Growth differentiation factor-15 level predicts major bleeding and cardiovascular events in patients with acute coronary syndromes: results from the PLATO study

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Aims Growth differentiation factor-15 (GDF-15) predicts death and composite cardiovascular (CV) events in patients with acute coronary syndrome (ACS). We investigated the independent associations between GDF-15 levels and major bleeding, the extent of coronary lesions and individual CV events in patients with ACS.

Methods and results Growth differentiation factor-15 was analysed at baseline (n = 16 876) in patients with ACS randomized to ticagrelor or clopidogrel in the PLATO (PLATelet inhibition and patient Outcomes) trial. Growth differentiation factor-15 levels were related to extent of coronary artery disease (CAD) and to all types of non-coronary artery bypass grafting (CABG)-related major bleeding, spontaneous myocardial infarction (MI), stroke, and death during 12-month follow-up. In Cox proportional hazards models adjusting for established risk factors for CV disease and prognostic biomarkers (N-terminal pro B-type natriuretic peptide, cystatin C, high-sensitive C-reactive protein, and high-sensitive troponin T), 1 SD increase in ln GDF-15 was associated with increased risk of major bleeding with a hazard ratio (HR) 1.37 (95% confidence interval: 1.25–1.51) and with a similar increase in risk across different bleeding locations. For the same increase in ln GDF-15, the HR for the composite of CV death, spontaneous MI, and stroke was 1.29 (1.21–1.37), CV death 1.41 (1.30–1.53), all-cause death 1.31 (1.30–1.53), spontaneous MI 1.15 (1.05–1.26), and stroke 1.19 (1.01–1.42). The C-statistic improved for the prediction of CV death and non-CABG-related major bleeding when adding GDF-15 to established risk factors.

Conclusions In patients with ACS, higher levels of GDF-15 are associated with raised risks of all types of major non-CABG-related bleeding, spontaneous MI, and stroke as well as CV and total mortality and seem to improve risk stratification for CV-mortality and major bleeding beyond established risk factors.

Clinical Trial Registration www.clinicaltrials.gov; NCT00391872.

Keywords GDF-15 • Major bleeding • Mortality • Myocardial infarction • Cardiovascular risk factors

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Introduction

Patients who have suffered from an acute coronary syndrome (ACS) are at high risk of recurrent cardiovascular (CV) morbidity and mortality. Patients with ACS are also at high risk for bleeding because of antithrombotic therapy, underlying CV disease and other comorbidities. The increased risk of ischaemic events is related to a wide range of clinical risk factors and to biomarkers associated with CV disease and other co-morbidities such as the growth differentiation factor-15 (GDF-15).

Multiple lines of evidence, from experimental and clinical studies, suggest that GDF-15 is associated with cellular oxidative stress, ischaemia, and strain although it is unknown if GDF-15 is causally involved in the pathological process leading to CV diseases or has a cellular protective function. Furthermore, several studies report associations between increased levels of GDF-15 and higher prevalence of CV risk factors as well as prevalence of CV diseases and death. Numerous risk factors predictive of CV events in patients with ACS are also prognostic for bleeding events, such as age and comorbidities. Previously, GDF-15 has been reported to be associated with the risk of bleeding in patients with atrial fibrillation treated with oral anticoagulation. However, no previous study has investigated whether the level of GDF-15 provides independent prognostic information concerning risk of bleeding as well as different types of CV events in patients with ACS receiving modern dual antiplatelet treatment and early revascularization. Therefore, the aim of this study was to investigate the GDF-15 level and its independent associations with major bleeding, extent of coronary artery disease (CAD), and specific CV outcomes in patients with ACS receiving dual antiplatelet treatment in the PLATO (PLATelet inhibition and patient Outcomes) trial.

Methods

Study population

The study is based on the PLATO trial of 18,624 patients with ST-elevation ACS (STE-ACS) or non-ST-elevation ACS (NSTE-ACS) randomized to either ticagrelor or clopidogrel in addition to established optimal medical or revascularization therapy. Ticagrelor was given with a loading dose of 180 mg followed by 90 mg twice daily. Clopidogrel was given with a maintenance dose of 75 mg daily and clopidogrel-naïve patients received a loading dose of 300–600 mg. All patients received acetylsalicylic acid unless intolerant. The randomized treatment continued from 6 to 12 months with a median duration of 9.1 months. The study excluded patients treated with acetylsalicylic acid unless intolerant. The randomized treatment continued from 6 to 12 months with a median duration of 9.1 months. The study excluded patients treated with acetylsalicylic acid unless intolerant.

Baseline characteristics, CV risk factors, previous medical history, and medication were recorded at baseline. Cardiovascular and bleeding events were recorded at discharge and at outpatient visits at 1, 3, 6, 9, and 12 months. The PLATO trial was approved by regulatory authorities in all participating countries and by participating sites’ institutional review boards. All participants provided written informed consent.

For laboratory evaluations and outcome assessments, see Supplementary material online.

Statistical analyses

Natural logarithmic (ln) transformations were performed for continuous variables with skewed distributions (all biomarkers). Baseline and inhospital patient characteristics were compared across GDF-15 quartile groups. Continuous variables are presented as medians and interquartile ranges (IQRs), and groups compared using Kruskal–Wallis tests, categorical variables as counts and percentages, and groups compared using χ² tests. A multivariable linear model was used to assess the relationship between natural log-transformed GDF-15 (below denoted as GDF-15, unless stated otherwise) and baseline characteristics, CV risk factors, and biomarkers. Geometric means and ratios were calculated using the antilog of the model-adjusted means.

Growth differentiation factor-15 levels (original scale) were evaluated using descriptive statistics. The relation of baseline GDF-15 level to each clinical outcome is displayed in Kaplan–Meier curves and analysed with Cox proportional hazards models [hazard ratios (HRs) 95% confidence intervals (CIs)] with GDF-15 as continuous or categorical variable divided into quartiles. Hazard ratios are expressed per 1 SD increase in GDF-15 level or relative to the lowest quartile group, respectively. The following models were used for adjustment:

- **Model 1:** Randomized treatment and risk factors for recurrent CV disease [age, gender, previous myocardial infarction (MI), previous stroke, previous peripheral arterial disease (PAD), previous percutaneous coronary intervention (PCI), previous coronary artery bypass grafting (CABG), congestive heart failure, diabetes mellitus, chronic kidney disease (CKD), ST-depression on admission ECG, hypertension, smoking, body mass index (BMI), hypercholesterolemia, antihypertensive medication, and lipid lowering medication].

- **Model 2:** Model 1 (excluding CKD) and prognostic biomarkers [hs-troponin T, cystatin C, c-reactive protein (CRP), N-terminal pro B-type natriuretic peptide (NT-proBNP)].

The functional form of the relationship between GDF-15 and outcomes was explored using cumulative sums of martingale residuals and restricted cubic splines. The assumption of proportional hazards was assessed visually using log-cumulative hazard plots and by use of the cumulative sum of martingale residuals.

The effects of GDF-15 levels on outcomes in relation to randomized treatment and ACS type, respectively, were evaluated using a Cox proportional hazards model that included GDF-15 transformed using restricted cubic splines and the treatment or ACS type (NSTE-ACS vs. STE-ACS), respectively, by GDF-15 interaction. In addition, we investigated the effect of GDF-15 on clinical outcomes in the subset of patients that underwent coronary angiography, taking into account the extent of CAD. The effects of GDF-15 levels on outcomes in relation to extent of CAD were analysed using a Cox proportional hazards model including extent of CAD, GDF-15 quartile group, and the CAD by GDF-15 interaction as independent variables. To assess the discriminatory ability of the models, Harrell’s C-index was estimated. Models with plasma GDF-15 level added were compared with models without GDF-15 in terms of global model fit using likelihood ratio (LR) tests.

P-Values <0.05 from two-sided tests were considered statistically significant. The P-values were not adjusted for multiple comparisons, due to the exploratory nature of the present study. All analyses were performed at the Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline and in-hospital characteristics

A total of 16,876 patients were included with a median concentration of (IQR) GDF-15 at randomization of 1550 ng/L (1145–2219). With higher quartiles of GDF-15, the prevalence of hypertension, diabetes mellitus, and CKD increased, as did the proportion of
individuals with previous MI, PAD, revascularization, and congestive heart failure. Furthermore, the levels of NT-proBNP, cystatin C, CRP, and hs-troponin T, increased with higher quartiles of GDF-15 (Table 1). Also, higher GDF-15 levels were associated with increasing age, and the prevalence of several risk factors and comorbidities (see Supplementary material online, Table S1).

Coronary artery disease assessment

The proportions of patients with 0- and 1-vessel CAD were larger, 30 and 45%, respectively, in the lowest compared with 21 and 32% in the highest quartile of GDF-15 (Table 1). Patients with 3-vessel CAD, compared with 0- or 1-vessel CAD, had higher levels of GDF-15 (see Supplementary material online, Table S1).

Non-coronary artery bypass grafting-related major bleeding

During follow-up, 607 patients had at least one non-CABG-related major bleeding. Higher levels of GDF-15 were associated with a higher risk of non-CABG-related bleeding. As illustrated in the Kaplan–Meier graphs, there were throughout follow-up, gradually increasing differences in bleeding rates between the GDF-15 quartiles.

Table 1 Baseline and in-hospital characteristics by growth differentiation factor-15 quartiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole population</th>
<th>GDF-15 quartile</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Q1 (&lt;1145 ng/L)</td>
<td>Q2 (1145–1550 ng/L)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (54–71)</td>
<td>56 (49–62)</td>
<td>61 (54–68)</td>
</tr>
<tr>
<td>Female</td>
<td>4840 (28.7%)</td>
<td>997 (23.7%)</td>
<td>1173 (27.8%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 (24.8–30.5)</td>
<td>27.7 (25.1–30.4)</td>
<td>27.4 (24.8–30.4)</td>
</tr>
<tr>
<td>Disease classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STE-ACS</td>
<td>6800 (40.3%)</td>
<td>1765 (41.9%)</td>
<td>1730 (41.0%)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>5994 (35.5%)</td>
<td>1587 (37.7%)</td>
<td>1620 (38.4%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>7945 (47.1%)</td>
<td>2064 (49.0%)</td>
<td>2009 (47.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11055 (65.5%)</td>
<td>2399 (56.9%)</td>
<td>2687 (63.6%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4219 (25.0%)</td>
<td>550 (13.1%)</td>
<td>828 (19.6%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3489 (20.7%)</td>
<td>675 (16.0%)</td>
<td>777 (18.4%)</td>
</tr>
<tr>
<td>Previous congestive heart failure</td>
<td>977 (5.8%)</td>
<td>88 (2.1%)</td>
<td>148 (3.5%)</td>
</tr>
<tr>
<td>Previous PCI or CABG</td>
<td>3232 (19.2%)</td>
<td>705 (16.7%)</td>
<td>733 (17.4%)</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>1103 (6.5%)</td>
<td>150 (3.6%)</td>
<td>216 (5.1%)</td>
</tr>
<tr>
<td>Previous PAD</td>
<td>1041 (6.2%)</td>
<td>137 (3.3%)</td>
<td>195 (4.6%)</td>
</tr>
<tr>
<td>CKD</td>
<td>708 (4.2%)</td>
<td>43 (1.0%)</td>
<td>65 (1.5%)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0-vessel disease</td>
<td>1026 (7.5%)</td>
<td>309 (30.1%)</td>
<td>279 (27.2%)</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>5361 (39.2%)</td>
<td>1630 (44.8%)</td>
<td>1461 (41.4%)</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>3891 (28.5%)</td>
<td>1034 (28.4%)</td>
<td>997 (28.2%)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>3387 (24.8%)</td>
<td>662 (18.2%)</td>
<td>796 (22.5%)</td>
</tr>
<tr>
<td>Biochemical analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs-Troponin T (ng/L)</td>
<td>182 (42.2–619)</td>
<td>144 (31.7–437)</td>
<td>160 (38.5–540)</td>
</tr>
<tr>
<td>NT-proBNP (pmol/L)</td>
<td>59.2 (19–185)</td>
<td>29.4 (11.4–77.2)</td>
<td>43.5 (15.9–118)</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.83 (0.68–1.01)</td>
<td>0.71 (0.60–0.83)</td>
<td>0.78 (0.66–0.91)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>104 (79–120)</td>
<td>120 (104–120)</td>
<td>114 (92.0–120.0)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.7 (1.6–9.5)</td>
<td>2.5 (1.2–5.6)</td>
<td>3.3 (1.5–7.6)</td>
</tr>
</tbody>
</table>

Values are medians (IQRs) and n (%) for categorical variables.

BMI, body mass index; MI, myocardial infarction; STE-ACS, ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischaemic attack; PAD, peripheral arterial disease; hs-Troponin T, high-sensitivity troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease.
Higher levels of GDF-15 were independently associated with a raised risk of bleeding and were 2.17 (95% CI 1.64–2.88) and 1.78 (95% CI 1.29–2.45) times higher in the highest, compared with the lowest quartile, when adjusting either for clinical characteristics alone or for clinical characteristics and other prognostic biomarkers, respectively (Table 2). The spline graph verified a consistent increase in the rate of non-CABG related bleeding from 700 to 3500 ng/L of growth differentiation factor-15 (ng/L). Abbreviations as in Table 1.

Figure 1  Kaplan–Meier estimated event rates of (A) the primary outcome (composite of cardiovascular death, spontaneous myocardial infarction, and stroke), (B) spontaneous myocardial infarction, (C) non-coronary artery bypass grafting-related major bleeding, (D) cardiovascular death, by quartiles of growth differentiation factor-15 (ng/L). Abbreviations as in Table 1.
GDF-15 (Figure 2). Higher level of GDF-15 was associated with higher rates of non-CABG related bleeding of all types and locations (see Supplementary material online, Table S3).

**Primary outcome**

During follow-up, 1446 patients suffered from the primary outcome (CV death, spontaneous MI, or stroke). Higher levels of GDF-15 at baseline were associated with a continuous increased risk of the primary outcome, and the estimates of event rates by quartiles showed gradually increasing differences between the event curves during follow-up (Figures 1A, 2 and Supplementary material online, Table S2). In adjusted models, higher quartiles of GDF-15 were associated with a gradually higher risk of the primary outcome (Table 2). Continuous GDF-15 level modelled in a spline graph suggested a linear...
Table 2

<table>
<thead>
<tr>
<th>GDF-15 quartile (Q1–Q4) within range of GDF-15</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (&lt;1145 ng/L)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Q2 (1145–1599 ng/L)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q3 (1599–2119 ng/L)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q4 (2119 ng/L)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P-values for the effect of GDF-15.

Estimates are HRs (95% CI). For continuous GDF-15, HRs are expressed per 1 SD GDF-15 increase.

The spline graph showed a consistent increase in event rate for CV and all-cause death at GDF-15 levels from 1000 to ~4000 ng/L (Figure 2).

Cardiovascular and all-cause death

Cardiovascular and all-cause death occurred in 677 and 782 patients, respectively. Higher levels of GDF-15 were associated with a higher risk of CV and all-cause death, and the differences in estimated event rates continued to increase throughout follow-up (Figure 1D and Supplementary material online, Figure S3A and Table S2). The spline graph showed a consistent increase in event rate for CV and all-cause death at GDF-15 levels from 1000 to ~4000 ng/L (Figure 2).

Spontaneous and procedure-related myocardial infarction

In the study, 742 patients suffered at least one spontaneous MI. Higher GDF-15 levels were associated with a higher risk of spontaneous MI. The differences in the estimated rates of spontaneous MI between the baseline GDF-15 quartiles gradually increased during the 12-month follow-up (Figure 1B and Supplementary material online, Table S2). Higher quartiles of GDF-15 were associated with a higher risk of spontaneous MI with 1.95 (95% CI 1.51–2.53) and 1.63 (95% CI 1.21–2.20) times increase of risk, respectively, in the highest compared with the lowest quartile using adjustment Models 1 and 2 (Table 2). The spline graph showed a consistent increase in event rate for spontaneous MI at GDF-15 levels ranging from 1000 to ~3500 ng/L (Figure 2). A total of 280 patients suffered a procedure-related MI. There was no significant association between the level of GDF-15 and the occurrence of procedure-related MI.

Stroke

A total of 207 patients had a stroke at least once during the study. Higher levels of GDF-15 were related to an elevated risk of stroke with a gradual increase in the difference in event rates between the GDF-15 quartiles during follow-up (see Supplementary material online, Figure S3 and Table S2). In both adjusted Models 1 and 2, higher GDF-15 quartiles were associated with a higher risk of stroke with a 1.8 times higher risk in the highest when compared with the lowest quartile for both adjustment models (Table 2).

Interactions

There was no interaction detected between the GDF-15 level and the effect of randomized treatment on any outcome (see Supplementary material online, Figure S1). Furthermore, no interaction between GDF-15 by type of ACS (NSTE-ACS vs. STE-ACS) was
observed for any outcome (see Supplementary material online, Figure S2).

The CAD category did not interact with the associations between the GDF-15 and the primary outcome \( P = 0.4695 \) or any of the separate outcomes \( P \geq 0.1763 \).

**Prognostic value of growth differentiation factor-15**

The model performance improved significantly for the prediction of the primary composite endpoint, CV death, all-cause death, and non-CABG-related major bleeding but not for stroke or MI (spontaneous and procedure-related), when plasma GDF-15 was incorporated into Model 1 (see Supplementary material online, Table S4).

**Discussion**

In this study, we observed that the GDF-15 level is associated with all types of non-CABG-related major bleeding in patients with ACS treated with dual antiplatelet medication. The increased risk of major bleeding was independent of a wide range of other indicators of raised risk of bleeding such as age, gender, and comorbidities and also of other biomarkers indicating organ dysfunction. We also showed that, in patients with ACS, the GDF-15 level is independently associated with a raised risk of spontaneous MI but not with procedure-related MI. In addition, we observed that the GDF-15 level in patients with ACS is independently associated with a raised risk of stroke. Finally, we verified that the GDF-15 level is independently and strongly associated with an increased risk of CV and total mortality in ACS.

In line with previous studies of patients with ACS, this study showed that higher levels of GDF-15 predicted the composite of CV death, spontaneous MI, and stroke beyond established risk factors and newer biomarkers.\(^1,3–5,20–22\) These previous findings were based on retrospective evaluations of smaller patient populations from a time when early revascularization and modern dual antiplatelet treatment were not standard of care. In the FRISC-2 study, GDF-15 predicted both short- and long-term risk of the composite of CV death and MI in non-revascularized patients,\(^2\) whereas only late events were prognosticated in revascularized patients.\(^{20}\) The present study corroborated the FRISC-2 findings that patients with elevated levels of GDF-15 had more severe CAD.\(^3\) In comparison with the findings in previous trials, this present large scale trial provided clear evidence that GDF-15 is not only independently related to total and CV mortality but also to recurrent spontaneous MI and stroke. The lack of association between GDF-15 and procedure-related MI strengthens a possible pathophysiological link between elevated GDF-15 and the development of
atherosclerotic disease, as procedure-related MI most often appears to be a minor mechanically induced event without important long-term consequences.\textsuperscript{22} We also observed that the associations between GDF-15 and disease development occur independent of intense platelet inhibition, early revascularization, and even extent of underlying CAD, as well as baseline characteristics, co-morbidities, and biomarkers associated with higher GDF-15 levels.

This study, for the first time in patients with ACS, showed that increasing levels of GDF-15 were independently associated with all types of bleeding complications during antiplatelet treatment. Reinforcing these associations are signs of causality with genetic effects on levels of GDF-15 and on non-CABG-related bleeding.\textsuperscript{23} These findings are in line with our recent report that the level of GDF-15 is an independent risk factor for major bleeding in anticoagulated patients with atrial fibrillation.\textsuperscript{16} The identification of a biomarker with a strong independent association with bleeding indicates an opportunity for an improved assessment of the balance between the risk of CV events and bleeding during antiplatelet treatments, which currently is associated with large difficulties when based on clinical variables alone.

In accordance with several previous studies of patients with ACS, GDF-15 was not only associated with prognosis, but also with a wide range of CV risk factors, such as age, male gender, smoking, diabetes mellitus, and comorbidities including myocardial and renal dysfunction as well as previous ischaemic events.\textsuperscript{1–3,5,19,20} In agreement with previous studies, the level of GDF-15 was associated with several biomarkers indicating myocardial damage and dysfunction (troponins, NTpro-BNP), renal dysfunction (cystatin C), and inflammatory activity (CRP).\textsuperscript{1–5,19,20} The increased C-indices and statistically significant LR tests for major bleeding, the composite ischaemic endpoint, and CV-death indicate that the addition of plasma GDF-15 to information from established cardiovascular risk factors, might represent an important improvement in risk stratification for several outcomes. If further validated and shown to influence selection of treatment, GDF-15 might be of clinical value in refining risk stratification and tailoring treatment of patients with ACS.

The underlying mechanisms explaining the independent associations between GDF-15 and CV disease and events are unknown. Part of the observed associations between GDF-15 and CV events probably is a reflection of the burden of risk given its association with several CV risk factors, established CV disease and other biomarkers reflecting CV disease. In addition, GDF-15 seems to be a downstream marker of established cell stress, such as inflammation, oxidation, tissue injury, and tissue aging. The mechanism for the association between GDF-15 and the risk of bleeding may be that GDF-15 is expressed as a consequence of cellular stress and vulnerability, which might be related to a raised risk of bleeding due to external or internal trauma. There is also a potential for a specific mechanism as GDF-15 has been shown to have an inhibitory effect on platelet activation mediated via a mechanism similar to glycoprotein IIb/IIIa inhibition resulting in a lower ability to form thrombus.\textsuperscript{24} Therefore, measurement of the GDF-15 level might provide unique information on underlying disease processes leading to a raised risk of severe events, e.g. fatal CV events and major bleeding during antithrombotic treatment.

Conclusions
In patients with ACS, higher levels of GDF-15 are associated with an increased risk of non-CABG-related major bleeding, a raised risk of recurrent spontaneous MI and stroke as well as with greater CV- and total mortality in models adjusting for established and newer risk factors. GDF-15 might in the future be a useful biomarker for tailoring antiplatelet treatment in patients with ACS. Furthermore, the association between GDF-15 and spontaneous MI, stroke and bleeding indicates a need for further investigations of possible direct effects of GDF-15 on the development and balance of these events in patients with ACS and other settings.

Supplementary material
Supplementary material is available at European Heart Journal online.

Authors’ contributions

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