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EDITORIAL COMMENT

Growth Differentiation Factor-15 in Asian IHD Patients

Should We Use to Guide Therapeutic Decision?*

Jae-Sik Jang, MD

Growth differentiation factor (GDF)-15 is a member of the transforming growth factor beta superfamily of cytokines that is secreted in response to cellular injury or ischemic stress.[1] Under normal circumstances, GDF-15 is detected at very low levels.[2] However, elevated levels of GDF-15 have been associated with cancer cachexia, chronic kidney disease, cardiovascular disease, and a host of other diseases with inflammatory etiologies.[3,4] Also, high GDF-15 levels have been related to an increased risk of adverse clinical outcomes, such as death, myocardial infarction, and heart failure in patients with ischemic heart disease (IHD).[5] Prior large non-ST-segment elevation acute coronary syndrome (ACS) studies suggested that GDF-15 levels have a meaningful predictive value in patients with ACS.[6,7]

In this issue of *JACC: Asia,* Kobayashi et al[8] analyzed the data set of 632 patients with IHD who were admitted to a single center between 2012 and 2018. They found a close association between plasma GDF-15 levels, the Japanese version of the high bleeding risk (J-HBR) criteria, and bleeding events in Japanese patients with IHD. Kobayashi et al also found that plasma GDF-15 levels improved the prediction capacity of all-cause mortality, major adverse cardiac events, heart failure-related rehospitalizations, and bleeding events. The authors suggested that plasma GDF-15 levels could serve as a discriminatory factor between thrombotic and bleeding risk in Asian patients with IHD.

This study[8] is in line with previous reports,[9,10] which found that higher levels of GDF-15 were associated with an increased risk of bleeding events in patients with atrial fibrillation receiving anticoagulation therapy, and another study[11] that revealed an association between higher level of GDF-15 and an increased risk of bleeding complications in patients with ACS after percutaneous coronary intervention (PCI). Kobayashi et al[8] found that, despite the close relationship between serum GDF-15 levels and severe coronary artery disease, GDF-15 was not significantly associated with thrombotic events. The authors focused on the association of serum GDF-15 levels with major J-HBR criteria and bleeding events, as they followed a previous study regarding this issue showing a low incidence of thrombotic events in an Asian population[12] and another study that revealed the importance of bleeding events in mortality.[13] Nonetheless, the feasibility and clinical utility of GDF-15 measurements are still doubted, and further research is required among different ethnic populations and across different geographical areas.

This study, for the first time in Asian patients with IHD, showed that increasing levels of GDF-15 were closely associated with J-HBR and bleeding events.[8] Kobayashi et al showed the prognostic usefulness of serum GDF-15 for mortality, major adverse cardiac events, heart failure development, and major bleeding events in Asian patients with IHD. The use of GDF-15 as a biomarker of bleeding risk is still an area of active investigation and is not yet widely used in clinical practice. There have been several risk scores developed to predict bleeding risk in this population, such as CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines),[14] ACUITY-HORIZONS (Acute Catheterization and Urgent Intervention Triage Strategy-Harmonizing

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From the Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea.

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Outcomes with Revascularization and Stents in Acute Myocardial Infarction),[15] and PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) scores.[16] Cardiac biomarkers are becoming important tools to predict cardiovascular risks and have been shown to be better than traditional risk factor-based models.[17] Biomarkers assessment is proposed as a potential way to predict bleeding risk in patients with IHD undergoing PCI, and elevated levels of high-sensitivity troponin and GDF-15 have been associated with increased risk of bleeding in several studies.[5,18]

There are several limitations to this study.[8] Because this was a nonrandomized observational study, a causal relationship could not be determined between plasma GDF-15 levels and adverse outcomes. In this study, GDF-15 level was not a significant predictor of thrombotic events, despite the close relationship between its plasma levels and severe coronary artery disease. Kobayashi et al focused on the association of plasma GDF-15 levels with bleeding events and all-cause mortality in Asian patients with IHD. Although bleeding events are important predictors of all-cause mortality, we should not underestimate the risk of thrombotic events. Moreover, several other factors contribute to the increased risk of bleeding in Asian patients with IHD, including genetic predisposition, comorbidities, and pharmacokinetic properties.

Although performance of the existing risk scores developed to estimate bleeding risk in ACS is rather poor,[19] the addition of GDF-15 to a previous risk scoring system may help identify vulnerable patients at high risk of bleeding who will benefit from a multifaceted approach to decrease bleeding complications (eg, shortened dual antiplatelet duration, radial access). Together with risk stratification tools and bleeding prediction models, it is important to consider patient-specific factors that may affect bleeding risk, such as comorbidities, medication use, and procedural factors during PCI. In other words, health care providers can better predict bleeding risk and develop strategies to minimize this risk by combining these tools and considering patient-specific factors in patients undergoing PCI.

Future randomized studies are strongly needed to evaluate the clinical utility of GDF-15 to guide therapeutic decisions, preferably in conjunction with other novel biomarkers and clinical variables. We could also expect a potential therapeutic effect from anti-inflammatory and anti-atherosclerotic agents. Moreover, new therapeutic targets could emerge based on the pathobiological property of GDF-15. Ultimately, therapeutic agents that can lower GDF-15 levels may result in better clinical and health-related outcomes in a broader population, including those of Asian ethnicity.

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ADDRESS FOR CORRESPONDENCE: Dr Jae-Sik Jang, Department of Internal Medicine, Busan Paik Hospital, University of Inje College of Medicine, 75, Bokji-ro, Busanjin-gu, Busan 47392, Republic of Korea. E-mail: jsjang71@gmail.com.

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