Novel Extracellular Matrix Biomarkers as Predictors of Adverse Outcome in Chronic Heart Failure: Association Between Biglycan and Response to Statin Therapy in the CORONA Trial

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ABSTRACT

Background: The extracellular matrix (ECM) plays an important role in left ventricular remodeling and progression of heart failure (HF). Biglycan and mimecan are ECM proteins that are abundantly expressed in cardiac tissue but have not been evaluated as prognostic markers in HF. We investigated their interaction with statin treatment and association with adverse outcome in chronic HF.

Methods and Results: The association between serum levels of biglycan and mimecan and the primary end point (cardiovascular [CV] death, nonfatal myocardial infarction, nonfatal stroke), all-cause mortality, CV death, the composite of all-cause mortality/hospitalization for worsening of HF, and the coronary end point was evaluated in 1,390 patients >60 years of age with ischemic systolic HF in the Controlled Rosuvastatin Multinational Trial in HF (CORONA) population, randomly assigned to 10 mg rosuvastatin or placebo. Serum biglycan and mimecan added no prognostic information beyond conventional risk factors, including N-terminal pro−B-type natriuretic peptide. However, statin treatment improved all outcomes except CV death in patients with low biglycan levels (ie, lower tertile), even after full multivariable adjustment.

Conclusions: Although circulating levels of mimecan and biglycan were of limited predictive value in patients with chronic HF, circulating biglycan could be a useful marker for targeting statin therapy in patients with HF. (*J Cardiac Fail 2015;21:153−159*)

Key Words: Heart failure, adverse outcome, extra cellular matrix, biglycan, mimecan.

Heart failure (HF) is a complex multisystem disorder in which a number of physiologic systems participate, acting on the myocyte and the myocardial interstitial cells. Inflammation and extracellular matrix (ECM) remodeling have been suggested to play an important role in left ventricular (LV) remodeling and changes in expression patterns of ECM proteins may contribute to the progression of HF.[1] Mimecan and biglycan are ECM-localized proteins that belong to the family of small leucine-rich proteoglycans (SLRPs). They have a similar structural organization but differ in their composition of tandem leucine-rich repeats and glycosaminoglycan side chains.[2,3] As a result, they may interact with different cytokines, growth factors, and ECM proteins and bind different collagens.[2] Biglycan binds to multiple collagens[3] and is universally expressed in the myocardium,[2] whereas mimecan predominately binds to collagen I[3] and has been localized to cardiac fibroblasts and smooth muscle cells.[4,5] Biglycan expression increases in response to pressure overload and myocardial infarction (MI),[6,7] whereas the expression of mimecan is markedly increased and shows a strong correlation with left ventricular (LV) mass.[8] Furthermore, these SLRPs may be involved in myocardial remodeling through modulation of the

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transforming growth factor (TGF) β pathway,[8,9] promoting both maladaptive and adaptive responses.[6,8–10]

Although there are ample data supporting a relationship between high circulating levels of ECM markers, such as matrix metalloproteinase and peptides of collagen metabolism, and poor outcomes in HF,[11] there are limited data on proteoglycans and adverse events in these patients. Recently, in a small HF cohort (n = 142) of mixed etiology, Motiwala et al found an univariate association between elevated mimecan, but not biglycan, and a composite end point of total CV events that did not persist after multivariable adjustment.[12] However, no large cohort studies involving HF patients have investigated the association between circulating levels of these ECM proteins and prespecified end points or investigated interactions with treatment modalities. Moreover, data on the ability of cardiovascular medication to modulate these markers are scarce.

In the present study we therefore evaluated the prognostic relevance of elevated levels of these ECM proteins on cause-specific outcomes in a substudy involving ∼30% of the patients enrolled in the CORONA trial.[13] Moreover, although rosuvastatin had no effect on the primary outcome in the whole study population, it is important to identify subgroups of HF patients that could benefit from such therapy. We therefore also examined whether serum levels of these ECM-related proteins could identify HF patients that might benefit from statin therapy.

Methods

Patients

The design and principal findings of CORONA have been reported in detail.[13] Briefly, patients ≥60 years of age with chronic HF attributed to ischemic heart disease, defined as (i) medical history or electrocardiographic evidence of established MI or (ii) other data indicating ischemic etiology of HF (ie, wall motion disturbances on echocardiography, left bundle branch block, or history of other occlusive atherosclerotic disease [ie, earlier stroke, intermittent claudication, percutaneous coronary intervention (PCI)]), who were in New York Heart Association (NYHA) functional class II–IV, and with an LV ejection fraction (LVEF) ≤40% (≤35% if NYHA II) were eligible, provided the investigator thought they did not need treatment with a cholesterol-lowering drug. The main criteria for exclusion were a recent CV event, current or planned procedures or operations, acute or chronic liver disease, a serum creatinine ≥2.5 mg/dL, contraindications to statin therapy or an unexplained increase in creatine kinase. Every patient provided written informed consent. Patients were randomly assigned to 10 mg/d rosuvastatin or matching placebo, once daily. There were only minor differences in the baseline characteristics between this substudy and the main CORONA study.[13]

Study Outcomes and Definitions

The primary predefined outcome for CORONA was the composite of death from CV causes, nonfatal MI, and nonfatal stroke, analyzed as time to the first event (n = 411). Of secondary outcomes, the following were used in the present substudy: all-cause mortality (n = 425), CV mortality (n = 347), composite of CV mortality and hospitalizations from worsening of HF (WHF; n = 542), and any coronary event (defined as sudden death, fatal or nonfatal MI, PCI, coronary artery bypass graft surgery, ventricular defibrillation by an implantable cardioverter-defibrillator, resuscitation from cardiac arrest, or hospitalization for unstable angina; n = 330).

Blood Sampling Protocol

Peripheral venous blood was drawn into pyrogen-free tubes without any additives. After coagulation at room temperature, the tubes were centrifuged at 1,500*g* for 10 minutes, and serum was stored at −80°C in multiple aliquots. Serum mimecan and biglycan were measured with the use of a microtiter prototype enzyme-linked immunosorbent assay (Roche Diagnostics, Penzberg, Germany). The limits of detection for biglycan and mimecan were, respectively, 0.08 ng/mL and 0.39 ng/mL, with inter- and intrarun coefficients of variation of, respectively, 6.6% and 3.9%, and 4.1% and 3.5%. N-Terminal pro–B-type natriuretic peptide (NT-proBNP) was analyzed with the use of a commercially available assay (Roche Diagnostics, Basel, Switzerland). A high-sensitivity immunonephelometric method was used to measure C-reactive protein (hsCRP; Dade Behring, Atterbury, United Kingdom; sensitivity 0.04 mg/L).

Ethics

All human studies conformed to the Declaration of Helsinki and were approved by the local Ethical Committee. Written informed consent was obtained from each individual.

Statistics

For comparing 2 groups, the Mann-Whitney *U* test was used. Kaplan-Meier curves were constructed to visualize and evaluate (log rank test) differences in survival. Trends across tertiles of ECM biomarkers were tested with the use of the Cuzick extension of the Wilcoxon rank sum test.

Survival analyses were performed with the use of Cox proportional hazard regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the ECM biomarkers included as log-transformed continuous variables at baseline or as nominal changes in a version of the model developed previously for the full CORONA population,[14] with the 8 clinical and 4 biochemical variables most associated with outcome including NT-proBNP and hsCRP. For investigating the effects of rosuvastatin treatment according to baseline levels of mimecan and biglycan, a formal interaction test was conducted comprising treatment group (binary variable), one of the ECM proteins (continuous), and the interaction term in a Cox model as indicated above. In addition, this interaction model was tested with interaction terms for NT-proBNP and hsCRP based on cutoffs for treatment responses identified in this population.[15,16] A subsequent Cox proportional hazard model was used to estimate the HRs and 95% CIs comparing rosuvastatin and placebo treatments within each tertile of ECM biomarker. Net reclassification improvement (NRI) and change in the Harrell C-index were calculated for the addition of ECM biomarker to all steps. A 2-sided *P* value of $<.05$ was considered to be significant in all cases, except for interaction terms, where $P < .1$ was considered to be significant.[17]