Limited Added Value of Circulating Inflammatory Biomarkers in Chronic Heart Failure

Ståle H. Nymo, MD,a Pål Aukrust, MD, PhD,a,b,c John Kjekshus, MD, PhD,d John J.V. McMurray, MD, PhD,e John G.F. Cleland, MD, PhD,f John Wikstrand, MD, PhD,g Pieter Muntendam, MD, PhD,h Ursula Wienhues-Thelen, PhD,i Roberto Latini, MD, PhD,j Erik Tandberg Askevold, MD, PhD,a Jørgen Gravning, MD, PhD, b Christen P. Dahl, MD, PhD, d Kaspar Broch, MD, PhD, d Arne Yndestad, MD, PhD, a,c,j Lars Gullesstad, MD, PhD, a,l Thor Ueland, PhD,a,c,m on behalf of the CORONA Study Group

ABSTRACT

OBJECTIVES This study sought to evaluate whether a panel of biomarkers improved prognostication in patients with heart failure (HF) and reduced ejection fraction of ischemic origin using a systematized approach according to suggested requirements for validation of new biomarkers.

BACKGROUND Modeling combinations of multiple circulating markers could potentially identify patients with HF at particularly high risk and aid in the selection of individualized therapy.

METHODS From a panel of 20 inflammatory and extracellular matrix biomarkers, 2 different biomarker panels were created and added to the Seattle HF score and the prognostic model from the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study (n = 1,497), which included conventional clinical characteristics and C-reactive protein and N-terminal pro-B-type natriuretic peptide. Interactions with statin treatment were also assessed.

RESULTS The two models—model 1 (endostatin, interleukin 8, soluble ST2, troponin T, galectin 3, and chemokine [C-C motif] ligand 21) and model 2 (troponin T, soluble ST2, galectin 3, pentraxin 3, and soluble tumor necrosis factor receptor 2)—significantly improved the CORONA and Seattle HF models but added only modestly to their Harrell’s C statistic and net reclassification index. In addition, rosuvastatin had no effect on the levels of a wide range of inflammatory and extracellular matrix markers, but there was a tendency for patients with a lower level of biomarkers in the 2 panels to have a positive effect from statin treatment.

CONCLUSIONS In the specific HF patient population studied, a multimarker approach using the particular panel of biomarkers measured was of limited clinical value for identifying future risk of adverse outcomes. (J Am Coll Cardiol HF 2017;5:256–64) © 2017 by the American College of Cardiology Foundation.
The prognosis in patient with heart failure (HF) remains poor despite improvements in disease management. Persistent inflammation and extracellular matrix (ECM) remodeling are considered central pathogenic elements in HF progression (1). As a result of their role in the pathogenesis of HF, circulating inflammatory and ECM markers may also be convenient, noninvasive tools for risk stratification and prognostication in these patients (2).

We previously evaluated a range of biomarkers in CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study, comprising elderly patients with moderate-to-severe ischemic HF (3-16). Classifying these markers according to categories proposed by Braunwald (2) revealed good coverage of the different pathological pathways activated in HF (Figure 1), with a focus on inflammation and matrix remodeling. When assessed separately, several of these markers provided independent prognostic information or identified subgroups of patients who seemed to benefit from rosuvastatin therapy. However, the improvement in prognostic discrimination as evaluated by net reclassification index (NRI) and Harrell’s C statistic (C), beyond established clinical risk factors and in particular N-terminal pro-B-type natriuretic peptide (NT-proBNP), was relatively modest and their clinical usefulness unclear.

Although measurements of individual markers of inflammation and the EMC so far have not improved risk stratification of patients with HF in a clinically meaningful way, combinations of multiple markers might help identify subjects with a clinically significantly increased risk. The combination of multiple markers might also help select patients for individualized therapy. The idea of a multimarker approach has been around for several years, but few studies have tested the power of such models, and most of these trials included few biomarkers or examined small populations. Moreover, the lack of optimal adjustment for existing tests and the lack of internal or external validation may have biased results (17-19).

In the present study, we used a systematized approach to assess the prognostic value of a combination of biomarkers from the CORONA trial (20).

RESULTS

MODEL BUILDING. Demographics of the CORONA inflammatory substudy and the training and validation set are given in Online Table 1. No significant differences between the training and validation sets were observed. All previously measured biomarkers in the CORONA database were entered as potential variables for the multimarker approach, that is, biglycan, mimecan, endostatin, YKL40, galectin-3, interleukin (IL)-8, monocyte chemotactic protein (MCP)-1, Chemokine (C-X-C motif) ligand 16 (CXCL16), chemokine (C-C motif) ligand-21, soluble ST2 (sST2), troponin T (TnT), secreted frizzled-related protein-3 (SFRP3), osteoprotegerin (OPG), neutrophil gelatinase-associated lipocalin (NGAL), pentraxin-3 (PTX3), soluble tumor necrosis factor receptor (sTNFR)-1, sTNFR2, IL-6, soluble glycoprotein-130, and tumor necrosis factor. The 3 different approaches to building a model from available biomarkers yielded 3 slightly different results. By keeping all variables as proposed by at least 2 methods, 6 variables remained in model 1: endostatin, IL-8, sST2, TnT, galectin-3, and chemokine (C-C motif) ligand 21 (Table 1). Testing the variable selection by bootstrapped model selection showed that all biomarkers chosen by an approach were selected in at least 50% of the repetitions, and no other biomarkers were selected by multiple approaches in more than 50% of the repetitions (see Online Table 2). For model 2, we included more established HF risk markers from the literature: TnT, sST2, galectin-3, PTX3, and sTNFR2 (Table 1) (7,23-27).
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