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ORIGINAL RESEARCH

Growth Differentiation Factor-15 Levels at Admission Provide Incremental Prognostic Information on All-Cause Long-term Mortality in ST-Segment Elevation Myocardial Infarction Patients Treated with Primary Percutaneous Coronary Intervention

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ABSTRACT

Introduction: To investigate the additive prognostic value of growth differentiation factor (GDF-15) levels in ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneously coronary intervention (pPCI) with 10-year mortality on top of clinical characteristics and known cardiac biomarkers.

Methods: Baseline serum GDF-15 levels were measured in 290 STEMI patients treated with pPCI in the MISSION! intervention trial conducted from February 1, 2004 through October 31, 2006. The incremental prognostic value of GDF-15 and NTproBNP levels was evaluated on top of clinical characteristics using Cox proportional hazards analysis, Chi-square models and C-index. Outcome was 10-year all-cause mortality.

Results: Mean age was 59.0 ± 11.5 years and 65 (22.4) patients were female. A total of 37 patients died during a follow-up of 9.4 (IQR 8.8–10.0) years. Multivariable Cox regression revealed GDF-15 and NTproBNP levels above median to be independently associated with 10-year all-cause mortality [HR GDF-15, 2.453 (95% CI 1.064–5.658), $P = 0.04$; HR NTproBNP, 2.413 (95% CI 1.043–5.564), $P = 0.04$] after correction for other clinical variables. Stratified by median GDF-15 (37.78 pmol/L) and NTproBNP (11.74 pmol/L) levels, Kaplan–Meier curves showed significant better survival for patients with GDF-15 and NTproBNP levels below the median versus above the median. The likelihood ratio test showed a significant incremental value of GDF-15 ($P = 0.03$) as compared with a model with clinically important variables and NTproBNP. The C-statistics for this model improved from 0.82 to 0.84 when adding GDF-15.

Christa M. Cobbaert and J. Wouter Jukema share senior co-authorship.

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Conclusion: GDF-15 levels at admission in STEMI patients are independently associated with 10-year all-cause mortality rates and could improve risk stratification on top of clinical variables and other cardiac biomarkers.

Keywords: GDF-15; Mortality; NTproBNP; Prognosis; Risk stratification; STEMI

INTRODUCTION

Long-term mortality rates in ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (pPCI) are declining owing to more frequent use of reperfusion therapy, modern antithrombotic therapy and secondary prevention measures [1, 2]. However, they are still substantial with a reported 1-year mortality rate of 10% [3, 4] and a 5-year mortality rate of about 23% [4].

Identification of high-risk patients is essential for optimal monitoring and initiation of appropriate treatment to reduce risk of events. Current risk assessment relies mainly on clinical characteristics such as age, infarct location, Killip class, cardiogenic shock, ejection fraction, diabetes, renal failure and time of ischemia [5–7]. In addition, traditional cardiac biomarkers such as cardiac troponin (cTn) and N-terminal pro-B-type natriuretic peptide (NTproBNP) have been shown to improve risk prediction in STEMI patients on top of clinical characteristics [8, 9].

Growth differentiation factor-15 (GDF-15) is a systemic stress-responsive member of the transforming growth factor beta (TGF-β) superfamily [10]. GDF-15 is a general, relatively novel biomarker which is induced in the myocardium after ischemia and reperfusion [11] and released as a result of haemodynamic stress [12]. However, GDF-15 is also released in the setting of inflammation or tissue damage and its overexpression has been found in a number of malignancies [11, 13].

Several studies have shown that GDF-15 levels in STEMI patients provide prognostic information on mortality rates within 1 year additional to established clinical and biochemical biomarkers [14–18]. Apart from this relatively short follow-up duration, these studies were limited since study populations were not always comparable because of differences with respect to timing of GDF-15 measurement, type of thrombolytic therapy and endpoints. So, whether GDF-15 levels at admission are also related to long-term mortality rate is unknown in STEMI patients treated with pPCI, especially on top of other more recently validated biomarkers such as cTn and NTproBNP.

Therefore, the additive prognostic value of GDF-15 levels at admission in STEMI patients treated with pPCI as to 10-year mortality rate is investigated on top of clinical characteristics and known cardiac biomarkers such as cTn and NTproBNP.

METHODS

Study Population

In this study, data is used from patients with STEMI, who were included in the prospective MISSION! intervention trial [19]. The MISSION! intervention trial was conducted from February 2004 to October 2006. In this randomized study, we evaluated clinical and angiographic results in patients with STEMI treated with either bare metal stents (BMS) or sirolimus-eluting stents (SES) during pPCI. In short, patients were eligible if STEMI symptoms started less than 9 h before the procedure and the electrocardiogram (ECG) showed ST elevation (at least 0.2 mV in at least two leads in V1–V3 or at least 0.1 mV in other leads) or presumed new left bundle branch block (LBBB). Patients were excluded if they were aged less than 18 years or over 80 years. The study protocol was approved by the Medical Ethical Committee in the Leiden University Medical Center (LUMC). This study was conducted according to the declaration of Helsinki and written informed consent was obtained from all patients before enrolment in the study.

Study Procedure

During the study, all subsequent patients were treated according to the institutional MISSION! protocol [20], based on guidelines of the

European Society of Cardiology, American College of Cardiology and the American Heart Association [21, 22]. The pre-hospital protocol included diagnosis by field triage by 12-lead ECG and in-ambulance treatment with a loading dose of clopidogrel, aspirin, heparin and intravenous glycoprotein IIb/IIIa inhibitors. pPCI was performed according to the clinical guidelines [21, 22]. If tolerated, patients received beta-blockers, ACE inhibitors and statins within 24 h. Additionally, patients were prescribed dual antiplatelet therapy, consisting of aspirin 100 mg daily for life and clopidogrel 75 mg daily for 12 months. More than 95% of the patients received a statin, an acetylsalicylic acid, and a thienopyridine and more than 85% of the patients received a beta-blocker and an ACE inhibitor within 24 h after admission. During admission, patients' demographic characteristics, risk factors and clinical features were collected. Clinical follow-up data was collected during the outpatient clinic visits at 30 days, 3, 6 and 12 months. Information on all-cause mortality was obtained from the Dutch Municipality Records registry at 2, 5 and 10 years after admission. Cause of death was retrieved from general practitioners. The primary outcome of this analysis was 10-year all-cause mortality.

GDF-15 and NTproBNP Measurement

GDF-15 and NTproBNP levels are expressed in picomoles per litre which represents the amount of substances. GDF-15 levels are converted to nanograms per litre by dividing the number by 0.02929. NTproBNP levels are converted to nanograms per litre by dividing the number by 0.118.

Blood samples were obtained at presentation before the pPCI procedure was performed. An extra serum sample was coagulated for at least 60 min before centrifugation at 1500 relative centrifugal force (RCF) for 10 min at 18 °C. Sera were pipetted into 1.1-mL Micronic tubes. Within 2 h after vena puncture, the serum samples were frozen at − 70/− 80 °C in a freezer.

For the in vitro quantitative determination of GDF-15 in human serum, a Roche electrochemiluminescence immunoassay (ECLIA) on Cobas e602 series (catalogue number 07125933190) is used (Roche Diagnostics, Mannheim, Germany). The test is based on the sandwich principle. Results are determined via a calibration curve which is instrument-specifically generated by two-point calibration and a master curve provided via the reagent barcode.

Serum fractions of 250 µL were used for parallel quantification of both serum GDF-15 and NTproBNP. GDF-15 values below the limit of detection were reported as less than 11.71 pmol/L. Values exceeding the measuring range were reported as greater than 585.8 pmol/L.

All GDF-15 measurements were performed at Leiden University Medical Center by investigators who were not aware of patients' characteristics and outcomes.

NTproBNP Measurements

A Roche ECLIA on Cobas e602 series (catalogue number 07125933190) is used (Roche Diagnostics, Mannheim, Germany) to determine NTproBNP levels. The test is based on the sandwich principle and has a detection limit of 0.59 pmol/L. Values exceeding the measuring range were reported as greater than 4130 pmol/L. Results are determined via a calibration curve which is instrument-specifically generated by two-point calibration and a master curve provided via the reagent barcode.

Statistical Analysis

Normally distributed data is presented as mean and standard deviation (SD). Non-normally distributed data is expressed as median with interquartile range (IQR). Categorical data is expressed as absolute numbers and percentages. Differences in baseline characteristics between patients below and above the median of GDF-15 were assessed with an independent *T* test, the Mann–Whitney *U* test or Chi-square test when appropriate. The Pearson correlation coefficient was used to analyse the correlation between GDF-15 and cTnT and NT-proBNP. Event-free survival was analysed with Kaplan–Meier curves

and compared between groups with the log-rank test. To assess the incremental value of GDF-15 levels at admission, we first investigated independent univariate Cox regression analyses to determine the association of potential confounding variables, like body mass index (BMI), hypertension, diabetes, hypercholesterolaemia, smoking, history of cardiovascular disease (CVD), prior MI, out of hospital cardiac arrest, cardiogenic shock, culprit vessel, number of vessel disease, type of stent, cTnT, creatine kinase (CK) and creatinine, on 10-year all-cause mortality. We then constructed a base multivariate Cox model which adjusts for age, gender and all variables with a $P < 0.10$ from the univariable analysis. The incremental prognostic value of GDF-15 and NTproBNP levels was then evaluated by independently adding these predictors to the base model and calculating the likelihood ratio for addition of these effects on top of clinical variables. In addition, the overall C-statistic as proposed by Harrell et al. [23] was calculated. Effects are reported as hazard ratios (HR) with 95% confidence intervals (CI). All statistical tests were performed with SPSS software (Version 24.0, IBM, Armonk, NY, USA). P values less than 0.05 assessed by two-sided tests were considered to be statistically significant.

RESULTS

Baseline and Clinical Characteristics

Baseline serum GDF-15 levels were available in 290 STEMI patients treated with pPCI in the MISSION! intervention trail. Mean age was 59.0 ± 11.5 years, 65 (22.4) patients were female and the median GDF-15 concentration was 37.78 pmol/L (IQR 26.88–55.83 pmol/L). Stratified by median GDF-15 levels, patients with values above the median were older, more often female and had higher NTproBNP, cTnT, creatine kinase (CK) and creatinine levels than the patients below the median (Table 1). The correlation coefficient between GDF-15 and NT-proBNP was 0.17 ($P = 0.004$) and that between GDF-15 and cTnT was 0.083 ($P = 0.191$).

Long-Term Clinical Outcome

A total of 37 patients reached the endpoint during a follow-up of 9.4 (IQR 8.8–10.0) years. The cause of death was adjudicated as cardiac origin in 10 patients, 4 patients died of likely cardiac origin, 19 patients died from a non-cardiac cause and the cause of death is unknown in 4 patients.

Survival Analysis

Univariable Cox regression analysis showed that age, diabetes, current smokers, patients with a family history of CVD, cardiogenic shock, more than one vessel disease at the time of STEMI, baseline levels of GDF-15 above the median, baseline NTproBNP level above the median (11.74 pmol/L), and renal dysfunction were associated with unfavourable outcome (Table 2). Infarct size expressed by the biomarkers cTnT and area under the curve of CK were not associated with higher mortality rates. Multivariable Cox regression revealed that GDF-15 and NTproBNP levels above median are independently associated with 10-year all-cause mortality [HR GDF-15, 2.453 (95% CI 1.064–5.658), $P = 0.04$; HR NTproBNP, 2.413 (95% CI 1.043–5.586), $P = 0.04$] after correction for clinical variables. Furthermore, age [HR 1.095 (95% CI 1.044–1.150), $P < 0.001$] and cardiogenic shock [HR 13.062 (95% CI 3.374–50.566), $P < 0.001$] remained significantly associated with all-cause mortality in the multivariable Cox regression analysis.

Stratified by median GDF-15 (37.78 pmol/L) and median NTproBNP (11.74 pmol/L) levels, Kaplan–Meier curves showed significantly better survival for patients with GDF-15 and NTproBNP levels below the median than for patients with GDF-15 and NTproBNP levels above the median. In the group with GDF-15 levels below the median, the event-free survival was 92.6%, compared to 79.8% in the group with GDF-15 levels above the median (log-rank $P < 0.001$) (Fig. 1a). Similar results were obtained with NTproBNP levels. The event-free survival rate was 93.5% with NTproBNP levels below the median, versus 78.8% event-free

Table 1 Demographic and clinical characteristics at baseline

Variable	Total group (n = 290)	Baseline GDF-15 median (37.8 pmol/L)		P
		< median (n = 145)	> median (n = 145)	
Age, mean (SD), years	59.0 (11.5)	55.7 (11.8)	62.4 (10.9)	< 0.001
Female gender, n (%)	65 (22.4)	18 (12.4)	47 (32.4)	< 0.001
Cardiovascular risk factors				
Current smoking	158 (54.5)	82 (56.6)	76 (52.4)	0.48
Ex-smoker	33 (11.4)	17 (11.7)	16 (11.0)	0.85
NIDDM, n (%)	19 (6.6)	6 (4.1)	13 (9.0)	0.10
IDDM, n (%)	11 (3.7)	6 (4.1)	5 (3.4)	0.76
Family history of CVD, n (%)	126 (43.4)	70 (48.3)	56 (38.6)	0.17
Treated hypercholesterolaemia, n (%)	56 (19.3)	25 (17.2)	31 (21.4)	0.37
Treated hypertension, n (%)	82 (28.3)	41 (28.3)	41 (28.3)	1.00
Body mass index, mean (SD), kg/m^2	26.6 (4.2)	26.7 (3.8)	26.6 (4.6)	0.87
Comorbidities				
Previous myocardial infarction, n (%)	11 (3.8)	6 (4.1)	5 (3.4)	0.76
Previous PCI, n (%)	5 (1.7)	3 (2.1)	2 (1.4)	0.65
Previous CABG, n (%)	2 (0.7)	2 (1.4)	0 (–)	0.16
History of cerebrovascular disease, n (%)	10 (3.4)	3 (2.1)	7 (4.8)	0.27
Previous medication use				
Beta-blocker, n (%)	36 (12.4)	20 (13.8)	16 (11.0)	0.48
ACE inhibitor/AT2 antagonist, n (%)	34 (11.7)	19 (13.1)	15 (10.3)	0.47
Statin, n (%)	31 (10.7)	14 (9.7)	17 (11.7)	0.51
Antiplatelet, n (%)	1 (0.3)	1 (0.7)	0 (–)	0.37
Ascal, n (%)	28 (9.7)	11 (7.6)	17 (11.7)	0.29
Clinical characteristics				
Time of ischemia, median (IQR), min	192 (146–257)	200 (147–260)	191 (146–248)	0.58
Number of narrowed coronary arteries				0.99
1	158 (54.5)	78 (53.8)	80 (55.2)	
2	115 (39.7)	58 (40.0)	57 (39.3)	
3	15 (5.2)	8 (5.5)	7 (4.8)	
Complete revascularization, n (%)	195 (67.5)	101 (71.1)	94 (65.7)	0.38
Killip class $\geq$ 2, n (%)	27 (9.3)	11 (7.6)	16 (11.0)	0.37

Table 1 continued

Variable	Total group (n = 290)	Baseline GDF-15 median (37.8 pmol/L)		P
		< median (n = 145)	> median (n = 145)	
Laboratory results				
Infarct size, median area under the CK curve (IQR), g/m^2	8.92 (4.26–15.82)	7.36 (2.93–14.45)	10.54 (5.73–16.99)	0.009
Peak cardiac troponin-T, median (IQR), μg/L	5.53 (2.28–10.22)	4.77 (1.64–8.84)	5.91 (3.08–10.72)	0.02
NTproBNP, median (IQR), pmol/L	11.74 (4.70–27.53)	9.46 (4.33–22.98)	14.49 (5.40–34.24)	0.02
Creatinine, mean (SD), μmol/L	81.6 (18.5)	78.2 (13.8)	85.1 (21.8)	0.002

Data are expressed as number (%), median (IQR) or mean ± standard deviation

Narrowed coronary artery, defined as ≥ 50% stenosis on baseline coronary angiogram. Treated hypercholesterolaemia, serum total cholesterol ≥ 6 mmol/L and/or serum TG ≥ 2.2 mmol/L or treatment with lipid -lowering drugs. Treated hypertension, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or the use of antihypertensive medication

ACE angiotensin-converting enzyme, *AT2* angiotensin II, *CABG* coronary artery bypass surgery, *CVD* cardiovascular disease, *GDF-15* growth differentiation factor-15, *IDDM* insulin-dependent diabetes mellitus, *IQR* interquartile range, *NIDDM* non-insulin-dependent diabetes mellitus, *NTproBNP* N-terminal pro b-type natriuretic peptide, *PCI* percutaneous coronary intervention, *SD* standard deviation

survival in patients with an NTproBNP level above the median (log rank $P < 0.001$). When these biomarkers are divided in four groups (both GDF-15 and NTproBNP < median; GDF-15 > median and NTproBNP < median; GDF-15 < median and NTproBNP > median; and both GDF-15 and NTproBNP > median), the prognostic value improved. In the group with both GDF-15 and NTproBNP levels below their medians the event-free survival was 95.7%, whereas in the group with both GDF-15 and NTproBNP levels above their medians (log rank $P < 0.001$) the event-free survival was 70.7% (Fig. 2).

Incremental Value of GDF-15

Figure 3 shows the incremental value of NTproBNP and GDF-15 on top of other clinically important risk factors for predicting the primary endpoint. Model 1 includes all variables that are significant in the univariable Cox regression analysis. The addition of NTproBNP to the basic model improved the likelihood ratio but this was not statistically significant ($P = 0.086$). The likelihood ratio test showed a significantly incremental value of GDF-15 ($P = 0.027$) as compared with a model with clinical important variables and NTproBNP. The C-statistics for this model improved from 0.82 to 0.84 when adding GDF-15 levels to the model with all clinically important risk factors and NTproBNP levels.

DISCUSSION

This study demonstrates that higher GDF-15 levels at admission are associated with 10-year all-cause mortality in STEMI patients treated with pPCI. This relation was independent of clinical risk factors and biomarkers. Moreover, GDF-15 levels at admission have additional prognostic value beyond identified risk factors and other cardiac biomarkers such as cTn and NTproBNP as analysed by Chi-square test and C-statistics.

When stratified by median GDF-15 levels, patients with a level below the median show an

Table 2 Univariable and multivariable Cox proportional hazard regression analysis to identify independent predictors of all-cause mortality

Parameter	Univariable analysis HR (95% CI)	*P*	Multivariable analysis HR (95% CI)	*P*
Age, mean, years	1.110 (1.069–1.153)	< 0.001	1.095 (1.044–1.150)	< 0.001
Female gender	0.761 (0.334–1.733)	0.51	0.413 (0.159–1.072)	0.07
Body mass index, mean, kg/m^2	0.962 (0.881–1.050)	0.39		
Treated hypertension	0.957 (0.463–1.978)	0.91		
Diabetes	2.176 (0.956–4.954)	0.06	2.374 (0.997–5.654)	0.05
Treated hypercholesterolaemia	0.875 (0.365–2.098)	0.765		
Current smoker	0.576 (0.299–1.109)	0.10	1.702 (0.821–3.525)	0.15
Family history of CVD	0.453 (0.219–0.936)	0.03	0.871 (0.384–1.974)	0.74
Prior myocardial infarction	1.322 (0.318–5.500)	0.70		
Out of hospital cardiac arrest	0.048 (0.000–568.83)	0.53		
Cardiogenic shock	10.76 (3.295–35.15)	< 0.001	13.062 (3.374–50.566)	< 0.001
Culprit vessel				
RCA	Ref	0.65		
RCX	0.944 (0.359–2.484)	0.91		
LAD	0.727 (0.356–1.483)	0.38		
Number of vessel disease (> 50%) > 1	1.914 (0.993–3.689)	0.05	1.383 (0.457–4.183)	0.57
Complete revascularization	0.480 (0.252–0.915)	0.026	0.977 (0.329–2.095)	0.97
Drug-eluting stent	1.256 (0.657–2.412)	0.49		
Peak cardiac troponin-T level, μg/L	1.023 (0.973–1.076)	0.37		
Infarct size, median under the CK curve (IQR), g/m^2	0.979 (0.940–1.019)	0.31		
Baseline GDF-15 > median	3.360 (1.585–7.121)	0.002	2.453 (1.064–5.658)	0.04
Baseline NTproBNP > median	3.332 (1.567–7.042)	0.002	2.413 (1.043–5.586)	0.04
Creatinine, μmol/L	1.023 (1.007–1.039)	0.004	1.005 (0.988–1.022)	0.56

Data are expressed as hazard ratios with 95% confidence interval

Treated hypercholesterolaemia, serum total cholesterol ≥ 6 mmol/L and/or serum TG ≥ 2.2 mmol/L or treatment with lipid-lowering drugs. Treated hypertension, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or the use of antihypertensive medication

CK creatine kinase, *CVD* cardiovascular disease, *GDF-15* growth differentiation factor-15, *NTproBNP* N-terminal pro b-type natriuretic peptide, *SD* standard deviation

excellent prognosis with a 10-year all-cause mortality rate of 6.2% compared to 19.3% in the group with a GDF-15 level above the median. NTproBNP levels stratified by the median show the same division of 10-year all-cause mortality rates as GDF-15 levels. However,

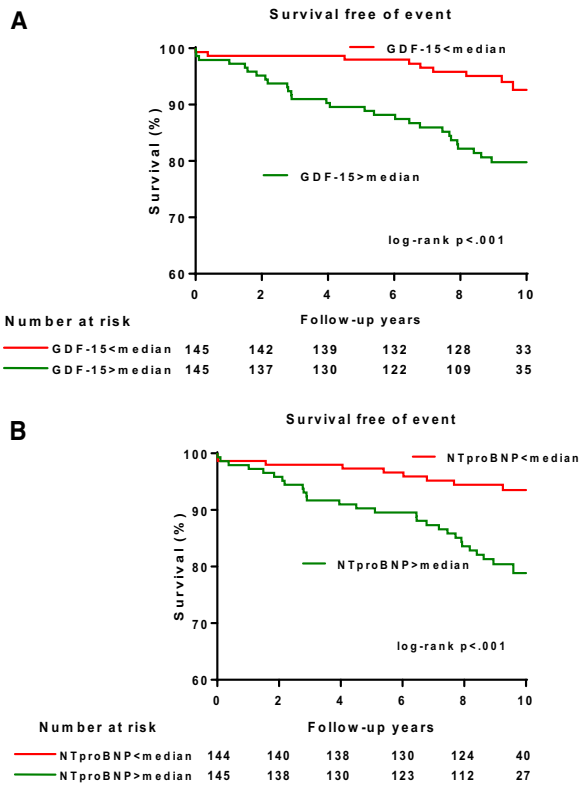

Fig. 1 Kaplan–Meier analysis to evaluate the survival free of the primary endpoint of all-cause mortality. **a** GDF-15. **b** NTproBNP. GDF-15 growth differentiation factor-15, NTproBNP N-terminal pro-B-type natriuretic peptide

combining these two biomarkers reveals that they have a complementary relation with 10-year all-cause mortality. So, the combination of these biomarkers seems to identify an interesting group of high-risk patients. In the group of patients with both GDF-15 and NTproBNP levels below the median, only 3 patients (3.8%) died within 10 years compared to 22 (27.8%) in the group with both GDF-15 and NTproBNP levels above the median. Furthermore, GDF-15 shows additional prognostic information when added to clinical information and NTproBNP.

Other studies in a broad spectrum of patients have shown that a high level of GDF-15 is independently associated with mortality and adds extra prognostic value on top of various clinical characteristics and biomarkers [12, 14–18, 24–26]. Several of these studies compared the GDF-15 levels of STEMI patients at admission with outcome [14–16]. Two of these studies used a comparable population with GDF-15 levels at admission of STEMI patients treated with pPCI. Eitel et al. demonstrated that GDF-15 levels at admission are a strong predictor of mortality after 6 years [16]. However, two important biomarkers, cTn and NTproBNP, were not available is this cohort. Recently, Velders et al. showed in a large cohort that GDF-15 is independently associated with cardiovascular death after 1 year after adjusting for these biomarkers, the severity of cardiovascular disease and other clinical information [14]. However, the number of studies that compared GDF-15 and NTproBNP levels at admission with all-cause mortality on the long term in STEMI patients treated with pPCI is virtually absent. To our knowledge the current study is the first that investigated these biomarkers at admission in relation to 10-year all-cause mortality in STEMI patients treated with pPCI.

A relatively low number of patients died in this cohort during the 10 years. In the first year of follow-up after STEMI only 5 patients (1.7%) died, of whom 4 died from a cardiac cause. In the years that followed, 32 more patients died, of whom 6 died from a cardiac cause and 4 patients' deaths were likely of cardiac origin. In total 19 patients died of a non-cardiac cause, of which 18 were after more than 1 year. By adding biomarkers that reflect a more general state of disease, one might not only capture patients prone to cardiovascular events but also patients prone to non-cardiac events.

Current risk assessment with for example the TIMI or GRACE risk scores is mainly based upon clinical characteristics [14]. Cardiac biomarkers such as cTn and NTproBNP have been shown to improve risk prediction [8, 9]. Using a multimarker strategy that captures a broader spectrum of diseases may have added value since it can reveal novel release mechanisms and therefore potential therapeutic targets. The relation of GDF-15 to cTn and NTproBNP has shown that GDF-15 is involved in cardiac pathologies. GDF-15 is induced in the myocardium after ischemia [11]. Several studies have demonstrated that plasma levels of GDF-15, just as NTproBNP, are associated with mechanical stretch, left ventricular mass,

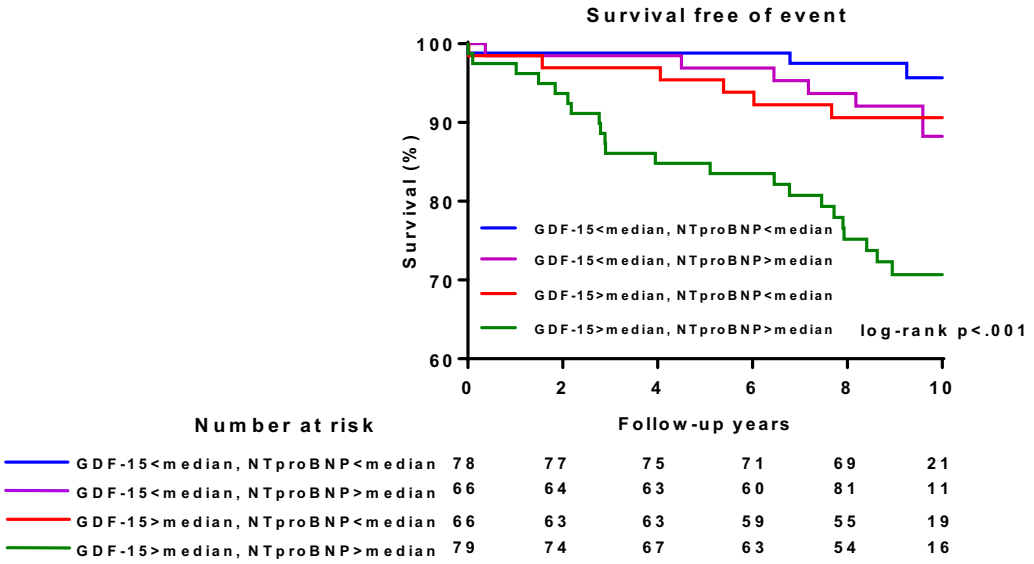

Fig. 2 Kaplan–Meier analysis to evaluate the survival free of experiencing the primary endpoint of all-cause mortality when combining assessment of GDF-15 and NTproBNP. GDF-15 growth differentiation factor-15, NTproBNP N-terminal pro-B-type natriuretic peptide

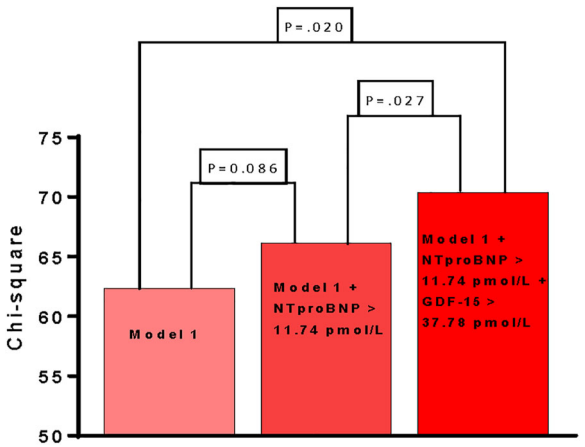

Fig. 3 The bar graphs show the incremental value of NTproBNP and GDF-15 on top of other clinically important risk factors for predicting the primary endpoint. Harrell C-statistics represent overall adequacy of the risk prediction. Model 1: Clinical variables (age, gender, previous diabetes mellitus, current smoking, family history of CVD, cardiogenic shock, > 1 number of vessel disease, complete revascularization, creatinine). Model 2: Model 1 + NTproBNP > median (11.74 pmol/L). Model 3: Model 1 + NTproBNP > median (11.74 pmol/L) + GDF-15 > median (37.78 pmol/L). CVD cardiovascular disease, GDF-15 growth differentiation factor-15, NTproBNP N-terminal pro-B-type natriuretic peptide

concentric left ventricular hypertrophy, reduced left ventricular ejection fraction, and heart failure [12, 15, 27]. Besides these similarities, the characteristics of GDF-15 release are distinct from those of NTproBNP and cTn. Earlier studies demonstrated that cTn release shows a typical rise and fall pattern, indicating the release from dying cardiomyocytes, whereas GDF-15 values increase within hours after ischemia [11] but remain remarkably stable over time during admission [28] and during 6 months of follow-up [24]. GDF-15 follows several stress pathways that differ from the cardiac-specific biomarkers, like NTproBNP and cTn [11, 29]. Plasma levels of GDF-15 may increase in response to pathological stress associated with vascular inflammation, endothelial activation or tissue damage, and its overexpression has been found in several malignancies [11, 24, 27, 30, 31]. Supported by epidemiological studies, this indicates that GDF-15 seems to be a marker of chronic cardiac and vascular pathologies, and is not per se related to acute injury [27, 32].

Over the last decade, a substantial amount of research has been performed that studied the role of GDF-15 levels for the risk assessment in acute coronary syndrome patients. However,

translation of novel biomarkers into clinical practice has been shown to be challenging. For example, after the discovery of NTproBNP as a marker for heart failure it took two decades to implement it into clinical practice [33]. Recently a multidisciplinary working group defined a strategy and checklist to better identify the clinical unmet needs and how novel biomarkers can satisfy them [34]. They provide a practical approach to help assess whether a new biomarker would provide clinical benefit. To give a purely hypothetical example, we designed a map for a clinical pathway using this checklist and clinical approach (supplemental figure) on how we could advance GDF-15 into clinical practice. In this figure we used GDF-15 as an add-on test on top of clinical characteristics and cTn and NTproBNP. We acknowledge that we cannot implement GDF-15 into clinical practice solely on the basis of the results of our study, especially since it is currently unclear how GDF-15 levels can be lowered by medical therapy or interventions and whether lowering these levels results in an improved outcome. However we do hope that we can encourage other stakeholders to follow this example in larger prospective intervention studies to target this unmet clinical need with the development and implementation of GDF-15 in clinical pathway mapping.

Before this can be considered, further research with regard to the pathophysiological mechanisms and the influence of common and novel medical therapies on plasma levels of GDF-15 should be explored. Two potentially ways to do so might be more aggressive lipid-lowering therapies or by anti-inflammatory therapy. The only study so far that investigated the relation between lipid lowering therapy by statin therapy and GDF-15 levels was conducted by Bonaca et al. [35]. They found no interaction of GDF-15 with different kind of statins and, moreover, GDF-15 levels did not decline after 4 months. Whether more aggressive medical therapy by for example PCSK-9 inhibitors has beneficial effects on GDF-15 is worth investigating. Another way to influence GDF-15 levels may be by anti-inflammatory therapy. In the recently published CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial it was shown that targeting the innate immunity pathway with canakinumab, independent of lipid level lowering, led to a significant lower rate of recurrent cardiovascular events than placebo [36]. It would be of interest to explore whether GDF-15 levels may act as biomarker-guided therapy to evaluate the effect of anti-inflammatory therapy.

Several limitations need to be mentioned. First of all, this study was a single-centre randomized trial with a limited number of patients; so, the results are limited to the patients eligible for the trial, although the results apply for a broad range of STEMI patients. All patients were treated according to the institutional MISSION! which provided an integrated approach of MI care to optimize treatment. This yielded a very homogeneous STEMI population. Secondly, limited data is available about the stability of GDF-15 samples after long-term storage at − 80 °C. However, an earlier study conducted by Daniels et al. [37] measured GDF-15 in 1391 serum samples that were stored for 14–18 years. The fact that GDF-15 levels were prognostic for outcome supports that there is sufficient stability to preserve a clinical signal [37]. Moreover, the median of the GDF-15 levels in the present cohort was 37.78 pmol/L which is comparable with the median levels of GDF-15 of 38.63 pmol/L in a similar cohort of STEMI patients [16]. Third, a relatively low number of events were noted during follow-up. To make the results more robust, larger cohorts of STEMI patients treated with pPCI should be followed. An explanation for the low number of events could be the exclusion criteria of patients older than 80 years. This could have led to a relatively young cohort with a mean age of 59 years. The last issue that should be addressed is the low number of events in relation to the multivariate Cox model. This paper has investigated the added value of GDF-15 for the prediction of 10-year all-cause mortality in addition to established risk factors as well as potential confounding variables identified from univariate analysis on our data. As opposed to fitting a prognostic model, a testing procedure was used, which first estimates a multivariate Cox model to account for the joint effect of these risk factors and potential confounders, after which the

added value was assessed from likelihood ratio testing for the addition of GDF-15 and NTproBNP to the base model.

CONCLUSIONS

Baseline GDF-15 levels are independently associated with 10-year all-cause mortality rates and improve long-term risk stratification in STEMI patients treated with pPCI on top of clinical variables and other cardiac biomarkers. Before implementation into clinical practice can be considered, the clinical utility needs to be further validated in prospective intervention studies.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to bad experiences regarding data hustling and cherry picking, but requests for collaborations are certainly welcome.

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