Circulation: Heart Failure

ORIGINAL RESEARCH

Multimarker Analysis of Serially Measured GDF-15, NT-proBNP, ST2, GAL-3, cTnI, Creatinine, and Prognosis in Acute Heart Failure

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BACKGROUND: Studies on serially measured GDF-15 (growth differentiation factor 15) in acute heart failure (HF) are limited. Moreover, several pathophysiological pathways contribute to HF. Therefore, we aimed to explore the (additional) prognostic value of serially measured GDF-15 using a multi-marker approach to more accurately predict HF risk.

METHODS: TRIUMPH (Translational Initiative on Unique and Novel Strategies for Management of Patients With Heart Failure) is a prospective cohort of 496 patients with acute HF who were enrolled in 14 hospitals in the Netherlands between 2009 and 2014. Blood sampling was scheduled at 7 moments during 1-year follow-up. GDF-15, NT-proBNP (N-terminal pro-B-type natriuretic peptide), ST2 (suppression of tumorigenicity 2), galectin-3, troponin I, and creatinine were measured in a central laboratory. We associated repeated measurements of these biomarkers with the composite primary end point of all-cause mortality and HF rehospitalization, using multivariable joint modeling.

RESULTS: Median age was 74 years, and 37% were women. Median baseline GDF-15 was 4632 pg/mL. The primary end point was reached in 188 (40%) patients. The average estimated GDF-15 level increased weeks before the primary end point was reached. The hazard ratio per 1 SD difference in log-GDF-15 was 2.14 (95% CI, 1.78–2.57) unadjusted, 1.96 (1.49–2.53) after adjustment for clinical confounders and 1.44 (1.05–1.91) when jointly modeled with all biomarkers. The adjusted HRs for NT-proBNP were 2.38 (1.78–3.33) and 1.52 (1.15–2.08), respectively. The multimarker model combining GDF-15, NT-proBNP, and troponin I provided a favorable risk discrimination (area under the curve=0.785).

CONCLUSIONS: Sequentially measured GDF-15 independently and dynamically predicts risk of adverse outcomes during 1-year follow-up after index admission for acute HF. NT-proBNP remains a robust predictor among potential candidates. Multiple biomarkers should be considered for stratification in clinical practice.

REGISTRATION: URL: https://www.trialregister.nl/trial/1783; Unique Identifier: NTR1893. (The trial can be found temporarily at https://trialsearch.who.int/Trial2.aspx?TrialID=NTR1893.)

Key Words: biomarkers ■ growth differentiation factor 15 ■ heart failure ■ prognosis

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Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Increase in GDF-15 (growth differentiation factor 15) level is strongly associated with an increased composite risk of all-cause mortality and heart failure hospitalization after admission for acute heart failure, independent of multiple biomarkers including NT-proBNP (N-terminal pro-B-type natriuretic peptide).
- Repeated measurements better reflect the dynamic pattern of biomarkers and take into account the natural disease progression compared with a single, baseline measurement.
- A multimarker panel of GDF-15, NT-proBNP, and troponin I has a stronger relation with the incidence of adverse outcomes during follow-up than a single-marker panel.

WHAT ARE THE CLINICAL IMPLICATIONS?

- A combination of multiple, serially measured (novel and established) biomarkers could improve risk stratification on top of existing risk prediction tools and further facilitate clinical decision-making.
- Frequent measurement of biomarkers during outpatient follow-up could provide an actionable window to anticipate and potentially prevent adverse events such as readmission, warranting further research into biomarker-guided management of heart failure.

Nonstandard Abbreviations and Acronyms

CHAMPION	CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients
GDF-15	growth differentiation factor 15
HF	heart failure
Hs-TnT	high-sensitivity troponin T
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RELAX-AHF	relaxin in acute heart failure
ST2	suppression of tumorigenicity 2
TRIUMPH	Translational Initiative on Unique and Novel Strategies for Management of Patients With Heart Failure

Heart failure (HF) increasingly burdens health care costs[1] due to high mortality rates and frequent hospitalization despite evidence-based treatment according to current guidelines.[2] In the context of reducing this growing burden, serum biomarkers, which reflect underlying biological processes, are becoming increasingly popular for risk stratification and treatment guidance. The most well-known and extensively studied biomarker in HF is NT-proBNP (N-terminal pro-B-type natriuretic peptide), which has been shown to provide incremental prognostic value to known clinical confounders. However, HF is a syndrome with a broad pathophysiological basis, and there is still need for novel circulating biomarkers that are expressed downstream several relevant molecular pathways.[3] Recent examples of such novel HF biomarkers include ST2 (suppression of tumorigenicity 2)[4] and galectin-3,[5] which we have previously investigated and shown to provide additional information to that conferred by NT-proBNP. Despite this evidence, these markers have not yet been adopted in the guidelines or routine clinical care.

A promising upcoming HF biomarker, which we have not previously investigated, is GDF-15 (growth differentiation factor 15). GDF-15 is a member of the transforming growth factor beta cytokine superfamily that is expressed in inflammatory state, under oxidative stress and reflects cardiac remodeling.[6,7] A meta-analysis of 8 clinical studies in patients with HF showed that elevated levels of GDF-15 were associated with increased mortality.[8] However, these studies relied on a single, baseline measurement of GDF-15, which fails to take into account disease progression and the dynamic pattern of biomarkers during follow-up. Studies on the longitudinal evolution of GDF-15 (≥3 measurements) and its relation with HF prognosis are limited[9–12] and even more so in patients with acute HF.[10] Furthermore, a multimarker approach might be necessary to account for the heterogeneity in pathophysiology and has been insufficiently applied in this context.[9,10] Thus, the full potency of serially measured GDF-15 remains unclear.

The current article describes our findings with respect to repeated measurements of several biomarkers, which we studied as prognostic markers for relevant clinical outcomes, with particular interest in the additional prognostic value of GDF-15 as part of a multimarker approach including NT-proBNP, ST2, galectin-3, troponin I, and creatinine. To this end, we used our TRIUMPH study (Translational Initiative on Unique and Novel Strategies for Management of Patients With HF), which was typically designed for this purpose; to identify and validate the prognostic value of temporal patterns of potentially relevant biomarkers in patients with acute HF.[4,5]

METHODS

Data Integrity and Sharing

The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Procedures

Full details of the TRIUMPH study have been published before[4,5] and are briefly mentioned here. TRIUMPH was a prospective, observational study conducted in 14 hospitals in the Netherlands between September 2009 and December 2013, enrolling patients admitted with acute HF. Patients were eligible if they were ≥18 years and hospitalized with a diagnosis of acute HF, either newly diagnosed or as an exacerbation of known, chronic HF. During hospitalization blood samples were collected at day 1 (admission), day 2 to 4, and on the day of discharge. Hereafter, blood samples were collected during regular outpatient follow-up visits at 2 to 4 weeks, 3, 6, and 9 to 12 months. The baseline blood sample was defined as the first measurement obtained within 48 hours after inclusion. HF status was assessed at each visit using New York Heart Association classification. Medication use was determined at discharge. Patients underwent physical examination, venipuncture, and imaging (including echocardiography), and all relevant variables were systematically measured during the scheduled moments described above. Follow-up was up to a maximum of 400 days after index admission to allow assessment of biomarker changes near the end point. The primary end point (PE) was the composite of all-cause mortality and HF hospitalization. The secondary outcome was all-cause mortality. An event adjudication committee, blinded to biomarker information, reviewed and adjudicated the study end points.

This study complies with the Declaration of Helsinki and was approved by the METC Erasmus MC institutional review board (MEC 2009-053) as well as the review boards at all other participating centers. It has been registered in the national trial register (NTR1893). All patients provided written informed consent before study procedures. The procedures followed were according to institutional guidelines. Patients received care as usual by the treating physician according to the prevailing HF guidelines at the time.[13] The treating physician was blinded to study-specific biomarker data, which was measured after study completion.

Blood Samples and Biomarker Measurements

Nonfasting blood samples were drawn by means of venipuncture and transported to the clinical chemistry laboratory of each participating center for further processing according to a standardized protocol. Samples were centrifuged at 1700 G/relative centrifugal force, after which heparin plasma and blood serum were separated. All blood aliquots were stored at a temperature of −80 °C within 2 hours after venipuncture.

All samples were measured in a single batch analysis of GDF-15, NT-proBNP, ST2, galectin-3, troponin I, and creatinine levels at a central laboratory. GDF-15 levels were determined in serum by the Cobas-e system using the Roche Diagnostics GDF-15 electro-chemiluminescent sandwich immunoassay (Elecsys GDF-15). NT-proBNP levels were determined in heparin plasma by using the Elecsys NT-proBNP electro-chemiluminescent sandwich immunoassay on a Cobas 8000 analyzer (Roche Diagnostics Ltd, Rotkreuz, Switzerland). ST2 levels were determined in serum using a quantitative sandwich monoclonal ELISA (Presage ST2 Assay; Critical Diagnostics Inc, San Diego, CA). Galectin-3 levels were determined in serum using the BGM galectin-3 Test (BG Medicine Inc, Waltham, MA). Troponin I levels were determined in heparin plasma on an Access 2 immunoassay system using the Access AccuTni assay procedure (Beckman Coulter Inc, Fullerton, CA). creatinine levels were determined in heparin plasma on the Cobas 8000 analyzer.

Analysts were blinded to patient characteristics and study end points.

Statistical Analysis

All continuous variables were non-normally distributed, as assessed by visual examination of histograms and Q-Q plots. Continuous variables are therefore presented as median and interquartile range (IQR), and differences in continuous variables between baseline GDF-15 quartiles were evaluated using the Jonckheere-Terpstra trend test. Categorical variables are presented as counts and percentages, and differences in categorical variables between baseline GDF-15 quartiles were evaluated with χ^2 trend tests using the Cochran-Armitage extension or the linear-by-linear association according to Mantel-Haenszel, as appropriate. The biomarkers were log-transformed and the correlation between biomarkers was calculated using Spearman correlation analyses. The log-transformed biomarkers were then standardized, and their Z-scores were used for longitudinal analyses.

The association between baseline biomarker measurement and study end points was assessed using Cox proportional hazards (PH) regression models. The PH assumption was evaluated based on the scaled Schoenfeld residuals. The association between repeated biomarker measurements and study end points was assessed using joint models, which combine a linear mixed effects model for the longitudinal evolution of the biomarker with a time-to-event model that relates the serially measured biomarker levels to the incidence of the end points.[14]

We ran the following models:

1. Univariable or unadjusted.
2. Adjusted for age, sex, systolic blood pressure, diabetes, left ventricular ejection fraction, previous HF hospitalization within last 6 months, ischemic HF etiology, body mass index, estimated glomerular filtration rate[15] (except in model with creatinine; clinical model).
3. Adjusted for clinical variables and NT-proBNP.
4. Adjusted for clinical variables and NT-proBNP plus an additional biomarker.
5. Only adjusted for all biomarkers (biomarker model).

The selection of potential confounders is based on previous analyses of TRIUMPH and represents some of the common variables also used in risk assessment tools like Meta-Analysis Global Group in Chronic HF[16] and Barcelona (BCN) Bio-HF calculator[17]. Both the linear mixed effects and Cox PH regression submodels were adjusted for the same variables. We used cubic splines with knots set at 1 week and 1 month after index admission for the linear mixed effects submodel, based on clinical data and biomarker evolution. The results of the models are presented as hazard ratios (HRs) per 1 SD difference of the biomarker level (on the log-scale) with 95% CIs. Measures of discrimination (C-index and area under the curve) are also presented for each of the models. The area under the curve was based on the "aucJM" function with measurements up to 7 days used to predict outcomes up to 30 days for short-term and similarly 30 to 400 days for long-term. Data on covariates were complete in at least 92%, except for left ventricular

ejection fraction with 78% completeness. Missing data in covariates were addressed by means of single imputation using the multivariate imputation by chained equations function.

For all tests, a $P<0.05$ was considered statistically significant. Data were analyzed using SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY) for data preparation and descriptive analyses. R Statistical Software version 3.6.3 (Vienna, Austria) was used for the main analyses; Cox regression analysis using the "survival" package, joint modelling with "mvJMBayes" function within the "JMBayes" package.[14]

RESULTS

Baseline Characteristics

The TRIUMPH cohort study enrolled 496 patients. However, 3 patients withdrew informed consent, whereas 18 patients were withdrawn from analysis due to a lack of evidence of sustained left ventricular dysfunction. Therefore, the analysis set included 475 patients; baseline characteristics are presented in Table 1. Median age was 74 years (IQR, 65–81), and 37% were women. The median left ventricular ejection fraction was 30% (IQR, 21–41), and most patients (83%) had HF with reduced ejection fraction according to the prevailing HF guidelines at the time[13] whereas this was 69% according to the updated guidelines.[2] More than half (55%) of the patients were in New York Heart Association class III. Median baseline levels of GDF-15, NT-proBNP, ST2, galectin-3, troponin I, and creatinine were 4632 pg/mL (IQR, 2859–7399), 4152 pg/mL (IQR, 2089–9387), 72 ng/mL (IQR, 47–103), 24 ng/mL (IQR, 18–34), 46 ng/mL (IQR, 24–99), and 126 µmol/L (IQR, 100–164), respectively.

Table 1 also shows the characteristics according to quartiles of baseline GDF-15. Kidney function was significantly worse in the highest quartile compared with the lowest (34 versus 63 mL/min per 1.73 m^2) and as expected, the prevalence of chronic kidney disease was higher (38% versus 7%; $P<0.001$). Similarly, more patients in the higher quartiles had undergone previous HF hospitalization in the last 6 months, had ischemic HF etiology and diabetes. Importantly, the opposite was true for patients with new-onset HF as nearly half of the patients in the lowest quartile of GDF-15 had new-onset HF compared with the highest (46% versus 22%; $P<0.001$). Most patients used diuretics (93%), beta-blocker (78%), or ACE-i/ARB (75%) and use of the latter was significantly lower in the highest quartile (67% versus 88%; $P=0.002$). Across the board, baseline biomarker levels were significantly higher in the highest quartile compared with the lowest.

Study End Points

The PE was reached in 188 (40%) of the patients during a median follow-up of 325 days (IQR, 85–401; Table 1). A total of 113 patients (24%) died of any cause (68% cardiovascular) during follow-up. In the highest GDF-15 quartile, 61% of the patients reached the PE, while this was 19% in the lowest ($P<0.001$). A similar pattern was observed for all-cause mortality.

Correlations Between Biomarkers

The correlation between all 6 biomarkers is shown in Figure 1. All biomarkers showed a near normal distribution on the log-scale. There was statistically significant correlation between all biomarkers on the log-scale. The correlation was strongest between GDF-15 and creatinine. The pairs GDF-15 and galectin-3, GDF-15 and ST2, as well as creatinine and galectin-3 also showed an association. Based on the coefficients, these relationships were moderate at best.

Baseline Measurement and Prognosis

The PH assumption of the Cox PH regression analyses appeared satisfied. Univariable HR (model 1) per 1 SD difference of GDF-15 for the PE was 1.67 ([95% CI, 1.39–2.02]; $P<0.001$; Table 2). According to the clinical model (2) the adjusted HR was 1.42 ([95% CI, 1.12–1.80]; $P=0.003$) and additionally adjusted for NT-proBNP (model 3) it was 1.28 ([95% CI, 1.00–1.63]; $P=0.05$). Jointly modeled with NT-proBNP, ST2, galectin-3, troponin I and creatinine (biomarker model 5) the HR was 1.41 ([95% CI, 1.11–1.80]; $P=0.005$). The multimarker model combining GDF-15, NT-proBNP, and troponin I provided a favorable risk discrimination (C-index=0.722) in comparison to a single-marker model. A similar pattern was observed for all-cause mortality (Table 3). Notably, the associations were stronger for the mortality end point than the composite PE. Overall, NT-proBNP was the strongest predictor and independently associated with the end points in all models followed by GDF-15 and ST2 as strong candidates. Furthermore, troponin I had significant incremental prognostic value for the mortality end point but not for the PE in combination model 4.

Repeated Measurements and Prognosis

The average number of repeated measurements per patient during follow-up was 3.6 for GDF-15, 3.9 for ST2 and 4.1 for NT-proBNP, galectin-3, troponin I, and creatinine. Figure 2 shows the longitudinal evolution of the average estimated GDF-15 level during index admission and during follow-up. The *x* axis is reversed in the bottom graph showing the period leading up to the PE or end of follow-up. The average estimated GDF-15 level was higher in patients who reached the PE versus those who did not and decreased during index admission in both groups following treatment for decompensation. The average estimated GDF-15 level increased weeks

Table 1. Characteristics and Study End Points Overall (n=475) and for Quartiles of Baseline GDF-15 Level (n=386)

	Overall	Q1	Q2	Q3	Q4	*P* value*
Demographic characteristics, median (IQR) or n (%)						
Age, y	74 (65–81)	70 (59–76)	76 (66–81)	75 (67–81)	73 (64–80)	0.029†
Sex, female	177 (37)	41 (42)	39 (41)	33 (34)	29 (30)	0.048†
Race, White	449 (95)	89 (92)	91 (95)	90 (94)	91 (94)	0.64
Intoxications, n (%)						
Smoking status						<0.001†
Current smoker	85 (18)	29 (30)	23 (25)	10 (11)	12 (12)	
Previous smoker	198 (43)	36 (37)	34 (37)	43 (46)	39 (40)	
Never smoker	179 (39)	32 (33)	36 (39)	40 (43)	46 (47)	
Alcohol abuse	57 (24)	9 (26)	6 (24)	6 (24)	6 (21)	0.57
Baseline measurements, median (IQR) or n (%)						
Body mass index, kg/m^2	27.5 (24.7–31.0)	27.4 (25.0–32.0)	26.8 (24.8–30.5)	28.1 (24.8–32.4)	26.8 (24.1–30.7)	0.58
Systolic blood pressure, mm Hg	125 (110–147)	129 (114–146)	130 (111–146)	130 (114–148)	116 (105–139)	0.014†
Diastolic blood pressure, mm Hg	74 (65–85)	80 (66–94)	71 (65–86)	75 (65–87)	70 (60–80)	0.003†
Heart rate, beats/min	85 (71–100)	90 (75–107)	85 (73–100)	86 (73–99)	80 (69–95)	0.010†
eGFR, mL/min per 1.73 m^2	46 (34–62)	63 (53–71)	49 (39–61)	43 (34–55)	34 (29–44)	<0.001†
Left ventricular ejection fraction, %	30 (21–41)	30 (20–40)	30 (23–42)	31 (25–45)	30 (20–41)	0.44
NYHA classification						0.010†
I	4 (1)	1 (1)	2 (2)	1 (1)	0 (0)	
II	76 (17)	28 (29)	16 (18)	8 (9)	11 (12)	
III	248 (55)	48 (50)	41 (45)	53 (58)	58 (63)	
IV	124 (27)	19 (20)	32 (35)	30 (33)	32 (25)	
History, n (%)						
Newly diagnosed heart failure	171 (36)	45 (46)	38 (40)	33 (35)	21 (22)	<0.001†
Heart failure with reduced ejection fraction‡	308 (83)	69 (88)	63 (86)	59 (82)	62 (82)	0.18
Heart failure with reduced ejection fraction§	254 (69)	58 (74)	50 (68)	46 (64)	54 (71)	0.54
Previous heart failure admission <6 mo	94 (20)	10 (10)	14 (15)	24 (25)	32 (33)	<0.001†
Ischemic heart failure	229 (49)	37 (38)	47 (49)	48 (51)	55 (57)	0.012†
Myocardial infarction	190 (40)	37 (38)	36 (38)	34 (35)	44 (45)	0.38
Hypertension	242 (51)	42 (43)	55 (57)	50 (52)	45 (46)	0.86
Atrial fibrillation	198 (42)	40 (41)	41 (43)	37 (39)	43 (44)	0.82
Diabetes	172 (36)	16 (16)	34 (35)	41 (43)	50 (52)	<0.001†
Stroke	81 (17)	13 (13)	16 (17)	16 (17)	15 (15)	0.71
Peripheral arterial disease	101 (21)	15 (15)	16 (17)	24 (25)	25 (26)	0.033†
Hypercholesterolemia	140 (30)	25 (26)	30 (31)	28 (29)	27 (28)	0.81
Chronic obstructive pulmonary disease	92 (20)	15 (15)	21 (22)	19 (20)	21 (20)	0.34
Obstructive sleep apnea syndrome	18 (4)	2 (2)	4 (4)	3 (3)	4 (4)	0.52
Chronic kidney disease	91 (19)	7 (7)	12 (12)	24 (25)	36 (38)	<0.001†
Episode of depression	31 (7)	10 (10)	5 (5)	5 (5)	5 (5)	0.17
Interventions, n(%)						
CABG	136 (29)	19 (20)	23 (24)	30 (41)	37 (48)	0.002†
Device implantation	141 (30)	31 (32)	24 (25)	27 (28)	34 (35)	0.56
ICD	81 (17)	13 (14)	12 (13)	14 (15)	27 (28)	0.008†
Pacemaker	58 (12)	17 (18)	11 (12)	12 (12)	8 (8)	0.07
CRT	26 (6)	5 (5)	5 (5)	6 (6)	6 (6)	0.70

(*Continued*)

Table 1. Continued

	Overall	Q1	Q2	Q3	Q4	*P* value*
Biomarkers (baseline), median (IQR)						
GDF-15, pg/mL	4632 (2859–7399)	2104 (1666–2447)	3752 (3341–4217)	5616 (5115–6226)	10323 (8468–16 725)	<0.001†
NT-proBNP, pg/mL	4152 (2127–9235)	2571 (1383–4749)	4042 (2072–7203)	5785 (2660–11 206)	8364 (4322–13 032)	<0.001†
ST2, ng/mL	72 (47–103)	50 (30–78)	72 (51–113)	83 (57–104)	94 (62–130)	<0.001†
Galectin-3, ng/mL	24 (18–34)	17 (15–21)	22 (18–28)	27 (20–34)	30 (23–38)	<0.001†
Troponin I, ng/mL	46 (24–99)	34 (19–77)	37 (22–81)	54 (35–128)	53 (24–95)	0.001†
Creatinine, µmol/L	126 (100–164)	100 (84–115)	118 (97–150)	135 (114–171)	161 (140–204)	<0.001†
Medication at discharge, n (%)						
ACE-i/ARB	330 (75)	82 (88)	67 (73)	65 (74)	61 (67)	0.002†
Beta-blocker	343 (78)	78 (84)	70 (76)	70 (80)	66 (73)	0.11
Diuretic	407 (93)	88 (95)	86 (93)	84 (95)	83 (91)	0.46
Digoxin	87 (20)	26 (28)	18 (20)	10 (11)	22 (24)	0.30
End points during follow-up, n (%)						
Primary end point‖	188 (40)	18 (19)	30 (31)	42 (44)	59 (61)	<0.001†
All-cause mortality	113 (24)	8 (8)	12 (12)	28 (29)	33 (34)	<0.001†

ACE-i indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; and ST2; suppression of tumorigenicity 2.

*P value for differences between quartiles of baseline GDF-15 level.

†Significant *P* values.

‡According to the European Society of Cardiology Heart Failure guidelines of 2012

§According to the European Society of Cardiology Heart Failure guidelines of 2016.

‖Primary end point is a composite of all-cause mortality and HF hospitalization.

before the PE was reached while levels remained stable in patients who did not reach the PE.

The univariable HR per 1 SD difference of GDF-15 for the PE was 2.14 ([95% CI, 1.78–2.57]; *P*<0.001; Table 4). According to the clinical model, the HR was 1.96 ([95% CI, 1.49–2.53]; *P*<0.001) and additionally adjusted for NT-proBNP it remained statistically significant. In the biomarker model, the HR was 1.44 ([95% CI, 1.05–1.91]; *P*=0.022). The multimarker model combining GDF-15, NT-proBNP, and troponin I provided a favorable risk discrimination (area under the curve=0.785) in comparison to a single-marker model. A largely similar pattern with stronger associations was observed for the mortality end point (Table 5). NT-proBNP was again the strongest predictor. Unlike the baseline analysis, serially measured troponin I had significant incremental prognostic value for the PE in the biomarker model and the association was largely driven by all-cause mortality. In both analyses, the additional prognostic value of galectin-3 and creatinine was mostly limited.

DISCUSSION

In this study of 475 patients with acute HF, we show that serially measured GDF-15 dynamically predicts the composite risk of all-cause mortality or HF rehospitalization during 1-year follow-up independent of several other serially measured biomarkers including NT-proBNP. Moreover, the multimarker model combining GDF-15, NT-proBNP, and troponin I provides a favorable risk discrimination. Troponin I provides incremental prognostic value mainly for all-cause mortality while galectin-3 and creatinine have limited additional value for both end points. Overall, NT-proBNP remains the robust predictor followed by GDF-15 and ST2.

GDF-15 reflects key processes like inflammation and cardiac remodeling in HF.[6,7] Previous studies have shown the prognostic value of baseline GDF-15 level for HF outcome.[8] Studies that have analyzed elevated GDF-15 specifically in patients with acute HF are limited in number.[10,18–20] Unlike a single timepoint-based measurement, repeated measurements take into account the temporal evolution as a result of the dynamic natural disease progression. Our study underscores the usefulness of repeated measurements GDF-15, which provided a better risk discrimination than a single (baseline) measurement alone. This is in accordance with the limited number of studies.[10–12] Fluschnik et al[11] demonstrated only a slight improvement with repeated measurements compared with our study, but there was a large interval between measurements, which could explain this discrepancy. A more frequent sampling schedule seems to be required to detect changes in biomarker level and assess risk adequately. As such, the temporal pattern revealed average GDF-15 level increased in the weeks leading up to the PE, whereas it stabilized in patients

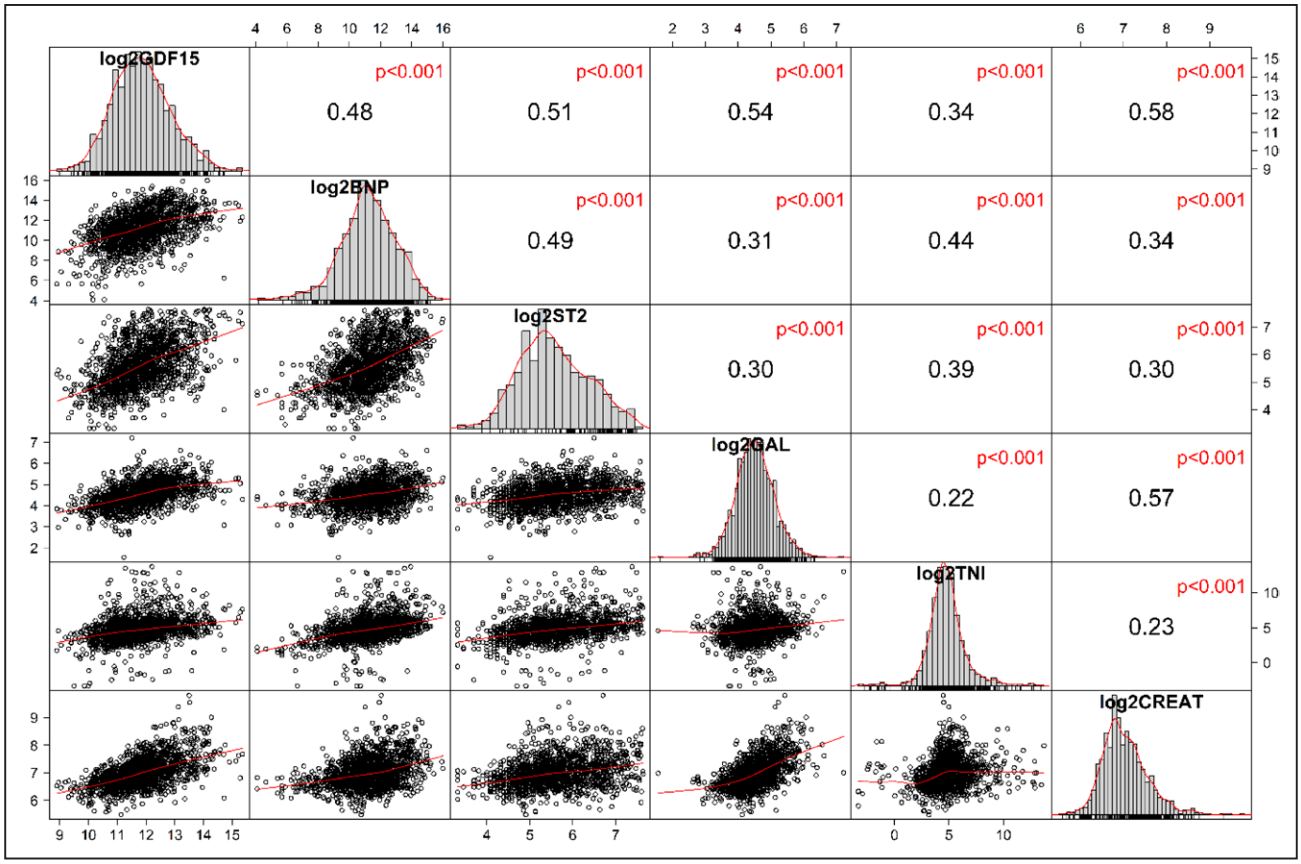

Figure 1. Correlation plot of all biomarkers.

Correlation plot showing the associations between biomarkers based on the log-transformed values. Diagonally depicted are the individual distributions of the biomarkers. Below the diagonal are presented the scatter plots of the correlations between biomarkers, and above the diagonal are presented the corresponding Spearman correlation coefficients with *P* values. BNP indicates N-terminal pro-B-type natriuretic peptide; CREAT, creatinine; GAL, galectin-3; GDF15, growth differentiation factor 15; log2, logarithm to the base 2; ST2, suppression of tumorigenicity 2; and TNI, troponin I.

who were event-free. A similar trend was observed for NT-proBNP,[4] ST2,[4] and galectin-3[5] in previous analyses of TRIUMPH. In the current study, serially measured troponin I was significantly associated with the PE but not baseline measurement, further supporting this notion.

Both baseline and repeated measurements of GDF-15 have been shown to have incremental prognostic value over NT-proBNP, the golden standard biomarker in HF.[10,12,18,20–22] Likewise, in our study, repeated measurements of GDF-15 were associated with the outcomes independent of repeated measurements of NT-proBNP. This further denotes several, different underlying pathophysiological pathways contribute to HF progression and suggests that GDF-15 as a marker of inflammation[6] provides additional information compared with NT-proBNP, which reflects volume overload and myocardial stretch.[23,24] To properly assess the incremental prognostic value of serially measured GDF-15 and more accurately predict HF risk, a multimarker approach with additional biomarkers is necessary. An analysis of 14 serum biomarkers in the Bio-SHiFT study in patients with chronic HF showed a strong association of repeated measurements of GDF-15, NT-proBNP, and ST2 with the composite end point of CV mortality, heart transplantation, left ventricular assisted device and HF hospitalization.[9] However, these associations were only analyzed separately in a clinical model and a biomarker-adjusted only model as opposed to our study where we also combined both into 1 single model. In the multimarker analysis of 7 circulating makers in the study performed by Demissei et al,[10] in patients with acute HF, the combination of GDF-15, NT-proBNP, soluble ST2, and Hs-TnT (high-sensitive troponin T) provided significant and independent prognostic information on cardiovascular mortality. Our results show that the combination of GDF-15, NT-proBNP, and troponin I provided a favorable risk discrimination for the end points, further emphasizing the utility of joint analysis of multiple biomarkers to capture several different underlying pathways. GDF-15 was not significant in model 4 with ST2 included, possibly due to correlation or synergistic pathways and the lower area under the curve, especially on the long term, indicates more ST2 measurements are needed as the event nears to properly assess risk.

Notably, GDF-15 was more strongly associated with the mortality end point than with the PE that also includes HF hospitalization, which is in line

Table 2. Association of Baseline Measurement of Biomarkers With the Primary End Point

Model*	GDF-15	NT-proBNP	ST2	Galectin-3	Troponin I†	Creatinine	C-index
1: Single biomarker, unadjusted	1.67 (1.39–2.02)						0.636
	P<0.001‡						
2: Single biomarker, adjusted for clinical variables (clinical model)	1.42 (1.12–1.80)						0.696
	P=0.003‡						
		1.68 (1.27–2.21)					0.707
		P<0.001‡					
			1.35 (1.11–1.63)				0.698
			P=0.002‡				
				1.11 (0.88–1.40)			0.683
				P=0.38			
					1.10 (0.95–1.27)		0.694
					P=0.19		
						1.56 (1.16–1.92)	0.682
						P<0.001‡	
3: Two biomarkers, adjusted for clinical variables	1.28 (1.00–1.63)	1.55 (1.17–2.06)					0.714
	P=0.05	*P*=0.003‡					
		1.54 (1.16–2.05)	1.25 (1.03–1.52)				0.713
		P=0.003‡	*P*=0.025‡				
		1.66 (1.26–2.20)		1.06 (0.84–1.34)			0.707
		P<0.001‡		*P*=0.64			
		1.70 (1.27–2.26)			1.06 (0.91–1.23)		0.718
		P<0.001‡			*P*=0.47		
		1.62 (1.22–2.14)				1.31 (1.05–1.65)	0.707
		P<0.001‡				*P*=0.019‡	
4: Three biomarkers, adjusted for clinical variables	1.23 (0.96–1.57)	1.47 (1.10–1.96)	1.22 (1.00–1.49)				0.713
	P=0.10	*P*=0.009‡	*P*=0.046‡				
	1.27 (0.99–1.63)	1.55 (1.16–2.06)		1.04 (0.82–1.31)			0.713
	P=0.06	*P*=0.003‡		*P*=0.76			
	1.35 (1.05–1.75)	1.54 (1.15–2.07)			1.07 (0.92–1.25)		0.722
	P=0.021‡	*P*=0.004‡			*P*=0.39		
	1.25 (0.97–1.59)	1.51 (1.13–2.02)				1.20 (0.94–1.54)	0.714
	P=0.08	*P*=0.005‡				*P*=0.15	
5: Six biomarkers, unadjusted (biomarker model)	1.41 (1.11–1.80)	1.33 (1.00–1.76)	1.20 (0.98–1.46)	0.98 (0.78–1.24)	1.03 (0.89–1.20)	1.10 (0.88–1.38)	0.679
	P=0.005‡	*P*=0.048‡	*P*=0.08	*P*=0.89	*P*=0.66	*P*=0.40	

Hazard ratios for the primary end point (composite of all-cause mortality and HF hospitalization) per 1 SD difference of baseline biomarker level (on the log scale) with corresponding (95% CIs) and *P* value. GDF-15 indicates growth differentiation factor 15; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and ST2, suppression of tumorigenicity 2.

*Clinical variables: age, sex, systolic blood pressure, diabetes, left ventricular ejection fraction, previous HF hospitalization within the last 6 months, ischemic HF etiology, body mass index, and estimated glomerular filtration rate (except in models including creatinine).

†Patients who had an ischemic event and/or underwent revascularization during index admission (n=18) were excluded from models including troponin I.

‡Significant *P* value.

with previous literature.[25] This phenomenon was also observed for other biomarkers, especially troponin I, which is a marker of cardiomyocyte injury or necrosis.[26] While it is routinely used in the diagnosis of acute coronary syndrome, previous studies have also shown the prognostic value of (isoforms of) this marker in HF.[27,28] A study of 238 patients with advanced HF even found a relative risk of 2 for mortality after adjustment for clinical factors and BNP.[29] Our observations confirm this independent prognostic utility of serially measured troponin I. It appears that elevated levels could possibly provide insight into the severity and etiology of acute decompensation.

Galectin-3 is another marker of systemic inflammation and fibrosis[30] and was significantly and independently associated with adverse outcome in previous studies.[5,31]

Table 3. Association of Baseline Measurement of Biomarkers With All-Cause Mortality

Model*	GDF-15	NT-proBNP	ST2	Galectin-3	Troponin I†	Creatinine	C-index
1: Single biomarker, unadjusted	1.84 (1.42–2.39)						0.649
	P<0.001‡						
2: Single biomarker, adjusted for clinical variables (clinical model)	1.58 (1.14–2.20)	2.29 (1.50–3.50)					0.744
	P=0.006‡	*P*<0.001‡					0.768
			1.65 (1.24–2.20)				0.756
			P<0.001‡				
				1.15 (0.83–1.58)			0.729
				P=0.41			
					1.26 (1.06–1.51)		0.753
					P=0.010‡		
						1.80 (1.32–2.45)	0.728
						P<0.001‡	
3: Two biomarkers, adjusted for clinical variables	1.41 (1.00–1.99)	2.11 (1.37–3.24)					0.772
	P=0.047‡	*P*<0.001‡					
		1.99 (1.30–3.07)	1.49 (1.11–1.99)				0.780
		P=0.002‡	*P*=0.007‡				
		2.27 (1.48–3.47)		1.10 (0.79–1.53)			0.768
		P<0.001‡		*P*=0.56			
		2.21 (1.43–3.43)			1.19 (0.98–1.44)		0.782
		P<0.001‡			*P*=0.08		
		2.19 (1.43–3.36)				1.36 (0.97–1.90)	0.766
		P<0.001‡				*P*=0.07	
4: Three biomarkers, adjusted for clinical variables	1.35 (0.96–1.89)	1.91 (1.25–2.94)	1.46 (1.09–1.96)				0.783
	P=0.08	*P*=0.003‡	*P*=0.011‡				
	1.40 (1.00–1.98)	2.11 (1.37–3.23)		1.07 (0.77–1.49)			0.773
	P=0.05	*P*<0.001‡		*P*=0.69			
	1.51 (1.06–2.15)	2.02 (1.30–3.13)			1.23 (1.01–1.50)		0.787
	P=0.024‡	*P*=0.002‡			*P*=0.038‡		
	1.37 (0.97–1.92)	2.04 (1.32–3.14)				1.19 (0.83–1.72)	0.771
	P=0.07	*P*=0.001‡				*P*=0.35	
5: Six biomarkers, unadjusted (biomarker model)	1.42 (1.01–1.99)	1.62 (1.08–2.44)	1.46 (1.09–1.94)	1.13 (0.84–1.53)	1.17 (0.97–1.41)	0.95 (0.70–1.29)	0.745
	P=0.042‡	*P*=0.021‡	*P*=0.010‡	*P*=0.41	*P*=0.10	*P*=0.73	

Hazard ratios for all-cause mortality per 1 SD difference of baseline biomarker level (on the log scale) with corresponding (95% CIs) and *P* value. GDF-15 indicates growth differentiation factor 15; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and ST2, suppression of tumorigenicity 2.

*Clinical variables: age, sex, systolic blood pressure, diabetes, left ventricular ejection fraction, previous HF hospitalization within the last 6 months, ischemic HF etiology, body mass index, and estimated glomerular filtration rate (except in models including creatinine).

†Patients who had an ischemic event and/or underwent revascularization during index admission (n=18) were excluded from models including troponin I.

‡Significant *P* value.

However, in our study, its incremental prognostic value was limited when jointly modeled with other biomarkers. This might be due to its more systemic and less cardiospecific nature.

Increases in creatinine, a measure of kidney function, were associated with higher 30-day mortality or HF hospitalization in patients admitted with acute HF.[32] However, creatinine also had limited prognostic value in our study after extensive adjustment. Nevertheless, creatinine remains important considering the close relation with HF and as a confounder due to the influence of renal clearance on biomarker levels.

HF remains a complex disease but despite GDF-15 being a pleiotropic protein involved in several pathological conditions,[34] it enables us to elucidate the disease status and impact on cardiac functioning. Noteworthy to mention is that GDF-15 has a lower intraindividual biological variation compared with NT-proBNP,[35,36] which is even lower in ST2, Hs-TnT, and galectin-3.[37] Therefore, the combination of biomarkers would more reliably

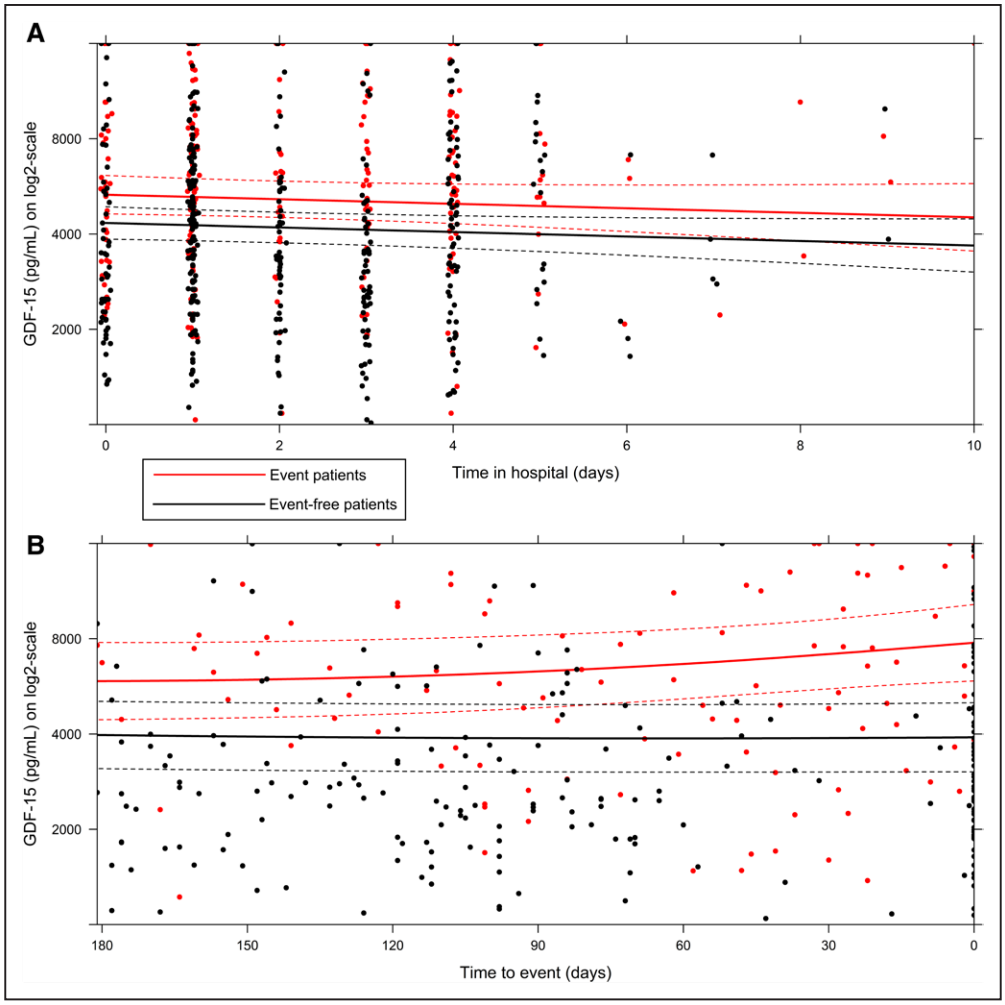

Figure 2. Temporal pattern of average estimated GDF-15 (growth differentiation factor 15) level during index admission and follow-up in patients with and without the primary end point.

A, Longitudinal evolution of average estimated GDF-15 level during index admission. **B**, Longitudinal evolution of average estimated GDF-15 level during follow-up until the event or end of follow-up. Patients who reached the primary end point during follow-up are shown in red and those who did not in black. The *y* axis is on a logarithmic scale with the raw values shown. Solid bold lines represent mean values; dashed lines represent the corresponding 95% CI. Dots represent individual measurements. The average GDF-15 level is based on a linear mixed effects model adjusted for age, sex, systolic blood pressure, diabetes, left ventricular ejection fraction, previous heart failure (HF) hospitalization within last 6 months, ischemic HF etiology, body mass index, estimated glomerular filtration rate, and NT-proBNP (N-terminal pro-B-type natriuretic peptide). log2 indicates logarithm to the base 2. Adapted from Abstracts of the Heart Failure 2021 and the World Congress on Acute Heart Failure[33] with permission. Copyright ©2021, European Society of Cardiology.

predict risk on an individual patient-level than relying on a single marker.

Clinical Implications and Future Research

Based on our findings, a combination of multiple, serially measured biomarkers could play a role in risk stratification in clinical practice to discriminate between patients at low or high risk for adverse outcomes. This individualized risk assessment could be performed with a mobile/online calculator app much like the Barcelona Bio-Heart Failure risk calculator to provide up-to-date risk scores based on repeated biomarker levels and clinical confounders, hereby facilitating clinical decision-making. Furthermore, they could also prove useful in monitoring of patients as medical therapy seems to lower the levels of GDF-15 as shown in the RELAX-AHF trial (Relaxin in Acute HF), a double-blinded randomized controlled trial where patients received serelaxin versus placebo.[19] In the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III HF Patients trial (CHAMPION), CardioMEMS sensor invasively measured and successfully identified HF patients with elevated pulmonary pressures up to 2 weeks before decompensation allowing the physician to uptitrate medication to prevent clinical worsening and subsequent hospitalization.[38] In our study, the longitudinal evolution of GDF-15 revealed a similar unique window to potentially, noninvasively anticipate adverse events and intervene accordingly. More research

Table 4. Association of Repeated Measurements of Biomarkers With the Primary End Point

Model*	GDF-15	NT-proBNP	ST2	Galectin-3	Troponin I†	Creatinine	AUCs‡	AUCI‡
1: Single biomarker, unadjusted	2.14 (1.78–2.57)						0.678	0.699
	P<0.001§							
2: Single biomarker, adjusted for clinical variables (clinical model)	1.96 (1.49–2.53)						0.741	0.713
	P<0.001§							
		2.38 (1.78–3.33)					0.763	0.712
		P<0.001§						
			2.58 (1.60–4.57)				0.727	0.679
			P<0.001§					
				1.56 (1.15–2.10)			0.736	0.688
				P=0.006§				
					1.70 (1.25–2.26)		0.781	0.695
					P<0.001§			
						1.71 (1.36–2.11)	0.718	0.682
						P<0.001§		
3: Two biomarkers, adjusted for clinical variables	1.98 (1.43–2.79)	2.26 (1.55–3.42)					0.737	0.668
	P<0.001§	*P*<0.001§						
		2.04 (1.48–2.83)	1.79 (1.27–2.53)				0.794	0.704
		P<0.001§	*P*<0.001§					
		2.27 (1.65–3.14)		1.21 (0.87–1.66)			0.766	0.731
		P<0.001§		*P*=0.24				
		2.25 (1.65–3.28)			1.39 (1.03–1.87)		0.786	0.726
		P<0.001§			*P*=0.042§			
		2.20 (1.64–2.92)				1.26 (0.99–1.58)	0.760	0.733
		P<0.001§				*P*=0.06		
4: Three biomarkers, adjusted for clinical variables	1.29 (0.73–2.07)	2.12 (1.38–3.55)	2.12 (1.11–4.87)				0.750	0.676
	P=0.33	*P*<0.001§	*P*=0.012§					
	1.63 (1.21–2.20)	1.89 (1.37–2.76)		1.23 (0.85–1.76)			0.768	0.729
	P=0.002§	*P*<0.001§		*P*=0.28				
	1.43 (1.03–2.00)	1.84 (1.27–2.75)			1.32 (0.92–1.87)		0.785	0.724
	P=0.022§	*P*<0.001§			*P*=0.14			
	1.51 (1.12–1.96)	2.00 (1.48–2.78)				1.06 (0.81–1.39)	0.771	0.734
	P=0.006§	*P*<0.001§				*P*=0.64		
5: Six biomarkers, unadjusted (biomarker model)	1.44 (1.05–1.91)	1.52 (1.15–2.08)	1.34 (0.98–1.85)	1.06 (0.79–1.47)	1.39 (1.01–1.93)	0.96 (0.74–1.22)	0.743	0.720
	P=0.022§	*P*=0.002§	*P*=0.06	*P*=0.69	*P*=0.044§	*P*=0.72		

Hazard ratios for the primary end point (composite of all-cause mortality and HF hospitalization) per 1 SD difference of repeatedly measured biomarker level (on the log scale) with corresponding (95% CIs) and *P* value. This represents the instantaneous risk for the end point at any given timepoint during follow-up. AUC indicates area under the curve; AUCI, area under the curve incremental; GDF-15, growth differentiation factor 15; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and ST2, suppression of tumorigenicity 2.

*Clinical variables: age, sex, systolic blood pressure, diabetes, left ventricular ejection fraction, previous HF hospitalization within the last 6 months, ischemic HF etiology, body mass index, and estimated glomerular filtration rate (except in models including creatinine).

†Patients who had an ischemic event and/or underwent revascularization during index admission (n=18) were excluded from models including troponin I.

‡AUCs: short-term (longitudinal information up to 7-day prediction until 30 days); AUCI: long-term (30–400 days).

§Significant *P* value.

into biomarker level-guided treatment of HF is therefore warranted.[39]

Strengths and Limitations

In this large, prospective, cohort study, specifically designed for the purpose of studying clinically relevant biomarkers in patients with acute HF, patients underwent a protocolized high-frequency (7) blood sampling during 1-year follow-up. Furthermore, a comprehensive overview is given with the analysis of both single and repeated measurements of multiple biomarkers further underscoring the merit of sequentially measuring a combination of biomarkers. Also, state-of-the-art statistical

Table 5. Association of Repeated Measurements of Biomarkers With All-Cause Mortality

Model*	GDF-15	NT-proBNP	ST2	Galectin-3	Troponin I†	Creatinine	AUCs‡	AUCI‡
1: Single biomarker, unadjusted	2.58 (1.95–3.33)						0.741	0.689
	P<0.001§							
2: Single biomarker, adjusted for clinical variables (clinical model)	2.61 (1.85–3.81)						0.734	0.752
	P<0.001§							
		3.38 (2.25–5.39)					0.799	0.759
		P<0.001§						
			3.90 (2.53–6.93)				0.733	0.733
			P<0.001§					
				1.70 (1.15–2.61)			0.625	0.749
				P=0.010§				
					2.55 (1.77–3.65)		0.759	0.768
					P<0.001§			
						1.70 (1.32–2.17)	0.639	0.719
						P=0.002§		
3: Two biomarkers, adjusted for clinical variables	2.08 (1.39–3.11)	2.53 (1.66–4.34)					0.822	0.779
	P=0.002§	*P*<0.001§						
		2.44 (1.57–3.88)	2.55 (1.61–4.05)				0.815	0.763
		P<0.001§	*P*<0.001§					
		3.12 (2.03–4.77)		1.29 (0.86–1.93)			0.790	0.781
		P<0.001§		*P*=0.21				
		2.37 (1.56–3.66)			1.90 (1.31–2.84)		0.817	0.802
		P<0.001§			*P*=0.004§			
		3.48 (2.22–5.47)				1.02 (0.72–1.43)	0.783	0.774
		P<0.001§				*P*=0.82		
4: Three biomarkers, adjusted for clinical variables	1.66 (1.03–2.59)	2.46 (1.53–4.13)	2.02 (1.23–3.36)				0.841	0.769
	P=0.042§	*P*<0.001§	*P*=0.006§					
	1.84 (1.21–2.79)	2.50 (1.56–4.06)		1.13 (0.72–1.78)			0.810	0.779
	P=0.012§	*P*<0.001§		*P*=0.58				
	1.87 (1.32–3.02)	1.84 (1.18–3.00)			2.12 (1.33–3.28)		0.836	0.795
	P=0.002§	*P*=0.010§			*P*<0.001§			
	2.07 (1.34–3.18)	2.82 (1.80–4.52)				0.76 (0.51–1.10)	0.817	0.780
	P<0.001§	*P*<0.001§				*P*=0.15		
5: Six biomarkers, unadjusted (biomarker model)	1.48 (0.92–2.29)	1.86 (1.16–3.04)	1.97 (1.17–3.40)	1.17 (0.80–1.74)	1.91 (1.20–2.88)	0.67 (0.45–0.96)	0.881	0.745
	P=0.11	*P*=0.008§	*P*=0.016§	*P*=0.48	*P*=0.010§	*P*=0.030§		

Hazard ratios for all-cause mortality per 1 SD difference of repeatedly measured biomarker level (on the log scale) with corresponding (95% CIs) and *P* value. This represents the instantaneous risk for the end point at any given timepoint during follow-up. AUC indicates area under the curve; AUCI, area under the curve incremental; GDF-15, growth differentiation factor 15; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and ST2, suppression of tumorigenicity 2.

*Clinical variables: age, sex, systolic blood pressure, diabetes, left ventricular ejection fraction, previous HF hospitalization within the last 6 months, ischemic HF etiology, body mass index, and estimated glomerular filtration rate (except in models including creatinine).

†Patients who had an ischemic event and/or underwent revascularization during index admission (n=18) were excluded from models including troponin I.

‡AUCs: short term (longitudinal information up to 7-day prediction until 30 days); AUCI: long term (30–400 days).

§Significant *P* value.

methods are applied to study the complex data that were generated by these measurements in relation to the incidence of clinically relevant end points.

Still, several limitations should also be acknowledged. First, TRIUMPH was an observational study in which the treating physician was recommended to provide HF management according to the prevailing guidelines[13]; however, adherence to these guidelines was not explicitly checked. Guideline-directed medical therapy has also been updated since (including quadruple therapy)[40] and could therefore also affect our results and generalizability of our findings to a contemporary cohort. Furthermore, while the observational nature of the study (no stringent exclusion criteria) allowed a wide range of consecutive patients to be included, the cohort might not be fully representative of the HF population at large, for example,

37% of the patients were women. Although, despite this difference in sex distribution, we did not observe an important relation of sex on the association between the biomarkers and outcomes. Finally, while the large number of events and measurements available enabled us to run various multimarker models with adjustment for a multitude of potential confounders, we were ultimately limited by model performance (convergence) and therefore we cannot exclude the possibility of residual confounding.

Conclusions

This multimarker analysis of the TRIUMPH study shows that repeated measurements of GDF-15 are associated with adverse outcomes in patients with acute HF, independent of several other biomarkers including NT-proBNP, which remained the most robust predictor. The multimarker model combining GDF-15, NT-proBNP, and troponin I provided a favorable risk discrimination for the end points. Our findings underscore the usefulness of both repeated measurements and a multimarker panel for improved individual patient-level prognostication. Additional studies are warranted to evaluate if these biomarkers can be (jointly) used for patient-tailored guided therapy.

ARTICLE INFORMATION

Received January 14, 2022; accepted August 19, 2022.

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Acknowledgments

The authors thank all participating centers for carrying out the study procedures and data collection. All authors have read and approved the final version of the article.

Sources of Funding

This work was supported within the framework of the Center for Translational Molecular Medicine, project TRIUMPH (grant 01C-103).

Disclosures

Dr Asselbergs is supported by University College London Hospitals NIH and Care Research Biomedical Research Center. Dr Orsel is an employee of Philips Healthcare. Dr Pinto serves as a consultant and speaker for biotechnology and pharmaceutical companies that develop molecules that target myocardial disease, including Pfizer, Roche, Novartis, and Forbion. Dr Pinto is named inventor on patents related to cardiomyopathy therapy and holds minor shares (<5%) and spin-off aimed at developing therapies for heart disease. All other authors have nothing to disclose.

REFERENCES

1. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004-2016. *BMC Cardiovasc Disord*. 2018;18:74. doi: 10.1186/s12872-018-0815-3
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128
3. Ahmad T, Fiuzat M, Pencina MJ, Geller NL, Zannad F, Cleland JG, Snider JV, Blankenberg S, Adams KF, Redberg RF, et al. Charting a roadmap for heart failure biomarker studies. *JACC Heart Fail*. 2014;2:477–488. doi: 10.1016/j.jchf.2014.02.005
4. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, Orsel JG, Westenbrink BD, Brunner-la Rocca HP, van Miltenburg AJM, Boersma E, et al. Prognostic value of serial ST2 measurements in patients with acute heart failure. *J Am Coll Cardiol*. 2017;70:2378–2388. doi: 10.1016/j.jacc.2017.09.026
5. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, de Boer RA, Asselbergs FW, Wajon EMCJ, Orsel JG, Boersma E, et al. Prognostic value of serial Galectin-3 measurements in patients with acute heart failure. *J Am Heart Assoc*. 2017;6:e003700. doi: 10.1161/JAHA.116.003700
6. Breit SN, Johnen H, Cook AD, Tsai VW, Mohammad MG, Kuffner T, Zhang HP, Marquis CP, Jiang L, Lockwood G, et al. The TGF-β superfamily cytokine, MIC-1/GDF15: a pleotrophic cytokine with roles in inflammation, cancer and metabolism. *Growth Factors*. 2011;29:187–195. doi: 10.3109/08977194.2011.607137
7. Wesseling M, de Poel JHC, de Jager SCA. Growth differentiation factor 15 in adverse cardiac remodelling: from biomarker to causal player. *ESC Heart Fail*. 2020;7:1488–1501. doi: 10.1002/ehf2.12728
8. Zeng X, Li L, Wen H, Bi Q. Growth-differentiation factor 15 as a predictor of mortality in patients with heart failure: a meta-analysis. *J Cardiovasc Med (Hagerstown)*. 2017;18:53–59. doi: 10.2459/JCM.0000000000000412
9. Bouwens E, Brankovic M, Mouthaan H, Baart S, Rizopoulos D, van Boven N, Caliskan K, Manintveld O, Germans T, van Ramshorst J, et al. Temporal patterns of 14 blood biomarker candidates of cardiac remodeling in relation to prognosis of patients with chronic heart failure-The Bio- SH i FT study. *J Am Heart Assoc*. 2019;8:e009555. doi: 10.1161/JAHA.118.009555
10. Demissei BG, Cotter G, Prescott MF, Felker GM, Filippatos G, Greenberg BH, Pang PS, Ponikowski P, Severin TM, Wang Y, et al. A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. *Eur J Heart Fail*. 2017;19:1001–1010. doi: 10.1002/ejhf.749
11. Fluschnik N, Ojeda F, Zeller T, Jørgensen T, Kuulasmaa K, Becher PM, Sinning C, Blankenberg S, Westermann D. Predictive value of long-term changes of growth differentiation factor-15 over a 27-year-period for heart failure and death due to coronary heart disease. *PLoS One*. 2018;13:e0197497. doi: 10.1371/journal.pone.0197497
12. Liu JX, Li YP, Liu BH, Zhao XJ, Zhang ZY, Wang JD, Jia Q, Liu CL, Gao XJ, Xu ZG, et al. Repeated measurement of growth-differentiation factor-15 in Chinese Han patients with post-myocardial infarction chronic heart failure. *J Geriatr Cardiol*. 2018;15:618–627. doi: 10.11909/j.issn.1671-5411.2018.10.002
13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787–1847. doi: 10.1093/eurheartj/ehs104
14. Rizopoulos D. The R package JMbayes for fitting joint models for longitudinal and time-to-event data using MCMC. *J Stat Softw*. 2016;72:46. doi: 10.18637/jss.v072.i07
15. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function–measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;354:2473–2483. doi: 10.1056/NEJMra054415

16. Rich JD, Burns J, Freed BH, Maurer MS, Burkhoff D, Shah SJ. Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: validation of a simple tool for the prediction of morbidity and mortality in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2018;7:e009594. doi: 10.1161/JAHA.118.009594
17. Bayés-Genís A, Lupón J. The barcelona Bio-HF calculator: a contemporary web-based heart failure risk score. *JACC Heart Fail*. 2018;6:808–810. doi: 10.1016/j.jchf.2018.06.001
18. Bettencourt P, Ferreira-Coimbra J, Rodrigues P, Marques P, Moreira H, Pinto MJ, Guimarães JT, Lourenço P. Towards a multi-marker prognostic strategy in acute heart failure: a role for GDF-15. *ESC Heart Fail*. 2018;5:1017–1022. doi: 10.1002/ehf2.12301
19. Cotter G, Voors AA, Prescott MF, Felker GM, Filippatos G, Greenberg BH, Pang PS, Ponikowski P, Milo O, Hua TA, et al. Growth differentiation factor 15 (GDF-15) in patients admitted for acute heart failure: results from the RELAX-AHF study. *Eur J Heart Fail*. 2015;17:1133–1143. doi: 10.1002/ejhf.331
20. Hao J, Cheang I, Zhang L, Wang K, Wang HM, Wu QY, Zhou YL, Zhou F, Xu DJ, Zhang HF, et al. Growth differentiation factor-15 combined with N-terminal prohormone of brain natriuretic peptide increase 1-year prognosis prediction value for patients with acute heart failure: a prospective cohort study. *Chin Med J (Engl)*. 2019;132:2278–2285. doi: 10.1097/CM9.0000000000000449
21. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, Kuskowski M, Cohn JN, Drexler H, Wollert KC. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. *Circulation*. 2010;122:1387–1395. doi: 10.1161/CIRCULATIONAHA.109.928846
22. Kempf T, von Haehling S, Peter T, Allhoff T, Cicoira M, Doehner W, Ponikowski P, Filippatos GS, Rozentryt P, Drexler H, et al. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol*. 2007;50:1054–1060. doi: 10.1016/j.jacc.2007.04.091
23. Gangji AS, Helal BA, Churchill DN, Brimble KS, Margetts PJ. Association between N-terminal propeptide B-type natriuretic peptide and markers of hypervolemia. *Perit Dial Int*. 2008;28:308–311. doi: 10.1177/089686080802800319
24. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis*. 2005;46:610–620. doi: 10.1053/j.ajkd.2005.06.017
25. Chan MM, Santhanakrishnan R, Chong JP, Chen Z, Tai BC, Liew OW, Ng TP, Ling LH, Sim D, Leong KT, et al. Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail*. 2016;18:81–88. doi: 10.1002/ejhf.431
26. Wettersten N, Maisel A. Role of cardiac troponin levels in acute heart failure. *Card Fail Rev*. 2015;1:102–106. doi: 10.15420/cfr.2015.1.2.102
27. Felker GM, Mentz RJ, Teerlink JR, Voors AA, Pang PS, Ponikowski P, Greenberg BH, Filippatos G, Davison BA, Cotter G, et al. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail*. 2015;17:1262–1270. doi: 10.1002/ejhf.341
28. Peacock WF 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH; ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358:2117–2126. doi: 10.1056/NEJMoa0706824
29. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833–838. doi: 10.1161/01.CIR.0000084543.79097.34
30. de Boer RA, Yu L, van Veldhuisen DJ. Galectin-3 in cardiac remodeling and heart failure. *Curr Heart Fail Rep*. 2010;7:1–8. doi: 10.1007/s11897-010-0004-x
31. van Kimmenade RR, Januzzi JL Jr, Ellinor PT, Sharma UC, Bakker JA, Low AF, Martinez A, Crijns HJ, MacRae CA, Menheere PP, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. *J Am Coll Cardiol*. 2006;48:1217–1224. doi: 10.1016/j.jacc.2006.03.061
32. Metra M, Cotter G, Senger S, Edwards C, Cleland JG, Ponikowski P, Cursack GC, Milo O, Teerlink JR, Givertz MM, et al. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post hoc analysis of the PROTECT data. *Circ Heart Fail*. 2018;11:e004644. doi: 10.1161/CIRCHEARTFAILURE.117.004644
33. Abstracts of the Heart Failure 2021 and the World Congress on Acute Heart Failure, 29 June–1 July 2021, Online Congress. *Eur J Heart Fail*. 2021;23 Suppl 2:2–322. doi: 10.1002/ejhf.2297
34. Arkoumani M, Papadopoulou-Marketou N, Nicolaides NC, Kanaka-Gantenbein C, Tentolouris N, Papassotiriou I. The clinical impact of growth differentiation factor-15 in heart disease: a 2019 update. *Crit Rev Clin Lab Sci*. 2020;57:114–125. doi: 10.1080/10408363.2019.1678565
35. Frankenstein L, Remppis A, Frankenstein J, Hess G, Zdunek D, Gut S, Slottje K, Katus HA, Zugck C. Reference change values and determinants of variability of NT-proANP and GDF15 in stable chronic heart failure. *Basic Res Cardiol*. 2009;104:731–738. doi: 10.1007/s00395-009-0027-1
36. Oremus M, McKelvie R, Don-Wauchope A, Santaguida PL, Ali U, Balion C, Hill S, Booth R, Brown JA, Bustamam A, et al. A systematic review of BNP and NT-proBNP in the management of heart failure: overview and methods. *Heart Fail Rev*. 2014;19:413–419. doi: 10.1007/s10741-014-9440-0
37. Meijers WC, van der Velde AR, Muller Kobold AC, Dijck-Brouwer J, Wu AH, Jaffe A, de Boer RA. Variability of biomarkers in patients with chronic heart failure and healthy controls. *Eur J Heart Fail*. 2017;19:357–365. doi: 10.1002/ejhf.669
38. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet*. 2016;387:453–461. doi: 10.1016/S0140-6736(15)00723-0
39. Kimmoun A, Cotter G, Davison B, Takagi K, Addad F, Celutkiene J, Chioncel O, Solal AC, Diaz R, Damasceno A, et al. Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF): rationale and design for a multicentre, randomized, parallel-group study. *Eur J Heart Fail*. 2019;21:1459–1467. doi: 10.1002/ejhf.1575
40. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368