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Clinical Investigation

Prognostic Value of Insulin-Like Growth Factor-Binding Protein 7 in Patients with Heart Failure and Preserved Ejection Fraction

PARUL U. GANDHI, MD,[1,2] SHERYL L. CHOW, PharmD,[3] THOMAS S. RECTOR, PhD,[4,5] HENRY KRUM, PhD FRACP,[6] HANNA K. GAGGIN, MD, MPH,[7] JOHN J. MCMURRAY, MD,[8] MICHAEL R. ZILE, MD,[9] MICHEL KOMAJDA, MD,[10] ROBERT S. MCKELVIE, MD, PhD,[11] PETER E. CARSON, MD,[12] JAMES L. JANUZZI Jr., MD,[7,*] AND INDER S. ANAND, MD, DPhil[4,5,*]

West Haven and New Haven, Connecticut; Pomona, California; Minneapolis, Minnesota; Melbourne, Australia; Boston, Massachusetts; Glasgow, United Kingdom; Charleston, South Carolina; Paris, France; Hamilton, Ontario, Canada; and Washington, DC

ABSTRACT

Background: The prognostic merit of insulin-like growth factor-binding protein 7 (IGFBP7) is unknown in heart failure and preserved ejection fraction (HFpEF).

Methods and Results: Baseline IGFBP7 (BL-IGFBP7; n = 302) and 6-month change (Δ; n = 293) were evaluated in the Irbesartan in Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial. Primary outcome was all-cause mortality or cardiovascular hospitalization with median follow-up of 3.6 years; secondary outcomes included HF events. Median BL-IGFBP7 concentration was 218 ng/mL. BL-IGFBP7 was significantly correlated with age ($R^2 = 0.13$; $P < .0001$), amino-terminal pro-B-type NP ($R^2 = 0.22$; $P < .0001$), and estimated glomerular filtration rate (eGFR; $R^2 = 0.14$; $P < .0001$), but not with signs/symptoms of HFpEF. BL-IGFBP7 was significantly associated with the primary outcome (hazard ratio [HR] = 1.007 per ng/mL; $P < .001$), all-cause mortality (HR = 1.008 per ng/mL; $P < .001$), and HF events (HR = 1.007 per ng/mL; $P < .001$). IGFBP7 remained significant for each outcome after adjustment for ln amino-terminal pro-B-type NP and eGFR but not all variables in the I-PRESERVE prediction model. After 6 months, IGFBP7 did not change significantly in either treatment group. ΔIGFBP7 was significantly associated with decrease in eGFR in patients randomized to irbesartan ($R^2 = 0.09$; $P = .002$). ΔIGFBP7 was not independently associated with outcome.

Conclusions: Higher concentrations of IGFBP7 were associated with increased risk of cardiovascular events, but after multivariable adjustment this association was no longer present. Further studies of IGFBP7 are needed to elucidate its mechanism.

Clinical Trial Registration: www.clinicaltrials.gov, NCT00095238 (*J Cardiac Fail 2016;■■:■■–■■*)

Key Words: Heart failure, biomarkers, preserved left ventricular function, prognosis, insulin-like growth factor-binding protein 7.

From the [1]Section of Cardiovascular Medicine, VA Connecticut, West Haven, Connecticut; [2]Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; [3]Western University of Health Sciences, Pomona, California; [4]Veterans Affairs Medical Center, Minneapolis, Minnesota; [5]University of Minnesota, Minneapolis, Minnesota; [6]CCRE Therapeutics, Monash University, Melbourne, Australia; [7]Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts; [8]British Heart Foundation Glasgow Cardiovascular Research Center, Glasgow, United Kingdom; [9]RHJ Department of Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, South Carolina; [10]Université Paris 6; Pitie Salpetriere Hospital, Paris, France; [11]Population Health Research Institute and McMaster University, Hamilton, Ontario, Canada and [12]Washington VAMC and Georgetown University, Washington, DC.

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Reprint requests: James L. Januzzi Jr., MD, Massachusetts General Hospital, 32 Fruit Street, Yawkey 5984, Boston, Massachusetts 02114. Tel: +1 617 726 3443; Fax: +1 617 643 1620. E-mail: jjanuzzi@partners.org

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*Contributed equally.

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Heart failure (HF) affects more than 5.7 million people in the United States alone, and the prevalence is increasing.[1] Approximately one-half of patients with HF have preserved ejection fraction (HFpEF); increasingly, reports suggest more patients who are hospitalized for HF are found to have HFpEF, rather than HF with reduced ejection fraction (HFrEF).[2,3] Furthermore, patients with HFpEF are at significant risk, given its considerable morbidity and mortality.[4–6] Many evidenced-based therapies and management strategies exist for those affected by HFrEF;[7] however, in spite of attempts to discover therapies for HFpEF, its management remains a clinical conundrum with multiple unrevealing trials,[8–10] possibly because of the heterogeneous nature of the affected population as well as the challenging diagnosis of this syndrome.[11] A more logical approach to evaluate and treat HFpEF may be strategies aimed at individual mechanism(s) of HF in these patients, rather than simply focusing on EF; in this regard, use of cardiac biomarkers may be helpful to characterize HFpEF phenotypes, assist in risk stratification, and provide insight into additional pathophysiologic mechanisms.

Natriuretic peptides (NP) remain useful for diagnosis and hold similar prognostic power in patients with HFpEF.[12] These peptides are also linked to echocardiographic parameters of diastolic dysfunction,[13,14] but NPs lack specificity for diastology, because other conditions including valvular abnormalities and left ventricular ejection fraction (LVEF) can contribute to their concentrations.[7] Therefore, a biomarker more reflective of diastolic dysfunction would provide improved options for diagnosis, prognosis, and possibly even management strategies for patients whose primary mechanism of HF is abnormal diastolic function.

Recent work has identified insulin-like growth factor-binding protein 7 (IGFBP7) as a novel biomarker associated with cardiac hypertrophy; elevated concentrations were detected in the serum of patients with both HFrEF and HFpEF.[15] We previously identified IGFBP7 to be prognostic in patients with HFrEF, and in adjusted analyses, IGFBP7 was incrementally additive to amino-terminal pro-B-type NP (NT-proBNP) for prognostication.[16] Notably, in these patients, we found IGFBP7 was significantly associated and correlated with stigmata of diastolic dysfunction, including transmitral E/A ratio, E/E′, left atrial volume index, and right ventricular systolic pressure; we also found an inverse relationship between therapy with angiotensin-converting enzyme inhibitors and IGFBP7.[17] Given the prognostic value of IGFBP7 in patients with HFrEF, along with its links to abnormalities of diastolic function, we sought to examine the prognostic ability of IGFBP7 in a subgroup of patients with HFpEF from the Irbesartan in Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial.[18] We hypothesized that IGFBP7 would provide significant prognostic information in this subset of patients.

Materials and Methods

Patient Population and Study Overview

The I-PRESERVE study enrolled 4128 patients with LVEF of at least 45%, as determined by the individual sites, who were age 60 or greater with symptomatic HF and recent hospitalization for HF or with persistent New York Heart Association class III/IV symptoms who were randomized to receive irbesartan or placebo. Patients were excluded if they had prior evidence of HFrEF (LVEF <40%), recent acute coronary syndrome with or without revascularization or stroke, significant valvular heart disease, hypertrophic or restrictive cardiomyopathy, pericardial disease, cor pulmonale, or significant hypertension (>160 mmHg systolic or >95 mmHg diastolic) or hypotension (<100 mmHg). Additional exclusion criteria included limited life expectancy, hemoglobin <11 gm/dL, creatinine >2.5 mg/dL, or liver function abnormalities. The primary outcome was the composite of all-cause mortality and protocol-specified cardiovascular hospitalizations.[8] The collagen marker substudy included 313 of these patients with blood samples at baseline and 6 months and examined concentrations of procollagen type I amino-terminal peptide (PINP), procollagen type 3 amino-terminal peptide (PIIINP), and osteopontin.[18] For the current analysis, 302 samples were available at baseline and 293 at 6 months. Using these samples, we evaluated the prognostic utility of baseline IGFBP7 concentrations as well as change from baseline to 6 months with respect to outcomes during a median follow-up of 3.6 (2.8 to 3.9) years. A flow diagram for the present study is depicted in Fig. 1. The current study complies with the Declaration of Helsinki, the research protocol has been approved by the ethics committee, and informed consent was obtained from all subjects.

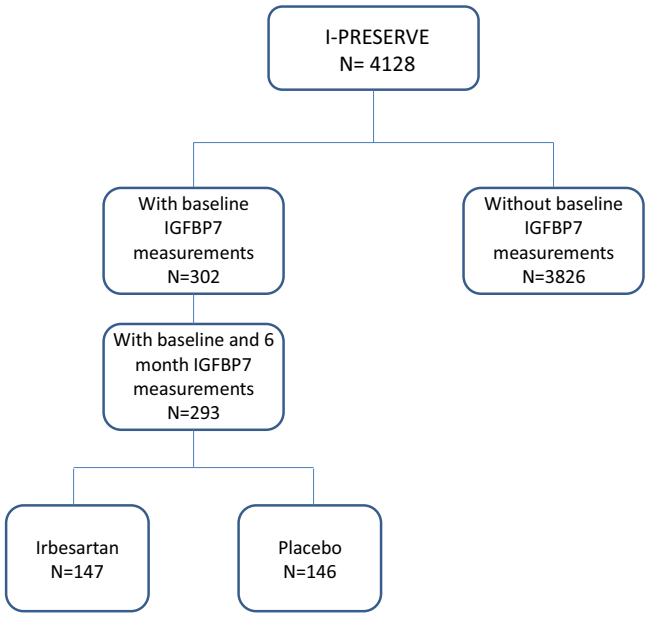

Fig. 1. Flow chart of patients from I-PRESERVE included in current analysis.
Of the 4128 patients in the I-PRESERVE study, baseline IGFBP7 measurements were available in 302 patients; baseline and 6-month samples were available in 293 patients. IGFBP7, insulin-like growth factor-binding protein 7; I-PRESERVE, Irbesartan in patients with heart failure and preserved ejection fraction.