International Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Biomarkers for characterization of heart failure – Distinction of heart failure with preserved and reduced ejection fraction

Christoph Sinning [a,1,2], Tibor Kempf [a,1,2], Michael Schwarzl [a,c,1], Simon Lanfermann [a,1], Francisco Ojeda [a,1], Renate B. Schnabel [a,c,1], Elvin Zengin [a,1], Philipp S. Wild [d,e,f,1], Karl-J. Lackner [g,1], Thomas Munzel [d,e,1], Stefan Blankenberg [a,c,1], Kai C. Wollert [b,1], Tanja Zeller [a,c,1,3], Dirk Westermann [a,c,*,1,3]

[a] University Heart Center Hamburg, Department of General and Interventional Cardiology, Hamburg, Germany
[b] Division of Molecular and Translational Cardiology, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany
[c] German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany
[d] German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Germany
[e] University Medical Center of the Johannes Gutenberg-University Mainz, Department of Medicine 2, Mainz, Germany
[f] Center for Thrombosis and Hemostasis, University Medical Center Mainz, Germany
[g] Institute of Chemistry and Laboratory Medicine, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

ARTICLE INFO

Article history:
Received 11 August 2016
Accepted 6 November 2016
Available online xxxx

Keywords:
Heart failure
Heart failure with reduced and preserved ejection fraction
Growth-differentiation factor-15
Soluble source of tumorigenicity 2
C-reactive protein

ABSTRACT

Background: Heart failure (HF) incidence is rising worldwide and HF with preserved ejection fraction (HFpEF) represents nearly half of all cases. Treatment options are still limited in HFpEF in comparison to HF with reduced ejection fraction (HFrEF).
Methods: We analyzed biomarkers in the general population to characterize HFpEF and HFrEF and defined a biomarker index to differentiate HFpEF from HFrEF. Growth differentiation factor-15 (GDF-15), soluble source of tumorigenicity 2 (sST2), C-reactive protein (CRP) and NT-proBNP were measured in 5000 individuals of the population-based Gutenberg Health Study (GHS). The median follow-up time for all-cause mortality was 7.3 years with 213 events.
Results: Identification of subjects with HF was improved by GDF-15 ($p < 0.001$) in addition to NT-proBNP with an odds ratio (OR) of 1.4 (95% confidence interval [CI]:1.1–1.7). Discrimination of subjects with and without HF was slightly higher for GDF-15 (area under the ROC curve [AUC]:0.79 [95%CI:0.75–0.83]) compared to NT-proBNP (AUC:0.77 [95% CI:0.72–0.82]). For subjects with HF, differentiating HFpEF from HFrEF was feasible with the index ((CRP + GDF-15 + sST2)/NT-proBNP) with an OR of 3.7 (95% CI:1.9–8.5) ($p < 0.001$). The best biomarkers predicting all-cause mortality were NT-proBNP and GDF-15 with a hazard ratio (HR) of 1.9 (95% CI:1.6–2.2) and 1.7 (95%CI:1.6–1.9) (both $p < 0.001$), respectively.
Conclusion: GDF-15 was useful to detect prevalent HF in addition to NT-proBNP and was elevated in HFrEF and HFpEF, whereas NT-proBNP was higher in HFrEF than in HFpEF. All biomarkers were useful to predict mortality in the general population. The index of ((CRP + GDF-15s + sST2)/NT-proBNP) was able to discriminate HFpEF from HFrEF.

1. Introduction

Studies have shown an increasing number of patients with heart failure (HF) symptoms and preserved ejection fraction (HFpEF), representing more than half of the HF population [1,2]. The morbidity and mortality of patients with HFpEF is nearly similar to patients with HF and reduced ejection fraction (HFrEF) [3,4].

Biomarkers are a cornerstone in establishing HF diagnosis and natriuretic peptides are still the standard biomarker recommended [3,4]. Elevated levels have been demonstrated in symptomatic patients with HFpEF and HFrEF [3,5]. The use of NT-proBNP was recently emphasized by the European Society of Cardiology HF guidelines [4] to rule out HF with a cut-off of <125 pg/mL, while no option exists to differentiate different heart failure subtypes with the application of distinct biomarkers. Current studies show that inflammatory stress is also relevant in HFrEF and HFpEF [6], which implies a potential for novel biomarkers. Such candidate biomarkers are growth-differentiation factor 15 (GDF-15)

* Corresponding author at: University Heart Center Hamburg, Department of General and Interventional Cardiology, Martinistr. 52, 202246 Hamburg, Germany.
E-mail address: d.westermann@uke.de (D. Westermann).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Both authors contributed equally as first author.
[3] Both authors were equally senior author.

http://dx.doi.org/10.1016/j.ijcard.2016.11.110
0167-5273/

for inflammation and oxidative stress [7], soluble source of tumorigenicity 2 (sST2) [8] for myocardial strain and fibrosis, and C-reactive protein (CRP) for inflammation [9].

The aims of the present study thus were (a) to characterize GDF-15, sST2, CRP and NT-proBNP in a large sample of the general population and in HF subgroups, (b) to investigate the prognostic influence of these biomarkers for predicting outcome and (c) to improve the discrimination of HFrEF from HFpEF by calculating an index with the suggested biomarkers.

2. Methods

2.1. Study population – Gutenberg Health Study (GHS)

Enrollment in the study was between April 2007 and April 2012, finally including 15,010 individuals. Study individuals aged 35 to 74 years and stratified according to gender and age were selected randomly by the registration office from the city of Mainz. The Gutenberg Health Study was approved by the ethics committee of Rhineland-Palatinate and the medical faculty of the Johannes Gutenberg-University, Mainz. Each study individual provided written informed consent before participating. The ethical application complied with the Declaration of Helsinki. The current analyses were performed on the first 5000 individuals of the GHS with available biomarker levels. Therefore 4821 subjects with measured values for all three biomarkers were included in this analysis and the median follow-up time of these individuals is 7.3 years.

2.2. Assessment of cardiovascular risk factors

Risk factors were assessed as outlined in the previous publication [10]. Former history of stroke, coronary artery disease, myocardial infarction, HF and peripheral artery disease were assessed in a standardized interview. Arterial hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg at rest obtained as the mean of the second and third measurement, or by taking any antihypertensive drugs within the last 2 weeks. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dl, a spontaneous glucose concentration of ≥200 mg/dl, or as diagnosed by a physician. Dyslipidemia was defined as a LDL/HDL-ratio of >3.5 or as diagnosed by a physician. Waist circumference ≥ 102 cm for men or ≥88 cm for women identified subjects with body mass index ≥30 and was used therefore for subjects being classified as to be obese [11]. Smokers were classified into daily smokers (≥1 cigarette/day), occasional smokers (<1 cigarette/day), former smokers, and non-smokers (never smoked). Any family history of myocardial infarction in first-degree relatives before the age of 60 years was defined as positive family history. For glomerular filtration rate (GFR), as the best marker for renal function in health and disease, we used the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [12].

2.3. Assessment of cardiac structure and function with echocardiography

All subjects underwent echocardiography with an iE33 echocardiography system (Royal Philips Electronics, Amsterdam, The Netherlands) [13]. Trained and certified medical technical assistants at a single center performed the examinations according to standard operating procedures. Measurements were according to recommendations by the American and European Societies of Echocardiography [14].

2.4. Selection of individuals with HF

According to our previous definition [15], participants with either shortness of breath (according to New York Heart Association [NYHA] functional class II-IV) or with medical treatment for HF were classified as either heart failure with reduced ejection fraction "HFrEF" (LV EF < 50%) or heart failure with preserved ejection fraction "HFpEF" (LV EF ≥ 50% and evidence of diastolic dysfunction: either ($E/e' \geq 12$) or [($8 \leq E/e' < 12$) and ($E/A \leq 0.5$)]). All other participants were defined as "No HF" [15]. Since the guidelines were updated recently, [4] the cohort of patients with HFmrEF was investigated additionally (n = 21). However, as the characteristics of HFrEF and HFmrEF were nearly similar (Supplemental Table 1), we included HFmrEF into the HFrEF cohort.

2.5. Definition of biomarker indices

As natriuretic peptides are the standard markers for HF assessment we calculated an index incorporating NT-proBNP to discriminate the sub-types of HFrEF and HFpEF. An index of GDF-15/NT-proBNP had already been described [16] and its relevance for discriminating HFrEF from HFpEF patients in a small patient study with known HF. We hypothesized to improve this model by adding novel biomarkers to this index.

2.5.1. Laboratory methods

Blood was drawn in supine position from the right or left forearm or the elbow flexure. The participants were asked to have an overnight fast of at least 8 h when the appointment to the study centre was before 12:00 noon and a prior fast of at least 5 h for appointments after 12:00 noon. All biomaterial was stored at −80 °C.

NT-proBNP levels were measured on the ELECSYS 2010 using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). The analytical range is 5–35.000 ng/L. Intra- and interassay coefficients of variants were 0.8%–3.0% and 2.2%–5.8%, respectively.

The concentration of sST2 was determined using the high-sensitivity ELISA assay with a detection limit of 2 ng/mL (Presage ST2, Critical Diagnostics). Intra- and inter assay coefficients of variants were 5.6 and 8.85%, respectively.

GDF-15 was measured by an immunoluminometric assay (ILMA) with a limit of detection of 24 ng/L and a linear range from 200 to 50,000 ng/L. The ILMA is technically identical to the previously described immunoradiometric assay (IRMA) [17] except that the GDF-15 detection antibody was labeled with acridinium ester and assay results were quantified in a luminometer. The ILMA has an intra-assay imprecision below 5.9% and an inter-assay imprecision below 10%.

CRP and serum creatinine were measured with the routine laboratory using an Abbott Architect c8000 system and the CRP Vario immunoassay, further the modified Jaffe method for creatinine.

2.5.2. Statistical analyses

Continuous variables were described by its quartiles and binary ones by absolute and relative frequencies. Skewed variables and therefore all biomarkers were log transformed before analyses.

Receiver operating characteristic (ROC) curves were generated for NT-proBNP, CRP, GDF-15 and sST2 for the outcomes HF vs. no HF and HFpEF vs. HFrEF. The outcomes HFpEF vs. no HF and HFrEF vs. no HF are shown in the online supplemental material. The area under the curve (AUC) was computed together with 95% confidence intervals.

The association between the markers CRP, GDF-15 and sST2 and the different HF types was examined with logistic regression analysis. First a model adjusted for cardiovascular risks factors (age, sex, BMI, GFR, hypertension, diabetes, dyslipidemia, current smoking) and NT-proBNP was used. For HFpEF vs. HFrEF additional logistic regressions were performed, using the quotients GDF-15/NT-proBNP, sST2/NT-proBNP and (CRP + GDF-15)/NT-proBNP as covariates of interest (for each quotient a model was calculated).

Unadjusted associations of NT-proBNP, CRP, GDF-15 and sST2 to mortality were examined, categorizing the markers using thirds, and then estimating the survival curves per category via the Kaplan-Meier method and performing the long-rank test. Multivariable associations of the aforementioned markers to mortality were calculated with Cox regressions adjusted for cardiovascular risk factors.

Please cite this article as: C. Sinning, et al., Biomarkers for characterization of heart failure – Distinction of heart failure with preserved and reduced ejection fraction, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.11.110