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Growth Differentiation Factor 15: A Prognostic Marker in Patients with Acute Chest Pain without Acute Myocardial Infarction

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BACKGROUND: Acute chest pain is associated with an increased risk of death and cardiovascular events even when acute myocardial infarction (AMI) has been excluded. Growth differentiation factor-15 (GDF-15) is a strong prognostic marker in patients with acute chest pain and AMI, but the prognostic value in patients without AMI is uncertain. This study sought to investigate the ability of GDF-15 to predict long-term prognosis in patients presenting with acute chest pain without AMI.

METHODS: In total, 1320 patients admitted with acute chest pain without AMI were followed for a median of 1523 days (range: 4 to 2208 days). The primary end point was all-cause mortality. Secondary end points included cardiovascular (CV) death, future AMI, heart failure hospitalization, and new-onset atrial fibrillation (AF).

RESULTS: Higher concentrations of GDF-15 were associated with increased risk of death from all causes (median concentration in non-survivors vs survivors: 2124 pg/mL vs 852 pg/mL, $P < 0.001$), and all secondary end points. By multivariable Cox regression, GDF-15 concentration ≥4th quartile (compared to <4th quartile) remained an independent predictor of all-cause death (adjusted hazard ratio (HR): 2.75; 95% CI, 1.69–4.45, $P < 0.001$), CV death (adjusted HR: 3.74; 95% CI, 1.31–10.63, $P = 0.013$), and heart failure hospitalization (adjusted HR: 2.60; 95% CI, 1.11–6.06, $P = 0.027$). Adding GDF-15 to a model consisting of established risk factors and high-sensitivity cardiac troponin T (hs-cTnT) led to a significant increase in C-statistics for prediction of all-cause mortality.

CONCLUSIONS: Higher concentrations of GDF-15 were associated with increased risk of mortality from all causes and risk of future CV events.

Introduction

Acute chest pain is a common complaint in the emergency department (ED) (1). Most patients presenting with acute chest pain are not diagnosed with acute myocardial infarction (AMI), but may still be at increased risk of cardiovascular (CV) disease or death (2, 3). Patients without AMI represent a large and heterogeneous group, and it may be difficult for clinicians to discern those at increased risk of CV events. As opposed to patients presenting with ST-segment elevation myocardial infarction (STEMI) (4) or non-ST-segment elevation-myocardial infarction (NSTEMI) (5), there are no clear guidelines for further follow-up of increased risk in patients without AMI. These patients usually present with stable cardiac troponin concentrations, and additional biomarkers may contribute to improved diagnostic pathways.

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Growth differentiation factor-15 (GDF-15) is a cytokine member of the transforming growth factor β superfamily (6). Under normal physiological conditions it is expressed at low levels and it is upregulated with aging and in various organs and tissues in response to oxidative stress, injury, inflammation, and hypoxia (7). Its role in the CV system is not fully understood, but the degree of atherosclerosis correlates with increasing levels of GDF-15 (8). It is also expressed in cardiomyocytes, and increased levels are found in patients with AMI (9), heart failure (HF) (10, 11), and cardiac hypertrophy (12), probably mediated through various pathophysiological mechanisms.

GDF-15 has a low biological variation (13), is stable during acute events (14), and has been extensively investigated as a prognostic marker, and an independent prognostic value has been shown in patients presenting with STEMI (15), NSTEMI (14), HF (10), and several non-cardiac diseases including cancer (16) and sepsis (17). In the current study, we compared the prognostic value of GDF-15 with that of existing risk factors and biomarkers that constitute the current standard of care in patients admitted with chest pain without AMI. Given the heterogeneity of pathologies causing acute chest pain in patients without AMI, we postulated that GDF-15 may provide important prognostic information given its upregulation in several cardiac pathophysiological pathways.

Materials and Methods

STUDY DESIGN AND POPULATION

The prospective observational WESTCOR study (Clinical Trials number: NCT02620202) included patients with suspected non-ST-elevation acute coronary syndrome (NSTE- ACS). Details of the study design are available in the Supplemental Material, and have been published previously (18). The current study includes data from 1506 patients ≥18 years who were admitted to the ED at Haukeland University Hospital in Bergen, Norway. Patients adjudicated as AMI according to the third universal definition of myocardial infarction (19) were excluded. An additional 3 patients were excluded due to missing biomarkers, and 1 patient was excluded due to a GDF-15 concentration >90 000 pg/mL. The remaining 1320 patients were followed for a median of 1523 days (range: 4 to 2208 days).

BIOCHEMICAL ANALYSIS

Blood samples were drawn at the ED at presentation. Samples were measured in fresh blood samples for high-sensitivity cardiac troponin T (hs-cTnT) from Roche Diagnostics, whilst GDF-15 (Roche Diagnostics) was analyzed using biobank samples stored at −80°C (see Supplemental Material for further information).

FOLLOW-UP AND STUDY END POINTS

Follow-up data were collected through the Norwegian Patient Register and Norwegian Cause of Death Registry, which according to Norwegian legislation register all deaths and hospital-provided healthcare. The primary prognostic end point was all-cause mortality and secondary end points included CV death, incident AMI, HF hospitalization, and new-onset AF. Patients with known AF and AF diagnosed during index hospitalization were excluded from all analyses with AF as an end point. CV death included causes of death coded I00 to I99 or R96 according to the International Classification of Diseases, Tenth revision (ICD-10) system. The cause of death was classified according to the principal condition that caused the death, not the immediate mode of death. All CV deaths were later reviewed and confirmed by an independent cardiologist, who was unaware of the patient's biomarker concentrations.

STATISTICAL ANALYSES

Patients were categorized into 4 groups based on quartiles of GDF-15 concentration at admission. Normality of distribution was examined using the Shapiro–Wilk normality test. Non-normally distributed continuous variables are reported as median (25th–75th percentile). ANOVA and the Kruskal–Wallis test were used to compare parametric and non-parametric variables as applicable. Categorical variables are given as a percentage, using Pearson χ^2 or Fisher exact test for comparison. Multiple linear regression was used to assess the relationship between GDF-15 (dependent variable) and predictor variables including age, N-terminal pro-B-type natriuretic peptide (NT-proBNP), hs-cTnT, estimated glomerular filtration rate (eGFR), previous AMI, hypertension, diabetes, female gender, ongoing smoking at baseline, and hyperlipidemia; skewed continuous variables were transformed by its natural logarithm. Kaplan–Meier survival plots were generated and cumulative event rates compared by the log-rank test. Cox proportional hazards regression was used to assess the association between GDF-15 concentration and study end points in unadjusted and adjusted models. Model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, eGFR, present smoker at baseline, hypertension, hyperlipidemia, diabetes, and previous AMI. In addition to analyses by GDF-15 quartiles, we used cutoff points of >1200 pg/mL and >1800 pg/mL, which have been used for other GDF-15 assays in earlier studies (14), GDF-15 in the 4th quartile, greater than median GDF-15

concentration, and the log2 of the GDF-15 continuous concentration. Youden indexes and optimal cutoff points for the different end points were estimated. Generalized additive model (GAM) curves were constructed to explore the association between different GDF-15 concentrations and unadjusted and adjusted (age) hazard ratios. C-statistics and the DeLong test were used for evaluating the incremental predictive value of GDF-15 compared to hs-cTnT, NT-proBNP, and established risk factors (age, sex, eGFR, present smoker, hypertension, hyperlipidemia, diabetes, and previous AMI). The predictor variables were entered into a binary logistic regression model and the resulting predicted probability was used to compute the area under the curve (AUC). Continuous net reclassification improvement (NRI) was calculated using previously defined methods (20) using the R package "hmisc." Categorical NRI was calculated using the 4th quartile as a cutoff point as well as the previously defined cutoff point of >1200 pg/mL, and compared with the hs-cTnT 99th percentile cutoff or the NT-proBNP cutoff for ruling out HF (300 ng/L). Interaction between age and GDF-15 was investigated by entering a multiplicative interaction term between age and GDF-15 into a Cox regression model containing age and GDF-15. Based on a significant interaction (primary end point) a subgroup analysis was performed investigating the prognostic value of GDF-15 stratified by median age. IBM SPSS statistics for Windows, version 26.0, MedCalc statistical software version 17.6, and R version 4.1.2 were used for statistical analysis. For all statistical testing, 2-sided *P*-values were reported, and a *P*-value <0.05 was considered statistically significant.

Results

PATIENT CHARACTERISTICS

A total of 1320 patients (41% female) were included in the analysis. The median age of the participants at the time of study enrollment was 61 (interquartile range (IQR): 51 to 72) years. Patients with GDF-15 in the upper quartile were older, had more comorbidities, lower LDL cholesterol, lower eGFR, and higher concentrations of hs-cTnT, NT-proBNP, and C-reactive protein (CRP) (Table 1). There were no differences in the distribution of gender, smoking status, and obesity (body mass index (BMI) > 30 kg/m^2) between different quartiles.

ASSOCIATION OF GDF-15 WITH OTHER VARIABLES

Multiple linear regression was performed to assess the relation between GDF-15 and other variables (online Supplemental Table 1). By using ln GDF-15 as the dependent variable, age, ln NT-proBNP, ln hs-cTnT, hypertension, previous AMI, and diabetes were positively associated while ln eGFR and female gender were negatively associated with increasing GDF-15 concentrations.

CLINICAL OUTCOMES

During follow-up, 114 (8.6%) patients met the primary end point of all-cause mortality, 28 (2%) died of CV causes, 45 (3.4%) suffered an AMI, 39 (3%) were hospitalized with HF, and 40 patients (3%) received a new diagnosis of AF (Table 1). The number of end points increased across the 1st–4th quartiles and the highest number was observed in the 4th quartile of GDF-15 concentrations (Table 1, Fig. 1, online Supplemental Fig. 1). Higher concentrations of GDF-15 were associated with a higher likelihood of being diagnosed with coronary and non-coronary cardiac disease, whereas patients with low GDF-15 were more likely to be diagnosed with non-cardiac chest pain (online Supplemental Table 2). Individuals reaching the primary and secondary end points had significantly higher GDF-15 concentrations at baseline than patients not reaching the end points (Table 1, online Supplemental Table 3).

Mortality prediction. In the 4th quartile of GDF-15 concentration, 26% of patients died compared to 0.6% in the 1st quartile (Table 1, Fig. 1). The log-rank test demonstrated a significant relationship between GDF-15 concentrations stratified by quartiles and all-cause mortality, CV death, and non-CV death (Fig. 2, A–2, C). Increasing concentrations of GDF-15 were associated with increased risk of death in unadjusted models (Table 2, Fig. 3). In the fully adjusted Cox regression model, GDF-15 in the 4th quartile was the strongest predictor for all-cause mortality with a HR of 2.75 (95% CI, 1.69–4.45, $P < 0.001$) (Table 2, online Supplemental Table 4), and for CV death (HR: 3.74; 95% CI, 1.31–10.63, $P = 0.013$). C-statistic for all-cause mortality for GDF-15 was 0.86 (0.84–0.88), and for CV death 0.84 (0.82–0.86), and did not differ significantly from that of hs-cTnT (online Supplemental Table 5). When added to a model consisting of established risk factors, GDF-15 significantly increased C-statistics from 0.86 to 0.89, $P < 0.001$, and there was a trend towards increase in overall NRI (borderline significant): 0.20 (0.00–0.38, $P = 0.052$) (Table 3).

Prediction of secondary end points. Similar to the primary end point, the log-rank test demonstrated a significant relationship between GDF-15 concentration stratified by quartiles and future AMI, HF hospitalization, and new-onset AF (Fig. 2, D–F). In predicting

Table 1. Baseline characteristics according to GDF-15 quartiles on admission. Categorical variables are given as number and percentage and continuous variables as median (25th–75th centile). A table presented in SI units is provided in online Supplemental Table 11.

	GDF-15 quartiles				
Characteristic[a]	1st quartile, n = 330 (<622 pg/mL)	2nd quartile n = 330 (622–899 pg/mL)	3rd quartile n = 330 (900–1430 pg/mL)	4th quartile n = 330 (>1430 pg/mL)	*P*
Age in years	48 (41–55)	58 (51–66)	67 (59–74)	75 (66–82)	<0.001
Female gender	124 (38%)	145 (44%)	138 (42%)	133 (40%)	0.419
Cardiovascular risk factors					
Obesity: BMI >30 kg/m^2, n = 770	41 (23%)	42 (25%)	42 (26%)	43 (29%)	0.758
Active smoker	66 (20%)	56 (17%)	66 (20%)	58 (18%)	0.637
Former smoker	141 (43%)	140 (42%)	152 (46%)	152 (46%)	0.587
Hyperlipidemia	52 (16%)	84 (25%)	96 (29%)	96 (29%)	<0.001
Diabetes mellitus	9 (3%)	15 (5%)	36 (11%)	51 (16%)	<0.001
Hypertension	63 (19%)	110 (33%)	152 (46%)	201 (61%)	<0.001
Medical history					
Previous AMI	14 (4%)	50 (15%)	72 (22%)	107 (32%)	<0.001
Atrial fibrillation	5 (1.5%)	15 (5%)	25 (8%)	33 (10%)	<0.001
Previous stroke	4 (1.2%)	6 (1.8%)	11 (3%)	15 (5%)	0.074
Family history of CAD	73 (22%)	67 (20%)	61 (19%)	43 (13%)	0.027
Renal failure: eGFR <60 mL/min/1.73m^2	2 (0.6%)	9 (3%)	37 (11%)	109 (33%)	<0.001
Peripheral arterial disease	1 (0.3%)	1 (0.3%)	5 (1.5%)	18 (6%)	<0.001
Known heart failure	5 (1.5%)	1 (0.3%)	7 (2%)	29 (9%)	<0.001
Laboratory parameters					
TC, mg/dL	193 (162–224)	193 (159–228)	182 (146–224)	166 (135–205)	<0.001
LDL-C, mg/dL	115 (86–142)	112 (82–145)	99 (70–137)	85 (61–120)	<0.001
HDL-C, mg/dL	50 (43–66)	54 (43–66)	50 (43–68)	54 (43– 66)	0.378
Troponin T, ng/L	3 (3–5)	5 (3–7)	7 (5–12)	14 (8–24)	<0.001
CRP, mg/L	1.0 (0.5–2)	1.0 (0.6–2)	2.0 (0.7–5.0)	2.0 (1.0–7.0)	<0.001
NT-proBNP, ng/L	37 (19–77)	62 (28–114)	87 (43–224)	278 (97–1130)	<0.001
eGFR, mL/min/1.73m^2	97 (87–106)	90 (81–98)	83 (70–93)	71 (53–86)	<0.001
End points					
All-cause mortality	2 (0.6%)	7 (2%)	21 (6%)	84 (26%)	<0.001
CV death	1 (0.3%)	1 (0.3%)	4 (1.2%)	22 (7%)	<0.001
AMI	3 (0.9%)	2 (0.6%)	17 (5%)	23 (7%)	<0.001
HF hospitalization	2 (0.6%)	0 (0%)	10 (3%)	27 (8%)	<0.001
New-AF	4 (1.2%)	5 (1.5%)	16 (5%)	15 (5%)	0.006

[a]Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein.

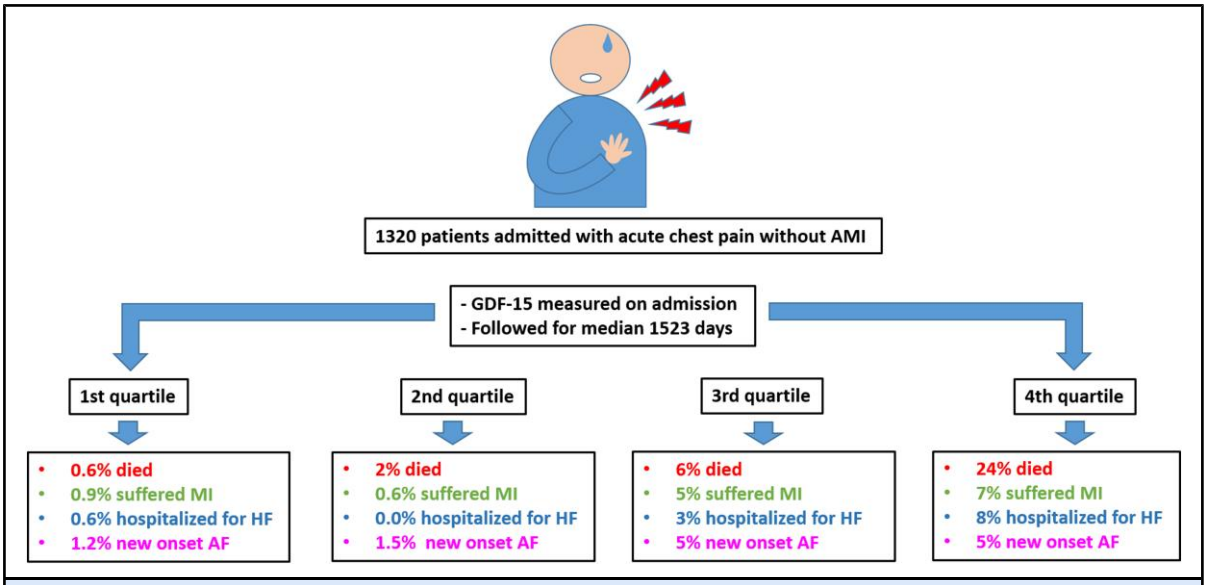

Fig. 1. Elevated GDF-15 concentration is associated with increased risk of death and CV events in patients presenting with acute chest pain without acute myocardial infarction. Color figure available online at clinchem.org.

future AMI, GDF-15 in the 4th quartile was associated with an unadjusted HR: 3.2 (95% CI, 1.78–5.74, $P < 0.001$), but the association was no longer significant in the adjusted model with a HR of 1.10 (95% CI, 0.53–2.30, $P = 0.797$) (Table 2). In predicting HF hospitalization, GDF-15 levels in the 4th quartile were associated with an adjusted HR of 2.60 (95% CI, 1.11–6.06, $P = 0.027$). GDF-15 levels in the 4th quartile were associated with an unadjusted HR of 2.25 (95% CI, 1.19–4.27, $P = 0.013$) in predicting AF. In adjusted models, high levels of GDF-15 were not significantly associated with the risk of developing AF. Hazard ratios for the previously used cutoff points of >1200 pg/mL and >1800 pg/mL are provided in online Supplemental Table 10. The C-statistic of GDF-15 in predicting AMI was: 0.73 (95% CI: 0.71–0.76), HF: 0.80 (95% CI: 0.78–0.82), and AF: 0.68 (95% CI: 0.65–0.71). These numbers did not differ significantly from those of hs-cTnT, whilst NT-proBNP showed higher AUC than hs-cTnT for CV mortality and hospitalization for HF (online Supplemental Table 5). Adding GDF-15 to established risk factors did not increase C-statistics in predicting AMI or HF, but led to an increase in prediction of AF from 0.80 (95% CI: 0.77−0.82) to 0.81 (95% CI: 0.78−0.83), $P = 0.032$ (Table 3). Adding GDF-15 to a model consisting of established risk factors did not lead to a significant increase in overall continuous NRI for any of the secondary end points except for new-onset AF (Table 3). The 2 × 2 table (online Supplemental Table 6) for hs-cTnT >14 ng/L vs ≤14 ng/L crossed with GDF-15 >1430 pg/mL (4th quartile) vs ≤1430 pg/mL gives the end point occurrences of 83/164 (51%) for both high, 32/165 (19%) for only GDF-15 high, 17/92 (19%) for only hs-cTnT high, and 55/899 (6%) for neither high, and an overall NRI of 0.029. Addition of NT-proBNP into the C-statistics or continuous/categorical NRI analysis did not show any clear benefit (Table 3, Supplemental Table 5, and Supplemental Table 7).

Long-term prognostic value of GDF-15 stratified by median age. There was an interaction between age and GDF-15 in the prediction of all-cause mortality (*P*-value for the interaction term was 0.035). For the other end points the *P*-value for the interaction term was non-significant: cardiovascular death, $P = 0.132$; HF hospitalization, $P = 0.982$; future AMI, $P = 0.192$; and new-onset AF, $P = 0.746$. GDF-15 seems to have a good prognostic value in the subgroup analysis stratified by median age (61 years). AUC for all-cause mortality was 0.84 in patients below 61 years and 0.79 in patients ≥61 years (online Supplemental Table 8). Increasing concentrations of GDF-15 were associated with increased risk of all-cause mortality, CV-death, and heart failure after age-adjustment (online Supplemental Fig. 2). The unadjusted hazard for GDF-15 (log2 transformed) in predicting all-cause mortality was 4.51 (95% CI, 2.70–7.54, $P < 0.001$) in patients below 61 years and 3.04 (95% CI, 2.53–3.66, $P < 0.001$) in patients ≥61 years. In patients above the median age, the Kaplan–Meier curves demonstrated increasing risk with increasing quartiles for

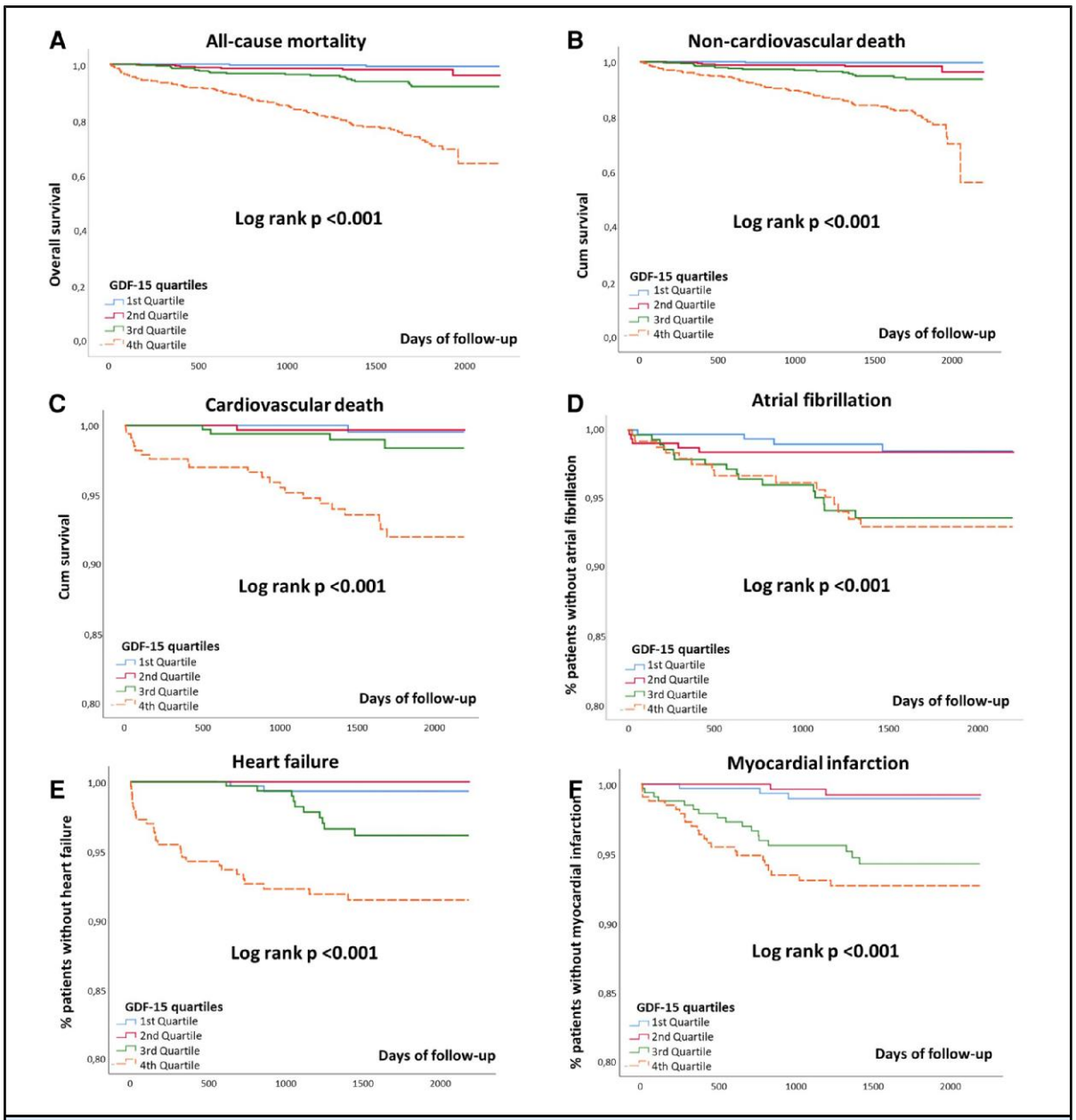

Fig. 2. Kaplan–Meier curves demonstrating overall survival (A), non-CV death (B), CV death (C), overall event-free survival for AF (D), HF hospitalization (E), and myocardial infarction (F), stratified by different quartiles of GDF-15. Color figure available online at clinchem.org.

all-cause mortality, CV-death, non-CV death, and HF hospitalization (online Supplemental Fig. 3).

Discussion

MAIN FINDINGS

This prospective observational study evaluated the prognostic value of GDF-15 in 1320 patients with acute chest pain without AMI. A total of 8.6% of the patients died and 9.4% reached a secondary end point, clearly demonstrating that this population is not without CV risk, even though AMI is excluded. Patients without AMI represent the majority of patients presenting with acute chest pain and are therefore of great interest to clinicians. We report 5 major findings, including low risk of death and CV events in patients with low

Table 2. Calculated HRs with 95% CI for primary and secondary end points in an unadjusted model, model 1 (adjusted for age and sex), and model 2 (adjusted for age, sex, eGFR, present smoker, hypertension, hyperlipidemia, diabetes, and previous myocardial infarction).

Calculated HRs			
Variable	**Unadjusted HR (95% CI)**	**Model 1, HR (95% CI)**	**Model 2, HR (95% CI)**
All-cause mortality			
Log2 GDF-15	3.56 (3.07–4.20), $P < 0.001$	2.78 (2.28–3.38), $P < 0.001$	2.80 (2.22–3.53), $P < 0.001$
GDF-15 > median	12.12 (6.13–23.95), $P < 0.001$	3.17 (1.52–6.63) $P = 0.002$	2.63 (1.24–5.60), $P = 0.012$
GDF-15 > 4th quartile	9.11 (6.00–13.83), $P < 0.001$	3.23 (2.02–5.14) $P < 0.001$	2.75 (1.69–4.45), $P < 0.001$
CV mortality			
Log2 GDF-15	3.19 (2.41–4.22), $P < 0.001$	2.49 (1.77–3.49), $P < 0.001$	2.70 (1.84–3.97), $P < 0.001$
GDF-15 > median	12.71 (3.02–53.56) $P < 0.001$	3.48 (0.74–16.38) $P = 0.115$	2.94 (0.61–14.18), $P = 0.180$
GDF-15 > 4th quartile	10.91 (4.42–26.92), $P < 0.001$	4.09 (1.49–11.257), $P = 0.006$	3.74 (1.31–10.63), $P = 0.013$
Future myocardial infarction			
Log2 GDF-15	1.81 (1.42–2.31), $P < 0.001$	1.23 (0.92–1.81), $P = 0.141$	1.09 (0.73–1.64), $P = 0.669$
GDF-15 > median	8.18 (3.23–20.73), $P < 0.001$	4.53 (1.63–12.60), $P = 0.004$	3.57 (1.27–10.00), $P = 0.016$
GDF-15 > 4th quartile	3.2 (1.78–5.74), $P < 0.001$	1.48 (0.74–2.94), $P = 0.268$	1.10 (0.53–2.30), $P = 0.797$
HF			
Log2 GDF-15	2.27 (1.77–2.89) $P < 0.001$	1.66 (1.21–2.29), $P = 0.002$	1.49 (1.00–2.22), $P = 0.051$
GDF-15 > median	18.79 (4.53–77.96), $P < 0.001$	8.18 (1.83–36.58), $P = 0.006$	7.23 (1.58–33.45), $P = 0.011$
GDF-15 > 4th quartile	7.00 (3.55–13.83), $P < 0.001$	3.18 (1.45–6.99), $P = 0.004$	2.60 (1.11–6.06), $P = 0.027$
AF			
Log2 GDF-15	1.66 (1.24–2.23), $P = 0.001$	0.87 (0.56–1.35) $P = 0.532$	0.67 (0.40–1.11), $P = 0.118$
GDF-15 > median	4.21 (2.00–8.83), $P < 0.001$	1.68 (0.72–3.96), $P = 0.124$	1.37 (0.56–3.35), $P = 0.488$
GDF-15 > 4th quartile	2.25 (1.19–4.27), $P = 0.013$	0.78 (0.37–1.63), $P = 0.506$	0.59 (0.27–1.31), $P = 0.198$

concentrations of GDF-15, the ability of GDF-15 to independently predict death, future MI, and HF hospitalization, and finally that GDF-15 was associated with future development of AF in an unadjusted model.

First, we demonstrated GDF-15's ability to reclassify patients into high or low long-term risk when added to traditional risk factors (Table 2), and that GDF-15 might provide additional information to hs-cTn and NT-proBNP (Table 3, Supplemental Table 6) in chest pain patients without AMI. Low levels of GDF-15 may imply less need of long-term follow-up in patients presenting with acute chest pain without AMI, and both the 1st and 2nd quartiles are associated with a very low risk of events (Fig. 1).

Second, GDF-15 is a strong and independent predictive marker for death and CV death. GDF-15 concentration in the 4th quartile was associated with a markedly increased risk of death (Table 2). Adding GDF-15 to established risk factors led to a significant increase in C-statistics in predicting all-cause mortality (Table 3), while adding hs-cTnT to established risk factors did not lead to an increase in C-statistics, suggesting that GDF-15 may be superior in mortality prediction. This may be because GDF-15 integrates information from several pathological conditions; in the myocardium, in atherosclerotic lesions, and in relation to other comorbidities and aging. Also, since GDF-15 is stable during acute cardiac events (14), it might be a better risk predictor in the proportion of patients who had acute myocardial injury (without NSTEMI), as the predictive ability of cTn in this group is less certain. However, an association between hs-cTn and all-cause mortality has been demonstrated in a similar but larger cohort (21).

Furthermore, our findings are consistent with previous studies of patients with acute chest pain and AMI. In a smaller study (n = 453, 30% with AMI), Eggers et al. demonstrated an HR of 2.1 per 1 SD increase in GDF-15 concentrations in predicting death during 5.8 years follow-up (22). Schaub et al. demonstrated similar findings in 645 patients with acute chest pain (18% AMI) with GDF-15 having a C-index of 0.85 for predicting death, being superior to hs-cTnT and BNP

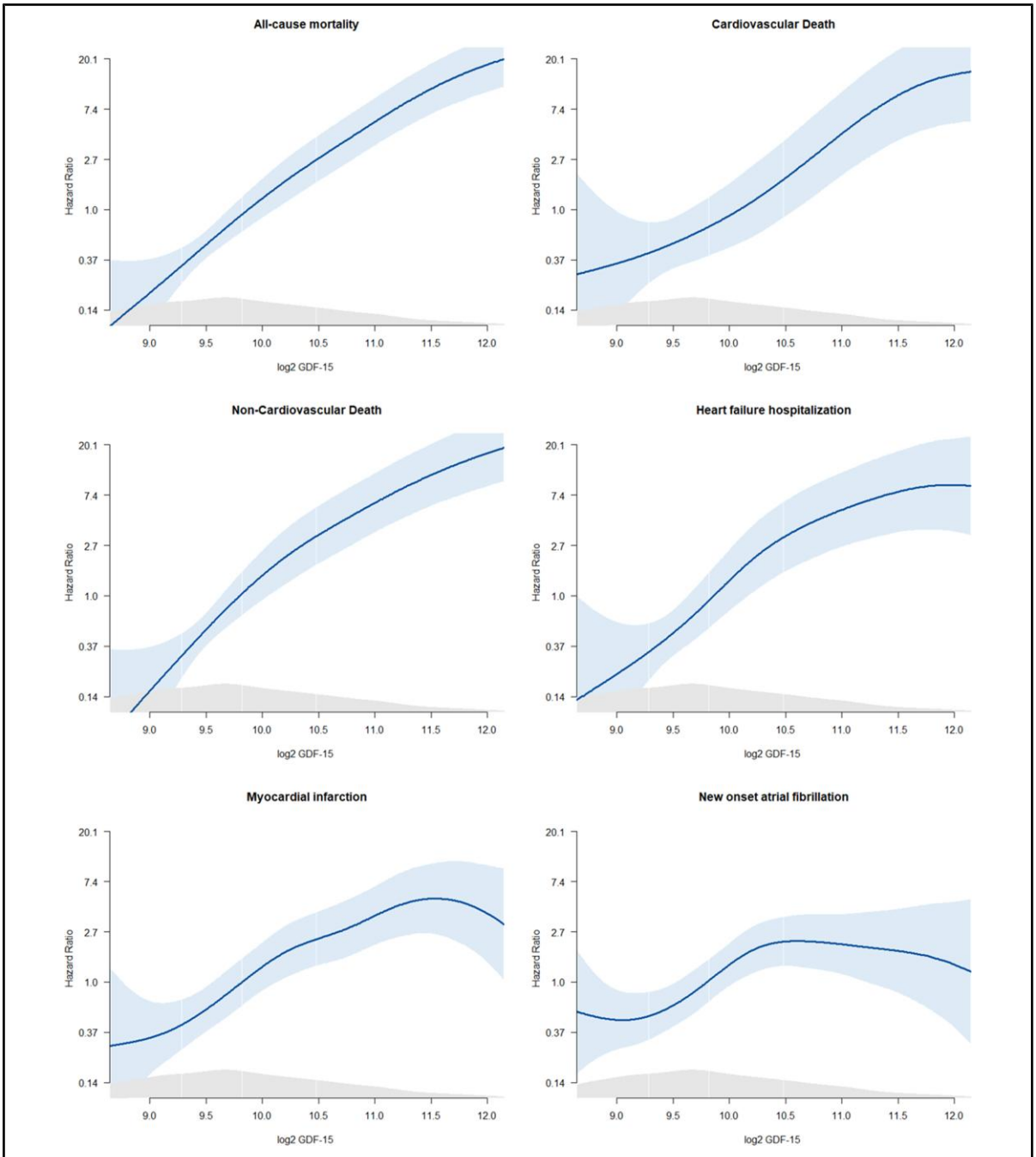

Fig. 3. Generalized additive models (GAM) curves demonstrating unadjusted HRs with 95% confidence intervals (shaded) for different end points along the *y*-axis and log2- transformed GDF-15 concentration (from 2.5th–97.5th percentile) along the *x*-axis. Density plots demonstrate the distribution of GDF-15 (shown on the x-axis).

(23). Schaub et al. also performed a subgroup analysis on patients without AMI (n = 531), demonstrating increased mortality and risk of AMI in patients with GDF-15 >1200 ng/L. This study had a smaller sample size, shorter follow-up, and included fewer end points than the current study.

Third, while GDF-15 in the 4th quartile was not associated with the risk of future AMI (Table 2),

Table 3. Incremental prognostic value of adding GDF-15 to established risk factors, hs-cTnT, and NT-proBNP. Risk factors include age, sex, eGFR, present smoker, hypertension, hyperlipidemia, diabetes, and previous myocardial infarction.

	C-statistic (95% CI)	*P*-value	Continuous NRI (95% CI)	*P*-value
All-cause mortality				
Risk factors	0.86 (0.84–0.88)	Reference	Reference	Reference
Risk factors + hs-cTnT	0.86 (0.84–0.88)	0.980	−0.13 (−0.32–0.06)	0.174
Risk factors + NT-proBNP	0.87 (0.85–0.89)	0.004	−0.08 (−0.27–0.11)	0.389
Risk factors + GDF-15	0.89 (0.87–0.90)	<0.001	0.20 (−0.00–0.38)	0.052
Risk factors + hs-cTnT and GDF-15	0.89 (0.87–0.90)	<0.001	0.20 (−0.00–0.38)	0.052
Risk factors + hs-cTnT + NT-proBNP + GDF-15	0.89 (0.87–0.91)	<0.001	0.14 (−0.05–0.33)	0.148
CV death				
Risk factors	0.85 (0.83–0.87)	Reference	Reference	Reference
Risk factors + hs-cTnT	0.85 (0.83–0.87)	0.432	0.30 (−0.07–0.68)	0.106
Risk factors + NT- proBNP	0.87 (0.85–0.89)	0.002	0.23 (−0.12–0.58)	0.198
Risk factors + GDF-15	0.89 (0.86–0.90)	0.023	0.38 (0.02–0.75)	0.038
Risk factors + hs-cTnT and GDF-15	0.89 (0.87–0.90)	0.023	0.42 (0.06–0.78)	0.024
Risk factors + hs-cTnT + NT-proBNP + GDF-15	0.89 (0.87–0.90)	0.019	0.40 (0.03–0.76)	0.034
Myocardial infarction				
Risk factors	0.80 (0.78–0.82)	Reference	Reference	Reference
Risk factors + hs-cTnT	0.80 (0.78–0.82)	0.601	0.25 (−0.03–0.54)	0.081
Risk factors + NT-proBNP	0.80 (0.78–0.82)	0.509	0.18 (−0.12–0.48)	0.246
Risk factors + GDF-15	0.80 (0.78–0.82)	0.706	0.12 (−0.18–0.42)	0.421
Risk factors + hs-cTnT and GDF-15	0.80 (0.78–0.82)	0.737	0.13 (−0.16–0.43)	0.386
Risk factors + hs-cTnT + NT-proBNP + GDF-15	0.80 (0.78–0.82)	0.724	0.13 (−0.16–0.43)	0.383
HF hospitalization				
Risk factors	0.82 (0.79–0.84)	Reference	Reference	Reference
Risk factors + hs-cTnT	0.82 (0.79–0.84)	0.764	−0.07 (−0.37–0.24)	0.673
Risk factors + NT-proBNP	0.82 (0.80–0.84)	0.022	−0.18 (−0.50–0.14)	0.264
Risk factors + GDF-15	0.82 (0.80–0.84)	0.737	−0.15 (−0.47–0.17)	0.367
Risk factors + hs-cTnT and GDF-15	0.82 (0.80–0.84)	0.746	−0.14 (−0.46–0.17)	0.377
Risk factors + hs-cTnT + NT-proBNP + GDF-15	0.82 (0.80–0.84)	0.461	−0.13 (−0.45–0.19)	0.431
AF				
Risk factors	0.75 (0.73–0.78)	Reference	Reference	Reference
Risk factors + hs-cTnT	0.76 (0.73–0.78)	0.204	0.37 (0.07–0.67)	0.015
Risk factors + NT-proBNP	0.77 (0.74–0.78)	0.063	0.58 (0.30–0.85)	<0.001
Risk factors + GDF-15	0.78 (0.75–0.80)	0.005	0.40 (0.10–0.70)	0.009
Risk factors + hs-cTnT and GDF-15	0.78 (0.75–0.80)	0.003	0.54 (0.25–0.83)	<0.001
Risk factors + hs-cTnT + NT-proBNP + GDF-15	0.78 (0.76–0.80)	0.005	0.50 (0.21–0.80)	<0.001

GDF-15 greater than median was associated with a HR of 3.57 (95% CI, 1.27–10.00, $P = 0.016$), indicating that GDF-15 may be a predictor of AMI as well, when lower cutoff values are used. This may be explained by the non-linear relationship between GDF-15 concentration and risk of AMI, which may be derived from the Kaplan–Meier curve and GAM curve (Fig. 2, F, Fig. 3). Previous studies have reported

conflicting data in patients with ACS (24). In our study GDF-15 was associated with an increased risk of future AMI, but did not add incremental value beyond that of traditional risk factors and hs-cTnT.

Fourth, we demonstrated that GDF-15 may independently predict HF as GDF-15 in the 4th quartile was associated with a markedly increased risk of future HF hospitalization (Table 2). A meta-analysis by Wang et al. (24) on the prognostic value of GDF-15 in patients with ACS included 13 studies. Only 2 studies included HF as an end point, and overall results demonstrated an elevated risk of developing HF with a relative risk (RR) of 6.66, and evident heterogeneity (I^2 of 87%), making it difficult to reach a clear conclusion with regard to a positive correlation. The current study further strengthens the theory that there is an association between elevated GDF-15 levels and the risk of developing HF.

Fifth, this study is the first to investigate the ability of GDF-15 to predict AF in an acute chest pain population. GDF-15 levels in the 4th quartile were associated with an unadjusted HR of 2.25 (95% CI, 1.19–4.27, $P = 0.013$) in predicting AF, but the association was not significant in adjusted models. There was no significant difference in C-statistics between hs-cTnT and GDF-15 in the prediction of AF. Previous studies have demonstrated that GDF-15 may be associated with left atrial fibrosis (25) and atrial matrix remodeling (26). Increased risk of AF has been seen with higher GDF-15 levels in community-based individuals (27, 28) and after coronary artery bypass grafting (29). On the other hand, one study showed that GDF-15 concentration in patients with HF was not influenced by the presence of atrial fibrillation (30). In sum, our study showed that higher GDF-15 concentration may predict future development of AF, but the association was not significant in the adjusted models. Further studies including larger cohorts with a higher number of patients reaching end points should be performed to validate our findings.

CLINICAL IMPLICATIONS

This study demonstrates that GDF-15 adds information to current standard of clinical care, and by being a nonspecific marker it may better reflect the heterogeneity of etiologies underlying the clinical presentation of acute chest pain. Measuring GDF-15 may further guide clinicians regarding who will benefit from aggressive risk reduction intervention and who could be discharged without further follow-up. Improved identification of patients at low risk is beneficial for clinical care. There has been a recognition that CV risk is a continuum starting at the level of detection of high-sensitivity (hs) troponins (31), thus limiting hs-troponin prognostic value when using the 99th percentile cutoff value. On the other hand, the use of low cutoffs for hs-troponins may falsely classify patients as high risk, leading to unnecessary diagnostic work-up such as coronary angiography (32). The use of additional biomarkers may better classify patients into risk categories, and as demonstrated in our study, GDF-15 may better classify patients into high or low risk when used in combination with cardiac troponins (Table 3, Supplemental Table 6).

Even though associated with age, GDF-15 seemingly also predicts risk of death and CV events in patients above 61 years (online Supplemental Table 8). GDF-15 in the lower quartiles is also associated with a low risk of events in higher age groups (Supplemental Fig. 3). Our evidence suggests that GDF-15 may be used as a prognostic marker regardless of age (Supplemental Table 8), although the hazard ratios in patients below the median age might be overestimated as a result of a low event rate in this group.

Another important observation is that GDF-15 seems to be as predictive of non-CV death as it is of CV death (Fig. 2, Fig. 3), in keeping with earlier studies which have demonstrated that the risk prediction value of GDF-15 is also related to non-cardiac conditions (16, 17). Accordingly, GDF-15 can serve as a predictor of mortality/general health, while traditional cardiac-specific biomarkers such as hs-cTnT and NT-proBNP may be better at diagnosing and ruling in/ruling out myocardial injury and HF, respectively.

A clinically highly relevant observation from our data is that the cutoff values for optimizing sensitivity and specificity in prediction of different end points varied widely (online Supplemental Table 9). This might become an important obstacle if GDF-15 is to be implemented in clinical practice. Another obstacle could be the lack of standardization between GDF-15 assays, although an earlier publication show a reasonable correlation/agreement between this assay from Roche Diagnostics and an earlier used immunoradiometric assay (33).

LIMITATIONS

Few patients met the secondary end points. In the regression analysis residual confounders might influence the data analysis. Previous studies have shown that GDF-15 correlates with BMI. We did not include BMI in our regression analysis because we had sufficient data to calculate BMI in only 660 patients. On the other hand, there were no differences in BMI between different quartiles of GDF-15 in the 660 patients where BMI was calculated, making it unlikely that it would have impacted the analysis. Patients with hyperlipidemia and hypertension were found to have reduced risk, and this somewhat paradoxical finding might be related to a very high number of patients receiving risk reduction treatment for these conditions. Furthermore, other

confounders, like cancer and autoimmune disorders, were not investigated. There was a strong association between age and GDF-15 as may be depicted from Table 1 and Supplemental Table 1, and this has to be taken into account in the interpretation of all the unadjusted results. However, the association between age and GDF-15 has been accounted for in all multivariable analysis and by age-stratified analysis. In contrast to many other countries, a proportion of low-risk chest pain patients in Norway are initially seen by a primary physician, thus excluding some of the lowest risk patients. The percentage of ACS and non-cardiac chest pain patients in the overall WESTCOR cohort were still similar to comparable studies e.g., APACE (34), so we do not expect this to have a major influence on our data.

Conclusion

GDF-15 is a robust prognostic marker in chest pain patients without AMI, and independently predicts future risk of death, AMI, and HF. GDF-15 provides additional prognostic information beyond established risk factors and biomarkers, and may aid in identifying patients at low risk and those at high risk who require further diagnostics and management.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: AMI, acute myocardial infarction; GDF-15, growth differentiation factor 15; CV, cardiovascular; AF, atrial fibrillation; HR, hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; NRI, net reclassification improvement; BMI, body mass index.

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