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Utility of temporal profiles of new cardio-renal and pulmonary candidate biomarkers in chronic heart failure

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ABSTRACT

Background: Our aim was to explore potential use of temporal profiles of seven emerging cardio-renal and two pulmonary candidate biomarkers for predicting future adverse clinical outcome in stable patients with chronic heart failure (CHF).
Methods: In 263 CHF patients, we determined the risk of a composite endpoint of HF-hospitalization, cardiac death, LVAD-placement and heart transplantation in relation to repeatedly assessed (567 samples in total) blood biomarker levels, and slopes of their temporal trajectories (i.e., rate of biomarker change per year). In each patient, we estimated biomarker trajectories using repeatedly measured osteopontin (OPN), osteoprotegerin (OPG), epidermal growth factor receptor (EGFR), heparin-binding protein (HBP), trefoil factor-3 (TFF3), kallikrein-6 (KLK-6), matrix extracellular phosphoglycoprotein (MEPE), pulmonary surfactant-associated protein-D (PSP-D), and secretoglobulin family 3A-member-2 (SCGB3A2).
Results: During 2.2 years of follow-up, OPN, OPG, and HBP levels predicted the composite endpoint (univariable hazard ratio [95% confidence interval] per 1SD increase: 2.31 [1.76–3.15], 2.23 [1.69–3.00], and 1.36[1.09–1.70]). Independently of the biomarkers' levels, the slopes of OPG, TFF-3, PSP-D trajectories were also strong clinical predictors (per 0.1SD increase: 1.24 [1.14–1.38], 1.31 [1.17–1.49], and 1.32 [1.21–1.47]). All associations persisted after multivariable adjustment for baseline characteristics, and repeatedly assessed CHF pharmacological treatment and cardiac biomarkers NT-proBNP and troponin T.
Conclusions: Repeatedly-measured levels of OPN, OPG, and HBP, and slopes of OPG, TFF-3, and PSP-D strongly predict clinical outcome. These candidate biomarkers may be clinically relevant as they could further define a patient's risk and provide additional pathophysiological insights into CHF.

1. Introduction

Chronic heart failure (CHF) is a clinical syndrome which often requires constant therapeutic interventions due to recurrent episodes of cardiac decompensation [1]. The failing heart also induces structural and functional changes in distant organs such as the kidneys and the lungs [2,3]. Eventually, a vicious circle of pathophysiological processes is formed between these organs leading to end-stage heart failure [4,5]. In this context, circulating biomarkers that reflect the status of this multi-organ pathophysiology may be a valuable clinical tool, as these biological signals precede decompensation and may provide early organ-specific information in CHF. Therefore, patient-specific biomarker profiles may further characterize the multi-organ involvement in CHF, but may also help in monitoring disease progression to allow timely adaptation of treatment to prevent impending decompensation.

Although previous biomarker-based studies have increased our understanding of CHF [6,7], several important aspects of biological signals in CHF remain to be addressed. Most previous studies have examined the prognostic value of a single baseline assessment which is unable to capture progression of CHF that naturally occurs over time. These studies also used conventional statistical models that do not allow for individualized risk prediction using patient-specific biomarker values and their change over time. Finally, similar sets of CHF biomarkers have been investigated by most of the existing studies such as natriuretic peptides, troponins, and markers representing certain aspects of CHF like galectin-3 and ST2.

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Data on the utility of new candidate biomarkers in CHF are scarce, and their clinical value remains uncertain. Therefore, in this study, our aim was to explore the prognostic utility of temporal profiles of several emerging cardio-renal and pulmonary candidate biomarkers in CHF patients during their outpatient follow-up.

Cardio-renal candidate biomarkers included osteopontin (OPN), which is associated with accumulation of monocytes/macrophages in injured renal tissues including both glomeruli and tubules [8], and which is mainly overexpressed in cardiac non-myocytes during pathological cardiac remodeling [9]; osteoprotegerin (OPG), which is involved in bone metabolism, endocrine function, and immunity [10], and is secreted mainly by osteoblasts and by vascular smooth muscle and endothelial cells, but also in the renal tissue [11]; matrix extracellular phosphoglycoprotein (MEPE), which is another molecule that regulates bone metabolism, and in particular phosphates handling in the renal tubules [12]; trefoil factor-3 (TFF3), which is a member of the trefoil factor peptide family secreted by the renal tubulocites in response to injury [13]; heparin-binding protein (HBP), which is released from neutrophils upon activation, after which it induces vascular leakage, edema formation, and inflammatory reactions which play a role in sepsis-induced acute kidney injury (AKI) [14–16]; epidermal growth factor receptor (EGFR), which is a tyrosine kinase receptor found to be involved in acute and chronic renal injury [17]; and kallikrein 6 (KLK-6) which is a recently identified member of the kallikrein gene family and is involved in degradation of extracellular matrix during tumor invasion and metastasis, but also in demyelization and spinal cord injury [18,19].

Pulmonary candidate biomarkers included pulmonary surfactant-associated protein-D (PSP-D), which was found to reduce alveolar macrophages apoptosis and to promote clearance of necrotic cells after lung injury [20], and secretoglobulin family 3A-member-2 (SCGB3A2), which is another newly discovered biomarker with prominent anti-inflammatory and anti-fibrotic activity in animal models of pulmonary fibrosis [21].

2. Methods

2.1. CHF cohort

The Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis (Bio-SHiFT) is a prospective cohort of stable patients with CHF, conducted in Erasmus MC, Rotterdam, and Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands [22,23]. Patients were included if aged ≥18 years, capable of understanding and signing informed consent, and if CHF had been diagnosed ≥3 months ago according to European Society of Cardiology guidelines (Fig. S1) [1,24,25]. Patients were ambulatory and stable, i.e. they had not been hospitalized for HF in the past three months. The study was approved by the medical ethics committees, conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov (NCT01851538). Written informed consent was obtained from all patients. This investigation comprised 263 CHF patients enrolled during the first inclusion period (October 2011 until June 2013).

2.2. Baseline and follow-up assessment

All patients were evaluated by research physicians, who collected information on HF-related symptoms, NYHA class, and performed a physical examination. Information on HF etiology, left ventricular ejection fraction (EF of 50% at inclusion used as a cut-off for HFrEF versus HFpEF) [25], cardiovascular risk factors, medical history and treatment was retrieved primarily from hospital records and was checked in case of ambiguities.

During the study, all patients were routinely followed at the outpatient clinic by their treating physicians. Additionally, study follow-up visits were predefined and scheduled every 3 months (±1 month). At each study follow-up visit, a short medical evaluation was performed and blood and urine samples were collected. During follow-up, all medication changes and occurrence of hospitalizations for HF, MI, PCI, CABG, arrhythmias, and CVA, cardiac transplantation, left ventricular assist device (LVAD) implantation and mortality, were recorded in the electronic case report forms, and associated hospital records and discharge letters were collected. Subsequently, a clinical event committee, blinded to the biomarker results, reviewed hospital records and discharge letters and adjudicated the study endpoints.

2.3. Study endpoints

The composite endpoint comprised of hospitalization for the management of acute or worsened HF, cardiac death, cardiac transplantation, and LVAD implantation, whichever occurred first. Cardiac death was defined as death from MI or other ischemic heart disease (ICD-10: I20-I25), death from other heart disease including HF (I30-I45 and I47-I52), sudden cardiac death (I46), sudden death undefined (R96) or unwitnessed or ill-described death (R98, R99). Hospitalization for acute or worsened HF was defined as a hospitalization for an exacerbation of HF symptoms, in combination with two or more of the following: BNP or NT-proBNP > 3× upper limit of normal, signs of worsening HF, such as pulmonary rales, raised jugular venous pressure or peripheral edema, increased dose or intravenous administration of diuretics, or administration of positive inotropic agents [24].

2.4. Study measurements and laboratory analysis

Blood samples were collected at baseline and at each 3-monthly study follow-up visit, and were processed and stored at −80 °C within 2 h after collection. Treating physicians were unaware of biomarker results as biomarkers were measured batchwise after completion of follow-up using methods described in the supplemental text. Thus, the biomarker measurements did not lead to drug adjustments. All patients received treatment according to the ESC guidelines on CHF [1,24]. All laboratory personnel was blinded for clinical data and patients outcomes. For efficiency, for the current investigation we selected all baseline samples, the two samples closest in time to the composite endpoint, and for patients in whom the primary endpoint did not occur during follow-up, the last sample available. Glomerular filtration rate (GFR) was determined by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation validated in HF patients [26].

2.5. The Olink multiplex PEA platform panel for new biomarkers

The Olink Cardiovascular (CVD) panel III was used for analysis of high-abundance proteins (Olink Proteomics AB, Uppsala, Sweden). The proteins present in this Olink panel were selected because either they have a proven pathophysiological role in cardiovascular disease, or because they are promising in this respect but yet unexplored. In the current investigation, biomarkers from the panel were chosen and grouped based on their previously described predominant tissue expression and involvement in renal [9,16,27–31] and/or pulmonary [32,33] pathophysiology.

The Olink panel is based on PEA (proximity extension assay) technology as described in the supplementary text [34]. The biomarkers are presented in normalized protein expression (NPX) units on a ^{2}log scale. In a validation study, the mean intra-assay and inter-assay coefficients of variation were 8% and 12%, respectively [34].

2.6. Statistical analysis

For the analysis, we used the Z-score (i.e. the standardized form) of the ^{2}log-transformed biomarkers to allow for direct comparisons of different biomarkers. We used a network analysis [35] to assess the relationships between biomarkers with Pearson's correlation coefficients $p < 0.05$ using a clustering coefficient as a measure of the degree to which biomarkers tend to cluster together (higher coefficients suggest a certain centrality of a biomarker within the network) [36].

To study the effect of baseline characteristics on repeatedly measured biomarkers, linear mixed-effects (LME) models were performed using biomarkers as the dependent variables and baseline characteristics as the independent variables (fixed part). The sampling time was entered into the fixed- and random parts of the models.

To estimate the associations between biomarker levels and survival, we applied a joint modeling (JM) prediction analysis that combines LME models for repeated measurements, and Cox survival analysis for time-to-event data [37]. For both the fixed- and random-effects parts of the LME models, linear terms were used for sampling times, and both intercepts and slopes were included in the random-effects design matrix. This allowed the markers' trajectories to differ at baseline and over time. We also estimated the time-dependent slope (i.e., rate of change) of each biomarker, indicating whether and by how much the levels are increasing or decreasing on a continuous scales.

Besides sampling time, all markers were adjusted as follows: (1) clinical model: Cox and LME models were adjusted for age, sex, diabetes, atrial fibrillation, baseline NYHA class, diuretics, systolic blood pressure, and eGFR; (2) clinical & time-varying HF medication model: after adjusting for clinical characteristics, biomarker values were extracted from the joint models and entered simultaneously with repeatedly assessed equivalent doses of carvedilol, enalapril, furosemide, and spironolactone (for details on conversion factors for equivalent doses see table S1) into a time-dependent Cox analysis to examine the incremental value of the new biomarkers over clinical characteristics and medication during follow-up; (3) time-dependent Cox model using the marker's fitted values adjusted for type of HF (HFrEF vs. HFpEF), and time-varying NT-proBNP and hs-cTnT collected at the same time points during follow-up as the biomarker of interest. Data on all variables were complete, except for systolic blood pressure which was missing in <5% of patients and for which imputations were applied using the patients' clinical and outcome data. Results are given as hazard ratios (HR) and 95% confidence intervals (CI) per 1SD increase of the marker's level and per 0.1SD increase of the slope at any time-point during follow-up.

To correct for multiple testing, we performed matrix spectral decomposition which has been used in genetic studies as it has been demonstrated to be more effective than Bonferroni correction [38]. In this way, we accounted for the correlations between the biomarkers by setting a significance level at $p < 0.008$ (0.05/6).

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All tests were two-tailed and were performed with R Statistical Software using packages nlme and JMbayes [37]. The network analysis was performed using Gephi software (https://gephi.org) and the matSpD application (https://gump.qimr.edu.au/general/daleN/matSpD) available online.

3. Results

3.1. Baseline characteristics

Patients who experienced the primary endpoint during follow-up were older, more frequently had diabetes, atrial fibrillation, lower systolic blood pressure, higher NYHA class, higher levels of NT-proBNP and cardiac troponin T, and were more frequently on diuretics (Table 1). All biomarkers showed significantly higher levels at baseline, except for EGFR which was lower, in patients who later experienced the endpoint than in endpoint-free patients (Fig. S2).

3.2. Follow-up and study endpoints

During a median (IQR) follow-up of 2.2 (1.4–2.5) years, we collected at fixed 3-month intervals a median (IQR) of 9 (5–10) blood samples per patient (1984 samples in total). Seventy (27%) patients reached the composite endpoint: 56 patients were re-hospitalized for acute or worsened HF, 3 patients underwent heart transplantation, 2 patients underwent LVAD placement, and 9 patients died of cardiovascular causes. For reasons of efficiency, we set out to select all baseline samples, the two samples closest in time to the composite endpoint, and the last sample available for event-free patients for biomarker measurement. Some of these samples were not available, for example in case an endpoint occurred early after baseline or before next scheduled study visit. Ultimately, 567 samples were used for biomarker measurement.

Table 1
Patients characteristics in relation to the occurrence of the composite endpoint.

Variable	Total	Composite endpoint		p-Value
		Yes	No	
N (%)	263 (100)	70 (27)	193 (73)	
Demographics				
Age, years	67 ± 13	69 ± 13	66 ± 12	0.05
Men, n (%)	189 (72)	53 (76)	136 (70)	0.41
Clinical characteristics				
BMI, kg/m2	27.5 ± 4.7	27.6 ± 4.8	27.4 ± 4.7	0.80
Heart rate, b.p.m.	67 ± 12	69 ± 13	67 ± 11	0.31
SBP, mm Hg	122 ± 20	117 ± 17	124 ± 21	0.02
DBP, mm Hg	72 ± 11	70 ± 10	73 ± 11	0.06
Features of heart failure				
NYHA class III or IV, n (%)	69 (26)	31 (44)	38 (20)	< 0.001
HF-rEF n (%)	250 (95)	66 (94)	184 (95)	0.75
HF-pEF n (%)	13 (5)	4 (6)	9 (5)	
LVEF, %	32 ± 11	30 ± 11	33 ± 10	0.18
NT pro-BNP (ng/L)[a]	1161 (439–2305)	2388 (1492–4376)	806 (268–1757)	< 0.001
Hs-cTnT (ng/L)[a]	18.0 (9.5–33.2)	31.9 (20.6–49.7)	13.9(8.4–26.7)	< 0.001
Etiology of heart failure, n (%)				
Ischemic	117 (44)	36 (51)	81 (42)	0.17
Hypertension	34 (13)	10 (14)	24 (12)	0.70
Secondary to valvular disease	12 (5)	5 (7)	7 (4)	0.23
Cardiomyopathy	68 (26)	15 (21)	53 (28)	0.32
Unknown or Others	32 (12)	4 (6)	28 (15)	
Medical history, n (%)				
Prior MI	96 (36)	32 (46)	64 (33)	0.06
Prior PCI	82 (31)	27 (39)	55 (28)	0.12
Prior CABG	43 (16)	13 (19)	30 (15)	0.57
Atrial fibrillation	106 (40)	36 (51)	70 (36)	0.03
Diabetes	81 (31)	32 (46)	49 (25)	0.002
Hypercholesterolemia	96 (36)	30 (43)	66 (34)	0.20
Hypertension	120 (46)	38 (54)	82 (42)	0.09
COPD	31 (12)	12 (17)	19 (10)	0.10
Medication use, n (%)				
Beta-blocker	236 (90)	61 (87)	175 (91)	0.40
ACE-I or ARB	245 (93)	63 (90)	182 (94)	0.22
Diuretics	237 (90)	68 (97)	169 (88)	0.02
Loop diuretics	236 (90)	68 (97)	168 (87)	0.02
Thiazides	7 (3)	3 (4)	4 (2)	0.28
Aldosterone antagonist	179 (68)	53 (76)	126 (65)	0.11
Glomerular function				
Creatinine, mg/dL	1.18 (0.99–1.49)	1.30(1.02–1.52)	1.17(0.98–1.45)	0.18
eGFR, mL/min/1.73m^2	58 (43–76)	53 (40–73)	59 (44–77)	0.16
KDOQI classification, n (%)				0.18
eGFR ≥ 90 mL/min/1.73m^2	28 (11)	7 (10)	21 (11)	
eGFR 60–89 mL/min/1.73m^2	95 (36)	20 (28)	75 (39)	
eGFR 30–59 mL/min/1.73m^2	119 (45)	37 (53)	82 (42)	
eGFR < 30 mL/min/1.73m^2	21 (8)	6 (9)	15 (8)	

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; NYHA class, New York Heart Association class; HF-rEF, Heart failure with reduced ejection fraction; HF-pEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; TIA, transitory ischemic attack; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and non-normally distributed variables as median and interquartile interval. Categorical variables are presented as numbers and percentages.

[a] Median with inter-quartile range (IQR).

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Table 2
Association between baseline characteristics and repeatedly measured levels of candidate biomarkers during follow-up.

	Dependent variable									
	OPN		OPG		EGFR		HBP		TFF3	
Independent variable	β(95% CI)	p-Value	β(95% CI)	p-Value	β(95% CI)	p-Value	β(95% CI)	p-Value	β(95% CI)	p-Value
Age per 10 yrs.		ns		ns	−0.29 (−0.38 to −0.20)	<0.001		ns		ns
Male sex		ns	−0.25 (−0.47 to −0.04)	0.022		ns		ns	−0.27 (−0.46 to −0.08)	0.006
NYHA class (per 1 point increase)		ns		ns	−0.16 (−0.28 to −0.04)	0.009		ns	0.20 (0.08 to 0.31)	0.001
DM		ns	0.27 (0.05 to 0.48)	0.015		ns		ns		ns
AF	0.28 (0.10 to 0.47)	0.003	0.37 (0.18 to 0.58)	<0.001		ns	0.23 (0.03 to 0.44)	0.026		ns
SBP per 10 mm Hg		ns		ns		ns		ns		ns
eGFR per 20 mL/min/1.73 m2		ns	−0.12 (−0.22 to −0.02)	0.015		ns	−0.10 (−0.20 to −0.01)	0.038	−0.21 (−0.30 to −0.13)	<0.001
NT-proBNP per doubling	0.10 (0.04 to 0.16)	<0.001		ns		ns		ns	0.13 (0.07 to 0.18)	<0.001
cTnT per doubling	0.18 (0.07 to 0.28)	<0.001	0.12 (0.01 to 0.23)	0.033		ns		ns	0.17 (0.07 to 0.26)	0.001
Carvedilol eqv. per 50 mg		ns		ns		ns		ns		ns
Enalapril eqv. per 40 mg		ns	−0.21 (−0.38 to −0.04)	0.015		ns		ns		ns
Furosemide eqv. per 40 mg	0.06 (0.04 to 0.09)	<0.001		ns		ns	0.06 (0.02 to 0.11)	0.009	0.06 (0.02 to 0.11)	0.002
Spironolactone eqv. per 25 mg	−0.16 (−0.29 to −0.02)	0.03		ns		ns	−0.21 (−0.37 to −0.05)	0.012		ns

	Dependent variable							
	KLK-6		MEPE		PSP-D		SCGB3A2	
Independent variable	β(95% CI)	p-Value	β(95% CI)	p-Value	β(95% CI)	p-Value	β(95% CI)	p-Value
Age per 10 yrs.		ns		ns		ns		ns
Male sex		ns		ns		ns	−0.41 (−0.66 to −0.16)	0.002
NYHA class		ns		ns		ns	0.19 (0.04 to 0.34)	0.013
DM		ns		ns		ns	−0.46 (−0.71 to −0.22)	<0.001
AF		ns		ns		ns		ns
SBP per 10 mm Hg	−0.05 (−0.10 to 0.00)	0.047	−0.06 (−0.11 to 0.00)	0.041		ns		ns
eGFR per 20 mL/min/1.73 m2	−0.23 (−0.33 to −0.14)	<0.001	−0.16 (−0.27 to −0.06)	0.002		ns		ns
NT-proBNP per doubling	0.08 (0.02 to 0.14)	0.007		ns	0.09 (0.02 to 0.17)	0.016		0.039
cTnT per doubling	0.21 (0.10 to 0.31)	<0.001	0.19 (0.06 to 0.31)	0.003		ns		ns
Carvedilol eqv. per 50 mg		ns	0.14 (0.01 to 0.27)	0.038		ns		ns
Enalapril eqv. per 40 mg		ns		ns		ns		ns
Furosemide eqv. per 40 mg		ns	0.06 (0.01 to 0.11)	0.016		ns		ns
Spironolactone eqv. per 25 mg	−0.43 (−0.59 to −0.28)	<0.001	−0.19 (−0.36 to −0.01)	0.034	−0.24 (−0.43 to −0.05)	0.013		ns

OPN, osteopontin; OPG, osteoprotegerin; EGFR, epidermal growth factor receptor; HBP, heparin-binding protein; TFF3, trefoil factor 3; PSP-D, pulmonary surfactant-associated protein D; SCGB3A2, secretoglobulin family 3A member 2; KLK-6, kallikrein-6; MEPE, matrix extracellular phosphoglycoprotein. The effects of patients' baseline characteristics are given as adjusted β (95% confidence interval) for 1SD differences of biomarkers as measured on the ^{2}log scale. This method allows a direct comparison of the effects on different biomarkers. All βs are adjusted for age, sex, diabetes mellitus (DM), atrial fibrillation (AF), baseline NYHA class, systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR), NT-proBNP levels, cardiac troponin T levels (cTnT), and equivalent doses of carvedilol, enalapril, furosemide, and spironolactone. Only the associations with significance level of p-value < 0.05 are presented.

3.3. Patients' clinical profile and biomarkers during follow-up

Table 2 shows the associations between the patients' baseline clinical profiles and the repeatedly-measured levels of candidate biomarkers during follow-up. Furthermore, we found a negative association between time-varying enalapril equivalent doses and OPN, OPG, PSP-D, and SCGB3A2 levels during follow-up (Table S2). Moreover, a negative association was observed between spironolactone equivalent doses and OPG, KLK-6, PSP-D, and SCGB3A2 levels, whereas furosemide equivalent doses correlated positively with OPN, TFF-3, KLK-6, and MEPE levels during follow-up.

3.4. Network analysis

The network analysis showed that OPN and TFF3 had the highest clustering coefficients which suggests that these two biomarkers had a certain centrality within the network, meaning that a large number of biomarker correlations are mediated thought these hubs (Fig. S3).

3.5. Temporal trends in biomarkers and relation to study endpoint

Fig. 1 shows the average temporal evolutions of candidate biomarkers in patients who reached the composite endpoint and those who remained endpoint-free. In patients who reached the endpoint, OPN, OPG, HBP, and TFF3, PSP-D, and SCGB3A2 showed higher baseline levels that increased further during follow-up as the endpoint approached. Patients with the endpoint also had constantly higher levels of KLK-6 and MEPE, but without a further increase in the approach to the endpoint. Table 3 shows the associations of these biomarkers with the composite endpoint.

After adjustment for clinical characteristics and repeatedly assessed CHF pharmacological treatment, OPN, OPG, HBP, TFF3, KLK-6, and PSP-D independently predicted the endpoint (per 1SD increase of marker levels: hazard ratio [95%CI] 2.78 [2.03–3.08], 2.31 [1.72–3.10], 1.65 [1.32–2.06], 2.35 [1.84–2.99], 1.61 [1.17–2.22], 1.12 [1.04–1.19], each $p < 0.008$). Levels of these biomarkers, except for KLK-6 and PSP-D, remained significant predictors after adjustment for time-varying levels of two established cardiac biomarkers (NT-proBNP and hs-cTnT). Independently of their absolute levels, the slopes of OPG, TFF3, and PSP-D remained robust clinical predictors after adjusting for clinical characteristics and repeatedly assessed CHF pharmacological treatment and cardiac biomarkers (Table 3).

4. Discussion

This study is the first to demonstrate that temporal trends in levels of OPN, OPG, and HBP strongly predict clinical outcome in CHF. Moreover, independent of the absolute level of the biomarker, higher slopes of OPG, TFF-3, and PSP-D trajectories were also strong clinical predictors. Importantly, all associations with adverse outcomes were independent of patients' clinical profiles, CHF pharmacological treatment and known cardiac biomarkers measured repeatedly during follow-up. Therefore, these candidate biomarkers may become relevant for clinical practice as they might further define a patient's risk, but also for future HF trials as they might help design more effective biomarker-guided therapy.

Recently, we have demonstrated in the same cohort that temporal patterns of NT-proBNP, troponin T and C-reactive protein are associated with adverse outcome [23]. Our current investigation extends these findings to several novel cardio-renal and pulmonary candidate biomarkers. OPN was previously found to be significantly increased in critically ill patients with AKI compared to those without AKI [27]. Moreover, both animal and human studies have shown that OPN is upregulated in left ventricular hypertrophy, diabetic and dilated cardiomyopathy [39–42]. Interestingly, a small-scale study of CHF patients undergoing cardiac resynchronization therapy (CRT) showed that CRT-responders had significantly lower circulating OPN levels than non-responders [43]. Thus, it is apparent that OPN is involved both in cardiac and renal damage. However, up till now, there have been insufficient data to address the temporal relationship of OPN with adverse clinical outcomes. To this end, our results demonstrate that repeatedly measured OPN levels, but not the slope, are clinically relevant for risk stratification of CHF patients. Taken together, the re-assessment of OPN levels might not only help to update a patient's risk estimates, but may also serve as a potential response-indicator to HF therapy, However, the latter application of OPN levels warrants confirmation in subsequent clinical studies.

OPG levels predicted progression of vascular calcification and survival in pre-dialysis, dialysis, and renal-transplant patients [11]. In CKD patients, OPG levels were found to be markedly increased in those who had diabetes, which was also observed in our CHF patients [28]. In patients with post-infarction or chronic HF, OPG levels predicted death after acute coronary syndrome and HF-hospitalizations [29,30,44]. However, it is here that our study extends existing evidence by showing that OPG levels dynamically increase as the adverse event such as HF-hospitalization or death approaches. Importantly, the patient's risk entailed by this temporal increase (i.e., higher slope of the OPG trajectory) was independent of OPG levels. In other words, in two patients who have the same "high" OPG levels, it is important whether the OPG levels were high but steady (zero slope) or were increasing prior to assessment (increasing slope). In the latter case, our study shows that every 0.1SD increase in the slope will translate into a 24% higher risk of the event. This information may be used to additionally refine the patients' risk assessment. Interestingly, we also found that patients who were on higher doses of renin-angiotensin-system (RAS) blockers had lower OPG levels. This is indirectly supported by Tsuruda et al. who demonstrated that OPG levels increase in response to cardiac damage during angiotensin II-induced hypertrophy in mice [45]. Therefore, the question is raised whether serial assessment of circulating OPG may be used to identify patients who respond poorly to RAS inhibition. In case OPG does not decrease after RAS inhibition, therapy might be intensified in order to prevent pathological cardiac remodeling.

TFF-3 was found to be upregulated after ischemic myocardial injury in mice [46]. The same authors showed that administration of TFF-3 significantly reduced the infarct size suggesting a cardioprotective effect. In CKD, TFF-3 was found to predict onset of CKD and poor survival [31]. However, data on the prognostic role of TFF-3 in CHF is currently lacking. Hence, this study is the first to demonstrate that increasing slope of the TFF-3 trajectory is a strong clinical predictor in CHF. The importance of TFF-3 in the pathophysiology of CHF is also supported by the network analysis that showed that TFF-3 was the hub within the currently investigated biomarker network. Still, the exact mechanisms of the actions of TFF-3 and its potential use for targeting HF therapy remain to be investigated.

In critically ill patients, HBP was found to be associated with respiratory and circulatory failure, infection-related organ dysfunction, and mortality [47,48]. However, to our best knowledge, there is no previous publication on the role of HBP in CHF. Our study provides strong evidence that HBP is also implicated in CHF by showing a significant association with cardiac decompensation and mortality. Although HBP was independently associated with eGFR, it is unclear whether renal dysfunction is the only factor that contributes to the pool of circulating HBP in CHF. Nevertheless, this study establishes a basis for further investigations on the role of HBP in CHF.

Finally, the pulmonary biomarkers were increased and associated with the primary endpoint independently of the patients' clinical profiles and pharmacological treatment during follow-up. However, only higher slope of PSP-D remained significant predictor after adjustment for time-varying cardiac biomarkers. The fact that the current study population was in a relatively good condition (74% was in NYHA class I-II) may have contributed to the inability to demonstrate robust associations, as lung damage may be expected to manifest itself prominently only with more advanced stages of CHF [3]. Taken together, PSP-D and

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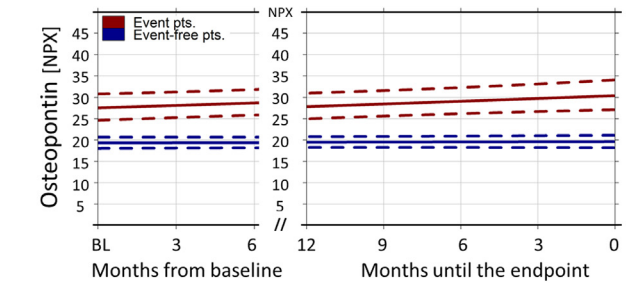

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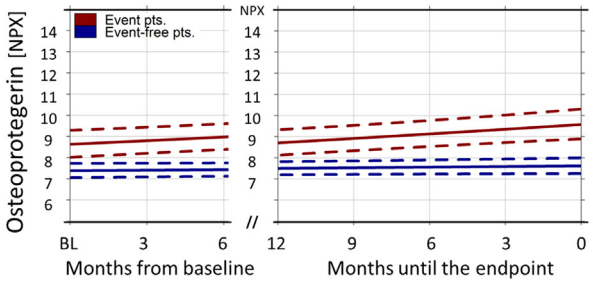

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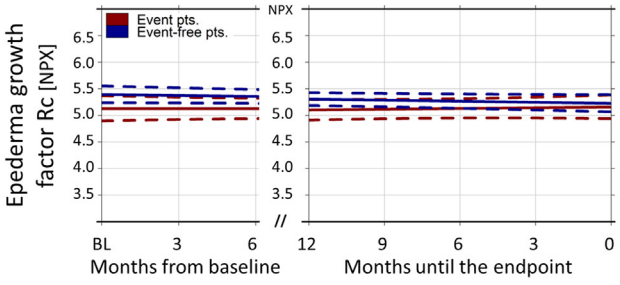

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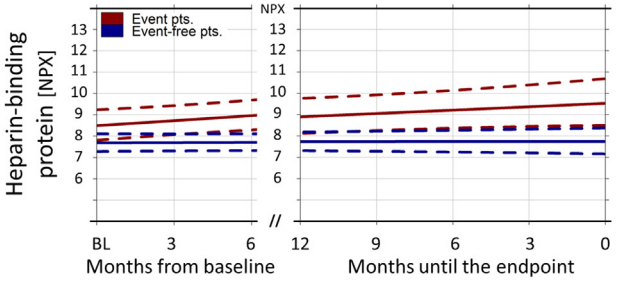

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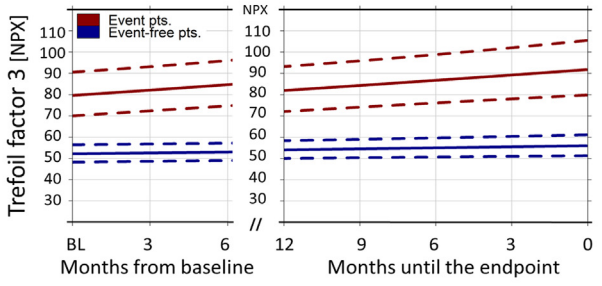

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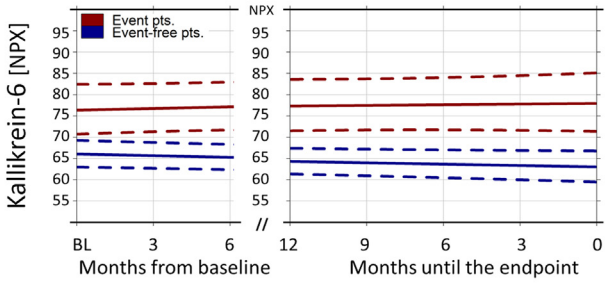

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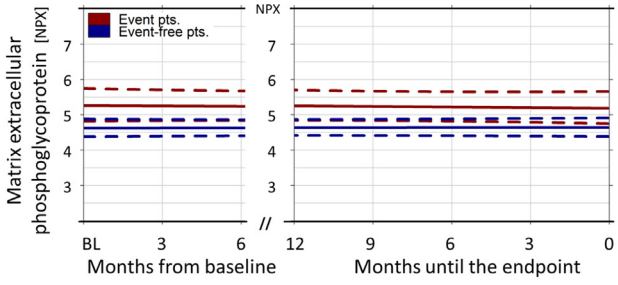

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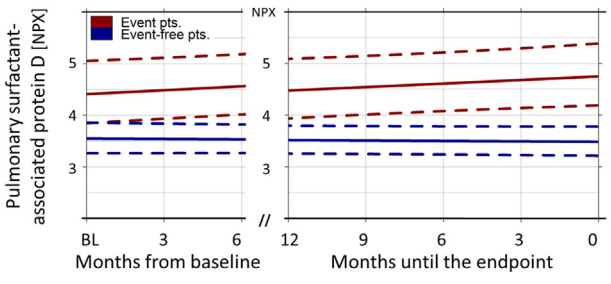

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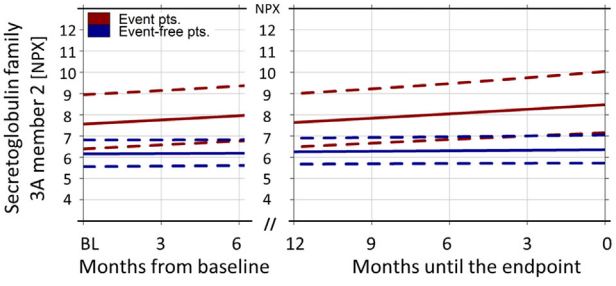

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Table 3
Associations between candidate biomarkers and the composite endpoint.

	Crude model		Clinical data		Clinical data & time-varying medication		Time-varying cardiac biomarkers & HF-type	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Levels (per 1SD increase)								
Cardiorenal biomarkers								
OPN	2.31 (1.76–3.15)	<0.001*	2.45 (1.64–3.68)	<0.001*	2.78 (2.03–3.80)	<0.001*	1.64 (1.16–2.32)	0.006*
OPG	2.23 (1.69–3.00)	<0.001*	2.76 (1.90–4.16)	<0.001*	2.31 (1.72–3.10)	<0.001*	1.68 (1.21–2.32)	0.002*
EGFR	0.77 (0.54–1.08)	0.13	x		xx		x	
HBP	1.36 (1.09–1.70)	0.006*	1.49 (1.15–1.88)	0.002*	1.65 (1.32–2.06)	<0.001*	1.60 (1.24–2.05)	<0.001*
TFF3	2.20 (1.75–2.82)	<0.001*	2.38 (1.73–3.33)	<0.001*	2.35 (1.84–2.99)	<0.001*	1.29 (0.94–1.77)	0.11
KLK-6	1.60 (1.25–2.04)	<0.001*	1.45 (1.07–1.94)	0.014	1.61 (1.17–2.22)	0.003*	0.95 (0.70–1.29)	0.74
MEPE	1.35 (1.04–1.75)	0.02	1.06 (0.79–1.42)	0.66	xx		0.76 (0.57–1.01)	0.05
Pulmonary biomarkers								
PSP-D	1.66 (1.28–2.12)	<0.001*	1.51 (1.15–1.95)	0.002*	1.63 (1.23–2.16)	0.001*	1.16 (0.89–1.50)	0.26
SCGB3A2	1.44 (1.17–1.77)	<0.001*	1.32 (1.02–1.69)	0.032	1.37 (1.08–1.73)	0.008	1.06 (0.81–1.40)	0.67
Slope (per 0.1SD increase/year)[a]								
Cardiorenal biomarkers								
OPN	1.14 (1.03–1.29)	0.010	1.12 (1.00–1.29)	0.046	1.08 (1.03–1.14)	0.003*	1.05 (1.00–1.12)	0.07
OPG	1.24 (1.14–1.38)	<0.001*	1.48 (1.19–1.88)	0.004*	1.15 (1.08–1.23)	<0.001*	1.09 (1.03–1.16)	0.003*
EGFR	x		x		xx		x	
HBP	0.87 (0.77–1.08)	0.19	0.92 (0.73–0.19)	0.62	xx		1.03 (0.99–1.07)	0.13
TFF3	1.31 (1.17–1.49)	<0.001*	1.55 (1.30–1.87)	<0.001*	1.19 (1.11–1.28)	<0.001*	1.15 (1.07–1.23)	<0.001*
KLK-6	1.01 (0.76–1.38)	0.99	1.05 (0.66–1.77)	0.90	xx		1.02 (0.95–1.10)	0.58
MEPE	0.96 (0.86–1.10)	0.57	1.03 (0.91–1.16)	0.66	xx		1.02 (0.95–1.09)	0.61
Pulmonary biomarkers								
PSP-D	1.32 (1.21–1.47)	<0.001*	1.52 (1.32–1.78)	<0.001*	1.12 (1.04–1.19)	0.001*	1.10 (1.04–1.16)	<0.001*
SCGB3A2	1.33 (1.18–1.53)	<0.001*	1.39 (1.19–1.67)	<0.001*	1.10 (1.102–1.20)	0.020	1.08 (1.00–1.17)	0.05

OPN, osteopontin; OPG, osteoprotegerin; EGFR, epidermal growth factor receptor; HBP, heparin-binding protein; TFF3, trefoil factor 3; PSP-D, pulmonary surfactant-associated protein D; SCGB3A2, secretoglobulin family 3A member 2; KLK-6, kallikrein-6; MEPE, matrix extracellular phosphoglycoprotein.
Hazard ratios (HRs) and 95% confidence intervals (CIs) are given per 1SD increase of the level and per 0.1SD increase of the annual slope at any point in time during follow-up. Crude model: Cox model unadjusted, LME model adjusted for sampling time. Clinical model: Cox and LME models adjusted for age, sex, diabetes, atrial fibrillation, baseline NYHA class, diuretics, systolic blood pressure, an eGFR, and sampling time (LME); Clinical & time-varying medication model: time-dependent Cox model using marker's fitted values from clinical model adjusted for total daily doses of equivalents of carvedilol, enalapril, furosemide, and spironolactone during follow-up. Time-varying cardiac biomarkers & HF-type model: time-dependent Cox model using marker's fitted values adjusted for type of HF (HFrEF vs. HFpEF) and time-varying NT-proBNP and cardiac troponin T collected at the same time points during follow-up as the biomarker of interest. Cox and LME models adjusted for baseline NT-proBNP and hs-cTnT, and sampling time (LME). x, not performed because repeatedly measured level was not significant. xx, not performed because marker's levels/slope was not significant in the clinical model.
[a] Annual slopes were additionally adjusted for the levels of repeatedly measured marker during follow-up.
* p-Value below the corrected significance level for multiple testing ($p < 0.007$).

SCGB3A2 are promising markers and warrant further exploration in more severe stages of CHF.

4.1. Clinical implications

We found that the new candidate biomarkers studied here are related to the patients' clinical characteristics. Limited data are available on this topic in patients with CHF. Secondly, in this study we utilized a network analysis which may help us to further specify the role of emerging biomarkers in heart failure by analyzing their inter-biomarker relations. In this regard, OPN and TFF-3 were identified as the hubs within the current network, and these findings were subsequently strengthened by the fact that these biomarkers also carried the highest crude risk of adverse events. Thirdly, this study is unique in showing that not only the levels, but also the slopes of biomarker trajectories (i.e., information on how much a marker was increasing, decreasing, or was stable in approach to a subsequent adverse cardiac event) are relevant for risk assessment. As such, temporal biomarker profiles may potentially help to identify the patients who respond poorly to treatment. This may enable timely adaptation of therapy, thereby preventing future events to occur. Finally, our results indicate a promising role of these new biomarkers in defining more effective biomarker-guided therapy, rather than the current approach where therapy is largely based on symptoms and ejection fraction [49].

4.2. Study limitations

Firstly, this cohort consisted mainly of HFrEF patients. The low number of HFpEF patients is most likely attributable to the fact that in the Netherlands, most HFpEF patients are followed in secondary referral centres or by the general practitioner, while the current study was performed in two tertiary referral centres. Potential inclusion bias is not a likely reason for the low HpEF rate, because all consecutive patients were screened in both participating centres. Secondly, enrolled CHF patients were in a better health condition than previously reported CHF populations. Yet, we were able to demonstrate, even in this 'less sick' CHF population, that several biomarkers are strongly associated with the clinical outcomes. Third, re-hospitalization for HF represented the majority of the composite endpoint. Investigation of individual, 'harder' endpoints such as cardiovascular mortality is advisable, but warrants larger numbers of such endpoints. Finally, future research should focus on better standardization of the assays and reproducibility in other CHF cohorts in order to successfully translate these emerging biomarkers into daily clinical practice.

Fig. 1. Average temporal evolution of candidate biomarkers during follow-up. Legend: Average evolution in patients who reached the composite endpoint (solid red line), and in endpoint-free patients (solid blue line). Dashed lines represent the 95% confidence interval. X-axis depicts the time from baseline (left part of the x-axis), and time remaining to the event (patients who experienced incident events) or last sample moment (patients who remained event-free) (right part of the x-axis). Biomarker levels are presented on the y-axis. a. Osteopontin (OPN), b. Osteoprotegerin (OPG), c. Epidermal growth factor receptor (EGFR), d. Heparin-binding protein (HBP), e. Trefoil factor-3 (TFF-3), f. Kallikrein-6 (KLK-6) g. Matrix extracellular phosphoglycoprotein (MEPE). h. Pulmonary surfactant-associated protein-D (PSP-D) i. Secretoglobulin family 3A-member-2 (SCGB3A2). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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5. Conclusion

Repeatedly-measured levels of OPN, OPG, and HBP, and slopes of OPG, TFF-3, and PSP-D strongly predict clinical outcome during outpatient follow-up in CHF. The use of these candidate markers may be clinically relevant as they may further refine a patient's risk assessment and provide additional pathophysiological insights into CHF.

Disclosure

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.001.

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