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Clinical Research

The Role of GDF-15 in Heart Failure Patients With Chronic Kidney Disease

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ABSTRACT

Background: Growth differentiation factor-15 (GDF-15) is a stress-inducible cytokine and member of the transforming growth factor-β cytokine superfamily that refines prognostic assessment in subgroups of patients with heart failure (HF). We evaluated its role in HF patients with chronic kidney disease (CKD, estimated glomerular filtration rate <60 mL/min/1.73 m^2).

Methods: A total of 358 patients with stable systolic HF were followed for a median of 1121 (interquartile range, 379-2600) days. Comprehensive evaluation including B-type natriuretic peptide (BNP) and GDF-15 testing was performed at study entry; the analysis was stratified according to kidney function.

Results: Patients with CKD (33.8%) were older, had more often diabetes, and were less often treated with angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB). GDF-15 was associated with estimated glomerular filtration rate, whereas BNP was associated with left ventricular-end diastolic diameter and ejection fraction ($P < 0.01$). During follow-up, 244 patients (68.2%)

RÉSUMÉ

Contexte : Le facteur de croissance et de différenciation cellulaire 15 (GDF-15) est une cytokine pouvant être induite par le stress. Elle fait partie d'une superfamille de cytokines, les facteurs de croissance transformant β, qui permet de raffiner l'établissement d'un pronostic chez des sous-groupes de patients atteints d'insuffisance cardiaque. Nous avons étudié son rôle chez des patients atteints d'insuffisance cardiaque et d'une néphropathie chronique (débit de filtration glomérulaire estimé : < 60 ml/min/1,73 m^2).

Méthodologie : Au total, 358 patients atteints d'une forme stable d'insuffisance cardiaque systolique ont été suivis pendant une période médiane de 1 121 jours (intervalle interquartile : de 379 à 2 600 jours). Une évaluation exhaustive comprenant, entre autres, des dosages du peptide natriurétique de type B (BNP) et du GDF-15 a été réalisée au moment de l'admission des patients à l'étude; les données analysées ont été stratifiées d'après la qualité de la fonction rénale.

Résultats : Les patients affligés d'une néphropathie chronique (33,8 %) étaient plus âgés, plus souvent atteints de diabète et moins souvent

Growth differentiation factor-15 (GDF-15) is a stress-inducible cytokine and member of the transforming growth factor-β cytokine superfamily. Plasma levels of GDF-15 are increased in response to multiple pathologic conditions such as inflammation, tissue injury, and oxidative stress.[1] Consequently, higher GDF-15 levels are associated with increased frequency of adverse events and higher mortality.[2] The source of GDF-15 in patients with heart failure (HF) has not been completely elucidated; however, it appears to be produced predominantly by peripheral tissues.[3] Previous studies in HF[4-6] showed that GDF-15 concentrations increase both with increasing HF severity and with various comorbidities. By reflecting several pathophysiological processes, GDF-15 functions as an integrator of both cardiac and noncardiac processes and may therefore serve as a biomarker in various clinical scenarios.[7,8] The exact role of GDF-15 in HF is still being investigated.

B-type natriuretic peptide (BNP) is a well-established biomarker of HF with excellent diagnostic and prognostic

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experienced an adverse outcome (death, urgent transplantation, implantation of mechanical circulatory support). In patients with HF and CKD, the Cox proportional hazard model identified BNP, GDF-15, sex, systolic blood pressure, sodium, total cholesterol, and ACEi/ARB treatment as significant variables associated with an adverse outcome ($P < 0.05$). In multivariable analysis, BNP was replaced by GDF-15. Net reclassification improvement confirmed prognostic superiority of the model encompassing GDF-15 (GDF-15, sodium, total cholesterol, ACEi/ARB treatment) compared with the model without GDF-15 (BNP, sex, sodium, ACEi/ARB treatment), net reclassification improvement 0.62, $P = 0.005$. In contrast, in patients with HF and normal kidney function, BNP remained superior to GDF-15 in a multivariable model. Conclusions: In patients with systolic HF and CKD, GDF-15 is more strongly associated with adverse outcomes than the conventionally used BNP.

traités par des inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA) et des antagonistes des récepteurs de l'angiotensine (ARA). Nous avons établi un parallèle entre le GDF-15 et le débit de filtration glomérulaire estimé et constaté que le BNP avait plutôt un lien avec le diamètre télédiastolique du ventricule gauche et la fraction d'éjection ($p < 0,01$). Pendant la période de suivi, 244 patients (68,2 %) ont été victimes de complications (décès, transplantation effectuée en urgence, implantation d'un dispositif d'assistance circulatoire mécanique). Chez les patients atteints d'insuffisance cardiaque et d'une néphropathie chronique, le modèle des risques proportionnels de Cox a permis de déterminer que le BNP, le GDF-15, le sexe, la pression artérielle systolique, le sodium, le cholestérol total et le traitement par un inhibiteur de l'ECA et par un ARA sont des variables importantes quant aux issues défavorables ($p < 0,05$). Lors d'une analyse multivariée, le BNP a été remplacé par le GDF-15. Une reclassification nettement améliorée a confirmé la supériorité pronostique du modèle tenant compte du GDF-15 (GDF-15, sodium, cholestérol total, traitement par un inhibiteur de l'ECA et par un ARA) comparativement au modèle ne le prenant pas en compte (BNP, sexe, sodium, traitement par un inhibiteur de l'ECA et par un ARA) (amélioration nette de la classification : 0,62; $p = 0,005$). En revanche, un modèle d'analyse multivariée a révélé que le BNP conservait sa supériorité sur le GDF-15 chez les patients atteints d'insuffisance cardiaque ayant une fonction rénale normale.
Conclusions : Chez les patients atteints d'insuffisance cardiaque systolique et d'une néphropathie chronique, le lien entre le GDF-15 et une issue défavorable est plus fort que celui observé avec le BNP, le marqueur qui est habituellement utilisé.

power. However, in a disease as complex as HF, prognosis is estimated using multiple types of predictor variables (laboratory, clinical, imaging, therapeutic) that are integrated into validated models (eg, Seattle HF model [SHFM]) rather than relying on a single parameter.

Chronic kidney disease (CKD) is a condition leading to increased oxidative stress and to multiple systemic sequelae[9] that confound some of the variables used (BNP, haemoglobin, creatinine). In patients with HF and CKD, additional laboratory biomarkers reflecting different pathophysiological pathways may thus refine the outcome prediction even when compared with a multimarker model.[10]

We hypothesized that in patients with HF and CKD, GDF-15 may improve prognostic utility of a multimarker model that already included BNP such as SHFM. The goal of the study was to identify variables associated with BNP and GDF-15 levels and to examine the association between BNP, GDF-15, and outcome in HF patients with CKD.

Methods

Study subjects

Patients with stable HF of at least 6-month duration resulting from left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] < 40%), hospitalized at the Institute for Clinical and Experimental Medicine in Prague for elective percutaneous coronary intervention, radiofrequency ablation, device implantation, or transplant eligibility evaluation, were screened. Those receiving stable medical therapy were enrolled into the study. Patients with recent HF decompensation (ie, diuretics in the previous month) or reversible LV dysfunction (planned valve surgery, revascularization, or tachycardia-induced cardiomyopathy) were excluded. Patients were prospectively followed for adverse outcome defined as the combined endpoint of death, urgent heart transplantation (patients with United Network for Organ Sharing [UNOS] status 1a/1b), or ventricular assist device implantation. Because the time to nonurgent transplantation (patients with UNOS status 2) reflects donor availability rather than the recipient's condition, patients who received a nonurgent heart transplant were censored as having no adverse outcome event at the day of transplantation.[11]

At the study enrollment, patients completed a Minnesota Living with Heart Failure Questionnaire and had anthropometric tests and echocardiographic study (Vivid-7; General Electric, Milwaukee, WI). LV function and dimensions were measured according to published recommendations.[12] A subgroup of 174 patients underwent right-heart catheterization at discretion of the examining cardiologist to help decide further therapeutic strategy. The investigation conforms with the principles outlined in the Declaration of Helsinki, the study protocol was approved by the Institutional Ethics Committee, and all subjects signed an informed consent.

Laboratory assessment

Blood was collected into ethylenediaminetetraacetic acid (EDTA)-anticoagulated tubes on patient enrollment. Basic biochemical parameters were assessed at the Institute for Clinical and Experimental Medicine. Sodium was measured by an indirect ion-specific electrode (ISE) method; creatinine (traceable to

the isotope dilution mass spectrometry (IDMS), Standard Reference Material (SRM) 967) and total cholesterol were measured by enzymatic methods (Abbott Architect; Abbott Laboratories Inc, Abbott Park, IL). Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation, based on serum creatinine levels, age, ethnicity, and sex.[13] BNP was measured on the ARCHITECT analyzer (Abbott Diagnostics, Abbott Park, IL) using a chemiluminescent immunoassay with a reportable range 10-25,000 ng/L. Intermediate precision was 6.8%, 5.6%, and 5.6% at 69.0, 286.0, and 1381.0 ng/L, respectively. GDF-15 was measured in the Biomarker Research and Clinical Trials Laboratory at Brigham and Women's Hospital. Patient specimens were diluted 4 times and 50 μL aliquots were tested in duplicates using the Quantikine Human GDF-15 Immunoassay (R&D Systems Inc, Minneapolis, MN). The reportable range was 94-6000 pg/mL and total imprecision was 8.3% at 162 pg/mL, 7.6% at 414 pg/mL, and 12.0% at 797 pg/mL.

Parameters used for an outcome analysis

In addition to BNP and GDF-15, we used the SHFM-derived set of validated variables to assess the prognosis of patients with HF: age, HF duration, sex, HF etiology, body mass index, systolic blood pressure, New York Heart Association (NYHA) functional class, heart rate, eGFR, sodium level, lymphocyte percentage, total cholesterol, uric acid, haemoglobin, Hb1Ac, LVEF, furosemide daily dose, use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), use of β-blockers, and presence of an implantable cardioverter defibrillator (ICD).[14,15]

Statistical analysis

The unpaired *t* test and/or Mann-Whitney *U* test was used to determine differences between parameters in patients with normal renal function and kidney disease. The Kolmogorov-Smirnov test was used to evaluate the Gaussian distribution. The χ^2 test was used to compare categorical variables. The association between variables was determined by linear regression. The effect of biomarker concentration on prognosis was tested using the univariate and multivariable Cox model; the forward Wald method was used for multivariable analysis. Because both BNP and GDF-15 showed markedly skewed distribution, log-normal values were used. Event-free survival of patients was analysed by Kaplan-Meier analysis with log-rank test comparison between groups. Calculations were performed using JMP 11 (SAS Institute Inc, Cary, NC) and SPSS version 19 software (Chicago, IL). Receiver operating characteristic (ROC) curves were analysed calculating C-statistics improvement using the method proposed by DeLong et al.[16] Net reclassification improvement was calculated by the method described by Pencina et al.[17]

Results

Patient characteristics

A total of 358 patients with systolic HF (LVEF 24.7% ± 5.0%, NYHA 2.8 ± 0.6) were followed for 1121 (interquartile range, 379-2600) days. During follow-up, 244 patients (68.2%) experienced an adverse outcome. Basic patient characteristics are summarized in Table 1.

Kidney function

Patients with CKD (eGFR < 60 mL/min/1.73 m^2, n = 121, 33.8% of total) were older, and had more often diabetes and ischemic etiology of HF and higher NYHA class. They were less often treated with ACEi or ARB but more frequently with cardiac resynchronization therapy. They also had borderline higher furosemide dose. No significant differences in any echocardiographic parameter were observed between the 2 groups. Patients with CKD had higher levels of both BNP and GDF-15 (Table 1). Patients with lower eGFR had significantly shorter event-free survival than those with normal kidney function (Supplemental Fig. S1).

Association of BNP and GDF-15 with clinical variables

There was a statistically significant but weak association between BNP and GDF-15 ($r = 0.49$, $P < 0.0001$). Both BNP and GDF-15 were negatively associated with systolic blood pressure and positively with NYHA class. There was a strong negative association between eGFR and GDF-15, whereas the association between eGFR and BNP was not significant ($P = 0.28$). Similarly, furosemide daily dose was associated with GDF-15 but not with BNP. BNP but not GDF-15 was associated with LVEF, LV end-diastolic diameter, and degree of mitral regurgitation (Table 2).

A subgroup of 174 patients underwent invasive haemodynamic assessment. Right atrial pressure, mean pulmonary pressure, and pulmonary capillary wedge pressure were associated with both BNP and GDF-15. In contrast, measured cardiac output was associated with BNP but not with GDF-15 (Table 2).

Outcome analysis

ROC analysis. Among patients with CKD, the ROC area under the curve (AUC) for GDF-15 (AUC 0.731, $P = 0.002$) was significantly higher (difference between areas 0.120, standard error 0.0548, $P = 0.03$, Fig. 1A) as compared with BNP (AUC 0.612, $P = 0.06$), which showed only a borderline association with the risk of adverse events. On the other hand, the ROC curves for GDF-15 (AUC 0.700, $P < 0.0001$) and BNP (AUC 0.705, $P < 0.0001$) did not differ in patients with normal kidney function (difference between areas 0.005, standard error 0.036, $P = 0.89$, Fig. 1B).

Kaplan-Meier analysis. We have further used ROC curve–derived cutoff values to stratify the cohort. For patients with CKD, BNP and GDF-15 levels of 652.7 ng/L and 1646.0 ng/L, respectively, were identified as optimal cutoffs. In patients with normal kidney function, the respective values were 264.0 ng/L for BNP and 1204.0 ng/L for GDF-15.

In patients with low BNP (both in patients with CKD and normal kidney function), those with high GDF-15 had substantially worse outcomes compared with those with low GDF-15 values (Fig. 2). In contrast, in patients with high BNP values, the difference between subjects with low and high GDF-15 was only small and did not reach statistical significance for patients with CKD (Supplemental Fig. S2). GDF-15 thus strengthens

Table 1. Basic characteristics of patients stratified according to the estimated glomerular filtration rate

Anthropometry	Total cohort (n = 358)	eGFR < 60 (n = 121)	eGFR > 60 (n = 237)	*P* value
Age (y)	58.92 ± 10.72	63.60 ± 8.85	56.53 ± 10.83	**< 0.0001**
Male gender	303 (84.6%)	103 (85.1%)	200 (84.4%)	0.85
BMI (kg/m^2)	27.7 ± 4.76	28.03 ± 4.89	27.60 ± 4.69	0.41
Heart failure and comorbidities				
Ischemic etiology	196 (54.7%)	78 (64.5%)	118 (49.8%)	**0.008**
HF duration (y)	8.25 ± 7.09	10.10 ± 8.08	7.28 ± 6.31	**0.0008**
NYHA functional class (1-4)	2.79 ± 0.55	2.88 ± 0.55	2.73 ± 0.55	**0.02**
Diabetes	122 (34.1%)	55 (45.5%)	67 (28.3%)	**0.001**
Obesity	102 (28.5 %)	34 (28.1%)	68 (28.7%)	0.91
Hb (g/L)	140.45 ± 16.63	137.12 ± 17.94	142.50 ± 15.59	**0.004**
eGFR (mL/min/1.73 m^2)	69.68 ± 22.91	47.22 ± 9.71	81.15 ± 18.85	**< 0.0001**
Hb1Ac (mmol/mol)	49.78 ± 16.11	51.90 ± 18.48	48.69 ± 14.67	0.07
Asthma/COPD	57 (15.9%)	21 (17.4%)	36 (15.2%)	0.60
BNP (ng/L)	562 (278; 1208)	653 (345; 1397)	515 (236; 1102)	**0.02**
GDF-15 (ng/L)	1503 (956; 2323)	2094 (1553; 3059)	1204 (835; 2641)	**< 0.0001**
Cardiac function				
Heart rate (min^{-1})	77.68 ± 9.09	77.26 ± 16.03	77.02 ± 14.14	0.89
Systolic blood pressure (mm Hg)	114.64 ± 18.91	114.51 ± 18.96	114.71 ± 18.93	0.93
LVEF (%)	24.68 ± 5.00	24.98 ± 5.44	24.54 ± 4.76	0.43
LV end-diastolic diameter (mm)	70.68 ± 9.09	70.52 ± 9.14	70.76 ± 9.08	0.82
RV dysfunction grade (0-3)	2 (1; 2)	2 (1; 2)	1 (1; 2)	0.16
Mitral regurgitation (0-2)	1 (0; 2)	1 (0; 1)	1 (0; 2)	0.13
Tricuspid regurgitation (0-2)	0 (0; 1)	0 (0; 1)	0 (0; 1)	0.49
IVC (mm)	20.03 ± 5.95	19.94 ± 6.26	20.08 ± 5.79	0.84
Medication				
Furosemide use (daily dose, mg)	96.55 ± 81.60	107.85 ± 85.04	90.56 ± 79.27	0.07
β-Blocker use	333 (93.0%)	110 (90.9%)	223 (94.1%)	0.27
ACEi/ARB use	310 (86.6%)	96 (79.3%)	214 (90.3%)	**0.005**
Aldosterone antag. use	282 (78.8%)	100 (82.6%)	182 (76.8%)	0.19
Triple therapy	228 (63.7%)	72 (59.5%)	156 (65.8%)	0.24
Devices				
ICD	239 (66.8%)	80 (66.1%)	159 (67.1%)	0.85
CRT	161 (45.0%)	64 (52.9%)	97 (40.9%)	**0.03**
Follow-up				
Follow-up length (d)	1121 (379; 2600)	802 (296; 2115)	1435 (470; 2740)	**0.002**
Survival	92 (25.7%)	20 (16.5%)	72 (30.4%)	–
Death	159 (44.4%)	68 (56.2%)	91 (38.4%)	–
Urgent HTx	54 (15.1%)	20 (16.5%)	34 (14.4%)	–
Normal HTx (%)	22 (6.1%)	7 (5.8%)	15 (6.3%)	–
LVAD implantation (%)	31 (8.7%)	6 (5.0%)	25 (10.5%)	–

Data are presented as means ± standard deviation or medians and interquartile ranges (if appropriate). Obesity was defined as BMI > 30. Triple therapy was defined as the therapy with β-blockers, ACEi/ARB, and aldosterone antagonist.

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HF, heart failure; HTx, heart transplantation; ICD, implantable cardioverter defibrillator; IVC, inferior vena cava; LVAD, left ventricle assist device; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association functional class; RV, right ventricle.

the association with adverse outcomes in patients with HF, in particular those with low BNP.

Cox proportional hazard model—patients with normal kidney function. In the Cox univariate analysis, BNP, GDF-15, sex, systolic blood pressure, sodium, furosemide daily dose, lymphocyte percentage in complete blood count, total cholesterol, the use of ACEi/ARB, uric acid, NYHA functional class, Hb1Ac level, LVEF, body mass index, and HF etiology were significantly associated with an adverse outcome in patients with HF and normal kidney function (Table 3). In contrast, heart rate, age, eGFR, haemoglobin, HF duration, the presence of ICD, and β-blocker therapy were not statistically significant. Multivariable analysis with BNP but without GDF-15 identified BNP, sex, sodium, and the presence of ACEi/ARB as significant predictors of an adverse outcome. The addition of GDF-15 into the model did not change the results (Table 3).

Cox proportional hazard model—patients with CKD. In patients with HF and CKD, BNP, GDF-15, sex, systolic blood pressure, sodium, total cholesterol, and the treatment with ACEi/ARB were significantly associated with an adverse outcome, whereas other variables were not (Table 4). Multivariable analysis using BNP but not GDF-15 identified BNP, sodium, and ACEi/ARB treatment as variables associated with an adverse outcome. When GDF-15 was added into the model, it replaced BNP that was no longer significant (Table 4).

Net reclassification improvement analysis. We used net reclassification improvement (NRI) analysis to compare both models (BNP, Na, ACEi/ARB treatment vs GDF-15, Na, total cholesterol, ACEi/ARB treatment). Among patients with CKD, an addition of GDF-15 to the model led to a significant NRI by 62% at *P* level = 0.005 (6.4% for event NRI and 55.6% for nonevent NRI). We thus conclude that in patients with HF and CKD, GDF-15 is not only an additive but also a superior variable associated with an adverse outcome compared with BNP.

Table 2. Association of clinical, echocardiographic, and haemodynamic variables with GDF-15 and BNP

	GDF-15		BNP	
n = 358	*r*	*P* value	*r*	*P* value
SBP (mm Hg)	−0.10	**0.048**	−0.27	**< 0.0001**
Age (y)	+ 0.24	**< 0.0001**	+ 0.02	0.78
NYHA (II-IV)	+ 0.54	**0.0012**	+ 0.13	**0.01**
Heart rate (min^{-1})	+ 0.08	0.13	+ 0.19	**0.0003**
BMI (kg/m^2)	−0.037	0.47	−0.31	**< 0.0001**
eGFR ($mL/min/1.73\ m^2$)	−0.40	**< 0.0001**	−0.06	0.28
FSM daily dose (mg)	+ 0.23	**< 0.0001**	+ 0.07	0.23
Echocardiography (n = 358)				
LVEF (%)	−0.09	0.08	−0.25	**< 0.0001**
LVEDd (mm)	+ 0.03	0.54	+ 0.14	**0.0057**
MiR (0-2)	+ 0.096	0.33	+ 0.2	**< 0.0001**
TriR (0-2)	+ 0.28	**< 0.0001**	+ 0.28	**< 0.0001**
RV dysfunction grade (0-3)	+ 0.23	**< 0.0001**	+ 0.3	**< 0.0001**
IVC (mm)	+ 0.99	**0.02**	+ 0.29	**< 0.0001**
Haemodynamics (n = 174)				
RAP (mm Hg)	+ 0.45	**< 0.0001**	+ 0.30	**< 0.0001**
MAP (mm Hg)	+ 0.17	**0.02**	+ 0.32	**< 0.0001**
PCWP (mm Hg)	+ 0.2	**0.01**	+ 0.35	**< 0.0001**
TPG (mm Hg)	+ 0.08	0.31	+ 0.13	0.09
CO (mm Hg)	+ 0.11	0.14	−0.29	**< 0.0001**

BMI, body mass index; BNP, B-type natriuretic peptide; CO, cardiac output; eGFR, estimated glomerular filtration rate; FSM, furosemide; GDF-15, growth differentiation factor-15; IVC, inferior vena cava; LVEDd, left-ventricle diameter in end-diastole; LVEF, left-ventricle ejection fraction; MAP, mean pulmonary artery pressure; MiR, mitral regurgitation; NYHA, New York Heart Association functional class; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RV, right ventricle; SBP, systolic blood pressure; TPG, transpulmonary gradient; TriR, tricuspid regurgitation.

Discussion

Our study compared association of BNP and GDF-15 with adverse outcomes in HF population. When taking into account kidney function, the main conclusion is that the addition of GDF-15 refines prognosis of patients with low BNP. In addition, in patients with systolic HF and CKD, GDF-15 is more strongly associated with adverse outcomes than the conventionally used BNP. Both biomarkers were associated with distinct clinical variables; BNP was associated with parameters of LV function, whereas GDF-15 was more strongly associated with glomerular filtration.

Therapy of patients with HF and CKD

CKD is a common comorbidity in patients with HF with a prevalence of approximately 40%,[18] which is similar to the CKD prevalence observed in our patient cohort (33.8%). Patients with CKD are less often treated with HF medication,[18] which was confirmed in our study as well; patients with CKD had a significantly lower prevalence of ACEi/ARB therapy. However, ACEi/ARB treatment was an important factor related to the prognosis of patients regardless of kidney function. Importantly, patients with CKD were reported to derive similar benefit from ACEi/ARB therapy as those with normal kidney function.[19]

Association of biomarkers with clinical variables

The study showed that BNP and GDF-15 were associated with distinct clinical variables likely reflecting different pathophysiological mechanisms responsible for their release. BNP is produced by ventricular and atrial cardiomyocytes on mechanical stress that is believed to be the main stimulus for its biosynthesis and release.[20] Consistently, we observed a significant association between BNP and LV diameter and ejection fraction. Compared with BNP, the stimuli for GDF-15 production are more diverse. Cardiac myocytes produce and secrete large amounts of GDF-15 in response to oxidative stress and ischemia,[21] but considerable amount of GDF-15 is also produced by other tissues such as macrophages,[22] vascular smooth muscle cells,[23] adipocytes,[24] and endothelial cells.[25] Although the main source of GDF-15 in patients with HF is less clear, it seems that the majority is produced by noncardiac tissues.[3] Accordingly, we documented no relation between GDF-15 and LV size or function but a significant association with GFR. Similarly, GDF-15 was associated with tricuspid regurgitation severity, right ventricle dysfunction grade, and inferior vena cava diameter (but not mitral

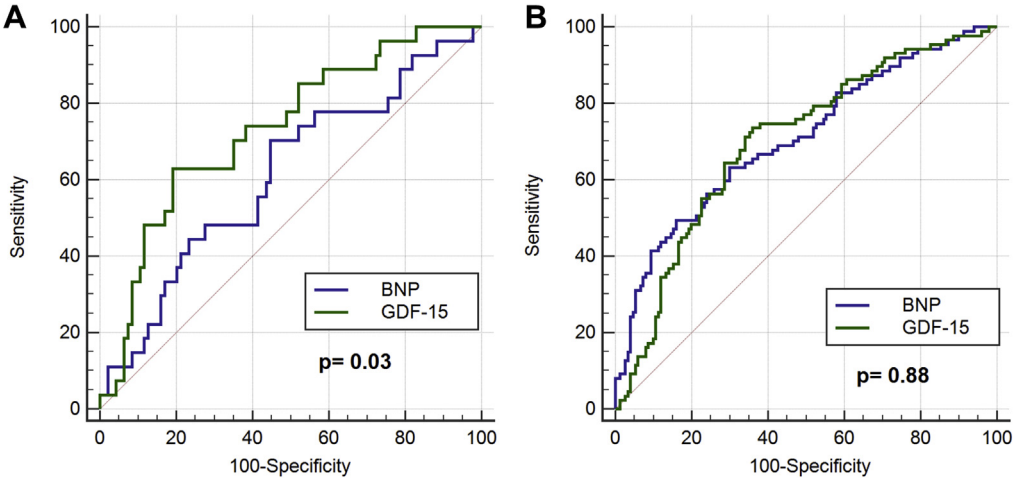

Figure 1. Receiver operating characteristic curve based on B-type natriuretic peptide (BNP) and growth differentiation factor-15 (GDF-15) in patients with chronic kidney disease (**A**) and in patients with normal kidney function (**B**).

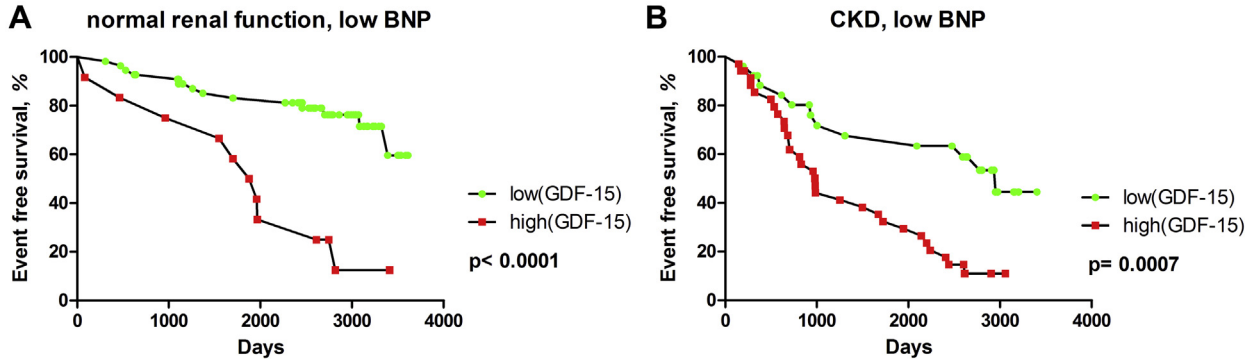

Figure 2. Kaplan-Meier analysis showing an outcome of patients with low B-type natriuretic peptide (BNP)/low growth differentiation factor-15 (GDF-15) compared with those with low BNP/high GDF-15 in patients with normal renal function (**A**) and chronic kidney disease (CKD) (**B**). Cutoff values to discriminate between high and low BNP and GDF-15 are based on receiver operating characteristic curve analysis and are as follows: BNP of 264.0 and 652.7 ng/L for patients with normal kidney function and CKD, respectively; GDF-15 of 1204.0 and 1646.0 ng/L for patients with normal kidney function and CKD, respectively.

regurgitation severity nor cardiac output), which likely reflects the degree of congestion and is thus related to renal function.

Patients with CKD had a higher level of both BNP and GDF-15. CKD is known to be associated with elevated levels of natriuretic peptides,[26] which can be only partially explained by decreased kidney clearance.[27,28] The association between increased GDF-15 levels and decreased kidney function is likely due to either increased production or decreased clearance. Kidneys produce GDF-15 in response to injury or metabolic stress, and increased concentration of GDF-15 in urine of patients with diabetic nephropathy has been described.[29]

The higher level of GDF-15 in HF patients with CKD thus probably reflects not only decreased clearance of GDF-15 but also increased production likely related to increased oxidative stress and inflammation.[4,30] A strong association between renal function and GDF-15 levels is in agreement with previous observations.[4,5,30]

Table 3. Variables associated with an adverse outcome in patients with HF and normal renal function

N = 237, 150 events	Univariate analysis			Multivariable analysis (excluding GDF-15)			Multivariable analysis (including GDF-15)		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
BNP (1 ln, ng/L)	1.82	1.55-2.16	**< 0.0001**	1.50	1.26-1.79	**< 0.0001**	1.50	1.26-1.79	**< 0.0001**
GDF-15 (1 ln, ng/L)	2.28	1.72-3.01	**< 0.0001**		**not included**				
Sex (males vs females)	3.37	1.91-6.62	**< 0.0001**	2.20	1.10-4.39	**0.025**	2.20	1.10-4.39	**0.025**
Systolic blood pressure (5 mm Hg)	0.88	0.84-0.93	**< 0.0001**						
Na (mmol/L)	0.89	0.86-0.93	**< 0.0001**	0.91	0.87-0.96	**< 0.0001**	0.91	0.87-0.96	**< 0.0001**
Furosemide daily dose (10 mg)	1.03	1.01-1.05	**0.001**						
Lymphocyte percentage (1%)	0.98	0.96-0.99	**0.009**						
Total cholesterol (mmol/L)	0.82	0.70-0.96	**0.02**						
ACEi or ARB (present vs absent)	0.32	0.20-0.54	**< 0.0001**	0.44	0.26-0.75	**0.002**	0.44	0.26-0.75	**0.002**
Uric acid (100 µmol/L)	1.27	1.10-1.46	**0.001**						
NYHA (I+II vs III+IV)	0.60	0.41-0.86	**0.005**						
Hb1Ac (mmol/mol)	1.02	1.008-1.025	**0.0002**						
LVEF (5%)	0.73	0.60-0.88	**0.0008**						
BMI (kg/m^2)	0.94	0.91-0.98	**0.002**						
Heart rate (min^{-1})	1.01	0.999-1.02	0.051						
Age (5 y)	0.99	0.92-1.08	0.90						
eGFR (mL/min/1.73 m^2)	0.99	0.99-1.004	0.34						
Haemoglobin (10 g/L)	1.05	0.95-1.17	0.35						
HF etiology (CAD vs non-CAD)	1.47	1.06-2.04	**0.02**						
HF duration (y)	1.01	0.98-1.03	0.53						
ICD (present vs absent)	0.98	0.70-1.39	0.89						
β-Blockers (present vs absent)	0.77	0.43-1.58	0.45						

Note that both models excluding and including GDF-15 are identical indicating that the inclusion of GDF-15 in the model has not changed the results of the model based on BNP.

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HF, heart failure; HR, hazard ratio; LVEF, left-ventricle ejection fraction; NYHA, New York Heart Association functional class.

Table 4. Variables associated with an adverse outcome in patients with HF and CKD

N = 121, 94 events	Univariate analysis			Multivariable analysis (excluding GDF-15)			Multivariable analysis (including GDF-15)		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
BNP (1 ln, ng/L)	1.65	1.31-2.07	**< 0.0001**	1.45	1.15-1.83	**0.002**			
GDF-15 (1 ln, ng/L)	2.87	1.90-4.30	**< 0.0001**	**not included**			2.05	1.29-3.26	**0.002**
Sex (males vs females)	2.20	1.17-4.73	**0.01**						
Systolic blood pressure (5 mm Hg)	0.92	0.87-0.98	**0.005**						
Na (mmol/L)	0.90	0.85-0.96	**0.001**	0.92	0.86-0.98	**0.009**	0.93	0.87-0.99	**0.02**
Furosemide daily dose (10 mg)	1.02	0.996-1.04	0.10						
Lymphocyte percentage (1%)	0.98	0.96-1.003	0.11						
Total cholesterol (mmol/L)	0.61	0.47-0.79	**< 0.0001**				0.76	0.59-0.98	**0.034**
ACEi or ARB (present vs absent)	0.32	0.20-0.52	**< 0.0001**	0.48	0.27-0.83	**0.008**	0.51	0.29-0.87	**0.014**
Uric acid (100 µmol/L)	1.04	0.90-1.22	0.53						
NYHA (I+II vs III+IV)	0.77	0.44-1.28	0.32						
Hb1Ac (mmol/mol)	1.00	0.996-1.02	0.18						
LVEF (5%)	0.94	0.78-1.12	0.50						
BMI (kg/m^2)	0.98	0.93-1.02	0.36						
Heart rate (min^{-1})	1.00	0.99-1.01	0.88						
Age (5 y)	0.96	0.86-1.07	0.42						
eGFR (mL/min/1.73 m^2)	0.98	0.96-1.30	0.15						
Haemoglobin (10 g/L)	0.97	0.86-1.09	0.60						
HF etiology (CAD vs non-CAD)	0.92	0.60-1.44	0.72						
HF duration (y)	1.00	0.98-1.03	0.76						
ICD (present vs absent)	1.06	0.70-1.64	0.79						
β-Blockers (present vs absent)	0.72	0.40-1.44	0.33						

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HF, heart failure; HR, hazard ratio; LVEF, left-ventricle ejection fraction; NYHA, New York Heart Association functional class.

The role of GDF-15 in outcome prediction of patients with HF

GDF-15 is elevated in many states reflecting primarily cardiac but also noncardiac pathology[31] and thus integrates multiple pathophysiological pathways.[30] GDF-15 captures different aspects of cardiovascular disease pathology that are not represented by established HF biomarkers that are related to outcome in HF. Although HF with reduced ejection fraction is caused primarily by a cardiac pathology, it is truly a syndrome rather than a disease and has many distinct subtypes.[1] Considering that HF affects multiple organ systems, biomarkers reflecting cardiac and extracardiac abnormalities may provide incremental information beyond purely cardiac markers such as natriuretic peptides in distinct HF subtypes. CKD is a condition accompanied by inflammation and increased oxidative stress; we have therefore hypothesized that an addition of GDF-15 (reflecting extracardiac component) to BNP (assessing cardiac component) would provide additional information compared with BNP alone. In our cohort, GDF-15 further stratified the outcome of patients with low BNP (< 264 ng/L in patients with normal kidney function and < 652.7 ng/L in patients with CKD). In patients with CKD, its association with an adverse outcome was superior to conventionally used BNP; such a strong role of GDF-15 was not observed in patients with HF and normal kidney function. Although we have observed a strong association between GDF-15 and eGFR, it was GDF-15 but not eGFR that was most tightly related to a poor outcome. GDF-15 thus seems to reflect qualitatively broader information beyond kidney function.

The fact that the majority of GDF-15 is produced outside the heart may explain why it adds so potently to a biomarker such as BNP that is produced exclusively in the cardiac tissue. Although the prognostic role of GDF-15 in patients with HF was already described in previous studies,[4,5,30] we believe that this is the first study specifically describing the role of GDF-15 in patients with HF and CKD.

Relationship to previous studies of GDF-15 in HF

Our study has several unique features. First, it had a long follow-up (upper quartile range 2600 days) during which more than two-thirds of patients (68.6%) experienced an outcome. Second, our cohort of patients had a considerably higher level of guideline-recommended HF therapy (93% β-blockers, 87% ACEi/ARB, 79% mineralocorticoid receptor antagonist, 67% ICD) than previously published studies. Kempf et al.[4] described that GDF-15 remained an independent predictor of mortality even after adjustment for clinical variables and established biomarkers of adverse prognosis including N-terminal type BNP. This study did not specifically focus on refinement of prognosis in certain HF subtypes and investigated a cohort with a lower level of guideline-recommended HF therapy (58.6% β-blocker, 23.7% spironolactone, no information about device therapy was provided). In a subanalysis of the **Val**sartan **He**art **F**ailure **T**rial (Val-HeFT) trial, GDF-15 predicted mortality independently of a comprehensive set of established prognostic variables including NYHA class, LVEF, renal function, haemoglobin, sodium, uric acid, HF medication, and prognostic biomarkers, including BNP, high-sensitivity troponin T, and C-reactive protein.[5] However, only 34.5% of patients were treated with β-blockers in the Val-HeFT trial compared with 67.1% treated with digoxin.[9] With the exception of neprilysin inhibitor therapy, BNP levels decrease with adequate HF pharmacotherapy (β-blockers, ACEi/ARB, mineralocorticoid receptor antagonist).[32] Additional biomarkers may therefore

refine the information about prognosis in patients treated with these agents. In comparison with previous studies,[4,5,30] our results thus provide an insight into the role of GDF-15 in an HF cohort treated according to the HF guidelines.

Study limitations

Our study was performed in a heart centre offering a complex cardiovascular program including ventricular assist device implantation and heart transplantation. Because this could introduce bias related to the analysis of prognostic value, urgent heart transplantation and LV assist device implantation were considered adverse outcomes,[11] whereas the patients receiving nonurgent heart transplant were censored as having no adverse outcome on the day of transplantation. In addition, it was a single-centre study with a substantial predominance of male patients. Because some of the patients were evaluated for heart transplant eligibility, this study cohort overall included patients with rather advanced HF. However, the prevalence of kidney disease was similar to other community-based cohorts.[18] Consequently, the results might not be fully applicable to patients with milder HF. Data about HF rehospitalizations were not available in all patients; this endpoint thus could not have been included in the analysis.

Conclusions

GDF-15 is strongly associated with adverse outcomes in patients with stable HF and optimized drug and device therapy. Regardless of kidney function, it refines risk stratification in subjects with low BNP. In patients with systolic HF and CKD, GDF-15 is more strongly related to an adverse outcome than conventionally used BNP.

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Supplementary Material

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