Growth Differentiation Factor 15 in Cardiovascular Diseases: Predicting Bleeding after Cardiac Surgery and Beyond That!

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Growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine-1, is a cytokine from the transforming growth factor β superfamily, the mature protein is secreted as a 25 kDa disulfide-linked dimer, which is strongly expressed and secreted in response to hypoxia, oxidative stress, inflammation, tissue injury, and remodeling.[1] Under pathological conditions, GDF-15 is expressed in various types of cardiovascular and noncardiovascular cells (macrophages, vascular smooth muscle cells, adipocytes, cardiomyocytes, endothelial cells, fibroblasts, prostate tissue, or intestinal mucosa) and therefore, GDF-15 levels provide information from both cardiac and extracardiac pathways.[2]

GDF-15 has gained attention during the recent years, particularly as a risk prediction biomarker (►**Fig. 1**). As for January 2022, more than 800 articles have been published in the last 3 years (period: 2019–2022) investigating GDF-15. An important part of the research on GDF-15 has focused on its potential relationship with worse prognosis in cardiovascular diseases. Thus, in outpatients with cardiovascular risk factors, GDF-15 was associated with an increased risk of stroke independently of conventional risk factors and other prognostic markers.[3] GDF-15 (among other circulating biomarkers) effectively predicted the risk of long-term mortality in patients with acute heart failure with preserved ejection fraction.[4] Similarly, in patients with acute coronary syndrome (ACS), baseline GDF-15 was a strong marker of all-cause mortality and major adverse cardiovascular events in previous studies,[5,6] and in patients with non-ST segment elevation myocardial infarction, GDF-15 was also related with cardiovascular death or heart failure.[7] Indeed, a meta-analysis showed a significant association between GDF-15 levels and mortality (relative risk [RR]: 6.75, 95% confidence interval [CI]: 5.81–7.84) or recurrent myocardial infarction (RR: 1.95, 95% CI: 1.72–2.21) in ACS patients.[8] Even in patients with suspected myocardial infarction, GDF-15 concentrations at emergency department have demonstrated to predict all-cause mortality and discriminate patients with very low mortality risk.[9]

Despite these findings, one of the main target uses of GDF-15 is the prediction of bleeding risk in different clinical scenarios (►**Table 1**). Thus, in patients with ACS from the PLATO trial, higher baseline levels of GDF-15 were associated with raised risks of major noncoronary artery bypass graft-related bleeding beyond established risk factors.[10] The same population was analyzed at 1 month after ACS, and again, elevated GDF-15 was related to the risk of major bleeding.[11] In patients with atrial fibrillation (AF), the impact of GDF-15 on bleeding outcomes has been extensively investigated.[12] Certainly, this interest motivated the inclusion of GDF-15 in the ABC (age, biomarkers, clinical history) bleeding score, which was derived and validated in the ARISTOTLE and RE-LY clinical trial cohorts.[13] In AF patients from the ENGAGE AF-TIMI 48, elevated GDF-15 levels at baseline were independently associated with a higher risk of major bleeding,[14] and a substantial increase in GDF-15 measured over 1 year was still associated with bleeding.[15] More recently, a massive screening of potential biomarkers associated with major bleeding in patients with AF from the ARISTOTLE and RE-LY revealed that GDF-15 and other biomarkers increased the risk of bleeding.[16]

However, GDF-15 is also related to bleeding in patients with other diseases. For example, a case/control study showed that high circulating GDF-15 levels at baseline were associated with incident intracerebral hemorrhage and incident subarachnoid hemorrhage, independently of
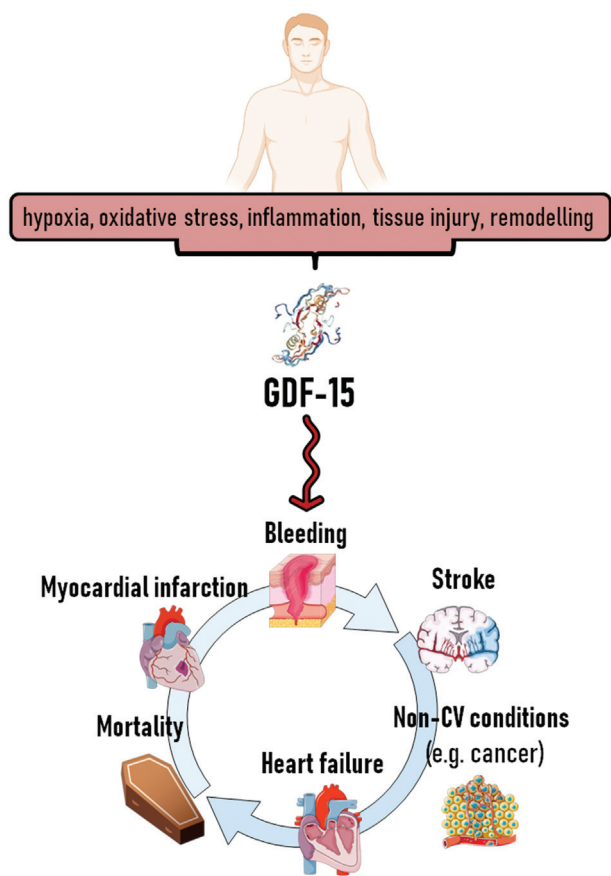
Fig. 1 Diseases associated with GDF-15. GDF-15, growth differentiation factor 15.

the main risk factors.[17] Another study found that GDF-15 concentrations were higher in patients with pulmonary embolism who experienced bleeding during hospitalization compared with those who did not experience bleeding, and GDF-15 was associated with a good prediction for bleeding (c-index: 0.783, 95% CI: 0.62–0.946).[18] Finally, GDF-15 also predicted bleeding in cancer patients receiving thromboprophylaxis from the AVERT trial.[19]

In this issue of *Thrombosis and Haemostasis*, Kazem and colleagues reported the outcomes of 504 prospective patients undergoing cardiac valve and/or coronary artery bypass graft surgery.[20] In brief, preoperative GDF-15 levels strongly associated with any intra- and postoperative red blood cell transfusion (adjusted odds ratio [aOR]: 1.62, 95% CI: 1.31–2.00) and ≥2 intra- and postoperative red blood cell transfusions (aOR: 1.75, 95% CI: 1.39–2.21). Importantly, preoperative GDF-15 levels were also related with the risk of composite of bleeding events (aOR: 1.33, 95% CI: 1.01–1.76), major or clinically relevant minor bleeding (aOR: 1.69, 95% CI: 1.08–4.46), and ≥2 red blood cell transfusions (aOR: 4.07, 95% CI: 1.78–9.28) during the first postoperative year. The authors therefore concluded that the preoperative GDF-15 level was an independent predictor for intra- and postoperative major bleeding, and major bleeding during the first year after cardiac surgery.[20]

The mechanisms underlying the association of GDF-15 and bleeding have not been fully discovered yet. One hypothesis is that GDF-15 specifically inhibits platelet integrin activation, thus increasing the risk of bleeding.[21] However, this is not specific of a particular condition but could be presented in different diseases. Since GDF-15 is expressed in

Table 1 Summary of studies about GDF-15 and bleeding outcomes

Study	Main disease of the included population	Sample size	Main results
Hagström et al[10]	Acute coronary syndrome	16,876	Increased GDF-15* was associated with higher risk of major bleeding (HR: 1.37, 95% CI: 1.25–1.51). *Per 1 SD increase in baseline ln GDF-15.
Lindholm et al[11]	Acute coronary syndrome	4,049	Increased GDF-15* at 1 month was associated with higher risk of non-CABG-related major bleeding (aHR: 3.38, 95% CI: 1.89–6.06). *Defined as GDF-15 > 1,800 ng/L.
Berg et al[14]	Atrial fibrillation	8,705	Increased GDF-15 was associated with higher risk of major bleeding (aHR: 2.12, 95% CI: 1.60–2.81)*/(aHR: 1.73, 95% CI: 1.46–2.04)** *Comparing the highest vs. lowest tertile category (≥1,800 vs. <1,200 ng/L). **Per 1 SD increase in baseline log GDF-15.
Oyama et al[15]	Atrial fibrillation	6,308	Increased GDF-15* at baseline and 12 months was associated with higher risk of major bleeding (aHR: 1.40, 95% CI: 1.02–1.92). *Per 1 SD increase in log2-transformed GDF-15.
Siegbahn et al[16]	Atrial fibrillation	4,200 (identification cohort) 1,368 (replication cohort)	Increased GDF-15* was associated with higher risk of major bleeding (aHR: 1.195 95% CI: 0.925–1.544) (identification cohort)/ (aHR: 1.574, 95% CI: 1.293–1.915) (replication cohort).

Table 1 (Continued)

Study	Main disease of the included population	Sample size	Main results
			*Comparing the highest vs. lowest quartile category.
Song et al[17]	Intracerebral hemorrhage, subarachnoid hemorrhage, controls	Incident ICH (220 cases, 244 controls) Incident SAH (79 cases, 261 controls)	Increased GDF-15* was associated with higher risk of incident ICH (aOR: 2.27, 95% CI: 1.52–3.41) and incident SAH (aOR: 2.16, 95% CI: 1.29–3.59). *Per 1 SD increase in log2-transformed GDF-15.
Skowrońska et al[18]	Pulmonary embolism	77	Patients with major bleeding/CRNMB had higher median GDF-15 levels (4,577 [3,588–11,877] vs. 2,179 [1,133–4,613] ng/L, $p = 0.03$). Increased GDF-15* increased risk of composite adverse outcomes** (aOR: 8.9, 95% CI: 1.03–77.76). *Defined as GDF-15 > 1,680 ng/L. **Including major bleeding/CRNMB.
Mulder et al[19]	Cancer	574	Increased GDF-15* was associated with higher risk of major bleeding (aHR: 2.80, 95% CI: 1.91–4.11), CRNMB (aHR: 1.67, 95% CI: 1.08–2.58), and any bleeding (aHR: 2.12, 95% CI: 1.38–3.25). *Comparing the highest vs. lowest tertile category.

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CABG, coronary artery bypass graft; CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; ICH, intracerebral hemorrhage; OR, odds ratio; SD, standard deviation; SAH, subarachnoid hemorrhage.

response to diverse signals (oxidative stress, inflammation, tissue injury, etc.), it can be equally predictive not only for bleeding, but also for stroke, mortality, heart failure, etc., as well as noncardiac events. Indeed, one of the classic criticisms of this biomarker is its nonspecific nature since it is upregulated because of injury of organs such as the liver, kidney, heart, and lung. In consequence, it has been associated with several conditions. Previous studies demonstrated that increased GDF-15 levels are related with glaucoma,[22] periodontal disease,[23] mental disorders (including poststroke depression and Alzheimer's disease),[24,25] different cancer types (lung, gastrointestinal, and colorectal),[26,27] and prognosis in COVID-19.[28–30] Thus, the predictive ability of biomarkers (and biomarker-based scores) beyond endpoints which they were designed for, could be very similar to what they were originally proposed (in the case of GDF-15, bleeding).[31] For this reason, it is not clear whether GDF-15 rises as reflective of a particular clinical outcome or is simply reflective of a "*sick heart*" or "*sick patient*." Such nonspecificity as well as the challenges of biomarker testing (cost, assay variability, diurnal and temporal variation, etc.) may discourage the incorporation of GDF-15 in guidelines related to antithrombotic therapy, where simplicity and practicality for decision making should be prioritized.[32–34]

Moreover, a limitation of GDF-15 is the lack of real-world studies given that most of the evidence is derived from randomized clinical trials. This is relevant for the particular issue of bleeding since one recent study suggested that differences in patient characteristics and risk profiles of patients from observational studies are important contrib-utors to the differences in bleeding outcomes between clinical practice and randomized trials.[35] In this sense, the study by Kazem et al adds new evidence to the field coming from a real-world population, what is needed at the moment.

In summary, GDF-15 is one promising biomarker amongst many others, but we are still far from its widespread use and some limitations need to be overcome. Factors such as the practicality of use, assay availability, elevated costs, and assay variability hamper its use in everyday clinical practice. Furthermore, aging and incident comorbidities increase the risk of bleeding, and risk assessment should be a dynamic process (and not a static "one-off" assessment). Therefore, the use of GDF-15 must be considered along with other variables that may increase the risks of bleeding (and other adverse nonbleeding events).

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