JACC: CARDIOONCOLOGY VOL. 7, NO. 2, 2025

EDITORIAL COMMENT

Growth Differentiation Factor-15

A Promising Biomarker and Target in Cancer Patients

Markus S. Anker, MD,[a,b,c,d] Lars Bullinger, MD,[e,f,g] Ulrich Keller, MD,[e,f,g] Muhammad Shahzeb Khan, MD, MSc[h,i,j]

Patients with cancer are predisposed to hemostatic dysfunction with resulting thromboembolic and bleeding complications. The current literature primarily focuses on risk prediction and biomarkers for venous thromboembolism (VTE), while there is a paucity of biomarkers for assessing bleeding events. Bleeding in cancer may be driven by local tumor invasion, angiogenesis, systemic effects of the malignancy, impairment of hepatic function due to liver metastasis, or anti-cancer treatments and may be worsened by treatment-emergent factors such as thromboprophylaxis or hematological abnormalities such as thrombocytopenia and myelosuppression from either the cancer or cancer therapies. The risk for a hemorrhagic complication in patients on anticoagulation is higher in cancer vs non-cancer cohorts regardless of the anticoagulant used.[1] Current guidelines suggest individual assessment of VTE risk before initiating primary thromboprophylaxis.[2] Hence, there is also a need for a reliable marker for bleeding risk assessment to reflect a cancer patient's hemostatic status and guide treatment decisions.

One promising biomarker seems to be growth differentiation factor (GDF)-15, a stress-response cytokine from the transforming growth factor β superfamily, which has shown prognostic value in predicting bleeding risk in malignancy.[3] Under normal conditions, there is minimal production of GDF-15. However, GDF-15 plays a role in energy balance regulation and immunomodulation in states of high stress such as infection, chronic disease, or malnutrition. In cancer, GDF-15 has been proposed to drive carcinogenesis through angiogenesis, metastasis, and impedance of chemotherapy, leading to disease progression. Clinically, it has been vastly studied as a prognostic biomarker, with potential to predict bleeding risk in a diverse patient population.[4]

In this issue of *JACC: CardioOncology*, Englisch et al[5] report their results from the CAT-BLED (Vienna Cancer, Thrombosis, and Bleeding) study, a prospective, observational cohort study including 779 cancer patients initiating systemic anticancer therapies. GDF-15 was recorded at baseline, 3 months, and 6 months, and the patients were followed for up to 2 years for thrombotic and bleeding events. The results showed that GDF-15 performed well in independently predicting major bleeding events at 12 months, with patients above the median GDF-15 level (1,864 ng/L) showing higher event rates (13% vs 5%; $P < 0.001$). Higher GDF-15 levels were also associated with increased all-cause mortality and any clinically relevant bleeding, but not associated with thromboembolic events.

The investigators should be congratulated for conducting this elegant study. Multiple cardiology scores are regularly used in the clinic to assess hemostatic status and risk. The CHA_2DS_2-VA score is one of the most commonly used assessment of thromboembolic risk and was recently updated to remove the

From the [a]Deutsches Herzzentrum der Charité, Department of Cardiology, Angiology and Intensive Care Medicine CBF, Berlin, Germany; [b]Charité – University Medicine Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [c]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; [d]Berlin Institute of Health Center for Regenerative Therapies (BCRT), Berlin, Germany; [e]Department of Hematology, Oncology, and Cancer Immunology, Charité – University Medicine Berlin, corporate member of Free University Berlin and Humboldt University Berlin, Berlin, Germany; [f]German Cancer Consortium (DKTK), partner site Berlin, and German Cancer Research Center (DKFZ), Heidelberg, Germany; [g]Max Delbrück Center for Molecular Medicine, Berlin, Germany; [h]Baylor College of Medicine, Temple, Texas, USA; [i]The Heart Hospital Plano, Plano, Texas, USA; and the [j]Baylor Scott and White Research Institute, Dallas, Texas, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2025.01.001

JACC: CARDIOONCOLOGY, VOL. 7, NO. 2, 2025
FEBRUARY 2025:153–156

female sex category from the score.[6] The risk of bleeding is assessed by tools like the widely established HAS-BLED score or the more contemporary CAT-BLEED score, specifically designed to evaluate bleeding risk in anticoagulation treatment of atrial fibrillation and cancer-associated thrombosis.[7,8] Deciding whether to initiate oral anticoagulation is always a careful clinical consideration made together by physicians and patients, guided by current clinical guidelines and tailored to the individual's risk profile and overall health status. Although thromboembolic risk can be reduced with effective oral or intravenous anticoagulation, there typically is an associated increased risk of bleeding events with anticoagulation.

Bleeding complications in cancer patients represent a significant clinical challenge, often complicating treatment strategies and impacting patient outcomes. Current predictive models to assess bleeding risk perform poorly in oncology populations.[8] Therefore, GDF-15 might be very useful for clinicians to get an additional objective measure for bleeding risk assessment. It is therefore especially interesting that the investigators compared the prognostic power of GDF-15 with the HAS-BLED and CAT-BLEED scores and found that a model using GDF-15 alone outperformed both scores in predicting major bleeding, represented by a higher c-statistic. The incorporation of GDF-15 also significantly improved the discriminatory power of the aforementioned scores.

GDF-15's integration into clinical practice holds promise for revolutionizing bleeding risk stratification in oncology. Cancer patients often face the dual challenge of high thromboembolic and bleeding risks, particularly when anticoagulation therapy is considered. By incorporating GDF-15, clinicians may achieve more precise risk assessments, enabling personalized therapeutic strategies. For example, in those at increased risk of bleeding, an alternative strategy that may be considered is left atrial appendage closure. Furthermore, GDF-15's objective measurement could serve as a valuable adjunct to clinician-patient discussions regarding the benefits and risks of anticoagulation therapy.

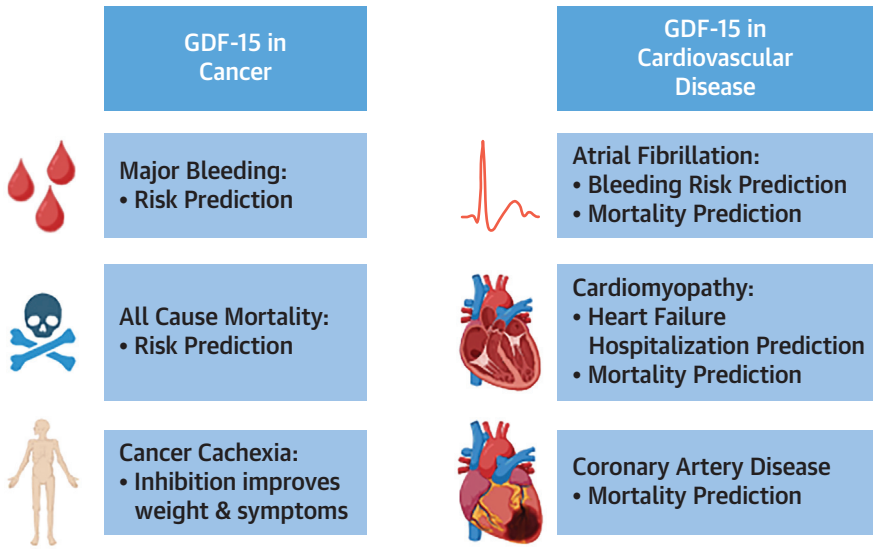
At the same time, it should also be accounted for that mortality was high in this study with 45% of patients dying over the 2-year follow-up. Notably, the patients who died could not have a bleeding event, thereby influencing the main outcome of the study. However, GDF-15 itself was a strong predictor of all-cause mortality. This is consistent with previous studies that have shown GDF-15's association with overall survival.[9] The absence of an association between GDF-15 and VTE further supports its applicability. Common hemostatic and inflammatory markers are often linked to both bleeding and thrombosis. This makes them less effective for independently assessing bleeding risk in cancer patients, who are frequently in a hypercoagulable state. In this context, GDF-15 may offer a more specific and reliable option, as it can better distinguish bleeding risk without being influenced by thrombotic status of the patient.

The role of GDF-15 in cancer goes beyond its association with hemorrhagic complications. Cancer cachexia is a devastating complication that affects 50% to 80% of advanced cancer patients and results in poor functional status, treatment tolerance, and survival.[10-12] Elevated GDF-15 levels are found in patients with cancer cachexia and are considered to be a main driver of anorexia and weight loss in solid cancers.[13] The potential of GDF-15 as a therapeutic target was recently investigated in a phase 2 clinical trial, which assessed the effects of ponsegromab, a humanized monoclonal antibody designed to inhibit GDF-15, in patients with non-small cell lung cancer, pancreatic cancer, or colorectal cancer.[14] The trial demonstrated that inhibiting GDF-15 led to significant improvements, including weight gain, increased physical activity, and a reduction in cachexia symptoms. These findings further underscore the potential role and novel therapeutic options of GDF-15 in cancer.

Beyond cancer, GDF-15 has been widely studied in the field of cardiovascular research. Before the evaluation of bleeding in cancer, GDF-15 is a well-established predictor of major bleeding, as well as adverse cardiovascular events and all-cause mortality in patients with atrial fibrillation on oral anticoagulation.[15] GDF-15 has thus already been incorporated into bleeding risk prediction scores in atrial fibrillation, such as in the ABC (Age, Biomarkers, Clinical History) risk score. With the current findings of the CAT-BLED study, this precedence can possibly be followed for bleeding risk prediction in cancer. In patients with ischemic or nonischemic cardiomyopathy, GDF-15 has been reported to also predict all-cause mortality as well as heart failure hospitalizations.[16] In patients with acute myocardial infarction, GDF-15 is associated with sudden cardiac death within 24 hours of the event.[17] The role of GDF-15 in cancer and cardiovascular disease is summarized in **Figure 1**.

In summary, this study by Englisch et al[5] highlights GDF-15 as a powerful biomarker for bleeding risk stratification in cancer patients. Its superior predictive performance compared with existing scores,

FIGURE 1 Potential Role of GDF-15 in Cardio-Oncology



GDF-15 is an emerging biomarker and therapeutic target in cardio-oncology with diverse applications. In cancer, GDF-15 may predict major bleeding risk and all-cause mortality, whereas in cardiovascular diseases, GDF-15 may serve as a prognostic marker for bleeding in atrial fibrillation, hospitalization in heart failure, and mortality in atrial fibrillation, cardiomyopathy, and coronary artery disease. Given the aging population and the frequent coexistence of cancer and cardiovascular disease, monitoring and targeting GDF-15 may provide significant benefits.

coupled with its specificity for bleeding over thrombotic events, makes it a valuable addition to clinical risk assessment tools. Beyond its prognostic role, GDF-15's involvement in cancer cachexia and its potential as a therapeutic target broaden its relevance in oncology. Moreover, GDF-15's established role in prediction of bleeding and death in various cardiovascular diseases such as atrial fibrillation, heart failure, and myocardial infarction further underscores its pathophysiologic role in systemic, chronic diseases. With the growing field of cardio-oncology and the increasing recognition of the shared pathophysiology and mutual risk amplification between cancer and heart disease, GDF-15 may be a promising biomarker for prognostic and therapeutic applications with the potential to address critical gaps in managing overlapping risks in these patient populations.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Bullinger has received honoraria from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Otsuka, Pfizer, Roche, and Sanofi, unrelated to this work; and research funding from Bayer and Jazz Pharmaceuticals, unrelated to this work. Dr Khan has received fees from Bayer and Novartis, unrelated to this work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Markus S. Anker, Charité-Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany. E-mail: markus.anker@charite.de. X handle: @ShahzebKhanMD.

REFERENCES

1. Angelini DE, Radivoyevitch T, McCrae KR, Khorana AA. Bleeding incidence and risk factors among cancer patients treated with anticoagulation. *Am J Hematol*. 2019;94(7):780–785. https://doi.org/10.1002/ajh.25494

2. Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol*. 2022;23(7):e334–e347. https://doi.org/10.1016/S1470-2045(22)00160-7

3. Mulder FI, Bosch FTM, Carrier M, et al. Growth differentiation factor-15 for prediction of bleeding in cancer patients. *J Thromb Haemost*. 2022;20(1):138–144. https://doi.org/10.1111/jth.15559

4. Mathews L, Hu X, Ding N, et al. Growth differentiation factor 15 and risk of bleeding events: the Atherosclerosis Risk in Communities study. *J Am Heart Assoc*. 2023;12(6):e023847. https://doi.org/10.1161/JAHA.121.023847

5. Englisch C, Nopp S, Moik F, et al. Growth Differentiation Factor-15 Predicts Major Bleeding in Cancer Patients. *JACC CardioOncol*. 2025;7(2):141–152.

6. Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45(36):3314–3414. https://doi.org/10.1093/eurheartj/ehae176

7. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1000. https://doi.org/10.1378/chest.10-0134

8. de Winter MA, Dorresteijn JAN, Ageno W, et al. Estimating bleeding risk in patients with cancer-associated thrombosis: evaluation of existing risk scores and development of a new risk score. *Thromb Haemost*. 2022;122(05):818–829. https://doi.org/10.1055/s-0041-1735251

9. Nopp S, Moik F, Kraler S, et al. Growth differentiation factor-15 and prediction of cancer-associated thrombosis and mortality: a prospective cohort study. *J Thromb Haemost*. 2023;21(9):2461–2472. https://doi.org/10.1016/j.jtha.2023.04.043

10. Hadzibegovic S, Sikorski P, Potthoff SK, Springer J, Lena A, Anker MS. Clinical problems of patients with cachexia due to chronic illness: a congress report. *ESC Heart Fail*. 2020;7(6):3414–3420.

11. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. *J Cachexia Sarcopenia Muscle*. 2016;7(5):507-509.

12. Lena A, Hadzibegovic S, von Haehling S, Springer J, Coats AJ, Anker MS. Sarcopenia and cachexia in chronic diseases: from mechanisms to treatment. *Pol Arch Intern Med*. 2021;131(12):16135.

13. Ling T, Zhang J, Ding F, Ma L. Role of growth differentiation factor 15 in cancer cachexia (Review). *Oncol Lett*. 2023;26(5):462. https://doi.org/10.3892/ol.2023.14049

14. Groarke JD, Crawford J, Collins SM, et al. Ponsegromab for the treatment of cancer cachexia. *N Engl J Med*. 2024;391(24):2291–2303. https://doi.org/10.1056/NEJMoa2409515

15. Nopp S, Königsbrügge O, Kraemmer D, Pabinger I, Ay C. Growth differentiation factor-15 predicts major adverse cardiac events and all-cause mortality in patients with atrial fibrillation. *Eur J Intern Med*. 2021;88:35–42. https://doi.org/10.1016/j.ejim.2021.02.011

16. Binder MS, Yanek LR, Yang W, et al. Growth differentiation factor-15 predicts mortality and heart failure exacerbation but not ventricular arrhythmias in patients with cardiomyopathy. *J Am Heart Assoc*. 2023;12(3):e8023. https://doi.org/10.1161/JAHA.122.026003

17. Andersson J, Fall T, Delicano R, Wennberg P, Jansson JH. GDF-15 is associated with sudden cardiac death due to incident myocardial infarction. *Resuscitation*. 2020;152:165–169. https://doi.org/10.1016/j.resuscitation.2020.05.001

KEY WORDS biomarkers, bleeding, cancer, hemorrhage, major bleeding, risk prediction