Growth Differentiation Factor 15: A Canary in a Coal Mine?

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It has been 50 years since Dr. William B. Kannel coined the term “factors of risk” in relation to cardiovascular disease (1). Since then, clinical risk assessment, including the use of circulating biomarkers, has become an integral part of medical practice. The current era of genomics, proteomics, and metabolomics is projected to lead to the discovery of an immense number of novel candidate biomarkers. With that in mind, the American Heart Association recently issued a statement emphasizing the critical appraisal of novel risk markers to determine their clinical utility (2). Although very few candidate biomarkers will likely survive the test of time (3), the study by Rohatgi et al. published in the present issue of Clinical Chemistry demonstrates the strengths of one such biomarker, growth differentiation factor 15 (GDF-15),² as a prognostic marker in the community (4).

In this study from the Dallas Heart Study, the authors investigated the association of GDF-15 with subclinical coronary atherosclerosis and mortality. Increasing circulating GDF-15 concentrations were cross-sectionally associated with cardiovascular risk factors and coronary artery calcium. More importantly, GDF-15 was a significant predictor of all-cause and cardiovascular mortality independently of traditional risk factors and other novel biomarkers (high-sensitivity C-reactive protein, N-terminal pro-B-type natriuretic peptide, and high-sensitivity cardiac troponin T).

This study is an important contribution to the mounting evidence that GDF-15 bears prognostic importance in the general population. GDF-15 has been shown to predict all-cause, cardiovascular, and non-cardiovascular mortality in older individuals in the Rancho Bernardo Study (5) and to be associated with endothelial and cardiac dysfunction in elderly participants in the Prospective Investigation of the Vasculature in Uppsala Seniors study (6). Although relatively underpowered for the end point of cardiovascular death (n = 48), the findings in the Dallas Heart Study certainly add to those of existing community-based studies and, importantly, extend the prognostic role of GDF-15 to a substantially younger population of mixed race. Also notable is that GDF-15 concentrations were measured with an assay different from what has been used in the majority of other published studies. The similarities in the distributions of GDF-15 values between different studies, as well as the robustness of findings, support the reproducibility and feasibility of GDF-15 measurement in ambulatory individuals.

In light of this growing body of evidence for GDF-15 as an emerging biomarker, 2 questions are worth addressing. First, what biological insights can be gathered, and, second, what is the clinical utility of measuring GDF-15?

What Biological Insights Can Be Gathered?

GDF-15 is a stress-responsive cytokine that is a part the transforming growth factor β superfamily (7). Weakly produced in most tissues under physiological conditions (8), GDF-15 is strongly produced by cardiac myocytes exposed to ischemia (9) or increased wall stress (10). GDF-15 appears to protect against cardiac injury in animal models (10), possibly because of anti-inflammatory (10), antiapoptotic (9), or antihypertrophic (8) effects. The fact that higher circulating GDF-15 concentrations are associated with adverse outcomes in clinical studies suggests that it is a marker, rather than a mediator, of cardiovascular disease in humans (11). That would make GDF-15 similar to the natriuretic peptides, which show increased concentrations in individuals at risk for cardiovascular disease, likely reflecting a response to increased hemodynamic stress.

GDF-15 is also thought to play an important role in carcinogenesis, in which both protective apoptotic effects and antiapoptotic actions have been demonstrated (12). Clinical studies have shown that GDF-15 is overproduced in several aggressive human cancers and that higher circulating concentrations portend a poor prognosis (13). In a post hoc analysis of the Rancho Bernardo Study, GDF-15 was associated with an increased risk of cancer death (5). The present study has demonstrated a strong association of GDF-15 with all-cause mortality. Although the investigators did not specifically examine noncardiovascular death, the ma-

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² Nonstandard abbreviations: GDF-15, growth differentiation factor 15; NRI, net reclassification improvement; IDI, integrated discrimination improvement.
The category-free NRI extends the category-based to the Adult Treatment Panel III guidelines (19%), and high-risk (8%). The value of the NRI is dependent on clinically discriminating improvement (IDI) metrics. The category-free NRI and the integrated discrimination improvement (NRI) are well defined, such as mortality (17). It is important to note that results of the category-based and category-free NRI analyses cannot be compared with each other.

In the Dallas Heart Study, the addition of GDF-15 to a model predicting all-cause mortality was associated with a category-free NRI of 0.42 (4). In comparison, the category-free NRI in the older individuals in the Rancho Bernardo Study was 0.30 (5). The maximum value for the category-free NRI is 2.0 (100% of events are moved up in risk + 100% of non-events are moved down in risk) (17). Importantly, the category-free NRI captures all changes in predicted risk, even very small ones that are unlikely to be of clinical importance. Thus, moving the predicted risk of an individual with a future event from 5% to 5.1% would be counted the same as moving it from 5% to 20%, although the latter is much more meaningful. The metric may be recalculated with different requirements used for defining a change in risk. For example, NRI(>1%) or NRI(>5%) would require that the change exceed 1% or 5%, respectively. Another key issue to address is the performance of GDF-15 in a multimarker approach, which might overcome the shortcomings of a single biomarker.

Lastly, given the assumption that the addition of GDF-15 leads to a meaningful reclassification of predicted risk for a given individual, the question that remains is how this information could alter clinical management. In the last century, mine workers brought canaries into coal mines to provide early warning of the presence of toxic gases. If the canary died, the workers would know to leave the mine. Whether GDF-15 measurement would be useful, like the proverbial canary, by changing clinical decisions or would serve merely as a harbinger of a poor outcome without specific therapeutic implications is unclear. Although a higher risk of coronary heart disease might prompt an aggressive modification of risk factors, a higher predicted risk of overall mortality may not translate directly into changes in therapy. That may be particularly true if the cause of higher mortality is cancer or another type of noncardiovascular death.

In summary, higher circulating GDF-15 concentrations are clearly associated with a worse prognosis, and knowledge of GDF-15 concentrations improves risk stratification. Nonetheless, the clinical utility of measuring GDF-15 concentrations in the general population remains unclear. Future studies that elucidate underlying biological pathways may help to identify specific therapies that would be useful in people with increased GDF-15 concentrations.
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