JACC: HEART FAILURE
VOL. 4, NO. 8, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.03.006

Plasma Corin as a Predictor of Cardiovascular Events in Patients With Chronic Heart Failure

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ABSTRACT

OBJECTIVES The aim of this study was to determine the prognostic value of plasma corin in patients with chronic heart failure (CHF).

BACKGROUND In recent years, accumulating evidence has indicated that corin plays a critical role in regulating blood pressure and cardiac function.

METHODS We enrolled 1,148 consecutive CHF patients in a prospective cohort study and explored the association between plasma corin levels and clinical prognosis using multivariate Cox regression analysis.

RESULTS Patients with low corin levels (<458 pg/ml) were more likely to be women and to be hypertensive. Low corin was found to be associated with an increase in New York Heart Association (NYHA) functional class and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and a decrease in left ventricular ejection fraction (LVEF) and the estimated glomerular filtration rate (eGFR). Multivariate Cox regression analysis suggested that log corin was an independent predictor of major adverse cardiac event(s) (MACE) (hazard ratio: 0.62; 95% confidence interval: 0.39 to 0.95), together with age, diabetes, NYHA functional class, LVEF, eGFR, and log NT-proBNP. In addition, log corin was also a significant predictor for cardiovascular death ($p = 0.041$) and heart failure rehospitalization ($p = 0.015$) after adjustment for clinical variables and established biomarkers of adverse prognosis. The Kaplan-Meier survival curves showed that low corin was a significant predictor of MACE in patients with NT-proBNP levels above and below the median.

CONCLUSIONS Our study demonstrates that plasma corin is a valuable prognostic marker of MACE in patients with CHF, independent of established conventional risk factors. (J Am Coll Cardiol HF 2016;4:664–9)

Corin is a type II transmembrane serine protease that is highly expressed in the heart, where it converts natriuretic peptides from inactive precursors to mature active forms (1). Human corin protein contains an N-terminal cytoplasmic tail of 45 amino acids, followed by a single-span transmembrane domain of 21 amino acids. The extracellular region consists of 2 frizzled-like, cysteine-rich domains, 8 low-density lipoprotein receptor repeats, a macrophage scavenger receptor-like domain, and a trypsin-like protease domain (2).

In recent years, there has been growing evidence that corin plays critical roles in the regulation of salt-water balance, blood pressure, and cardiac function. Chan et al. (3) reported that corin knockout mice eventually developed spontaneous hypertension and exhibited cardiac hypertrophy and dysfunction. Gladysheva et al. (4) showed that corin overexpression could attenuate myocardial fibrosis and improve cardiac function in transgenic mice with dilated cardiomyopathy. Pang et al. (5) indicated that corin was down-regulated and exerted cardioprotective action

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Manuscript received February 3, 2016; revised manuscript received March 8, 2016, accepted March 10, 2016.

via activating the atrial natriuretic peptide (ANP) pathway in diabetic cardiomyopathy. In African Americans, the corin variant with impaired natriuretic peptide processing activity was correlated with hypertension, cardiac hypertrophy, and adverse outcomes of heart failure (HF) (6–8).

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A clinical study conducted by Dong et al. (9) revealed that corin deficiency might contribute to the pathogenesis of HF and that plasma corin could be used as a biomarker in the diagnosis of HF. Moreover, Ibebuogu et al. (10) showed that decompensated HF was associated with reduced corin levels and decreased cleavage of pro-ANP. However, until now, it has remained unclear whether low corin is correlated with a poor prognosis in patients with chronic heart failure (CHF). Therefore, we carried out a prospective cohort study to evaluate the prognostic usefulness of plasma corin in CHF patients.

METHODS

STUDY POPULATION. A total of 1,148 consecutive patients with CHF admitted to the affiliated hospitals of Nanjing Medical University were recruited between January 1, 2010 and August 31, 2013. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Nanjing Medical University. The diagnosis of CHF was on the basis of typical symptoms and signs and evidence of left ventricular enlargement and systolic functional impairment by echocardiography, according to the American College of Cardiology/American Heart Association guidelines (11). All patients had a history of CHF for at least 6 months and were in stable condition on medication for at least 2 weeks before blood sampling. Patients with known malignancy or end-stage renal disease were excluded from the study. Demographic, clinical, and biochemical data were obtained from the medical records. All patients received standard medical treatment, and written informed consent was obtained from each participant.

MEASUREMENT OF PLASMA CORIN. Blood samples were collected from CHF patients and transferred into tubes containing ethylenediaminetetraacetic acid as an anticoagulant agent. Plasma was obtained by centrifugation for 10 min at 3,000 rpm and stored at −80°C. An enzyme-linked immunoabsorbent assay kit (R&D Systems, Minneapolis, Minnesota) was used to measure plasma soluble corin as previously described (9).

ENDPOINTS. The primary composite endpoint was major adverse cardiac event(s) (MACE), which was defined as cardiovascular death and rehospitalization due to worsening HF. The secondary endpoints were the individual components of the primary outcome, including cardiovascular mortality and HF rehospitalization. Endpoints were obtained by reviewing the hospital database and by contacting each patient individually.

STATISTICAL ANALYSIS. Statistical analyses were performed using SPSS version 18.0 (IBM, Armonk, New York). Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. Normality of continuous variables was assessed by the Kolmogorov-Smirnov test. The association between baseline variables and MACE was evaluated using univariable and multivariable Cox proportional hazards analysis. The factors entered into the Cox regression model were age, sex, ischemic etiology, hypertension, diabetes, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and corin. Levels of NT-proBNP and corin were normalized by $\log_{10}$ transformation. Kaplan-Meier analysis was conducted to compare the differences in survival rates between patients with high and low levels of corin using the log-rank test. The effect of adding corin to the reference model for the prediction of MACE was evaluated using integrated discrimination improvement (IDI). In this study, a 2-tailed p value <0.05 was considered to be statistically significant.

RESULTS

PATIENT CHARACTERISTICS. The baseline characteristics of the study population are shown in Table 1. CHF patients were divided into 2 groups according to the median levels of plasma corin. Patients with low corin levels (<458 pg/ml) were more likely to be women and to be hypertensive, and less likely to be treated with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers. Low corin was found to be associated with an increase in NYHA functional class and NT-proBNP levels and a decrease in LVEF and eGFR. In this study, the median length of follow-up was 569 days (range 64 to 1,932 days). No patient was lost to follow-up.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ANP = atrial natriuretic peptide

ARB = angiotensin receptor blocker

BNP = brain natriuretic peptide

CHF = chronic heart failure

CI = confidence interval

eGFR = estimated glomerular filtration rate

HF = heart failure

HR = hazard ratio

IDI = integrated discrimination improvement

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac event(s)

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association