**Growth-Differentiation Factor-15 in the Early Diagnosis and Risk Stratification of Patients with Acute Chest Pain**

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**BACKGROUND:** Growth-differentiation factor-15 (GDF-15) is a stress-responsive marker that might aid in the early diagnosis and risk stratification of patients with suspected acute myocardial infarction (AMI).

**METHODS:** In a prospective, international multicenter study, GDF-15, high-sensitivity cardiac troponin T (hs-cTnT), and B-type natriuretic peptide (BNP) were measured in 646 unselected patients presenting to the emergency department with acute chest pain. The final diagnosis was adjudicated by 2 independent cardiologists. The primary prognostic end point was all-cause mortality during a median follow-up of 26 months.

**RESULTS:** AMI was the adjudicated final diagnosis in 115 patients (18%). GDF-15 concentrations at presentation were significantly higher in AMI patients compared to patients with other diagnoses. The diagnostic accuracy of GDF-15 at presentation for the diagnosis of AMI as quantified by the area under the ROC curve (AUC) was lower (AUC 0.69, 95% CI 0.64 – 0.74) compared to hs-cTnT (AUC 0.96, 95% CI 0.94 – 0.98, P < 0.001) and BNP (AUC 0.74, 95% CI 0.69 – 0.80, P = 0.02). A total of 55 deaths occurred during follow-up. GDF-15 predicted all-cause mortality independently of and more accurately than hs-cTnT [AUC 0.85 (95% CI 0.81 – 0.90) vs 0.77 (95% CI 0.72 – 0.83), P = 0.002] and BNP (AUC 0.75, 95% CI 0.68 – 0.82, P = 0.007). Net reclassification improvement was 0.15 (P = 0.01), and the absolute integrated discrimination improvement was 0.07, yielding a relative integrated discrimination improvement of 0.36 (P = 0.07).

**CONCLUSIONS:** GDF-15 predicts all-cause mortality in unselected patients with acute chest pain independently of and more accurately than hs-cTnT and BNP. However, GDF-15 does not seem to help in the early diagnosis of AMI.

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omyocytes in the setting of myocardial ischemia and reperfusion suggests that it might be a protective factor after AMI. This hypothesis was supported by a mouse model showing GDF-15-deficient mice developed greater infarct size and more cardiomyocyte apoptosis after simulated ischemia/reperfusion in vivo (12). GDF-15 concentrations are independently related to age, smoking, diabetes, impaired renal function, C-reactive protein, and BNP, suggesting that GDF-15 is a general biomarker of cardiovascular risk and inflammation (14, 15). Initial pilot studies have shown that GDF-15 may provide powerful prognostic information in multiple cardiovascular disorders (14–20). The diagnostic and prognostic performance of GDF-15 in unselected patients presenting with acute chest pain to the ED is unknown, particularly when compared with high-sensitivity cardiac troponin T (hs-cTnT) and BNP.

We performed a large multicenter study to examine the diagnostic and prognostic performance of GDF-15 in unselected patients presenting to the ED with acute chest pain.

**Methods**

**STUDY DESIGN AND POPULATION**

APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital Basel, Switzerland (21–23). From April 2006 to May 2008, a total of 689 consecutive patients presenting to the ED with symptoms suggestive of AMI such as acute chest pain and angina pectoris were recruited. GDF-15 and hs-cTnT values at presentation were available in 646 (93%) of these patients. Patients with terminal kidney failure requiring dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

**ROUTINE CLINICAL ASSESSMENT**

All patients underwent an initial clinical assessment including clinical history, physical examination, 12-lead ECG, pulse oximetry, standard blood tests, and chest radiography. Standard cardiac troponin as determined by the local hospital assays, the MB fraction of creatine kinase, and myoglobin were measured at presentation, and thereafter as long as clinically indicated. Treatment of patients was left at the discretion of the attending physicians.

**ADJUDICATED FINAL DIAGNOSIS**

Final diagnoses were adjudicated centrally by 2 independent cardiologists after review of all available medical records (including patient history, physical examination, results of laboratory and radiologic testing, ECG, echocardiography, cardiac exercise test, and coronary angiography) pertaining to the patient from the time of ED presentation to 60-day follow-up. Cases were reviewed and adjudicated in conjunction with a third cardiologist in situations of diagnostic disagreement.

AMI was defined as recommended in current guidelines (5, 24). In brief, AMI was diagnosed when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Cardiac necrosis was diagnosed by at least 1 value of the local cardiac troponin above the 99th percentile (or above the 10% imprecision value if not fulfilled at the 99th percentile) (5, 24–26). A significant rise and/or fall was defined as a change of at least 30% of the 99th percentile (or the 10% CV level) within 6–9 h (5, 24–26). The following local standard cardiac troponin assays were used for the adjudication of the final diagnosis: Abbott Axsym cTnI ADV, Beckmann Coulter Accu cTnI, and Roche cTnT fourth generation. All 3 are well-validated current standard cardiac troponin assays with comparable performance in the diagnosis of AMI (25, 26). Unstable angina was diagnosed in cases of cardiac troponin concentrations within reference intervals and typical angina at rest, deterioration of a previously stable angina, positive cardiac exercise testing, or cardiac catheterization with coronary arteries found to have stenosis ≥70% and in ambiguous cases in which follow-up information revealed AMI or a sudden unexpected cardiac death within 60 days. Furthermore, predefined diagnostic categories included cardiac but not coronary symptoms (e.g., perimyocarditis, tachyarrhythmias) and noncardiac symptoms. If AMI was excluded in the ED but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified to be of unknown origin.

**BIOCHEMICAL ANALYSIS**

At presentation to the ED patient blood samples were collected in serum tubes for determination of GDF-15 and hs-cTnT and in EDTA-plasma for determination of BNP. After centrifugation, samples were frozen at −80 °C until assayed in a blinded fashion in a dedicated core laboratory.

GDF-15 was measured by using a precommercial sandwich immunoassay based on the enhanced chemiluminescence immunoassay principle. The assay used a polyclonal biotinylated goat capture antibody and a monoclonal detection antibody linked to a ruthenium complex. According to the manufacturer the lower limit of detection of the GDF-15 assay was <90 ng/L and the between-run imprecision of the assay was 2.8% (CV) at a concentration of 480 ng/L. The assay was
standardized to the immunoradiometric GDF-15 assay described by Kempf et al., with reported median GDF-15 concentrations in healthy, elderly individuals of 762 ng/L [interquartile range (IQR) 600–959 ng/L] (27). On the basis of previously established and published cutoff concentrations, patients were stratified according to 2 prespecified GDF-15 cutoffs, 1200 and 1800 ng/L (17).

hs-cTnT was measured on the Elecsys 2010 (Roche Diagnostics). For hs-cTnT the limit of blank and limit of detection have been determined to be 3 and 5 ng/L, respectively; an imprecision corresponding to 10% CV was reported at 13 ng/L and the 99th-percentile of a healthy reference population at 14 ng/L (28).

BNP was measured by using the AxSYM BNP assay (Abbott Laboratories) (29). The analytical range for the AxSYM assay as reported by the manufacturer extends from 15 000 to 20 000 pg/mL. Glomerular filtration rate was calculated by using the abbreviated Modification of Diet in Renal Disease formula (30).

**FOLLOW-UP AND CLINICAL END POINTS**
After hospital discharge patients were contacted after 3, 12, 24, and 36 months by telephone calls or in writing. Information regarding death was obtained from the national registry on mortality, the hospital’s diagnosis registry, and the family physician’s records. The primary end point was all-cause mortality in all patients; secondary end points were cardiovascular mortality in all patients and a composite end point of all-cause mortality or first AMI in chest pain patients without AMI at the initial presentation. Deaths were considered to be of cardiovascular cause unless specific information was available that death was attributable to other causes including cancer, infection, and trauma.

**STATISTICAL ANALYSIS**
Continuous variables are presented as mean or medians with IQR and categorical variables as numbers and percentages. Comparisons between groups were made by using χ² analysis for categorical and Mann–Whitney U-tests for continuous variables. ROC curves (and associated 95% CIs) were constructed to assess the sensitivity and specificity throughout the concentration range of GDF-15 and hs-cTnT to compare their individual or combined ability to diagnose AMI and to predict the probability of all-cause death and AMI during follow-up. Comparison of areas under the ROC curves (AUCs) was performed as recommended by DeLong (31). Kaplan–Meier analysis was performed for survival, and log-rank values were used to assess statistical significance. Cox proportional hazards analysis was used to compute hazard ratios and 95% CI of potential predictors of all-cause death, cardiovascular death, and death or AMI in patients without AMI at the initial presentation. All significant variables were then tested in a multivariable model by using forward stepwise variable selection. Improvements in mortality risk classification were evaluated by using the net reclassification improvement method developed by Pencina et al. (32). The net reclassification improvement represents the percentage change in predicted mortality risk after the inclusion of a new marker in a survival model. Model 1 was adjusted for age, established cardiovascular risk factors (hypertension, dyslipidemia, smoking, and diabetes mellitus), hs-cTnT, and BNP. Model 2 was additionally adjusted for GDF-15. We categorized mortality risk at 1 year of follow-up and compared the proportion of patients whose new mortality prediction was improved to those whose prediction became less accurate with the use of the new survival model. A related parameter, the integrated discrimination improvement, represents the increase in discriminatory power obtained by comparing average predicted probabilities between survivors and nonsurvivors of the 2 models without first categorizing the probabilities (33).

All hypothesis testing was 2-tailed, and a P-value of <0.05 was considered statistically significant. All statistical analyses were performed by using SPSS for Windows 15.0 (SPSS) and MedCalc 9.6.4.0 (MedCalc Software).

**Results**

**CHARACTERISTICS OF PATIENTS**
Baseline characteristics of the 646 patients enrolled are shown in Table 1. The adjudicated final diagnosis was AMI in 115 patients (18%) (30% ST-elevation MI, 70% non–ST-elevation MI), unstable angina in 98 (15%), cardiac symptoms of origin other than coronary artery disease (CAD) in 83 (13%), noncardiac symptoms in 298 (46%), and symptoms of unknown origin in 52 (8%). The overall median value at presentation of GDF-15 was 1225 ng/L (IQR 798–2013), of hs-cTnT 7.8 ng/L (IQR 3.4–23.6), and of BNP 77 pg/mL (IQR 26–211). Baseline characteristics according to GDF-15 concentrations at presentation are displayed in Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol58/issue2.

**CONCENTRATIONS OF GDF-15 IN DIFFERENT DIAGNOSTIC GROUPS OF CHEST PAIN PATIENTS**
Concentrations of GDF-15 at presentation are displayed in Fig. 1. Patients with AMI had higher presentation GDF-15 (median 1910 ng/L, IQR 1150–3060 ng/L) compared to patients with unstable angina (median 1325 ng/L, IQR 976–1835 ng/L, P < 0.001) and patients without ACS (median 1040 ng/L, IQR 783–1785 ng/L, P < 0.001). In patients with cardiac but not
coronary disease, median GDF-15 values were 1450 ng/L (IQR 974–2410 ng/L), which was lower compared to patients with AMI ($P < 0.05$) and similar compared to unstable angina patients ($P = 0.30$). There were no significant differences regarding GDF-15-values in patients with ST-elevation MI and non–ST-elevation MI ($P = 0.55$).

**GDF-15 FOR THE DIAGNOSIS OF AMI**

The diagnostic accuracy of GDF-15 at presentation for the diagnosis of AMI as quantified by the AUC was 0.69 (95% CI 0.64–0.74), which was lower compared to hs-cTnT at presentation (AUC 0.96, 95% CI 0.94–0.98, $P < 0.001$ for comparison). BNP was available in 513 of the 646 patients and had a higher diagnostic accuracy than GDF-15 (AUC 0.74, 95% CI 0.69–0.80, $P = 0.02$ for comparison). The additional use of GDF-15 in combination with hs-cTnT did not increase the diagnostic accuracy provided by hs-cTnT alone (data not shown).

**GDF-15 FOR THE PREDICTION OF ALL-CAUSE DEATH**

During a median (SD) follow-up time in survivors of 26 (5) months, there were 55 deaths in the whole cohort. Median GDF-15 values in deceased patients (3070 ng/L, IQR 1900–5210) were significantly higher compared to those in survivors (1140 ng/L, IQR 775–1823, $P < 0.001$).

Cumulative 24-month all-cause mortality rates were 0.7%, 6.3%, and 21.1% in patients with low (<1200 ng/L), moderately increased (1200–1800 ng/L), and markedly increased (>1800 ng/L) concentra-

| Table 1. Baseline characteristics of the patients.a |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | All patients     | AMI             |                  |                  |
|                  | (n = 646)        | Yes (n = 115)   | No (n = 531)    |                  |
| Age, y           | 64 (51–76)       | 73 (62–82)      | 62 (49–74)      | $<0.001$         |
| Male sex, n (%)  | 426 (66)         | 82 (71)         | 344 (35)        | 0.18             |
| Risk factors, n (%) |                |                  |                  |                  |
| Hypertension     | 397 (62)         | 86 (75)         | 311 (59)        | 0.001            |
| Hyperlipidemia   | 282 (44)         | 58 (50)         | 224 (42)        | 0.11             |
| Diabetes mellitus| 110 (17)         | 26 (23)         | 84 (16)         | 0.12             |
| Current smoking  | 155 (24)         | 30 (26)         | 125 (24)        | 0.56             |
| History of smoking | 212 (33)        | 32 (28)         | 183 (35)        | 0.17             |
| History, n (%)   |                |                  |                  |                  |
| CAD              | 228 (35)         | 42 (37)         | 186 (35)        | 0.76             |
| Previous MI      | 167 (26)         | 31 (27)         | 136 (26)        | 0.77             |
| Previous revascularization (percutaneous intervention, coronary artery bypass graft) | 181 (28) | 27 (24) | 154 (29) | 0.23 |
| Peripheral artery disease | 43 (7) | 12 (10) | 31 (6) | 0.07 |
| Previous stroke  | 40 (6)           | 15 (13)         | 25 (5)          | 0.001            |
| Vital status, median (IQR) |           |                  |                  |                  |
| Heart rate, bpm  | 75 (66–88)       | 80 (66–91)      | 75 (66–87)      | 0.07             |
| Systolic blood pressure, mmHg | 141 (127–160) | 136 (123–162) | 142 (128–160) | 0.07 |
| Diastolic blood pressure, mmHg | 85 (77–94) | 84 (76–96) | 86 (77–94) | 0.29 |
| Body mass index, kg/m², median (IQR) | 26 (24–29) | 26 (24–29) | 26 (24–29) | 0.94 |
| Glomerular filtration rate, mL·min⁻¹·(1.73 m²)⁻¹, median (IQR) | 91 (74–109) | 78 (59–103) | 93 (76–111) | $<0.001$ |
| Electrocardiographic findings, n (%) |                  |                  |                  |                  |
| Left bundle branch block | 24 (3) | 12 (11) | 12 (2) | $<0.001$ |
| ST-segment elevation | 42 (7) | 33 (29) | 9 (2) | $<0.001$ |
| ST-segment depression | 66 (10) | 22 (19) | 44 (8) | $<0.001$ |
| T-wave inversion  | 39 (6)          | 13 (11)         | 26 (5)          | 0.01             |
| No relevant ECG findings | 475 (74) | 35 (30) | 440 (83) | $<0.001$ |

* Data are displayed as absolute numbers (percentage) or median (IQR).
tions of GDF-15 at presentation (log rank $P < 0.001$, Fig. 2 A). The same predictive value of GDF-15 concentrations for all-cause mortality was observed in Kaplan–Meier analyses for the important subgroups of patients with baseline hs-cTnT below the 99th percentile (troponin-negative patients, $P < 0.001$), patients with AMI ($P < 0.001$), patients with nonischemic cardiac chest pain ($P = 0.008$), and with noncardiac chest pain ($P < 0.001$), but not for patients with unstable angina ($P = 0.20$).

Assessing the prognostic value for the prediction of all-cause death by ROC-curve analysis showed a significantly higher AUC for presentation values of GDF-15 (AUC 0.85, 95% CI 0.81–0.90) compared to both hs-cTnT (AUC 0.77, 95% CI 0.72–0.83, $P = 0.002$) and BNP (AUC 0.75, 95% CI 0.68–0.82, $P = 0.007$). A value of 1375 ng/L emerged as the best prognostic cutoff value of GDF-15 to predict death, with a sensitivity of 95% and a specificity of 61%. All 3 markers showed highest accuracy in predicting midterm mortality (180 days of follow up, AUC for GDF-15 0.90, for hs-cTnT 0.82, for BNP 0.83, Fig. 3). At 360, 540, and 720 days, the prognostic performance of GDF-15 was significantly better compared to hs-cTnT and BNP.

According to multivariable Cox proportional hazard analysis GDF-15 at presentation significantly predicted all-cause mortality independently of other predictors including hs-cTnT and BNP (Table 2). Reclassification tables for predicting death according to age, cardiovascular risk factors, and presentation values of hs-cTnT and BNP (model 1) and the additional use of GDF-15 (model 2) yielded a net reclassification improvement of 0.15 ($P = 0.01$; see online Supplemental Table 2). The absolute integrated discrimination improvement was 0.07, yielding a relative integrated discrimination improvement of 0.36 ($P = 0.07$).

GDF-15 for the Prediction of Cardiovascular Death

Of the 55 deceased patients, 34 (62%) died from cardiovascular causes, 10 (18%) from cancer, 10 (18%) from infectious diseases, and 1 (2%) from suicide. Cumulative 24-month cardiovascular mortality rates were 0.7%, 4.5%, and 13.3% in patients with low (<1200 ng/L), moderately increased (1200–1800 ng/L), and markedly increased (>1800 ng/L) concentrations of GDF-15 at presentation (log rank $P < 0.001$, Fig. 2B).

In ROC analysis, GDF-15 was prognostically superior to hs-cTnT (AUC 0.81 vs 0.75, $P = 0.04$ for comparison) and similar to BNP (AUC 0.77, $P = 0.35$ for comparison). In univariate Cox–proportional hazard analysis, concentrations of GDF-15 predicted cardiovascular death ($P < 0.001$), as did BNP ($P < 0.001$) and hs-cTnT ($P = 0.05$). In multivariable analysis, however, none of the 3 markers was significant (all $P$ values >0.05), and only age ($P = 0.001$) and history of CAD ($P = 0.01$) remained significant predictors of cardiovascular mortality.
GDF-15 FOR THE PREDICTION OF DEATH OR AMI IN CHEST PAIN PATIENTS WITHOUT AMI

In patients without AMI at the initial presentation (n = 531, 82%), there were 30 (5.6%) deaths and 35 (6.6%) first AMIs during follow up, resulting in a composite end point of death or AMI in 52 patients (9.8%). Median GDF-15 concentrations of patients reaching the composite end point were significantly higher compared to those in patients who did not (median 1800 ng/L, IQR 1190–3070 ng/L vs median 1045 ng/L, IQR 739–1730 ng/L, P < 0.001). Whereas only 3.6% of chest pain patients without AMI with low GDF-15 concentrations (<1200 ng/L) reached the combined end point of death or AMI, 12.3% with moderately increased concentrations (1200–1800 ng/L) and 16.8% with markedly increased GDF-15 concentrations (>1800 ng/L, P < 0.001) reached the combined end point.

Fig. 2. Kaplan–Meier curves for the cumulative rates of all-cause death (A) and cardiovascular death (B) in all chest pain patients.

Kaplan–Meier analysis displaying cumulative rates of all-cause death (A) and cardiovascular death (B) during follow-up in all chest pain patients according to concentrations of GDF-15.

Fig. 3. Prognostic performance of GDF-15, hs-cTnT, and BNP measurements at presentation for the prediction of all-cause death at different time points.

The prognostic accuracy of GDF-15, hs-cTnT, and BNP at presentation for the prediction of all-cause death as quantified by the AUC according to different time points of follow-up.

Fig. 4. Kaplan–Meier curves for the cumulative rates of death or AMI in patients without AMI at initial presentation.

Kaplan–Meier analysis displaying cumulative rates of death or AMI in patients without AMI at initial presentation according to levels of GDF-15.
Analysis of diagnostic subgroups revealed that concentrations of GDF-15 predicted the combined end point of death or AMI during follow-up in patients with nonischemic cardiac chest pain \((P = 0.008)\) and noncardiac chest pain \((P < 0.001)\), but not in patients with unstable angina \((P = 0.54)\).

In ROC analysis, the 3 markers performed similarly (AUC 0.73 for GDF-15, 0.72 for hs-cTnT, and 0.67 for BNP; \(P > 0.05\) for all comparisons). Although all 3 markers were significant predictors in univariate Cox proportional hazards analysis, only GDF-15 \((P = 0.005)\) and hs-cTnT \((P = 0.02)\), but not BNP \((P = 0.72)\), remained significant predictors after multivariable adjustment.

Discussion

In this prospective, international multicenter study of 646 consecutive patients presenting to the ED with acute chest pain, we examined the diagnostic and prognostic value of GDF-15. We report 3 major findings:

First, GDF-15 concentrations at presentation were significantly higher in patients with AMI compared to patients with other diagnoses. The diagnostic accuracy of GDF-15 at presentation for the diagnosis of AMI, however, was markedly lower compared to hs-cTnT. Second, GDF-15 at presentation was a powerful predictor of all-cause death and cardiovascular death in all patients, and a powerful predictor of death or AMI in patients without AMI at the initial presentation. Importantly, these associations also held in the subgroups of patients with AMI, nonischemic cardiac chest pain, and noncardiac chest pain. Third, the prognostic value of GDF-15 for adverse outcomes was more accurate than, and independent of, hs-cTnT and BNP.

These results are of clinical importance: GDF-15 constitutes a strong, valuable, and independent prognostic indicator in unselected patients with acute chest pain regardless of the underlying disease.

### Table 2. Cox proportional hazard analysis for prediction of all-cause death during follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
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<th>Multivariable analysis</th>
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<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>(P)</td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>(P)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.10 (1.07–1.13)</td>
<td>&lt;0.001</td>
<td></td>
<td>1.10 (1.06–1.14)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Female sex</td>
<td>0.71 (0.39–1.28)</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (per increase of 1 unit)</td>
<td>0.95 (0.89–1.01)</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>2.58 (1.41–4.35)</td>
<td>0.002</td>
<td></td>
<td>1.78 (0.90–3.50)</td>
<td>0.10</td>
<td></td>
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<tr>
<td>History of coronary artery disease</td>
<td>4.80 (2.68–8.59)</td>
<td>&lt;0.001</td>
<td></td>
<td>3.00 (1.54–5.87)</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Active smoking</td>
<td>0.69 (0.35–1.38)</td>
<td>0.69</td>
<td></td>
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<tr>
<td>Systolic blood pressure (per mmHg)</td>
<td>0.98 (0.97–1.00)</td>
<td>0.006</td>
<td></td>
<td>0.99 (0.98–1.01)</td>
<td>0.22</td>
<td></td>
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<tr>
<td>Estimated glomerular filtration rate [per increase in mL·min(^{-1}·(1.73 m^2)^{-1})]</td>
<td>0.97 (0.96–0.98)</td>
<td>&lt;0.001</td>
<td></td>
<td>0.99 (0.99–1.01)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>GDF-15 (per increase of 100 ng/L)</td>
<td>1.02 (1.01–1.02)</td>
<td>&lt;0.001</td>
<td></td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>hs-cTnT (per increase of 100 ng/L)</td>
<td>1.04 (1.00–1.09)</td>
<td>0.07</td>
<td></td>
<td>1.05 (0.99–1.12)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>BNP (per increase of 100 pg/mL)</td>
<td>1.09 (1.06–1.13)</td>
<td>&lt;0.001</td>
<td></td>
<td>1.10 (0.96–1.05)</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

Reliable markers for short- as well as long-term risk stratification of a heterogeneous group of patients presenting with acute chest pain remain an unmet need. One of the validated bedside risk stratification tools is the TIMI (Thrombolysis in Myocardial Infarction) risk score that estimates the risk of death and MI and the need for urgent coronary revascularization in patients with ACS (7). According to the findings of 2 recent studies, the TIMI risk score may also be useful in an unselected cohort of patients with chest pain (7, 8). Although cardiac troponin is the most well-established marker for prediction of short- and long-term adverse cardiac events in patients with ACS (2, 6–9), an increased cardiac troponin concentration implies that cardiac necrosis has already occurred. An ideal prognostic marker would identify patients at an earlier stage, when preventive or therapeutic measures might influence the course of the disease. In the heart, GDF-15 concentrations increase in response to stress associated with tissue injury or inflammation, and myocardial ischemia seems to be such a stressor (12, 13). Results of earlier studies demonstrated a powerful predictive value of GDF-15 in patients with various cardiovascular disorders, including acute chest pain (14–20). Wollert et al. showed that increasing concentrations of GDF-15 were associated with an increasing risk of
DIAGNOSTIC VALUE OF GDF-15

GDF-15 is not expressed in the heart under normal physiological conditions, but has been shown to be strongly induced in the myocardium after ischemic injury (12). This inducibility suggested that GDF-15 could be a valuable marker for the diagnosis of AMI. To our knowledge, this is the first study to prospectively analyze the performance of GDF-15 in the diagnosis of AMI in comparison to the novel hs-cTnT. Our data clearly showed that GDF-15 concentrations do not have added diagnostic utility over that provided by hs-cTnT.

Our data provide further support to the concept of using a multiple-marker approach in patients with acute chest pain. GDF-15 provided additional prognostic value when used in combination with hs-cTnT, whereas previous studies had suggested that copeptin, another novel biomarker, seemed to provide additional diagnostic value when used in combination with cTnT and cTnI (23, 34).

Potential limitations of the current study merit consideration. First, because this was a prospective observational study, we were unable to quantify exactly the clinical benefit associated with improved risk stratification. A further unknown was how to best avoid adverse outcome in patients with acute chest pain identified to be at increased risk by increased concentrations of GDF-15. Second, given that escalating GDF-15 concentrations were linked to factors also linked to increased morbidity and mortality, residual confounding may be present in the reported data. Third, we cannot comment on the diagnostic and prognostic accuracy among patients with terminal kidney failure requiring dialysis, because such patients were excluded from our study. Fourth, because the final diagnosis was adjudicated according to cardiac troponin concentrations as suggested in the universal definition of AMI, there was a bias favoring hs-cTnT over the other biomarkers. Fifth, the total number of events was relatively small (n = 55 deaths). This limited statistical power, particularly for subgroup analyses.

In conclusion, GDF-15 predicts all-cause mortality in unselected patients with acute chest pain independently of and more accurately than hs-cTnT and BNP regardless of the adjudicated final diagnosis. It furthermore predicts cardiovascular mortality in all patients and the composite of death and AMI in chest pain patients without AMI at initial presentation. However, GDF-15 does not seem to help in the early diagnosis of AMI.

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