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Reviews

Growth Differentiation Factor 15 as a Biomarker in Cardiovascular Disease

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BACKGROUND: Growth differentiation factor 15 (GDF-15) is expressed and secreted in response to inflammation, oxidative stress, hypoxia, telomere erosion, and oncogene activation. Cardiovascular (CV) disease is a major driver of GDF-15 production. GDF-15 has favorable preanalytic characteristics and can be measured in serum and plasma by immunoassay.

CONTENT: In community-dwelling individuals higher concentrations of GDF-15 are associated with increased risks of developing CV disease, chronic kidney disease, and cancer, independent of traditional CV risk factors, renal function, and other biomarkers (C-reactive protein, B-type natriuretic peptide, cardiac troponin). Low concentrations of GDF-15 are closely associated with longevity. GDF-15 is as an independent marker of all-cause mortality and CV events in patients with coronary artery disease, and may help select patients with non–ST-elevation acute coronary syndrome for early revascularization and more intensive medical therapies. GDF-15 is independently associated with mortality and nonfatal events in atrial fibrillation and heart failure (HF) with preserved or reduced ejection fraction. GDF-15 reflects chronic disease burden and acute perturbations in HF and responds to improvements in hemodynamic status. GDF-15 is independently associated with major bleeding in patients receiving antithrombotic therapies and has been included in a new bleeding risk score, which may become useful for decision support.

SUMMARY: GDF-15 captures distinct aspects of CV disease development, progression, and prognosis, which are not represented by clinical risk predictors and other biomarkers. The usefulness of GDF-15 to guide management decisions and discover new treatment targets should be further explored.

Growth differentiation factor 15 (GDF-15)[3] is a stress-responsive member of the transforming growth factor-β (TGF-β) cytokine superfamily. GDF-15 is synthesized as a precursor protein that undergoes disulfide-linked dimerization. Proteolytic cleavage releases the N-terminal propeptide from the mature GDF-15 protein, which is then secreted as a dimer with a predicted molecular mass of 25 kDa *(1, 2)*.

In health GDF-15 is weakly expressed in human tissues with the notable exception of the placenta *(3)*, resulting in very high circulating concentrations of GDF-15 during pregnancy *(4)*. Under pathological conditions, GDF-15 can be produced by many cardiovascular (CV) and noncardiovascular cell types. The biological effects of GDF-15 are context-dependent and may vary with the stage of the disease *(5–11)*. For example, GDF-15 mediates antiinflammatory effects in mice with acute MI by directly inhibiting myeloid cell recruitment *(7)*, but promotes indirect proinflammatory effects in atherosclerosis models *(8, 9)*.

Although GDF-15 and TGF-β can signal via the same receptor complex *(12)*, the upstream signals leading to the expression of GDF-15 are quite distinct. The

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[3] Nonstandard abbreviations: GDF-15, growth differentiation factor 15; TGF-β, transforming growth factor-β; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; hs-CRP, high-sensitivity-C-reactive protein; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; cTnI, cardiac troponin I; cTnT, cardiac troponin T; sST2, soluble suppression of tumorigenicity 2; HR, hazard ratio; ULSAM, Uppsala Longitudinal Study of Adult Men; CAD, coronary artery disease; ACS, acute coronary syndrome; FRISC-2, Fragmin and Fast Revascularization During Instability in Coronary Artery Disease-2 trial; PROVE IT–TIMI-22, Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction-22 trial; GUSTO-4, Global Utilization of Strategies to Open Occluded Arteries-4 trial; NSTE-ACS, non–ST-elevation ACS; STEMI, ST-elevation MI; PLATO, Platelet Inhibition and Patient Outcomes trial; CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; STABILITY, Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial; GRACE, Global Registry of Acute Coronary Events; HFrEF, HF with reduced ejection fraction; LVAD, left ventricular assist device; NYHA, New York Heart Association; HFpEF, HF with preserved ejection fraction; SHOP, Singapore Heart Failure Outcomes and Phenotypes study; Val-HeFT, Valsartan Heart Failure Trial; RELAX-AHF, Relaxin in Acute Heart Failure trial; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy trial; NRI(>0), continuous net reclassification improvement; ASSENT, Assessment of the Safety and Efficacy of a New Thrombolytic trial.

GDF-15 promoter contains 2 p53 transcription factor binding sites that are required and sufficient for the induction of GDF-15 expression *(13)*. Activation of p53 is a fundamental cellular response to inflammation, oxidative stress, hypoxia, telomere erosion, and oncogene activation. Although p53 is strongly induced by sporadic and severe stress, it also responds to low-level, constitutive stress that is encountered during the everyday rigors of normal human life *(14)*. The circulating levels of GDF-15 reflect these acute and chronic cellular stressors, which are associated with aging and disease.

Immunoassays and Preanalytical Characteristics of GDF-15

GDF-15 concentrations in human serum and plasma have been measured with a research ELISA *(4)*, a research IRMA *(15)*, an ELISA using antibodies from R&D Systems (now marketed as a Quantikine® ELISA), and a Luminex sandwich assay developed by Alere (Table 1). These assays are for research use only. Recently, an automated electrochemiluminescence (Elecsys®) immunoassay has been developed by Roche Diagnostics. This assay is now available for clinical use in Europe. Precommercial versions of this assay have been used in several investigations (Table 1). GDF-15 concentrations measured with the Elecsys assay correlate well with concentrations measured by the IRMA or Quantikine ELISA (Roche, personal communication). The preanalytic characteristics of GDF-15 have been assessed with the IRMA *(15)* and the Elecsys assay (Roche, personal communication): concentrations of GDF-15 measured in Li-heparin, K_2-EDTA, K_3-EDTA, or citrated plasma do not differ significantly from the concentrations obtained in serum. GDF-15 immunoreactivity is resistant to freezing and thawing and storage at room temperature for at least 48 h, which should facilitate measurements of the analyte under routine conditions.

Expression of GDF-15 in CV Disease

With the development of specific immunoassays, CV disease has emerged as a major driver of increased circulating concentrations of GDF-15 in community-dwelling individuals and patients (Fig. 1). So far, little is known about the tissues that produce GDF-15 in patients with CV disease. Visceral and subcutaneous adipose tissues are a source of GDF-15 in obese individuals *(16)*. GDF-15 is also expressed in atherosclerotic plaques in the carotid or coronary arteries *(8, 17)*. Moreover, GDF-15 is upregulated in the heart after an acute myocardial infarction (MI) *(6)*. In patients with chronic nonischemic heart failure (HF), GDF-15 appears to be produced mainly in peripheral tissues *(18)*. Based on its biology as a stress/p53-regulated gene and its induction in different disease settings (Table 2), GDF-15 has limited usefulness as a diagnostic marker, for example in patients with acute chest pain or dyspnea *(19, 20)*. However, this lack of cardiac specificity may turn into a strength when it comes to prediction of CV risk, which is determined by cardiac, peripheral, and systemic abnormalities, and by lifestyle, comorbidities, and aging.

GDF-15 in Community-Dwelling Individuals

The circulating concentrations of GDF-15 in community-dwelling elderly individuals are related to CV risk factors, most consistently to age, diabetes, and current smoking, in some studies also to arterial hypertension and low HDL-cholesterol levels. Independent of these conventional risk factors, GDF-15 is modestly related to biomarkers of inflammation [high-sensitivity-C-reactive protein (hs-CRP)], heart disease [B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), cardiac troponin I (cTnI), cardiac troponin T (cTnT)], and renal dysfunction (estimated glomerular filtration rate, cystatin C) *(21–27)*. Together, these risk factors and biomarkers of CV and renal dysfunction account for less than half of the interindividual variation in circulating GDF-15, suggesting that the marker carries additional information.

A study in elderly, community-dwelling twins concluded that genetic factors contribute to the interindividual variations in GDF-15 *(28)*. Indeed, a genomewide association study identified several single nucleotide polymorphisms associated with circulating GDF-15 *(25)*.

Community-dwelling individuals with CV risk factors or established CV disease have higher levels of GDF-15 than those without such conditions *(22)*. Along this line, GDF-15 is related to subclinical CV disease in apparently healthy middle-aged and elderly individuals. Indeed, associations of GDF-15 with vascular and cardiac pathologies (increased arterial stiffness, endothelial dysfunction, atherosclerotic plaque burden in the carotid artery, coronary artery calcification, left ventricular hypertrophy, left ventricular systolic dysfunction) have been reported *(22, 26, 29, 30)*. These associations persist after adjustment for conventional CV risk factors, implying that GDF-15 provides nonoverlapping information on CV disease burden.

GDF-15 concentrations increase with age but do not vary by sex in carefully selected cohorts of apparently healthy elderly individuals *(15, 25)*. As indicated by correlations with hs-CRP and cystatin C, apparently healthy individuals with GDF-15 concentrations at the upper end of the spectrum may have occult disease *(15)*. In 1 study that included 288 men and 141 women with a median age of 65 years, the median GDF-15 concentration was 762 ng/L, and 1188 ng/L marked the 90th percentile

Table 1. GDF-15 in relation to outcome events in exemplary studies.[a]

Study	Population	GDF-15 assay and concentration	Risks associated with increased GDF-15[b]
Community-dwelling individuals			
Women's Health Study, Brown et al. *(21)*	514 women Age, 60.2 ± 8.6 years No history of CVD Follow-up 4 years Case-control design	Research ELISA 618 (474–833) ng/L in women who developed a CV event vs 538 (431–670) ng/L in those who did not	Fatal or nonfatal CV events ++
Swedish population and twin registries, Wiklund et al. *(28)*	876 men Age range, 46–80 years Follow-up 5.3 years (median) 324 twins Age range, 63–93 years Follow-up 9.1 years (median)	Research ELISA 935 (156–9638) ng/L Research ELISA 1393 (428–8064) ng/L	All-cause mortality ++ CV mortality +[c] Cancer mortality +[c]
Rancho Bernardo Study, Daniels et al. *(23)*	1391 individuals Age, 70 ± 11 years No history of CVD Follow-up 11 years (mean)	Luminex assay (Alere) 1268 (962–1781) ng/L	All-cause mortality ++ CV mortality ++ Non-CV mortality ++ Cancer mortality ++
Dallas Heart Study, Rohatgi et al. *(26)*	3219 multiethnic individuals Age range, 30–65 years 17% with a history of CVD Follow-up 7.3 years (median)	Luminex assay (Alere) 670 (490–930) ng/L	All-cause mortality ++ CV mortality +
Framingham Offspring Study, Wang et al. *(24)*	3428 individuals Age, 59 ± 10 years 6% with a history of CVD Follow-up 11.3 years (mean)	Elecsys assay (Roche) 1066 (821–1414) ng/L (men) 1022 (812–1304) ng/L (women)	All-cause mortality ++ Fatal or nonfatal CV events ++ Incident HF ++ Coronary heart disease events −−
Framingham Offspring Study, Ho et al. *(31)*	2614 individuals without chronic kidney disease Age, 57 ± 9 years Follow-up 9.5 years (mean)	Elecsys assay (Roche) 983 (790–1261) ng/L	Incident chronic kidney disease ++ Rapid decline in renal function ++
ULSAM, Wallentin et al. *(27)*	940 men Age, 71 years 40% with a history of CVD 6% with a history of cancer Follow-up 9.8 years (median)	Elecsys assay (Roche) 1494 (1216–1882) ng/L	All-cause mortality ++ CV mortality ++ Fatal or nonfatal CV events ++ Cancer mortality ++
Stable coronary artery disease			
AtheroGene, Kempf et al. *(44)*	1352 patients with stable angina pectoris undergoing coronary angiography Follow-up 3.6 years (median)	Research IRMA 1128 (850–1553) ng/L	Coronary heart disease mortality ++ Nonfatal MI −−
Heart and Soul Study, Schopfer et al. *(50)*	984 patients with stable CAD Follow-up 8.9 years (mean)	Luminex assay (Alere) 2166 (1589–3057) ng/L	All-cause mortality ++ CV events ++ MI ++, HF hospitalization ++
KAROLA, Dallmeier et al. *(46)*	1029 patients with stable CAD 58% with a history of MI 47% with a history of CABG Follow-up 10 years (median)	Elecsys assay (Roche) 1232 (916–1674) ng/L	All-cause mortality ++ CV events +
STABILITY, Hagström et al. *(47)*	14 577 patients with stable CAD and at least one additional predictor of CV risk Follow-up 3.7 years (median)	Elecsys assay (Roche) 1253 (915–1827) ng/L	All-cause mortality ++ CV mortality ++ HF mortality ++, HF hospitalization ++ MI +, stroke + Non-CV-mortality ++ Cancer mortality ++
Acute coronary syndrome			
GUSTO-4, Wollert et al. *(40)*	2081 patients with NSTE-ACS, ~9–15 h after symptom onset Follow-up 1 year	Research IRMA 1499 (1151–2203) ng/L (derivation set) 1434 (1035–2078) ng/L (validation set)	All-cause mortality ++ MI −−

Continued on page 143

Table 1. GDF-15 in relation to outcome events in exemplary studies.[a] *(Continued from page 142)*

Study	Population	GDF-15 assay and concentration	Risks associated with increased GDF-15[b]
ASSENT-2 and ASSENT-plus Kempf et al. *(42)*[d]	741 patients with STEMI, before thrombolysis Follow-up 1 year	Research IRMA 1635 (1164–2309) ng/L	All-cause mortality ++
Leicester Royal Infirmary infarct registry, Khan et al. *(43)*	1142 patients with NSTEMI or STEMI, 3–5 days after symptom onset Follow-up 1.4 years (median)	ELISA (antibodies from R&D) 1470 (240–31 860) ng/L	All-cause mortality ++ HF hospitalization ++, MI −−
PROVE IT-TIMI–22, Bonaca et al. *(49)*	3501 patients with NSTE-ACS or STEMI, prior to discharge Follow-up 2 years (mean)	Research IRMA 1362 (1032–1844) ng/L	All-cause mortality ++ MI ++, HF hospitalization ++
IABP-SHOCK-2, Fuernau et al. *(51)*	190 patients with NSTEMI or STEMI and cardiogenic shock undergoing primary PCI Follow-up 30 days	Quantikine ELISA (R&D) 7662 ng/L (median)	All-cause mortality ++
PLATO, Hagström et al. *(48)*	16 876 patients with NSTE-ACS or STEMI, within 24 h after symptom onset Follow-up 1 year	Elecsys assay (Roche) 1550 (1145–2219) ng/L	All-cause mortality ++ CV mortality ++ MI ++, stroke ++ Non-CABG-related major bleeding ++
Heart failure			
European HF registry, Kempf et al. *(59)*	455 patients with HFrEF Median LVEF 32% Follow-up 3.3 years (median)	Research IRMA 1949 (1194–3577) ng/L	All-cause mortality ++
Val-HeFT, Anand et al. *(60)*	1734 patients with HFrEF Mean LVEF 26% Follow-up 1.9 years (median)	Research IRMA 2040 (1426–3027) ng/L	All-cause mortality ++ Death or nonfatal HF event ++
SHOP, Chan et al. *(64)*	730 patients with HFrEF Mean LVEF 28% 186 patients with HFpEF Mean LVEF 60% Follow-up 1.9 years (median)	Quantikine ELISA (R&D) 2517 (1555–4030) ng/L in HFrEF 2862 (1812–4176) ng/L in HFpEF	Death or HF hospitalization ++
RELAX-AHF, Cotter et al. *(72)*	1088 patients with acute HF Follow-up 180 days	Elecsys assay (Roche) Baseline, 4013 ng/L (median) day 2, 3608 ng/L (median) day 14, 3502 ng/L (median)[e]	CV death or rehospitalization with HF or renal failure at 60 days: GDF-15 at baseline: +[f] GDF-15 change: ++ CV death at 180 days: GDF-15 at baseline: +[f] GDF-15 change: ++
Atrial fibrillation			
ARISTOTLE, Wallentin et al. *(76)*	14 798 patients with atrial fibrillation Follow-up 1.9 years (median)	Elecsys assay (Roche) 1383 (977–2052) ng/L	All-cause mortality ++ Cardiac mortality ++ MI +, stroke + Major bleeding ++

[a] Continuous data are presented as median with 25th and 75th percentiles or mean ± SD, unless otherwise stated.
[b] ++, association persists after adjustment for clinical risk predictors and other plasma biomarker(s); + association persists after adjustment for clinical risk predictors; −−, association is lost after adjustment.
[c] Association after adjustment for clinical risk predictors and other plasma biomarker(s) not reported.
[d] ASSENT, Assessment of the Safety and Efficacy of a New Thrombolytic trial.
[e] Data are from the placebo group.
[f] Unadjusted (model adjusted for clinical risk predictors only was not reported).

(15). 1200 ng/L, the rounded 90th percentile in that study, was proposed as the upper limit of the reference interval in healthy elderly adults *(15)*. This value corresponded to the 79th percentile in a second study *(25)*.

ASSOCIATION WITH CV AND CANCER MORBIDITY AND MORTALITY

GDF-15 is a strong and independent predictor of CV and cancer morbidity and mortality in community-dwelling individuals (Table 1). An association of GDF-15 with future CV events was first observed in 514 apparently healthy middle-aged women from the Women's Health Study *(21)*. GDF-15 was modestly correlated with hs-CRP, but the relationship between GDF-15 and CV events persisted after controlling for hs-CRP and CV risk factors *(21)*, suggesting that hs-CRP and GDF-15 reflect nonoverlapping disease pathways.

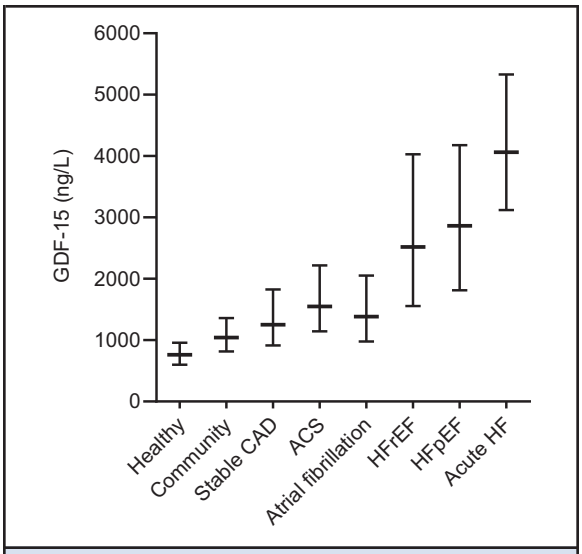

Fig. 1. Circulating GDF-15 concentrations in carefully selected apparently healthy individuals *(15)*, more unselected community-dwelling individuals *(24)*, stable CAD *(47)*, ACS *(48)*, atrial fibrillation *(76)*, chronic HFrEF and HFpEF *(64)*, and acute HF *(72)*.

GDF-15 was measured with the IRMA, Quantikine ELISA, or Elecsys assay. Data are presented as median with 25th and 75th percentiles (33rd and 66th percentiles in acute HF).

The relation of GDF-15 to CV outcomes was further analyzed in 3428 middle-aged individuals from the Framingham Offspring Study *(24)*. In models adjusted for CV risk factors, prevalent CV disease, and other biomarkers [BNP, hs-CRP, hs-cTnI, soluble suppression of tumorigenicity 2 (sST2)], GDF-15 was associated with all-cause mortality, incident HF, and major CV events, but not with coronary heart disease events. The association of GDF-15 with all-cause mortality was particularly strong compared with the other biomarkers [hazard ratio (HR) per 1 SD increase in log-transformed biomarkers in the fully adjusted model: GDF-15, 1.52 (95% CI, 1.37–1.67); hs-CRP, 1.18 (1.07–1.30); BNP, 1.13 (1.02–1.24); sST2, 1.12 (1.02–1.24); hs-cTnI, 1.06 (0.97–1.16)]. Regarding incident HF, BNP, GDF-15, hs-cTnI, and sST2 performed comparably well, and each biomarker offered independent information *(24)*. In a related analysis, GDF-15, but not hs-cTnI or sST2, predicted a rapid decline in renal function and the development of chronic kidney disease independent of known risk factors for renal disease, such as diabetes, hypertension, baseline proteinuria, and cystatin C *(31)*. While the Framingham Offspring Study included mostly participants of European ancestry, GDF-15 was also associated with all-cause mortality and CV mortality in the Dallas Heart Study that investigated individuals from different ethnic backgrounds *(26)*.

Table 2. Conditions associated with higher GDF-15 concentrations.

Higher age
Current smoking
Diabetes mellitus (metabolic syndrome)
Genetic factors
Acute inflammation (e.g. sepsis)
Chronic inflammation (e.g. rheumatoid arthritis)
Chronic kidney disease
Anemia and bleeding
Vascular disease
Heart failure
Atrial fibrillation
Solid cancers
Terminal illness, cachexia

The association of GDF-15 with all-cause mortality was further explored in the Rancho Bernardo Study which included 1391 mostly elderly individuals with no antecedent CV disease *(23)*. GDF-15 was independently associated with all-cause mortality and both CV and noncardiovascular mortality. GDF-15 added to the predictive value of conventional CV risk factors, hs-CRP, and NT-proBNP [HR per 1 SD increase in log GDF-15: all-cause mortality, 1.5 (1.3–1.8); CV mortality, 1.4 (1.1–1.8); non-CV mortality, 1.6 (1.4–2.0); cancer mortality, 1.8 (1.3–2.4)]. GDF-15 was a stronger predictor of all-cause mortality than hs-CRP or NT-proBNP and was the only 1 of the 3 markers to predict noncardiovascular mortality and cancer mortality in the fully-adjusted model *(23)*.

Similarly, GDF-15 was an independent predictor of all-cause mortality, CV mortality, and cancer mortality in the Uppsala Longitudinal Study of Adult Men (ULSAM) *(27)*. ULSAM included an unselected cohort of 940 71 years-old community-dwelling men, 40% of whom had a history of CV disease, and 6% a history of cancer. GDF-15 was analyzed in the context of conventional risk factors, hs-CRP, NT-proBNP, hs-cTnT, and cystatin C. Of these biomarkers, only GDF-15 independently predicted fatal or nonfatal CV events in men without a history of CV disease [HR per 1 SD increase in log GDF-15, 1.44 (1.22–1.71)], and incident cancer or cancer death in men without a history of cancer [1.24 (1.05–1.47)] *(27)*.

Although increased GDF-15 may be an indication of subclinical CV or malignant disease, GDF-15 alone appears not to be useful as a screening marker owing to its lack of tissue specificity *(30, 32, 33)*. However, the presence of subclinical disease may partly explain the associ-

ations of GDF-15 with future events. In addition, increased GDF-15 concentrations also seem to indicate a heightened susceptibility to develop CV disease and cancer. This is suggested, for example, by the continued separation of the cumulative CV event curves in patients with high as compared to low GDF-15 several years after the marker was measured *(23, 26, 27)*. Along this line, increased concentrations of GDF-15 were also associated with incident cancer when patients diagnosed with cancer within 2 years after the initial blood draw were excluded from the analyses *(27, 34)*.

POTENTIAL IMPLICATIONS FOR RISK MANAGEMENT

The close and independent associations of GDF-15 with CV disease and cancer are notable and distinguish GDF-15 from other biomarkers, including hs-CRP and the natriuretic peptides *(23, 27, 28)*. These relations are reflected by the robust association of GDF-15 with all-cause mortality which appears to be stronger than that of other biomarkers *(24)*. CV disease and cancer are the most common causes of death in high-income countries. CV disease and cancer accounted for 39% and 25% of all deaths in the Rancho Bernardo Study and for 43% and 40% of all deaths in the ULSAM population, respectively *(23, 27)*. Although commonly regarded as separate disease entities, there is a growing recognition that CV disease and cancer have various similarities, including shared risk factors (age, diabetes, smoking, physical inactivity, unhealthy diet) that suggest a common biology *(35)*. Chronic inflammation appears to be 1 unifying causal factor in both diseases. Inflammation is involved in all stages of atherosclerosis, from its initiation and progression to its thrombotic complications. Inflammation also plays a fundamental role in promoting malignant transformation and tumor progression *(35)*.

The American Heart Association endorses 7 metrics of ideal health that include a combination of health behaviors (no smoking, physical activity, healthy diet) and risk factors (blood pressure, total cholesterol, blood glucose, obesity). Poor adherence to these modifiable health metrics is associated with higher circulating concentrations of GDF-15 *(36)*. Conversely, adherence to these health metrics reduces CV risk *(36)* and the risk of incident cancer *(37)*. Increased GDF-15 concentrations could therefore provide individuals with an incentive to make healthier lifestyle choices and may justify more intense risk factor control and monitoring.

There are also medical therapies that reduce the risk of CV disease and cancer. For example, use of daily aspirin for the primary prevention of major CV events also reduces the incidence of cancer and cancer mortality, although more research is required to identify which individuals are likely to benefit most *(38)*. GDF-15 may ultimately help target high-risk individuals to preventive therapies such as aspirin. In fact, a prospective, nested case-control study has recently suggested that aspirin and nonsteroidal antiinflammatory drugs are associated with a lower risk of colorectal cancer specifically in patients with high GDF-15 concentrations *(34)*.

Given its associations with an unhealthy lifestyle, CV risk factors, and several age-related chronic diseases, including CV disease, renal disease, cancer, and even cognitive decline *(39)*, GDF-15 may be conceptualized as marker of biological age. In apparently healthy individuals, a low GDF-15 concentration as an indicator of general health and longevity may be more desirable than a low hs-CRP which is associated primarily with a lower risk of CV events *(23, 27)*.

GDF-15 in Coronary Artery Disease

Similar to what has been shown in community-dwelling elderly individuals, GDF-15 concentrations are independently related to age, diabetes, current smoking, hs-CRP, natriuretic peptides, and renal dysfunction in patients with established coronary artery disease (CAD) *(40–47)*. GDF-15 concentrations are higher in patients with multivessel disease *(41, 48)*, and in those with a history of MI or HF *(40–43, 48–50)*. Although GDF-15 is expressed in the infarcted human heart *(6)*, GDF-15 concentrations in acute coronary syndrome (ACS) appear not to be independently related to the extent of myocardial damage as reflected by necrosis biomarkers *(40, 41, 43, 51)* or infarct size *(52)*.

Circulating GDF-15 remains remarkably stable over time in patients with ACS and no acute HF. The average GDF-15 concentrations decreased by only 4% over the course of 4–6 months in patients from the Fragmin and Fast Revascularization During Instability in Coronary Artery Disease-2 trial (FRISC-2) or the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22 trial (PROVE IT–TIMI-22) *(45, 49)*, suggesting that GDF-15 primarily reflects chronic disease burden in these patients. This is in contrast to what has been observed with cardiac troponin, hs-CRP, and the natriuretic peptides, which increase and decrease during and after an episode of ACS *(45)*.

GDF-15 IN ACS

GDF-15 has been recognized as a consistent biomarker of mortality and CV events in patients with ACS *(40–44, 48, 49, 51)* or stable CAD *(44–47, 50)* (Table 1). As first shown in 2081 patients from the GUSTO-4 (Global Utilization of Strategies to Open Occluded Arteries-4 trial), admission GDF-15 concentrations are closely related to all-cause mortality in non–ST-segment elevation ACS (NSTE-ACS) *(40)*. Cumulative 1-year mortality rates were 1.5, 5.0, and 14.1% in patients with low (below 1200 ng/L), moderately increased (1200–

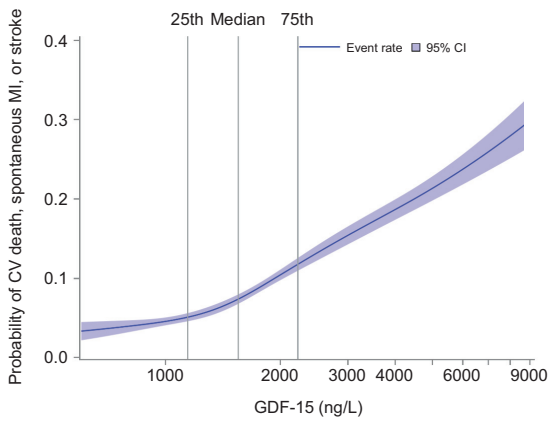

Fig. 2. Spline plot illustrating the association of circulating GDF-15 with the composite endpoint of CV death, spontaneous MI, or stroke after 12 months in 16 876 patients with ACS in PLATO *(48)*.

Event rate is shown with 95% CI. Median and 25th and 75th percentiles are indicated.

1800 ng/L), and markedly increased (above 1800 ng/L) concentrations of GDF-15. GDF-15 provided prognostic information beyond that provided by clinical predictors and other prognostic biomarkers, including cTnT, NT-proBNP, hs-CRP, and creatinine clearance *(40)*. The independent association of GDF-15 with mortality was later confirmed in other patient populations presenting with NSTE-ACS or ST-elevation MI (STEMI) *(42, 43)*.

Lately, the prognostic value of GDF-15 has been reevaluated in 16876 patients with NSTE-ACS or STEMI randomized to ticagrelor or clopidogrel in the Platelet Inhibition and Patient Outcomes trial (PLATO) (Fig. 2) *(48)*. Based on the large number of patients and outcome events, the PLATO biomarker study was able to explore the relation of GDF-15 to specific outcome events during follow-up. After adjustment for clinical predictors and other biomarkers (hs-cTnT, NT-proBNP, hs-CRP, and cystatin C), higher GDF-15 concentrations were associated with an increased risk of all-cause mortality [HR per 1 SD increase in log GDF-15, 1.41 (1.31–1.53)], CV mortality [1.41 (1.30–1.53)], MI [1.15 (1.05–1.26)], and stroke [1.19 (1.01–1.42)] *(48)*.

Increased concentrations of GDF-15 also identify patients at increased risk for adverse left ventricular remodeling and hospitalization for HF after ACS *(43, 49, 53)*. In 3501 patients from PROVE IT–TIMI-22, GDF-15 measured before hospital discharge was associated with the risks of all-cause mortality, recurrent MI, and hospitalization for new or worsening HF *(49)*. The prognostic information provided by GDF-15 was independent of clinical predictors and other biomarkers including hs-CRP and BNP, indicating that GDF-15 reflects nonoverlapping disease pathway(s) contributing to the development of HF after ACS. Notably, GDF-15, in contrast to hs-CRP *(54)*, did not decline over time in response to more intensive statin therapy in PROVE IT–TIMI-22 *(49)*.

GDF-15 IN STABLE CAD

GDF-15 maintains its close association with an adverse prognosis in patients with ACS when measured at initial presentation *(40–42, 44, 48)*, during the hospital course *(40, 43)*, before discharge *(49)*, and during the transition to the chronic stage of CAD *(45, 46)*. In a serial analysis from FRISC-2, GDF-15 provided similar independent prognostic information on the composite endpoint of death or recurrent MI on admission and up to 6 months after an episode of NSTE-ACS *(41, 45)*. Correspondingly, GDF-15 independently predicted all-cause mortality and CV events in 1029 patients admitted to a cardiac rehabilitation program approximately 6 weeks after an acute MI or coronary artery bypass graft surgery (CABG) *(46)*.

In the AtheroGene study, which included 1352 patients with stable angina pectoris undergoing coronary angiography, GDF-15 was associated with coronary heart disease mortality independent of CV risk factors, clinical predictors, the number of diseased vessels, left ventricular ejection fraction (LVEF), and other biomarkers (cTnI, NT-proBNP, hs-CRP) *(44)*. Similarly, GDF-15 was independently associated with all-cause mortality, fatal and nonfatal CV events, and HF hospitalization in 984 patients with stable CAD from the Heart and Soul Study *(50)*.

The relations of GDF-15 to specific outcome events have recently been reexamined in 14577 patients with stable CAD and at least 1 additional predictor of increased CV risk from the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial (STABILITY) *(47)*. GDF-15 concentrations were associated with all-cause mortality [HR 4th quartile vs 1st quartile, 2.00 (1.53–2.62)], CV mortality [1.61 (1.15–2.24)], and the composite endpoint of CV mortality, MI, or stroke [1.36 (1.11–1.67)], independent of clinical predictors and other prognostic biomarkers (hs-cTnT, NT-proBNP, hs-CRP, cystatin C). GDF-15 similarly predicted HF death [1.75 (1.30–2.35)], and hospitalization for HF [3.19 (1.71–5.98)] in fully-adjusted models. Likewise, GDF-15 predicted noncardiovascular mortality [2.62 (1.60–4.29)] and cancer mortality [2.35 (1.23–4.50)], although the prognosis of these high-risk patients with established CAD was primarily determined by CV events (CV mortality and cancer mortality accounted for 62% and 16% of all deaths, respectively) *(47)*.

POTENTIAL IMPLICATIONS FOR PATIENT MANAGEMENT

Based on its close and independent association with adverse outcomes, GDF-15 may ultimately support triage and management decisions in patients with suspected ACS. Several studies illustrate the potential of the marker to risk stratify unselected contemporary patient populations treated outside clinical trials. In a recent investigation that compared the incremental prognostic value of 9 biomarkers on top of the Global Registry of Acute Coronary Events (GRACE) score in unselected patients with NSTE-ACS, GDF-15 emerged as the most promising biomarker *(55)*. Underscoring its potential to add information to what is clinically available, GDF-15 also added discriminatory information to GRACE when hs-cTnT was considered as an additional continuous variable *(55)*. In another study in patients presenting to the emergency room with acute chest pain, GDF-15 predicted all-cause mortality more accurately than and independently of hs-cTnT and NT-proBNP. Using 1200 ng/L and 1800 ng/L as cutoff values, patient subgroups with greatly different 24-month mortality rates could be identified (0.7%, 6.3%, 21.1%) *(19)*.

In the FRISC-2 trial that randomized patients with NSTE-ACS to an early invasive vs a noninvasive treatment strategy, increased concentrations of both troponin and GDF-15 identified the patients who derived the largest benefit from early revascularization procedures *(41, 56)*. Early revascularization reduced the risks of death or recurrent MI in patients with GDF-15 above 1200 ng/L, with the greatest benefit observed in patients with GDF-15 above 1800 ng/L. Conversely, patients with GDF-15 below 1200 ng/L were at low risk and did not benefit from an early invasive strategy (Fig. 3) *(41, 56)*. In the NSTE-ACS subgroup of the PLATO trial, GDF-15 above 1200 ng/L was associated with an increased risk of CV death and MI and indicated larger absolute benefits from more intense treatments, i.e., with more intense platelet inhibition with ticagrelor as compared to clopidogrel as well as with planned early revascularization *(57)*.

Thresholds offer a convenient way to classify patients into risk categories that may be linked to treatment decisions. However, the use of thresholds may reduce statistical power given the continuous association of GDF-15 with CV risk (Fig.2). Alternatively, GDF-15 might be incorporated as a continuous variable into established or novel risk scores that can be presented as nomograms or applications on (handheld) electronic devices. A new bleeding risk score containing GDF-15 provides an example in this regard (discussed below) *(58)*. New algorithms for decision support in ACS are currently under evaluation (including variables such as troponin and GDF-15 showing a significant interaction with the effects of an early invasive treatment strategy).

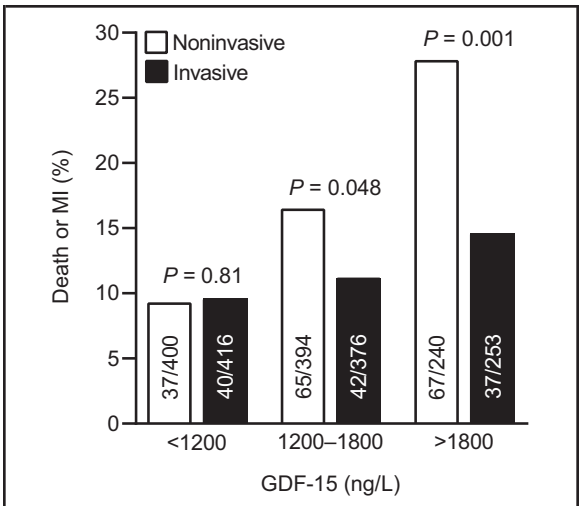

Fig. 3. Composite endpoint of death or MI after 2 years according to GDF-15 concentration at baseline and randomized treatment strategy in patients with NSTE-ACS in FRISC-2 *(41)*.
The number of events and number of patients are indicated in each group.

GDF-15 in Heart Failure

Most patients with HF with reduced ejection fraction (HFrEF) have increased concentrations of GDF-15 *(59–61)*, although a great interindividual variability is observed even in patients with advanced disease scheduled for left ventricular assist device (LVAD) implantation *(18)*. GDF-15 concentrations increase in relation to HF severity as reflected by New York Heart Association (NYHA) class, peripheral edema, and increased concentrations of BNP or NT-proBNP and hs-cTnT *(59, 60)*. GDF-15 concentrations are higher in patients with comorbidities such as diabetes, renal dysfunction, cachexia, and anemia. GDF-15 levels are also related to age and biomarkers of inflammation (hs-CRP, uric acid) and neurohormonal activation (plasma norepinephrine) *(59, 60)*.

Notably, measured GDF-15 is increased to a similar degree in patients with HF with preserved ejection fraction (HFpEF) or HFrEF *(62–64)*. In contrast, the circulating concentrations of NT-proBNP and hs-cTnT are generally lower in HFpEF than in HFrEF *(63)*. Systemic inflammation related to aging, diabetes, and hypertension has been put forward as a central pathomechanism in HFpEF *(65)*, raising the possibility that GDF-15 reflects this inflammatory state. GDF-15 concentrations in HFpEF are related to echocardiographic indices of diastolic dysfunction, and it has been suggested that GDF-15 in combination with BNP or NT-proBNP may support the diagnosis of HFpEF and the differential diagnosis of HFpEF vs HFrEF *(62, 63)*; larger studies in

heterogeneous patient populations with dyspnea and suspected HF are lacking, however.

GDF-15 concentrations in HFrEF *(59–61, 64)* or HFpEF *(64)* are associated with all-cause mortality and composite endpoints of death or HF events (Table 1) independent of clinical predictors such as NYHA class, LVEF, renal function, and prognostic biomarkers, including BNP or NT-proBNP, hs-cTnT, and hs-CRP. For example, in the recent Singapore Heart Failure Outcomes and Phenotypes study (SHOP), GDF-15 was associated with the composite endpoint of all-cause mortality or HF hospitalization independent of clinical predictors, HF type (HFrEF or HFpEF), NT-proBNP, and hs-cTnT [HR per 1 unit increase in ln-transformed GDF-15, 1.76 (1.39–2. 21)] *(64)*. In a biomarker substudy from the Valsartan Heart Failure Trial (Val-HeFT) in 1734 patients with HFrEF, GDF-15 concentrations increased by approximately 8% during the course of 12 months, with similar increases in patients randomized to placebo or valsartan *(60)*. Notably, the magnitude of the increase in GDF-15 was associated with worsening functional status and adverse outcomes after multivariable adjustment for baseline variables and biomarkers and their concurrent changes. By contrast, BNP concentrations showed a significant decrease in the valsartan group, indicating a distinct responsiveness of GDF-15 and BNP to angiotensin receptor blockade. These data emphasize that GDF-15 reflects a disease pathway that is not fully addressed by the therapies prescribed to the patients in Val-HeFT *(60)*. Notably, the intraindividual variation of GDF-15 in stable HF is lower compared with the intraindividual variation of the natriuretic peptides, which may facilitate the interpretation of temporal changes in GDF-15 *(66, 67)*.

Although pharmacological treatments reducing GDF-15 concentrations in chronic HF remain elusive, LVAD implantation can lead to a significant decrease of circulating GDF-15 in patients with advanced HFrEF *(18, 68)*, showing that even large increases in GDF-15 are to some extent reversible in response to a potentially life-saving therapeutic intervention. In 1 study which focused on patients with end-stage nonischemic cardiomyopathy, GDF-15 expression in the left ventricle was very low, suggesting that GDF-15 is mainly produced in peripheral organs *(18)*. Patients with advanced HF who require mechanical circulatory support often present with end-organ dysfunction as a consequence of tissue hypoperfusion, inflammation, oxidative stress, and neurohormonal activation. LVAD support improves renal and hepatic function and augments cerebral blood flow and leg perfusion in these patients *(69, 70)*. Decreases in GDF-15 may therefore mirror the peripheral effects of left ventricular unloading *(18)*, which contrasts with BNP, which is reflecting the cardiac effects of LVAD support *(71)*.

Patients with acute decompensated HF present with higher GDF-15 concentrations than patients with HF who are hemodynamically stable *(72)*. Similarly, patients with ACS and acute HF can have very high GDF-15 *(42, 43)*, especially patients in cardiogenic shock *(43, 51)*, and those who have been resuscitated or are mechanically ventilated *(51)*. GDF-15 concentrations in cardiogenic shock are related to serum lactate, indicating that GDF-15, to some extent, reflects peripheral hypoperfusion in these patients *(51)*. Circulating GDF-15 in cardiogenic shock is independently associated with 30-day mortality independent of other relevant risk factors including serum lactate *(51)*. In the Relaxin in Acute Heart Failure trial (RELAX-AHF) in patients with acute decompensated HF, GDF-15 decreased from admission to day 14 as the patients' clinical status gradually improved *(72)*. This decrease was faster and more pronounced in patients randomized to the investigational vasodilator drug serelaxin, showing, again, that GDF-15 levels may respond to therapeutic interventions *(72)*. Patients experiencing a greater reduction in GDF-15 had better outcomes in terms of reduced risks of CV death or rehospitalization with HF or renal failure, even after adjustment for baseline variables and for changes in other biomarkers (NT-proBNP, hs-cTnT, blood urea nitrogen) *(72)*.

GDF-15 has also been explored in patients with right-sided HF. In acute pulmonary embolism, GDF-15, but not NT-proBNP, enhanced the prognostic information provided by an echocardiographic assessment of right ventricular function *(73)*. In patients with idiopathic pulmonary arterial hypertension, GDF-15 added prognostic information to hemodynamic variables and NT-proBNP regarding the long-term risk of death or lung transplantation *(74)*. Changes in GDF-15 over time after initiation of medical therapy were inversely related to changes in mixed venous oxygen saturation, indicating that GDF-15 tracks changes in functional status in response to contemporary treatment regimens *(74)*. Based on these initial studies, further research on GDF-15 and its potential therapeutic implications in right-sided HF is warranted.

GDF-15 and Bleeding

A strong association of GDF-15 with the risk of bleeding was observed in patients with ACS receiving dual antiplatelet therapy in PLATO *(48)*. Higher GDF-15 concentrations, measured within 24 h after symptom onset, were associated with non-CABG-related major bleeding complications. The relation of GDF-15 to bleeding was consistent across different bleeding locations and independent of a comprehensive set of clinical predictors and other biomarkers (hs-cTnT, NT-proBNP, hs-CRP, and cystatin C) *(48)*. Clinical practice guidelines provide spe-

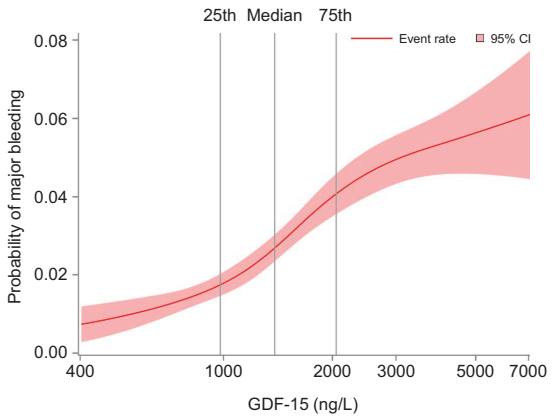

Fig. 4. Spline plot illustrating the association of GDF-15 with the occurrence of major bleeding after 12 months in 14 798 patients with atrial fibrillation in ARISTOTLE *(76)*.

Event rate is shown with 95% CI. Median and 25th and 75th percentiles are indicated.

cific recommendations for ACS patients deemed at high risk of bleeding, for example, regarding the length of dual antiplatelet therapy or the choice of parenteral and oral anticoagulants. Risk scores have been developed to estimate bleeding risk in ACS but the performance of these scores is rather poor *(75)*. Ultimately, GDF-15 may help identify patients at higher risk of bleeding who will benefit from closer monitoring and specific measures to reduce bleeding complications (e.g., radial vascular access, shorter duration of dual antiplatelet or triple therapies, proton pump inhibition).

The close and independent association of GDF-15 with the risk of major bleeding was verified in 14798 patients with atrial fibrillation treated with oral anticoagulation therapy in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE) (Fig. 4) *(76)*. These findings have led to the development of the biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation receiving oral anticoagulant therapy *(58)*. The score was developed in the ARISTOTLE population and validated in another 8468 patients with atrial fibrillation from the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY). The score is based on 5 variables (age, GDF-15, hs-cTnT or hs-cTnI, hemoglobin, history of previous bleeding), with GDF-15 being the strongest contributing factor. The ABC-bleeding risk score performed better than current bleeding risk scores in atrial fibrillation, and could become useful as decision support regarding indications for and selection of treatment with oral anticoagulants in patients with atrial fibrillation *(58)*.

Conclusion and Future Directions

There is now a large evidence base documenting a strong association of GDF-15 with future CV events in the community and in patients. GDF-15 captures distinct aspects of CV disease development, progression, and prognosis that are not represented by established risk predictors.

GDF-15 has been shown in multiple settings to add predictive information to traditional risk factors and other plasma biomarkers, to improve discrimination of patients with or without events, and to reclassify patients in the appropriate directions *(23, 26, 27, 31, 48, 55, 60, 64, 76, 77)*, indicating that the marker provides incremental value *(78)*. For example, GDF-15 adds substantial information to the GRACE score and hs-cTnT in patients with NSTE-ACS [increase in *c* statistic, from 0.763 to 0.791; continuous net reclassification improvement (NRI(>0)), 53%] *(55)*. Similarly, GDF-15 enhances the HAS-BLED bleeding risk score [increase in *c* statistic, from 0.633 to 0.677; NRI(>0), 30%] *(76)*, an observation that has spurred the development of the new ABC-bleeding risk score *(58)*.

Prospective and preferably randomized studies are needed to further evaluate the utility of GDF-15 for guiding management decisions and treatment selection, in comparison to and in combination with other biomarkers and clinical predictors. Considering the pathobiology of the marker, patients with increased GDF-15 concentrations may potentially benefit from antiinflammatory, antioxidant, or antiaging therapies. With a better understanding of the upstream disease pathways reflected by GDF-15, new treatment targets may emerge. Increasing GDF-15 concentrations over time are indicative of a worse prognosis in the community and in patients with CAD or HF *(45, 46, 60, 79, 80)*. Further evaluations of the impact of environmental influences, lifestyle changes, and (medical) treatments on GDF-15 concentrations over time are eagerly awaited. Eventually, interventions that lower GDF-15 may be associated with better health and improved outcomes. Prospective randomized studies of such interventions stratified for and monitored by GDF-15 concentrations therefore appear to be an exciting opportunity.

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