Clinical Chemistry 58:1
3–5 (2012)

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

Jennifer E. Ho[1] and Thomas J. Wang[1*]

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 report from the Dallas Heart Study, the authors describe their investigation of 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 independent 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 information in the general population. GDF-15 has been shown to predict all-cause, cardiovascular, and noncardiovascular mortality in older individuals in the Rancho Bernardo Study *(5)* and was associated with endothelial and cardiac dysfunction in elderly participants in the Prospective Investigation of the Vasculature in Uppsala Seniors study *(6)*. 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 expressed in most tissues under physiological conditions *(8)*, growth differentiation factor 15 (*GDF15*) is strongly expressed 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 antiinflammatory *(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 majority of the deaths were noncardiovascular, and it may

[1] Cardiology Division, Massachusetts General Hospital, Boston, MA.
* Address correspondence to this author at: Cardiology Division, GRB-800, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114. Fax 617-726-4105; e-mail tjwang@partners.org.
Received September 26, 2011; accepted October 3, 2011.
Previously published online at DOI: 10.1373/clinchem.2011.175406
[2] Nonstandard abbreviations: GDF-15, growth differentiation factor 15; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

be that increased GDF-15 reflects multiple different pathophysiological perturbations. This supposition is corroborated by the fact that the association of GDF-15 with all-cause mortality was stronger than the association with cardiovascular mortality in the Dallas Heart Study. Future clinical studies examining nonfatal end points (cardiovascular and noncardiovascular) will be useful for clarifying the relationship between circulating GDF-15 concentrations and specific conditions in a way that might inform management, and may guide targeted therapy.

What Is the Clinical Utility of Measuring GDF-15?

Beyond demonstration of a robust association between a novel biomarker and the predicted outcome, a key question is how to best assess the incremental prognostic information that is added to that of existing risk factors. Although there is no accepted standard, several statistical metrics have increasingly been used to evaluate the performance of a new biomarker. These metrics are well illustrated in the report by Rohatgi et al.

A key measure of a risk-prediction model is its ability to discriminate those who will develop an event from those who will not. This ability is commonly assessed with the *c* statistic. In the Dallas Heart Study, the value of the *c* statistic for a model including only clinical risk factors was 0.822 and increased to 0.839 with the addition of GDF-15 *(4)*. The base model within the Dallas Heart Study has very good discriminatory capability—in comparison, the value for the Framingham Risk Score *c* statistic is approximately 0.75 *(14)*. In general, an increase of 0.05 in the *c* statistic may be considered "clinically useful"; however, in the presence of several powerful predictors in the base model and a resulting high value for the *c* statistic, further increases would be very difficult to achieve *(15)*. Whether a statistically significant but modest improvement of 0.017 in the *c* statistic with the addition of GDF-15 is clinically meaningful is thus less clear.

The limitations of the *c* statistic have led to proposals of new metrics *(15)*, including the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) metrics. The NRI summarizes individuals who were correctly reclassified (upclassifying those with events and downclassifying those without events) and those incorrectly reclassified with the addition of a new marker. The value of the NRI is dependent on clinically meaningful categories of risk, such as the 10-year risk of coronary heart disease used to guide treatment of low-risk ($<$10%), intermediate-risk (10%–19%), and high-risk ($\geq$20%) individuals according to the Adult Treatment Panel III guidelines *(16)*. The category-free NRI extends the category-based NRI to outcomes for which risk categories are not 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 nonevents 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.

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. Whether GDF-15 measurement would be useful, like the proverbial canary in the coal mine, by changing clinical decisions, or whether it 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. The evaluation of GDF-15 in a multimarker approach might shed further light on potential clinical utility. Future studies that elucidate underlying biological pathways may help to identify specific therapies that would be useful in people with increased GDF-15 concentrations.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design,*

acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: T.J. Wang, Diasorin.
Stock Ownership: None declared.
Honoraria: T.J. Wang, Roche Diagnostics, Diasorin, and Quest Diagnostics.
Research Funding: T.J. Wang, NIH grants R01-HL086875, R01-HL102780, R01-DK081572, R01-HL098283, and R01-HL083197.
Expert Testimony: None declared.
Other Remuneration: T.J. Wang, Coinventor on patent applications relating to the use of metabolomic and neurohormonal biomarkers in risk prediction.

References

1. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd. Factors of risk in the development of coronary heart disease—six year follow-up experience. The Framingham Study. Ann Intern Med 1961;55:33–50.
2. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009; 119:2408–16.
3. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation 2007;115:949–52.
4. Rohatgi A, Patel P, Das SR, Ayers CR, Khera A, Martinez-Rumayor A, et al. Association of growth differentiation factor-15 with coronary atherosclerosis and mortality in a young, multiethnic population: observations from the Dallas Heart Study. Clin Chem 2012;58:172–82.
5. Daniels LB, Clopton P, Laughlin GA, Maisel AS, Barrett-Connor E. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the Rancho Bernardo Study. Circulation 2011;123:2101–10.
6. Lind L, Wallentin L, Kempf T, Tapken H, Quint A, Lindahl B, et al. Growth-differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Eur Heart J 2009;30:2346–53.
7. Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-β superfamily. Proc Natl Acad Sci U S A 1997;94:11514–9.
8. Xu J, Kimball TR, Lorenz JN, Brown DA, Bauskin AR, Klevitsky R, et al. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. Circ Res 2006;98:342–50.
9. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, et al. The transforming growth factor-β superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res 2006; 98:351–60.
10. Kempf T, Zarbock A, Widera C, Butz S, Stadtmann A, Rossaint J, et al. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. Nat Med 2011;17:581–8.
11. Taddei S, Virdis A. Growth differentiation factor-15 and cardiovascular dysfunction and disease: malefactor or innocent bystander? Eur Heart J 2010;31:1168–71.
12. Xu X, Li Z, Gao W. Growth differentiation factor 15 in cardiovascular diseases: from bench to bedside. Biomarkers 2011;16:466–75.
13. Mimeault M, Batra SK. Divergent molecular mechanisms underlying the pleiotropic functions of macrophage inhibitory cytokine-1 in cancer. J Cell Physiol 2010;224:626–35.
14. Wilson PW. Prediction of cardiovascular disease events. Cardiol Clin 2011; 29:1–13.
15. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
17. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.