levels, in agreement with findings on dapagliflozin,[9] while treatment with sacubitril/valsartan resulted in lower IGFBP7 concentrations compared with valsartan in patients with HF and preserved ejection fraction (HFpEF).[8]

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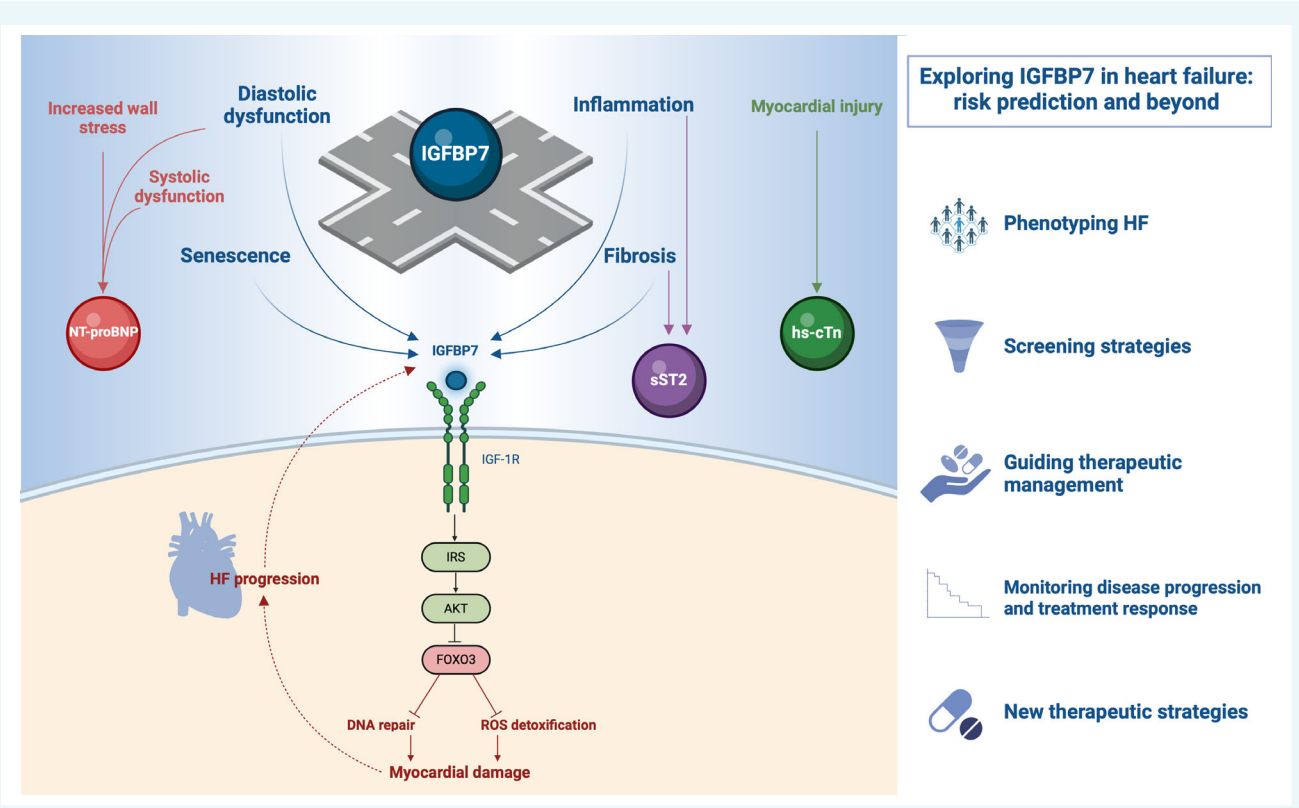

Figure 1 Insulin-like growth factor binding protein-7 (IGFBP7): biology and possible roles as a biomarker of heart failure (HF). See text for details. FOXO3, forkhead box O3; hs-cTn, high-sensitivity cardiac troponin; IGF-1R, insulin-like growth factor-1 receptor; IRS, insulin receptor substrate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROS, reactive oxygen species; sST2, soluble suppression of tumorigenesis-2.

IGFBP7 is known as part of the senescence-associated secretome, promoting cell-cycle arrest, oxidative stress, and fibrosis[11] (*Figure 1*). Overexpression of IGFBP7 is thus at the crossroad with aging, inflammation, insulin resistance and metabolic dysregulation. Under this respect, IGFBP7 elevation in HF patients emphasizes the relevance of immune dysregulation and metabolic derangement in HF pathogenesis, which is increasingly acknowledged. Interestingly, in a pressure-overload mouse HF model, IGFBP7 knock-out attenuated cardiac dysfunction by reducing cardiac inflammatory injury, tissue fibrosis and cellular senescence. The study also demonstrated that antibody-mediated IGFBP7 neutralization *in vivo* restored DNA repair and reactive oxygen species detoxification signals and attenuated pressure overload-induced HF.[12] Thus, targeting IGFBP7 could be a promising therapeutic target in HF.

IGFBP7 levels were previously associated with measures of diastolic dysfunction,[13] but the strongest association with risk in the present study was observed in patients with HF with reduced ejection fraction, challenging the notion that IGFBP7 elevation would mainly epitomize the aging-associated comorbidity burden and the immune-metabolic alterations that are distinct features of HFpEF.[14] Additionally, the prognostic value of IGFBP7 may arise from its distinct production and release mechanisms, unlike natriuretic peptides, which primarily indicate wall stress, and hs-cTn, which is released following myocardial injury.[2]

The lack of effect of empagliflozin on IGFBP7 is unexpected considering the direct cardioprotective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors and the proposed relationship between circulating levels of IGFBP7 and the degree of activation of these mechanisms. By promoting glucose excretion, SGLT2 inhibitors induce a state of starvation mimicry secondary to the urinary loss of calories. Consequently, the cardiorenal benefits of SGLT2 inhibitors are related to the activation of nutrient deprivation signalling, which promotes autophagy and improves mitochondrial function, reduces the generation of reactive oxygen species, blunts inflammation and fibrosis, and enhances the viability of cardiomyocytes and renal parenchymal cells.[15] These beneficial effects stem largely from their ability to regulate nutrient signalling pathways, increasing the activity of AMPK and sirtuins, among others. A possible explanation for the lack of effect of SGLT2 inhibitors on IGFBP7 is that the cardiorenal protective effects of SGLT2 inhibitors act on pathways different from those associated with IGFBP7-related senescence. IGFBP7 promotes cardiac senescence by stimulating IGF-1R/IRS/AKT-dependent suppression of FOXO3a, whereas SGLT2 inhibitors may inhibit cellular senescence and oxidative stress via ketone-induced NRF2 activation.[16]

Overall, Ferreira *et al.* confirm previous observations about the prognostic value of IGFBP7 in HF with a robust methodology, focusing also on the role of IGFBP7 across the entire

LVEF spectrum and changes in IGFBP7 over time, and generating hypotheses for future mechanistic studies. As a possible limitation, we may consider the risk of unknown confounders, which is particularly worrisome when evaluating molecules with pleiotropic effects like IGFBP7. Moreover, many open questions remain, first of all how to translate the prognostic value of IGFBP7 into our daily practice and how to leverage IGFBP7 for clinical use or therapeutic innovation.

Numerous biomarkers with established prognostic value, such as hs-cTn and sST2, remain underutilized in clinical practice. This gap primarily stems from practical barriers such as cost and the need for specific assay methods, but also from the lack of conclusive evidence that biomarker-guided prognostic stratification, including the use of NT-proBNP,[17] may inform the therapeutic strategy resulting in better patient outcomes.[2] Consequently, the European Society of Cardiology guidelines currently do not recommend using these biomarkers, including NT-proBNP, for risk stratification.[18] There is also a growing interest in identifying homogeneous phenotypes beyond traditional HF classifications, particularly in HFpEF.[19] Although these novel strategies have been proposed, they have yet to be translated into actionable clinical or research applications. To advance the integration of biomarkers into clinical settings, we should focus on identifying those that not only aid in risk stratification, but also suggest specific therapeutic interventions. For example, biomarkers that signal the activation of profibrotic pathways could potentially guide the use of antifibrotic medications. To truly realize the benefits of these biomarkers, it is crucial to rigorously evaluate the prognostic benefits of biomarker-driven treatment strategies. Additionally, exploring potential therapeutic targets within the pathways indicated by these biomarkers could pave the way for a precision medicine approach in HF. This strategy would likely incorporate specialized treatments in addition to established therapies, akin to approaches seen in cancer treatments.

In conclusion, the research conducted by Ferreira *et al.* represents a substantial advancement in our understanding and management of HF. It underscores the importance of further research into biomarkers that can predict outcomes and inform treatment strategies. There is a need to explore effective methods for incorporating IGFBP7 and other prognostically valuable biomarkers into clinical practice. By examining the correlations between biomarker profiles and responses to specific treatments, we can advance toward a precision medicine approach. This strategy, which tailors treatment to the individual's phenotype, holds promise for improving patient outcomes.

Conflict of interest: none declared.

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