**Growth-Differentiation Factor-15 for Long-Term Risk Prediction in Patients Stabilized After an Episode of Non–ST-Segment–Elevation Acute Coronary Syndrome**

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**Background**—Growth-differentiation factor-15 (GDF-15) has emerged as a prognostic biomarker in patients with non–ST-segment–elevation acute coronary syndrome. This study assessed the time course and the long-term prognostic relevance of GDF-15 levels measured repetitively in patients with non–ST-segment–elevation acute coronary syndrome during 6 months after the acute event.

**Methods and Results**—GDF-15 and other biomarkers were measured at randomization, after 6 weeks, and after 3 and 6 months in 950 patients with non–ST-segment–elevation acute coronary syndrome included in the FRagmin and Fast Revascularization during InStability in Coronary artery disease II study. Study end points were death, recurrent myocardial infarction, and their composite during 5-year follow-up. Median GDF-15 levels decreased slightly from 1357 ng/L at randomization to 1302 ng/L at 6 months ($P<0.001$). GDF-15 was consistently related to cardiovascular risk factors and biochemical markers of hemodynamic stress, renal dysfunction, and inflammation. Moreover, GDF-15 was independently related to the 5-year risk of the composite end point when measured at both 3 months (adjusted hazard ratio, 1.8 [1.0 to 3.0]) and 6 months (adjusted hazard ratio, 2.3 [1.3 to 4.1]). Serial measurements of GDF-15 at randomization and 6 months helped to identify patient cohorts at different levels of risk, with patients with persistently elevated GDF-15 levels >1800 ng/L having the highest rate of the composite end point.

**Conclusions**—GDF-15 is independently related to adverse events in non–ST-segment–elevation acute coronary syndrome both in the acute setting and for at least 6 months after clinical stabilization. Therefore, continued research on GDF-15 should be focused on the usefulness of GDF-15 for support of clinical management in acute and chronic ischemic heart disease. *(Circ Cardiovasc Genet. 2010;3:88-96.)*

**Key Words:** follow-up studies ▪ prognosis ▪ acute coronary syndrome ▪ growth-differentiation factor-15 ▪ risk assessment ▪ stable coronary artery disease

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Measurement of biochemical markers is a cornerstone of the evaluation of patients with ongoing non–ST-segment–elevation acute coronary syndrome (NSTE-ACS). The purpose is mainly the identification of subjects at high risk for adverse events who should be targeted to more aggressive therapies aimed at reducing morbidity and mortality. However, even after an acute ischemic event, biochemical markers provide valuable information and could therefore be used to further optimize treatment strategies during the transition of the disease from acute instability to its chronic stage.

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**Clinical Perspective on p 96**

Growth-differentiation factor-15 (GDF-15) is a stress-responsive member of the transforming growth factor-β cytokine superfamily that is induced in the myocardium, atherosclerotic plaques, and other tissues in response to pathological stress associated with inflammation or tissue injury. GDF-15 levels are related to biochemical indicators of myocardial and renal dysfunction and inflammatory activity in patients with stable angina, NSTE-ACS, ST-segment–elevation myocardial infarction (MI), and chronic heart fail-
ure, populations in which GDF-15 also has been shown to provide incremental prognostic information beyond clinical findings and established biochemical risk markers.8–12 Moreover, GDF-15 identifies patients with NSTE-ACS who derive the largest benefit from an early invasive treatment strategy.9 However, until now, GDF-15 levels have not been evaluated after an episode of NSTE-ACS. Therefore, we conducted this analysis in a subset of patients from the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) study who participated in a blood sampling program over a 6-month period after randomization. The purpose of this analysis was to assess the time course of GDF-15 levels after the index event; their associations to other clinical risk indicators, biomarkers, and treatment strategies; and their relations to clinical outcome.

Methods

Patients and Study Design

The protocol and results of the FRISC II trial, including the 5-year follow-up data, have been published elsewhere.13–15 In brief, the FRISC II trial was a prospective, multicenter study in which 3489 patients with NSTE-ACS were randomized in a factorial design to an early invasive or noninvasive strategy and to 3-month treatment with dalteparin or placebo. Patients were included in case of symptoms of unstable coronary artery disease with objective signs of myocardial ischemia, such as electrocardiographic changes (ST-segment depression ≥0.1 mV or T-wave inversion ≥0.1 mV), or elevated biomarkers of myocardial necrosis. Major exclusion criteria were increased risk of bleeding, serum creatinine >150 μmol/L, percutaneous coronary intervention during the past 6 months, and a decision to perform coronary angiography or percutaneous coronary intervention before randomization. Patients with a history of previous open heart surgery, advanced age, or poor general health and those included after completion of recruitment to the invasive versus noninvasive arm were treated primarily noninvasively and randomized only to either extended treatment with dalteparin or placebo.

In the invasive strategy, the aim was to perform coronary angiography and, if appropriate, revascularization within 7 days of admission. Patients randomized to the noninvasive strategy underwent coronary angiography only in case of refractory or recurrent angina or if they showed signs of severe ischemia on a predischarge exercise test. Informed consent was obtained from all patients, and the study protocol was approved by all local ethics committees.

Patients were followed up after randomization by outpatient visits after 6 weeks (range, 4 to 7 weeks) and after 3 and 6 months. At follow-up, a blood sampling program was performed, which included 1380 patients randomized at selected study centers. For the present analysis, all patients who had paired plasma samples available at randomization and 6 weeks, and thereafter at 3 and 6 months follow-up were considered, unless a patient died between the 6 weeks and 6 months. Thus, the total sample population was 950 patients. Further follow-up at 12 and 24 months was performed by telephone contact. Thereafter and up to 5 years after randomization, all information on events was based on mandatory national registries run by the Swedish Health Authority.

Laboratory Analysis

GDF-15 levels were determined with an immunoradiometric assay16 in frozen (−70°C), not previously thawed, samples of EDTA-plasma obtained at randomization, at 6 weeks, and at 3 and 6 months. Based on previous experiences, 2 prespecified GDF-15 cutoff points, 1200 and 1800 ng/L, were used in this analysis.8–10,12 These cutoff points have been found to be useful in identifying patient subgroups at low (<1200 ng/L), intermediate (1200 to 1800 ng/L), or high risk (>1800 ng/L) of adverse events.

N-terminal pro B-type natriuretic peptide (NT-proBNP) was analyzed with the Elecsys proBNP sandwich immunoassay on an Elecsys 2010 instrument. Cardiac troponin I (cTnI) was measured using the Access AccuTnI assay. For randomization samples, the original version of this assay was used, and results were dichotomized at its 99th percentile of 0.04 μg/L.17 Samples obtained at the other measurement instances were analyzed with an improved version of the assay and by applying a prognostic cTnI cutoff point of 0.01 μg/L following previous experiences.18 C-reactive protein (CRP) was determined on the Immulite CRP assay for all analyses except the 3-month follow-up because of a shortage of available samples. Serum creatinine was measured locally, and from that, the estimated glomerular filtration rate (eGFR) was calculated according to the 4-variable version of the Modification of Diet in Renal Disease formula.19

Statistical Analysis

Continuous variables are reported as medians with 25th and 75th percentiles. Between-group comparisons of medians were performed with the Mann–Whitney U test and within-group comparisons with the Wilcoxon signed-rank test. Categoric variables are expressed as...
frequencies and percentages, and differences were analyzed with Pearson χ² test. To evaluate the associations between GDF-15 levels and clinical variables (age, gender, current smoking, hypertension, heart failure, diabetes, previous MI, and previous stroke) and biomarker results (cTnI above the respective prognostic cutoff point, NT-proBNP, and eGFR), multiple linear regression analysis was used.

The end points for this analysis were total mortality and recurrent MI, alone or as a composite, after each respective measurement instance. For patients with an MI before any of the 3 follow-up instances, the time to the next MI was calculated, if applicable. To assess the prognostic value of GDF-15 levels obtained at the respective follow-up instances, we calculated the c-statistics and used Cox regression models, applying a landmark approach. The linearity assumptions and proportional hazard assumptions of these models were checked using the Shapiro-Wilk test and graphical methods. Adjustment was made for age, gender, diabetes, a history of heart failure, and a history of MI (model 1). Covariates were defined as follows:

- Diabetes at randomization: history of diabetes.
- Diabetes at the follow-up instances: history of diabetes, antidiabetic treatment, or a pretest fasting glucose ≥6.1 mmol/L.
- Heart failure at randomization: history of heart failure.
- Heart failure at the follow-up instances: history of heart failure or left-ventricular ejection fraction ≤0.45 during the index hospitalization.
- Previous MI at randomization: history of MI.
- Previous MI at the follow-up instances: history of MI, MI as index event (defined as cTnI ≥0.04 g/L at randomization), or recurrent MI during follow-up and before the respective measurement instance.

### Table 1. Clinical Characteristics of the Study Population at Randomization and After 6 Weeks and at 3 and 6 Months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomization (n=950)</th>
<th>6 wk (n=950)</th>
<th>3 mo (n=946)</th>
<th>6 mo (n=938)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.1 (58.9–73.9)</td>
<td>67.2 (59.0–74.0)</td>
<td>67.4 (59.1–74.1)</td>
<td>67.6 (59.4–74.3)</td>
</tr>
<tr>
<td>Male gender</td>
<td>686 (72.2)</td>
<td>686 (72.2)</td>
<td>684 (72.3)</td>
<td>676 (72.1)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>229 (24.1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension</td>
<td>305 (32.1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Heart failure</td>
<td>39 (4.1)</td>
<td>152 (16.0)</td>
<td>152 (16.1)</td>
<td>148 (15.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>120 (12.6)</td>
<td>174 (18.3)</td>
<td>193 (20.4)</td>
<td>164 (17.5)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>266 (28.0)</td>
<td>776 (81.7)</td>
<td>775 (81.9)</td>
<td>769 (82.0)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>55 (5.8)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Biomarker results:

- **GDF-15, ng/L**: 1357 (1023–1794) 1357 (1030–1800) 1351 (1042–1788) 1302 (996–1757)
- **cTnI**: 686 (72.2) ...
- **NT-proBNP, ng/L**: 534 (208–1251) 346 (144–798) 256 (127–591) 238 (115–510)
- **CRP, mg/L**: 6.0 (3.0–13.9) ...
- **eGFR, mL/min/1.73 m²**: 75.6 (63.9–87.6) 72.6 (61.1–84.6) 73.0 (61.6–83.6) 72.9 (62.0–85.5)

Values are shown as n (%) or medians with 25th to 75th percentiles. Smoking status, the prevalence of hypertension, and new strokes have not been systematically assessed during follow-up.

### Table 2. Change of GDF-15 Levels (ng/L) in Invasive Strategy and Noninvasive Strategy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Dalteparin Group (n=190)</th>
<th>Placebo Group (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Difference From Baseline</td>
<td>Median Difference From Baseline</td>
</tr>
<tr>
<td><strong>Invasive strategy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>1229 (974–1615)</td>
<td>1376 (1061–1724)</td>
</tr>
<tr>
<td>6 wk</td>
<td>1384 (1029–1816)</td>
<td>+155*</td>
</tr>
<tr>
<td>3 mo</td>
<td>1347 (1041–1727)</td>
<td>+118*</td>
</tr>
<tr>
<td>6 mo</td>
<td>1210 (975–1577)</td>
<td>−19</td>
</tr>
<tr>
<td><strong>Noninvasive strategy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>1294 (1004–1731)</td>
<td>1324 (981–1720)</td>
</tr>
<tr>
<td>6 wk</td>
<td>1315 (1040–1856)</td>
<td>+21†</td>
</tr>
<tr>
<td>3 mo</td>
<td>1311 (1031–1862)</td>
<td>+17</td>
</tr>
<tr>
<td>6 mo</td>
<td>1278 (1022–1805)</td>
<td>−16</td>
</tr>
</tbody>
</table>

GDF-15 levels are given as medians with 25th and 75th percentiles. Significance levels are determined based on the difference of GDF-15 levels from baseline to measurement at follow-up. P values were obtained using nonparametric tests.

*P<0.001.
†P<0.01.
‡P<0.05.
median of 1357 ng/L (25th to 75th percentiles, 1023 to 1794 ng/L) at randomization to 1302 ng/L (996 to 1757 ng/L) at 6-month follow-up ($P<0.001$). Applying multiple linear regression analysis using ln-transformed GDF-15 results obtained at randomization as the dependent variable, significant relations to age ($P<0.001$), male gender ($P<0.001$), current smoking ($P<0.001$), diabetes ($P<0.001$), higher levels of NT-proBNP ($P<0.001$), and a lower eGFR ($P<0.001$) were found, as previously reported.

At the 3 follow-up instances, there remained consistent significant associations between GDF-15 and age ($P<0.001$), male gender ($P<0.04$), current smoking ($P<0.002$), diabetes ($P<0.001$), NT-proBNP ($P<0.002$), and eGFR ($P<0.001$). At 6 weeks, there were also significant relationships between GDF-15 and hypertension ($P=0.044$) and cTnI $>0.01 \mu g/L$ ($P=0.007$). The $R^2$ values of these models were 0.38 at randomization, 0.39 at 6 weeks, 0.39 at 3 months, and 0.36 at 6 months. Higher CRP levels were significantly associated to GDF-15 at randomization, 6 weeks, and 6 months ($P<0.001$), when added to the models as an additional variable. However, inclusion of CRP did not appreciably change the $R^2$ values (data not shown).

### Change of GDF-15 Levels During the Observation Period

The median change of GDF-15 levels from randomization to 6 months was $-47$ ng/L ($-252$ to $+158$ ng/L; $P<0.001$). The only variables that were independently related to the
difference of ln-transformed GDF-15 levels from randomization to 6 months according to multiple linear regression were the difference for ln NT-proBNP from randomization to 6 months ($P=0.004$) and the difference for ln CRP from baseline to 6 months ($P<0.001$).

**GDF-15 Levels in Relation to Treatment Strategy**
GDF-15 levels decreased slightly from randomization to 6 months in patients randomized to the invasive strategy (median difference, $54 \text{ ng/L}; P=0.001$), whereas no considerable change was found in patients randomized to the noninvasive strategy (median difference, $36 \text{ ng/L}; P=0.111$). In contrast, a slight increase of GDF-15 levels from randomization to 3 months was noted in patients randomized to 3-month treatment with dalteparin (median difference, $62 \text{ ng/L}; P=0.001$), whereas patients in the placebo group had a slight decrease of GDF-15 levels during the same period (median difference, $94 \text{ ng/L}; P<0.001$). The temporal change of GDF-15 levels in relation to the different randomization arms is presented in Table 2.

**GDF-15 in Relation to Adverse Events**
From randomization to end of 5-year follow-up, 90 patients (9.5%) died, 166 (17.5%) had at least 1 recurrent MI, and 220 (23.2%) suffered the composite end point of death and MI. The occurrence of events in relation to the respective measurement instances is included in Figure 1.

The c-statistics of GDF-15 measured at 6 weeks and at 3 and 6 months follow-up regarding mortality were 0.69 (95% CI, 0.64 to 0.74), 0.72 (95% CI, 0.67 to 0.77), and 0.71 (95% CI, 0.66 to 0.77), respectively. The corresponding c-statistics regarding the composite end point were 0.65 (95% CI, 0.61 to 0.69), 0.67 (95% CI, 0.63 to 0.71), and 0.68 (95% CI, 0.63 to 0.72). Applying the preestablished cutoff points of 1200 and 1800 ng/L, there was a graded relationship between GDF-15 levels and subsequent events at all observation time points from 6 weeks to 6 months (Figures 2A through 2C). Although the 6-month results added

<table>
<thead>
<tr>
<th>6 wk</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>946</td>
<td>946</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>3.4 (2.0–5.8)</td>
<td>4.2 (2.6–6.9)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>946</td>
<td>946</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.4 (0.9–2.3)</td>
<td>1.7 (1.1–2.8)</td>
</tr>
<tr>
<td><strong>Death/MI</strong></td>
<td>946</td>
<td>946</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.9 (1.3–2.8)</td>
<td>2.5 (1.7–3.7)</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>938</td>
<td>938</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.2 (1.2–4.1)</td>
<td>2.5 (1.4–4.4)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td><strong>Model 2</strong></td>
<td><strong>Model 1</strong></td>
</tr>
<tr>
<td>n</td>
<td>622</td>
<td>622</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>4.0 (2.3–6.7)</td>
<td>4.0 (2.3–6.7)</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 3.** Cox Regression Analysis: Prognostic Value of GDF-15 During 5-Year Follow-Up

Model 1 was adjusted for age, gender, diabetes, heart failure and previous MI. Model 2 was adjusted for the same variables as in model 1 with the addition of cTnI >0.01 ng/L, ln NT-proBNP, and eGFR <75 mL × min⁻¹ × 1.73 m⁻². HR indicates hazard ratio for 1 ln-unit increase in GDF-15.
limited information for patients with GDF-15 levels <1200 ng/L at randomization, significant gradients of risk were found for patients with moderately and markedly elevated randomization GDF-15 levels (≥1200 ng/L), with patients with persistently elevated GDF-15 levels >1800 ng/L having the highest event rates (Figures 4C and 5C). The rate of events in relation to increasing, decreasing, or unchanged GDF-15 results with regard to these preestablished cutoff points is presented in the online-only Data Supplement, Table I.

**Discussion**

Risk prediction in patients with NSTE-ACS is a complex issue, considering not only the heterogeneity of patient subgroups and applied treatments, but also the prognostic information provided by established risk indicators that change as time passes from the acute phase to the chronic stage of the disease.5,21 Risk prediction thus could be facilitated if a risk indicator was available that provided consistent prognostic information over time. Our results indicate that GDF-15 might be a useful marker in this context. We have previously demonstrated that GDF-15 is an independent predictor of adverse events in ongoing NSTE-ACS.8,9 In this report, these findings are extended to the first months after an episode of NSTE-ACS. According to our results, GDF-15 exhibited a strong relation to mortality and the composite end point of mortality and recurrent MI, even when measured within 6 months after clinical stabilization and in the context of other cardiovascular risk factors and biochemical risk markers.

Similar to the acute situation,8,9,12 GDF-15 levels after the index event correlated with cardiovascular risk factors (ie, age, smoking, and diabetes) and biochemical markers of left-ventricular dysfunction (NT-proBNP), renal dysfunction (eGFR), and inflammation (CRP). However, these variables explained only 36 to 39% of the variability of the GDF-15 levels, indicating that this biomarker might provide unique additional information. This finding was supported by the remaining prognostic value of GDF-15 after adjustment for these and other established risk indicators.

During the 6-month follow-up, there were only minor median changes (approximately 5%) of the GDF-15 levels compared with the initial levels. This finding is in contrast to

**Figure 4.** Five-year mortality after 6 months in relation to GDF-15 levels at randomization of <1200 ng/L (A), 1200 to 1800 ng/L (B), and >1800 ng/L (C) and GDF-15 levels at 6 months. Mortality after 6 months in relation to levels of GDF-15 cutoff points at randomization (left bar) and at 6 months (right bars). The number of events per number of patients in the respective categories is given for each bar.
what has been shown for NT-proBNP levels that decrease substantially during the first months after an NSTE-ACS.\textsuperscript{3,4} The relative stability of the GDF-15 levels over time suggests that GDF-15 may be an indicator of a chronic underlying condition, explaining also its persistent relation to long-term outcome. Elevated GDF-15 levels may be related, in part, to a prolonged myocardial expression of this marker that is caused by oxidative stress, inflammation, and remodeling processes\textsuperscript{22,23} as supported by the significant and persistent association between GDF-15 and NT-proBNP levels. Moreover, because GDF-15 is expressed in human atherosclerotic plaque tissue,\textsuperscript{6} persistently elevated levels of GDF-15 also may be related to the extent of underlying atherosclerotic disease. Such a relation of GDF-15 to chronic cardiac and vascular pathologies is supported by a recent epidemiological study in elderly individuals from the community.\textsuperscript{24}

Of note, GDF-15 levels decreased slightly but significantly in patients randomized to the invasive strategy. This finding indicates that GDF-15 may reflect some of the benefits associated with an invasive treatment strategy.\textsuperscript{13–15} Intrigu-}


gingly, during the 3 months of dalteparin treatment, there was a slight increase of GDF-15 levels. This finding might have some bearing on the lack of sustained benefit by long-term dalteparin treatment.\textsuperscript{14} Other biomarkers also have indicated adverse effects of dalteparin, such as the reported increase of the concentration of von Willebrand factor, which might be related to a more pronounced endothelial activation by dalteparin.\textsuperscript{25} However, the possible interplay between GDF-15 levels and the coagulation system needs closer evaluation.

As reported earlier by our group, there was a significant interaction between baseline GDF-15 levels and the effects of an invasive versus noninvasive strategy on 2-year outcome in the FRISC II trial.\textsuperscript{9} As shown in this study, the interaction terms between GDF-15 at any follow-up measurement instance and the effects of the randomized treatment strategies were not significant, which may be due to differences in the underlying pathobiology (acute versus chronic setting), the smaller sample size, and an overall lower risk of the current study population that included only 6-week survivors.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure5}
\caption{Five-year rate of mortality and/or recurrent MI after 6 months in relation to GDF-15 levels at randomization of $<1200$ ng/L (A), 1200 to 1800 ng/L (B), and $>1800$ ng/L (C) and GDF-15 levels at 6 months. Rate of mortality and/or recurrent MI after 6 months in relation to levels of GDF-15 cutoff points at randomization (left bar) and at 6 months (right bars). The number of events per number of patients in the respective categories is given for each bar.}
\end{figure}
As in other patient populations, we found that the previously established GDF-15 cutoff points of 1200 and 1800 ng/L were practically useful for risk prediction,8–10,12 with a gradient of risk after increasing GDF-15 strata. Patients with a randomization GDF-15 level <1200 ng/L could be identified as low-risk subjects already at this time point, and retesting for GDF-15 at later follow-up provided only limited additive prognostic information. In contrast, patients with markedly elevated randomization GDF-15 levels (>1800 ng/L) had the highest event rates. This was particularly evident in cases of persistent GDF-15 increase >1800 ng/L at 6 months, with 1 of 3 patients in this cohort suffering the composite end point. Even with a decrease of GDF-15 to ≤1800 ng/L at 6 months, the risk for the composite end point was still almost twice as high as that for patients with GDF-15 ≤1800 ng/L at randomization. Even in patients with moderately elevated randomization GDF-15 levels (1200 to 1800 ng/L), retesting of GDF-15 at 6 months allowed for the identification of different patterns of risk. However, whether and in which way serial measurements of GDF-15 might improve patient management after an episode of NSTE-ACS remain to be evaluated by further prospective investigations.

Limitations

This study is based on an NSTE-ACS population randomized >10 years ago, that is, before the current era of intense secondary prevention with ADP inhibition, angiotensin-converting enzyme inhibitors, and high-dose statins. Moreover, our analysis is of a descriptive nature and needs to be regarded as hypothesis generating. Thus, a prospective validation in a contemporary sample of patients with NSTE-ACS is warranted. Because of a lack of remaining blood samples, we could not perform reanalyses of cTnI at randomization using the improved version of the AccuTnI assay. As a consequence, cTnI results were obtained using 2 iterations of this assay with different cutoff points, which limits the transferability of results obtained at randomization to follow-up results.

Conclusions

Based on the current and previously published results from our group,8–10,12 GDF-15 appears to be an important risk predictor in all stages of coronary artery disease from stable angina to acute instability and subsequent clinical stabilization, even when added to contemporary prognostic biomarkers. Continued research on GDF-15 now should be focused on its usefulness for support of decision making on management and an improved understanding of the underlying pathophysiology of GDF-15 as a potential treatment target.

Sources of Funding

This study was supported by grants from the German Ministry of Education and Research to Dr Wollert (BMFB, BioChancePlus) and the Swedish Heart-Lung Foundation to Dr Wallentin. The FRISC II trial was supported and organized in collaboration with Pharmacia and Upjohn. The reagents for analysis of cTnI at follow-up measurements were provided by Beckman Coulter, Inc.

Disclosures

Drs Wollert, Kempf, and Wallentin have filed a patent and have a contract with Roche Diagnostics to develop a GDF-15 assay for cardiovascular applications. Dr Venge has received research honoraria from Beckman Coulter, Inc, and Dr Lindahl has served as a consultant for that company.

References


**CLINICAL PERSPECTIVE**

Growth-differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β cytokine superfamily that is induced in the myocardium in response to oxidative stress, inflammation, or tissue injury. Circulating GDF-15 has been shown to be a strong predictor of adverse outcome in patients with chronic heart failure and acute manifestations of ischemic heart disease. In this study, the evidence regarding the prognostic significance of circulating GDF-15 is extended to patients who had been stabilized after an episode of non–ST-segment–elevation acute coronary syndrome and who were followed for 5 years. We observed that circulating GDF-15 levels, despite a slight, but significant decrease during the first 6 months after non–ST-segment–elevation acute coronary syndrome, were consistently related to cardiovascular risk factors and biochemical markers of hemodynamic stress, renal dysfunction, and inflammation. Moreover, higher blood GDF-15 concentration was independently related to an increased risk of developing adverse outcomes (ie, mortality) and the composite of mortality and recurrent ischemic events. The associations of GDF-15 with risk were remarkably consistent over time. This finding distinguishes GDF-15 from other established biochemical risk indicators, which often exhibit changing relationships to outcome as time passes after an acute ischemic event. Overall, our data underscore the potential role of GDF-15 as a prognostic biomarker over the entire time course of acute ischemic heart disease from the phase of acute coronary instability to the subsequent phase of clinical stabilization and extending into the chronic stage of coronary artery disease.
Growth-Differentiation Factor-15 for Long-Term Risk Prediction in Patients Stabilized After an Episode of Non–ST-Segment–Elevation Acute Coronary Syndrome
Kai M. Eggers, Tibor Kempf, Bo Lagerqvist, Bertil Lindahl, Sylvia Olofsson, Franziska Jantzen, Timo Peter, Tim Allhoff, Agneta Siegbahn, Per Venge, Kai C. Wollert and Lars Wallentin

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**SUPPLEMENTAL MATERIAL**

**Table.** Prognostic implications of the change of GDF-15 levels from randomization to 6 months.

<table>
<thead>
<tr>
<th>cut-off:</th>
<th>Low (n=276)</th>
<th>Increasing (n=81)</th>
<th>Decreasing (n=112)</th>
<th>High (n=469)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200 ng/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>9 (3.3%)</td>
<td>6 (7.4%)</td>
<td>3 (2.7%)</td>
<td>60 (12.8%)***</td>
</tr>
<tr>
<td>MI</td>
<td>15 (5.4%)</td>
<td>6 (7.4%)</td>
<td>5 (4.5%)</td>
<td>63 (13.4%)***</td>
</tr>
<tr>
<td>death/MI</td>
<td>22 (8.0%)</td>
<td>9 (11.1%)</td>
<td>8 (7.1%)</td>
<td>100 (21.3%)***</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cut-off:</th>
<th>Low (n=638)</th>
<th>Increasing (n=73)</th>
<th>Decreasing (n=86)</th>
<th>High (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1800 ng/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>31 (4.9%)</td>
<td>6 (8.2%)</td>
<td>10 (11.6%)*</td>
<td>31 (22.0%)***</td>
</tr>
<tr>
<td>MI</td>
<td>39 (6.1%)</td>
<td>10 (13.7%)*</td>
<td>11 (12.8%)*</td>
<td>29 (20.6%)***</td>
</tr>
<tr>
<td>death/MI</td>
<td>61 (9.6%)</td>
<td>14 (19.3%)*</td>
<td>17 (19.8%)**</td>
<td>47 (33.3%)***</td>
</tr>
</tbody>
</table>

‘Low’ denotes a GDF-15 level under the respective cut-offs at randomization and 6 months. ‘Increasing’ denotes a GDF-15 level below the respective cut-offs at randomization and above the cut-offs at 6 months. ‘Decreasing’ denotes a GDF-15 level above the respective cut-offs at randomization and below the cut-offs at 6 months. ‘High’ denotes a GDF-15 level above the respective cut-offs at randomization and 6 months.

Asterisks refer to significance levels compared to patients with low GDF-15 levels: * p<0.05; ** p<0.01; *** p<0.001.