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Review article

Growth differentiation factor-15, a novel systemic biomarker of oxidative stress, inflammation, and cellular aging: Potential role in cardiovascular diseases

Angelo Michele di Candia [a], Diane Xavier de Avila [a], Gustavo Rodolfo Moreira [a], Humberto Villacorta [a,*], Alan S. Maisel [b]

[a] Postgraduate Program in Cardiovascular Sciences, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil
[b] Division of Cardiovascular Medicine, University of California San Diego, La Jolla, United States of America

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ABSTRACT

Growth differentiation factor-15 (GDF-15) is a cytokine upregulated in multiple pathological conditions where oxidative stress, endothelial dysfunction, tissue aging, and chronic inflammation are the hallmarks. GDF-15 has many sources of production, including cardiac and vascular myocytes, endothelial cells, adipocytes and macrophages in response to metabolic stress, oncogenic transformation and the burden of proinflammatory cytokines or reactive oxygen species. Although the main sources of GDF-15 are extracardiac tissues, it has been shown to be elevated in many cardiac disorders. In experimental models of heart disease, GDF-15 release is induced after an ischemic insult and in pressure overload scenarios. Likewise, in recent years, an increasing body of evidence has emerged linking GDF-15 to the risk of mortality in acute coronary syndromes, atrial fibrillation and heart failure. Additionally, GDF-15 has been shown to add prognostic information beyond other conventional biomarkers such as natriuretic peptides and cardiac troponins. Further studies are needed to assess whether the incorporation of GDF-15 into clinical practice can improve cardiovascular outcomes.

1. Introduction

Cardiovascular diseases affect a considerable number of individuals and, along with cancer, represent the main cause of death in the occidental world. Cardiovascular events can be predicted by clinical variables and imaging tests, such as echocardiogram. However, the introduction of biomarkers increases prognostic value and refines risk stratification. Natriuretic peptides and cardiac troponins are well-established cardiovascular biomarkers, but new candidates have been proposed. In this group of emerging biomarkers, growth differentiation factor 15 (GDF-15) is a promising one. Although not a specific cardiac marker, it is elevated in many cardiovascular disorders and has been shown to predict cardiovascular events in some studies. In this article, we review the literature on GDF-15 and discuss its limitations and potential role in cardiovascular diseases.

2. What is GDF-15?

GDF-15, originally termed macrophage inhibitory cytokine-1 (MIC-1), is a divergent member of the transforming growth factor beta (TGF-β) superfamily, a group of cytokines that act on tissue homeostasis [1–3]. The TGF-β superfamily comprises more than 40 members, originally identified as molecules important for regulating development, differentiation, and tissue repair in various organs [2]. Although GDF-15 belongs to this superfamily, it has no strong homology to other existing families, indicating that it is a divergent member [3]. Its enhanced expression is believed to inhibit the latter phases of macrophage activation, thereby exerting an overall anti-inflammatory effect [2].

In normal situations, GDF-15 is weakly expressed in human tissues, except by the placenta, during pregnancy [4]. The concentrations of GDF-15 in healthy individuals increase slowly with aging and seem to be less influenced by race or sex [5]. On the other hand, GDF-15 is rapidly produced by various cell types, including hepatocytes, cardiomyocytes, macrophages, endothelial and smooth cells, among others, in response to other cytokines, cellular stress or tissue injury, hypoxia and oncogene activation [6]. Upregulation of GDF-15 has been demonstrated after various cardiovascular events that trigger inflammation and oxidative stress, including pressure overload, heart failure (HF), atrial fibrillation

* Corresponding author at: Rua Marquês do Paraná 303, Cardiology Division, CEP 24033-900 Niterói, Rio de Janeiro State, Brazil.
E-mail address: hvillacorta@id.uff.br (H. Villacorta).

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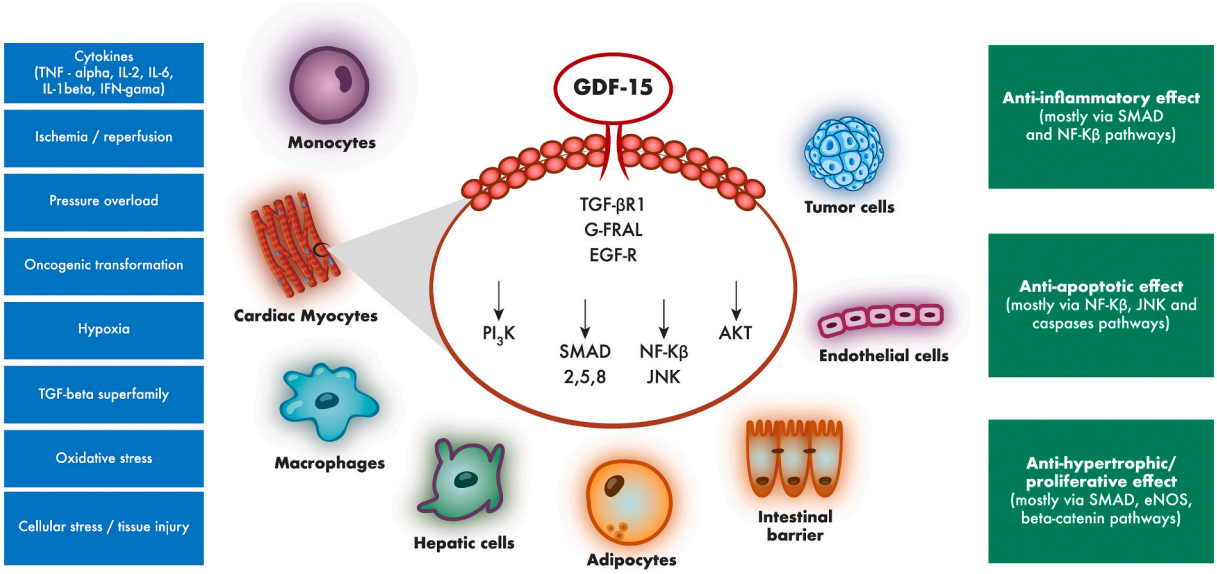

Fig. 1. Summary of known stimulators (in the left corner), transcriptional intracellular signaling pathways (inside the cell), cell types involved, and tissular effects (in the right corner) of GDF-15. GFRAL: GDNF-family receptor alpha-like, TGF-beta R1: TGF beta receptor-1, EGF-R: Epidermal growth factor receptor, PI3K: phosphoinositide 3 kinase, SMAD: small mother against decapentaplegic signaling pathway, NF-KB: Nuclear factor kappa B, JNK: c-Jun N-terminal kinase, AKT: Protein kinase B, eNOS: Endothelial Nitric oxide synthase.

Table 1
Summary of clinical disorders associated with GDF-15.

Cardiovascular conditions
Heart failure (Ref. [42–48])
Coronary artery disease (Ref. [31–36])
Atrial fibrillation (Ref. [37–39])
Stroke (Ref. [32,39])
Physiologic conditions
Aging and frailty (Ref. [5,38])
Inflammation and metabolic disorders
Acute and chronic inflammatory diseases (Ref. [1,4,8,12,40])
Metabolic syndrome, diabetes mellitus, obesity (Ref. [8,9])
Hematologic conditions
Anemia (Ref. [38,40])
Bleeding (Ref. [33,37–39])
Consumptive syndromes
Terminal illness (Ref. [1,4,10])
Neoplasia (Ref. [10,21–23])
Others
Renal insufficiency (Ref. [40])
Genetic diseases (Ref. [5])
COVID-19 (Ref. [28–30])

and atherosclerosis [1,6]. Of note, although GDF-15 can be produced by the heart, the main sources of this biomarker seem to be extracardiac tissues. In animal studies, after myocardial infarction (MI) or transverse aortic constriction, the GDF-15 gene expression was about 100-fold higher in the liver as compared with left ventricle tissue [7]. Strong expression was also found in the kidneys and in the lungs. Additionally, in a mouse model of obesity and hypertension, GDF-15 expression was readily detected in visceral adipose tissue [7]. These findings indicate that the elevated plasma levels observed in cardiac disorders reflect not only the heart damage itself but also the systemic repercussion of the cardiac injury.

After secretion, GDF-15 can act on neighboring cells regulating inflammatory interactions, in autocrine, paracrine and endocrine manners [2]. Those vast biological effects are context-dependent and may vary according to the stage of disease and tissue involved. In most cases GDF-15 triggers an adaptive response of tissular protection, with emphatic antiproliferative, anti-inflammatory and anti-apoptotic actions [8].

Fig. 1 highlights the relationships involved in the synthesis and known effects of GDF-15. Heart diseases, diabetes, obesity, stroke and various forms of cancer are the most studied descriptions found in the growing clinical literature of GDF-15, as summarized in Table 1. In the following sections we will review the pre-clinical and clinical studies on GDF-15. It is important to note that the values shown in these studies are method-dependent and cannot be indistinctively used. For this reason, no specific cutpoints have been proposed.

3. Expression of GDF-15 in cardiovascular disease: pre-clinical evidence

Recent findings from experimental studies focused on the discovery of an endogenous receptor for GDF-15, the GDNF-family alpha-like (GFRAL) receptor. Emmerson et al. [6] found that transgenic mice overexpressing GDF-15 invariably have a lean phenotype driven by decreased food intake and other improvements in energy metabolism, mediated through GFRAL receptors in the hindbrain. Yang et al. administered GDF-15 to obese mice and observed a robust and dose-dependent reduction in body weight, effect largely driven by the GFRAL pathway [8], which also reduced food intake and resulted in significant cachexia, reversed by antibodies neutralizing GDF-15, in tumor xenograft models [9]. These relevant findings clarify a role for GDF-15 in weight loss in response to stress, tissular damage and cancer, opening the possibility of future research on treatments for obesity and type 2 diabetes, with a focus on the GFRAL receptor or GDF-15 itself [8,10].

Although experimental sustained activation of TGF-beta1, the prototype of TGF-beta superfamily, causes structural remodeling and angiotensin-II induced hypertrophy and apoptosis, eventually leading to cardiac failure [2], in-vivo studies suggest that GDF-15 act in the opposite way, preventing cardiomyocyte cell death, limiting ischemic scar and protecting against hypertrophy and apoptosis induced by angiotensin-II, nitric oxide or even TGF-beta1 [11].

Kempf et al. observed that mice lacking GDF-15 were more susceptible to ischemia/reperfusion damage, with greater MI and higher chance of myocardial rupture thereafter [12]. In the same experiment, infusion of recombinant GDF-15 in the gene-targeted mice prevented cardiomyocyte cell death and tissue scar formation [13].

4. Expression of GDF-15 in the prediction of cardiovascular risk: clinical evidence

GDF-15 has shown only limited diagnostic usefulness in patients with chest pain, dyspnea, HF or MI [14,15]. However, its widespread production and lack of specificity perhaps explains why it is a strong predictor of cardiovascular events, considering that those are determined by abnormalities generally affected by lifestyle, comorbidities, and aging – in processes that reflect, ultimately, oxidative stress, apoptosis, chronic inflammation and repair [4,12]. In most studies, those associations remained statistically significant even after adjustments for age, sex, body mass index, diabetes, hypertension, smoking, left ventricular ejection fraction (LVEF), natriuretic peptides, cardiac troponins, renal function or the use of medications.

Brown et al. were the first to report a relation between GDF-15 and cardiovascular risk in 514 apparently healthy women when GDF-15 concentrations above >856 ng/L were independently associated with a 2.7-fold risk of fatal or nonfatal cardiovascular events (HR 1.6–4.9, 95% CI) [16]. In the Framingham Heart Study, after a mean follow-up of 11.3 years, GDF-15 was independently associated with all-cause mortality, incident HF and other major cardiovascular events; the association with all-cause mortality (HR 1.66, 95% CI 1.51–1.81) remained the strongest among other widely used biomarkers, notably high-sensitivity C-reactive protein (hs-CRP), B-type natriuretic peptide (BNP), high sensitivity cardiac troponin I (hs-TnI) and soluble suppression of tumorigenicity 2 (sST2) [17]. These findings support that GDF-15 can predict cardiovascular injury and dysfunction several years before the event in the unselected general population.

Recent trials advise that GDF-15 could be used as a prognostic biomarker (and potential therapeutic target) in diabetes and obesity. Schernthaner et al. [18] evaluated GDF15 concentrations in 160 obese subjects who underwent a 75 g oral glucose tolerance test. GDF15 was higher in the prediabetes and diabetes subgroups and correlated with HbA1c, glucose and baseline and dynamic indices of insulin sensitivity, signaling early disturbances in insulin resistance and future occurrence of diabetes, independently to its prognostic value regarding cardiovascular risk.

Kempf et al. [19] measured GDF-15 concentrations in a large longitudinal cohort of 496 obese nondiabetic individuals enrolled in the XENDOS trial. Baseline GDF-15 predicted the risk to have prediabetes or diabetes at 4 years and was independently related to the occurrence of insulin resistance after multivariate adjustments.

5. The relations between GDF-15, cancer and cardiovascular disease

Differentiating normal tissues to a neoplastic state requires an imbalance between the activation of oncogenes and the protective inhibition of tumor suppressor genes. Therefore, the transformed tissues attract immune cells (notably macrophages) that infiltrate the tumor site and orchestrate elimination functions, as part of an “immune surveillance” operation [20,21]. Much of this dynamic interaction between tumor cells and macrophages is integrally linked to GDF-15. GDF-15 acts in vitro by suppressing the pro-apoptotic activity mediated by NF-KB in macrophages, inhibiting the production of TNF-alpha and nitric oxide (NO), thus regulating tumor proliferation, among other beneficial effects [10,21]. Increased GDF-15 expression is a feature of many cancers including breast, colon, pancreas, and prostate [10].

Furthermore, there are close associations between cardiovascular disease, cancer and GDF-15; cardiovascular disease and most forms of cancer share the same risk factors, suggesting chronic inflammation, endothelial dysfunction and oxidative stress as unifying causal factors with a significant role in both diseases [10,22].

GDF-15 has a vital role in the connections of subcellular signaling between aging, obesity, CHIP (clonal hematopoiesis of indeterminate potential), neoplasia and cardiovascular risk [22,23]. Given these associations, GDF-15 is well regarded as an indicator of biological age. As seen in prospective cohorts of unselected individuals, low GDF-15 concentrations are usually related to longevity and health; on the other hand, when elevated, GDF-15 concentrations may act as a warning of developing pathological processes that imply increased risk and will need further investigation [16,17].

6. COVID-19, the heart and GDF-15

Several studies have reported that Coronavirus disease 2019 (COVID-19), a disorder caused by the SARS-CoV-2 infection, has both a higher incidence of cardiac arrhythmias, acute coronary syndromes (ACS) and heart-failure related events [24]; furthermore, among survivors, some type of heart damage has been widely observed, even if they didn't have previous underlying heart disease [24,25]. The mechanisms behind these acute and long-term processes are yet uncertain, although hypoperfusion, microvascular coagulopathy, adrenergic overdrive, and cytokines mediated injury have all been hypothesized [26].

It is well established that both occurrence and severity of COVID-19 increases with age and the presence of comorbidities like hypertension, diabetes, obesity and cardiovascular diseases – conditions also largely related to the production of GDF-15 [24,26]. Furthermore, as angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2 and its down-regulation appears to promote cardiac dysfunction in experimental models, a link between ACE2 and SARS-CoV-2 provides one theoretical mechanism for the cardiac dysfunction seen in COVID-19 patients [27]. In two large cohorts of patients with atrial fibrillation, GDF-15 was strongly associated with ACE2 concentrations, a finding that might contribute to better identification of risk for cardiac complications and severe COVID-19 infection [27].

GDF-15 is associated with more severe disease in COVID-19 and in some studies has been shown to be a predictor of outcomes [28–30]. In a prospective series of 66 patients admitted to a hospital with COVID-19, GDF-15 emerged as the inflammatory marker with the best ability to predict the risk of death, with excellent discriminatory capacity, superior to hs-CRP, d-dimer and ferritin, for example (AUC 0.89, 0.79–0.96, 95% CI) [29].

In one observational study of 123 patients, GDF-15 was elevated in patients hospitalized with COVID-19, and its concentrations were independently associated with poor outcome [30]. GDF-15 was superior to IL-6, hs-CRP, procalcitonin, high-sensitivity cardiac troponin T (hs-TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and other biomarkers, in the prediction of admission to intensive care unit or death during hospitalization. These patients had significantly higher GDF-15 concentrations than those that did not reach the endpoint (4225 vs. 2187 ng/L; C-statistic value, 0.78; 95% CI, 0.70–0.86). Additionally, SARS-CoV-2 viremia was associated with higher concentrations of GDF-15, but not with all other biomarkers, suggesting a direct link between the cytopathic effects of the viremia and the widespread expression of GDF-15 in multiple tissues [30]. More studies are necessary to consolidate the role of GDF-15 in COVID-19 either during the acute phase of the disease or in the prediction of post-COVID syndromes.

7. GDF-15 and coronary artery disease

GDF-15 is considered a good predictor of mortality in both patients with ACS or stable coronary artery disease (CAD) and is generally higher in ACS patients with a history of earlier MI or multivessel disease [31,32]. In the longitudinal cohort of 14,577 patients with stable CAD from the STABILITY trial, GDF-15 concentrations were related to all-cause mortality (HR 2.00, CI 95% 1.53–2.62 4th quartile vs 1st quartile) and the composite endpoint of cardiovascular mortality, MI, or stroke (HR 1.36, CI 95% 1.11–1.67), independent of other prognostic biomarkers, such as NT-proBNP, hs-TnT, or cystatin C [32].

Hagstrom et al. randomized non-ST-Elevation ACS patients to ticagrelor or clopidogrel in the PLATO trial and observed that higher GDF-

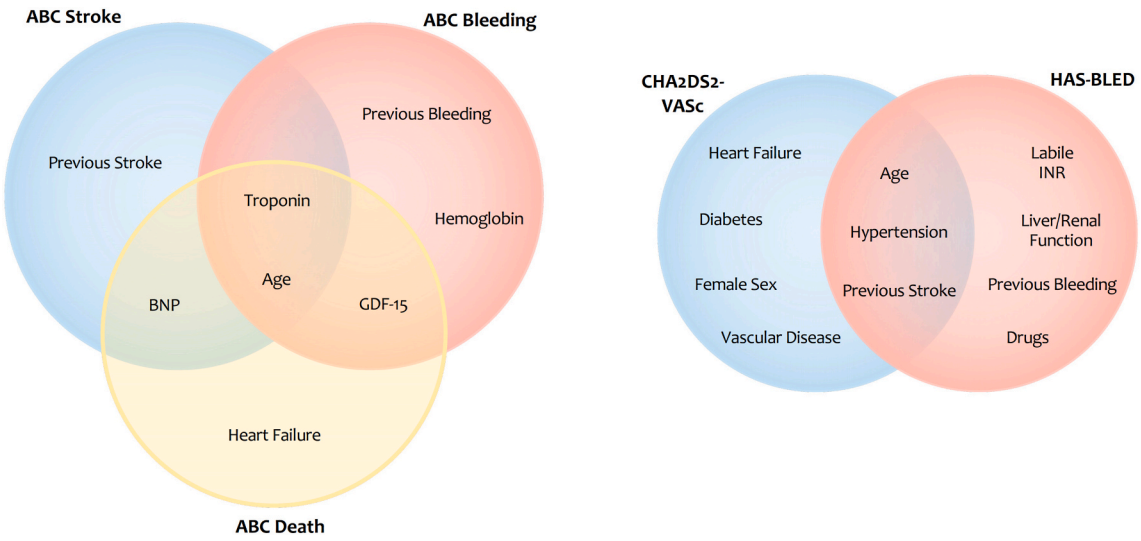

Fig. 2. Venn's diagrams showing dimensions of risk and overlapping of factors in the ABC (stroke, bleeding and death) and CHA2DS2-VASc/HAS-BLED risk scores.

15 concentrations were independently related to an increased risk of mortality, MI and bleeding in both groups [33]. A single measurement of GDF-15 at admission improved risk stratification for mortality and bleeding risk. Based on these findings, future studies should assess whether GDF-15 could help with difficult decisions in clinical practice, like the best duration of dual antithrombotic therapy for each patient.

Eggers et al. [34] and Schaub et al. [35] reported that GDF-15 predicts all-cause mortality more accurately than hs-TnT or natriuretic peptides in the emergency triage of patients with chest pain. Using 1200 ng/L and 1800 ng/L as cutoffs, Eggers et al. [34] observed that GDF-15 remained as an independent predictor of death or MI after 6 months in 479 patients (1.3% for the under 1200 ng/L group, 5.1% for the 1200–1800 ng/L group, and 12.6% for the above 1800 ng/L group, all $p < 0.05$). Similarly, Schaub et al. divided 646 unselected patients in 3 subgroups using the same cutoff values and reported substantial differences in mortality during the 2-year follow-up (0.7%, 6.3%, 21.1% for the 3 terciles, all $p < 0.05$). Moreover, GDF-15 concentrations enriched discrimination in the former cohort since they improved the C-statistic power of ECG and cardiac troponin data combined from 0.74 to 0.83 ($p < 0.01$) [34].

In a recent meta-analysis of 43,547 ACS patients, Wang et al. [36] observed a significant correlation between GDF-15 and mortality (RR 6.75, 95% CI 5.81–7.84), and recurrent MI (RR 1.95, 95% CI 1.72–2.21) in the overall Forest plot analysis, proposing GDF-15 as a valuable tool for early risk stratification.

8. GDF-15 and atrial fibrillation

Walletin et al. [37] were the first to propose, in the ARISTOTLE study, that GDF-15 concentrations in patients with AF added independent prognostic information regarding mortality and bleeding risk. After multivariate adjustments and throughout a follow-up of 1.9 years, the annual rates of major bleeding ranged from 1.22% to 4.53% ($p < 0.001$); and of mortality, from 1.34% to 7.19% ($p < 0.001$) in the lowest compared with the highest GDF-15 quartile groups. From that data they developed a bleeding risk score, based on clinical information and the use of biomarkers: the ABC-bleeding score [38]. The ABC-bleeding score reached agreement levels (C-index) higher than the HAS-BLED and ORBIT scores, improved risk stratification and reclassified patients within the range of the HAS-BLED and ORBIT score risk classes, including patients with low HAS-BLED and ORBIT scores. Conversely, neither HAS-BLED nor ORBIT scores improved the risk stratification within the different classes of ABC score bleeding risk [38].

These findings were then externally validated by Berg et al. [39] in the ENGAGE-TIMI 48 study, where GDF-15 was independently associated with both the risk of thrombosis and major bleeding. Furthermore, increases in GDF-15, NT-proBNP and hs-TnI after 12 months in relation to baseline values were able to reclassify the risk of thrombosis and bleeding in these patients; compared with the CHA2DS2-VASc and HAS-BLED scores, the ABC scores provided both correct upward and downward reclassification of stroke risk, and correct downward reclassification of bleeding risk, findings that offer a better risk-benefit profile in favor of treatment and should improve some management gaps in AF patients. Indeed, that decision-making process on anticoagulation of these patients must be more accurate when using the ABC scores, since they have less intersection and overlapping of variables than the CHADS2-VASC and HAS BLED clinical scores, as shown in Fig. 2.

Table 2
Summary of possible interactions between GDF-15 and cardiovascular diseases.

Possible interactions between GDF-15 and cardiovascular disease progression
Improvement of glucose tolerance and insulin resistance
Limitation of ischemia/reperfusion damage
Protection against hypertrophy and apoptosis induced by angiotensin-II
Reduction of collagen turnover and fibroblast growth
Impairing of microvascular relaxation
Inhibition of apoptosis in heart, adipose and muscular tissues
Regulation of atherosclerosis and plaque progression
Limitation of remodeling

Although the associations between GDF15 and bleeding risk observed by these authors are not yet fully understood, it seems certain that by signaling general frailty, systemic tissue aging and organ dysfunction, GDF-15 improves the bleeding risk estimation and adds clues to the early identification of complications directly related to the antithrombotic treatment. Furthermore, GDF-15 could help track the changes over time in modifiable risk factors (e.g., anemia, myocardial ischemia, renal dysfunction, obesity) [40] or treatments with the potential to reduce complications (catheter ablation, auricular closure).

A major gap we need to clarify is the role of GDF-15 in patients with AF who, for distinct reasons, are not under anticoagulant treatment. Additionally, there is no robust evidence for patients with AF outside the controlled setting of the recent clinical studies with new oral anticoagulants, where patients with severe renal disease, cognitive dysfunction, short life expectancy, frailty, among others, were excluded or underrepresented.

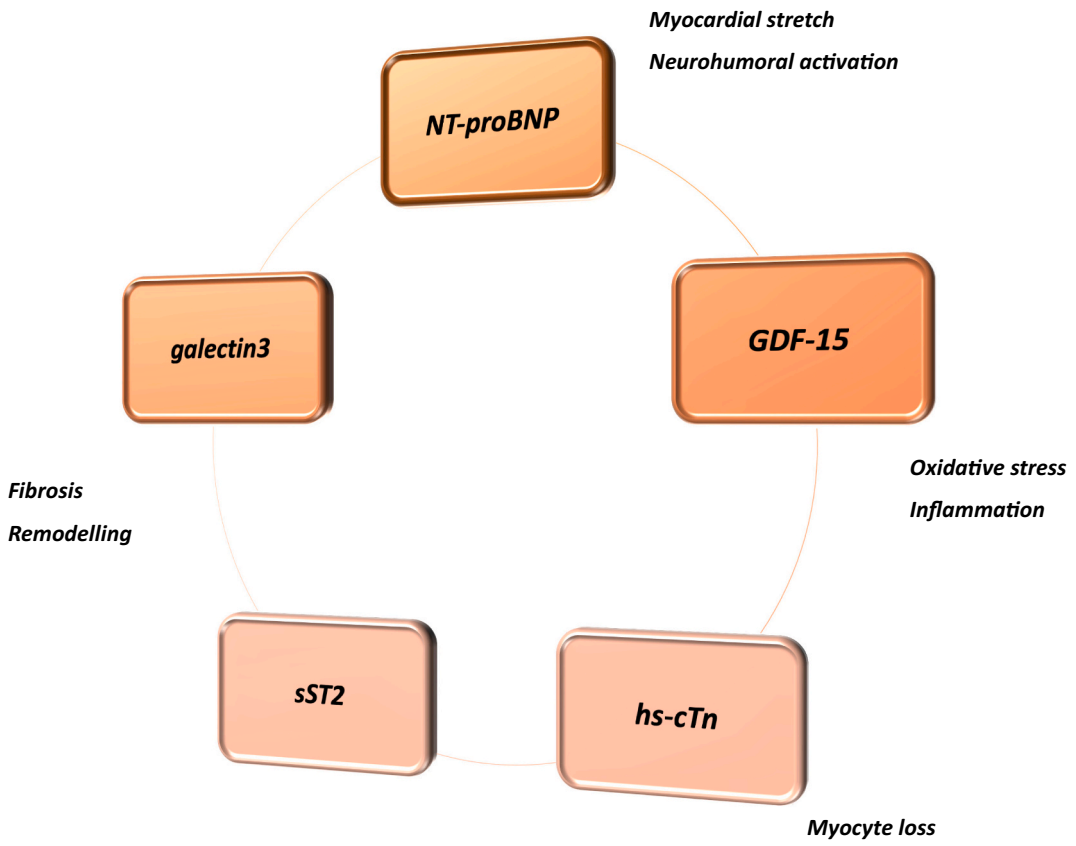

Fig. 3. Biomarkers suggested in a multimarker approach model for risk stratification in heart failure.

9. GDF-15 and heart failure

HF has a complex pathology, with pluriorganic involvement, a progressive worsening character that hinders its proper treatment and a growing demand for new and discriminative biomarkers to help manage it [41]. Table 2 summarizes the possible interactions between GDF-15 and cardiovascular diseases, notably HF.

Most patients with HF have increased concentrations of GDF-15, which are directly related to the stage of disease and functional status and independently associated with the risk of hospitalization and mortality [42,43]. GDF-15 is similarly increased in patients with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF), while the concentrations of BNP, NT-proBNP or hs-TnT are generally lower in the latter [43]. As HFpEF is a growing phenotype most related to a chronic inflammatory state involving aging, hypertension, metabolic syndrome and obesity, GDF-15 seems to better reflect this continued low-grade inflammatory condition than other usual biomarkers [43,44].

In 455 chronic HF patients Kempf et al. [44] demonstrated that the two-year mortality rate increased across GDF-15 quartiles (9.4%, 10%, 33.4% and 56.2%, respectively, $p < 0.001$). Even after multivariate adjustments, including NT-proBNP correction, GDF-15 remained an independent predictor of mortality. Bouabdallaoui et al. [45] measured GDF-15 concentrations at baseline, 1- and 8-months of 1935 ambulatory patients with HFrEF in the PARADIGM trial. Each 20% increase in baseline GDF-15 value was related to the mortality risk (HR 1.13, 95% CI 1.08–1.18) and to the combined endpoint of death or hospitalization (HR 1.09, 95% CI 1.05–1.14), all $p < 0.001$.

Some groups report the incremental ability of GDF-15 in addition to other conventional markers of cardiovascular risk, such as natriuretic peptides or cardiac troponins, with promising results of the combination surpassing the ability of either biomarker isolated in predicting all-cause mortality [46,47]. Bettencourt et al. [47] reported that higher GDF-15 values were associated with worse prognosis independently of the BNP concentrations in patients with acute HF. Indeed, when both biomarkers were elevated at discharge, the 2-year mortality risk increased over 4-fold (HR 4.33, 95% CI 2.1–9.1, $p < 0.001$) when compared with the reference category (both BNP and GDF-15 below the mean value).

In a prospective series of 209 patients with chronic HF, Lok et al. [48] evaluated the prognostic power of NT-proBNP, GDF-15, hs-CRP, galectin-3 and hs-TnT. In multivariate analysis, elevated concentrations of GDF-15 (HR 1.41, 95% CI 1.1 to 1.69), hs-CRP (HR 1.38, 95% CI 1.15 to 1.67), and hs-TnT (HR 1.27, 95% CI 1.06 to 1.53), all $p < 0.005$, were independently related to mortality. All biomarkers increased the prognostic value of NT-proBNP, using the integrated discrimination improvement. In this study, GDF-15 was the most powerful predictive marker, even stronger than NT-proBNP.

Nonetheless, in the group of 1161 acute HF patients enrolled in the RELAX-AHF trial, the use of a multiple-biomarker approach provided the greatest prognostic improvement, unmatched by a single time point-based single biomarker strategy [46]. However, this multiple-biomarker strategy needs to be tested in more clinical trials [49]. Fig. 3 provides a broad perspective of this proposal, gathering all pathophysiological axes associated with each biomarker.

10. Caveats and future directions

Although GDF-15 holds a potential role in cardiovascular medicine, some points still need clarification. The pathophysiology of this biomarker is not completely understood. For example, GDF-15 is an excellent predictor of bleeding in patients with atrial fibrillation [37–39]. At the same time, GDF15 in bleeding reflects very different biology compared to myocardial and vascular structural abnormalities observed in CAD, atrial fibrillation, and HF. Why a single marker could

indicate pathophysiological changes in such different domains remains a matter of debate. It is possible that inflammation, endothelium dysfunction, and oxidative stress, which are common pathways in these disorders, are a link between them. Therefore, GDF-15 is likely to represent an integrated biomarker of multiple comorbidities rather than a specific reflection of cardiovascular health, similar to that observed with hs-CRP.

In addition, the role of GDF-15 in cardiovascular diseases is not clear. Although it has been shown to predict cardiovascular events in some studies, other studies have failed to show this relationship. In the ACTION-HF study, GDF-15 predicted all-cause mortality but not cardiovascular mortality nor HF hospitalization [50]. Another example of this discordance is the findings from the PARADIGM-HF study. Although GDF-15 was a strong predictor of all-cause mortality, cardiac death, and HF hospitalization, it was not modified by sacubitril/valsartan, a drug that reduced all such events as compared with placebo [45]. The major determinants of GDF-15 concentrations in this clinical trial were age, diabetes, renal function, NT-proBNP, hs-TnT, and NYHA class III/IV. These findings reinforce the systemic nature of this biomarker rather than a specific cardiovascular marker.

As a result of the above limitations, the role of GDF-15 in clinical practice still needs to be defined. Further studies are needed to assess whether the use of GDF-15 can improve cardiovascular outcomes. Its role in predicting bleeding makes a strong case for using the ABC-bleeding risk score in patients with atrial fibrillation but no study so far has been carried out to assess reduction in events with this strategy. Likewise, future studies are necessary to establish its role in aiding in medical decision making in cardiovascular diseases such as CAD and HF.

11. Conclusion

GDF-15 is a biomarker with unquestionable predictive power in several scenarios involving cardiovascular disease. It provides a quantitative measure of the severity of multiple pathophysiological mechanisms underlying mortality risk in these patients. However, its exact function in cardiovascular system is still not clearly understood; whether it is a causative mediator or a passive, indirect risk biomarker, or even if it plays an adaptive or maladaptive role are yet uncertain fields of knowledge, and further studies are needed to access these controversies. Nonetheless, the recent discovery of the endogenous receptor for GDF-15 may allow advances in the understanding of its actions, especially in relation to energy metabolism, with future implications on therapies for obesity, cardiovascular disease and cancer. Additionally, incorporating GDF-15 on clinical panels with other biomarkers, such as cardiac troponins, galectin-3 and natriuretic peptides, appears a promising strategy since it can better reflect the multiple and complex disorders related to the progression of HF stages, of coronary disease, and of atrial fibrillation. Moreover, analyses that link all those axes involved, combining machine learning and biomarkers, have an enormous potential to better tailor cardiovascular therapy in the next precision medicine era.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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