Published in final edited form as:
Clin Chem. 2012 January ; 58(1): 3–5. doi:10.1373/clinchem.2011.175406.

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

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

[1]Cardiology Division, Massachusetts General Hospital, Boston, MA

It has been 50 years since the term ‘factors of risk’ in relation to cardiovascular disease was coined by Dr. William B. Kannel (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 this in mind, the American Heart Association issued a recent statement emphasizing the critical appraisal of novel risk markers to determine 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) as a prognostic marker in the community.

In this report, the authors investigated the association of GDF-15 with subclinical coronary atherosclerosis and mortality in the Dallas Heart Study. Increasing circulating GDF-15 levels were associated with cardiovascular risk factors and coronary artery calcium cross-sectionally. More importantly, GDF-15 significantly predicted 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 significance in the general population. GDF-15 has been shown to predict all-cause, cardiovascular, and non-cardiovascular mortality in older individuals in the Ranch Bernardo Study (4), and was associated with endothelial and cardiac dysfunction in elderly participants in the Prospective Investigation of the Vasculature in Uppsala Seniors study (5). While relatively underpowered for the endpoint of cardiovascular death (n=48), the findings in the Dallas Heart Study certainly add to existing community-based studies, and importantly extend the prognostic role of GDF-15 to a significantly younger population of mixed race. It is also notable that GDF-15 levels were measured using a different assay than what has been used in the majority of other published studies. The similarities in the distribution of GDF-15 values between different studies and the robustness of findings

Correspondence: Thomas J. Wang, MD, Cardiology Division, GRB-800, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114, Phone: (617) 726-6158, Fax: (617) 726-4105, tjwang@partners.org.

Disclosures: Dr. Wang has received research or assay support from Diasorin, Brahms, Singulex, Critical Diagnostics, Siemens Diagnostics, and LabCorp. Dr. Wang has served on the scientific advisory board for Diasorin,Inc, and received honoraria from Roche and Quest Diagnostics. Dr. Wang is named as a co-inventor on patent applications relating to the use of metabolomic and neurohormonal biomarkers in risk prediction. Dr. Ho has no relationships to disclose.

support the reproducibility and feasibility of GDF-15 measurement in ambulatory individuals.

In light of this growing body of evidence around GDF-15 as an emerging biomarker, there are two questions 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 (6). Weakly produced in most tissues under physiologic conditions (7), GDF-15 is strongly expressed by cardiac myocytes exposed to ischemia (8) or increased wall stress (7). GDF-15 appears to protect against cardiac injury in animal models (9), possibly due to anti-inflammatory (9), anti-apoptotic (8), or anti-hypertrophic (7) effects. The fact that *higher* circulating GDF-15 is associated with adverse outcomes in clinical studies, suggests that it is a marker, rather than a mediator, of cardiovascular disease in humans (10). This would make GDF-15 similar to the natriuretic peptides, which are elevated 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, where both protective apoptotic effects, as well as anti-apoptotic actions have been demonstrated (11). In clinical studies, GDF-15 is overexpressed in a number of aggressive human cancers, and higher circulating levels portend a poor prognosis (12). In a *post hoc* analysis of the Rancho Bernardo Study, GDF-15 was associated with an increased risk of cancer death (4). The present study demonstrates a strong association of GDF-15 with all-cause mortality. Although investigators did not specifically examine non-cardiovascular death, the majority of deaths were non-cardiovascular, and it may be that elevated GDF-15 reflects multiple different pathophysiological perturbations. This is corroborated by the fact that the association of GDF-15 with all-cause mortality was stronger than the association with cardiovascular mortality. Future clinical studies examining non-fatal endpoints (cardiovascular and non-cardiovascular) will be useful to clarify the relation between circulating GDF-15 concentrations and specific conditions, in a way that might inform management.

What is the clinical utility of measuring GDF-15?

Beyond showing 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 existing risk factors. While there is no accepted standard, several statistical metrics have been increasingly used to evaluate the performance of a new biomarker, which are well illustrated in the paper 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, which is commonly assessed using the c-statistic. In the Dallas Heart Study, the c-statistic for a model including only clinical risk factors was 0.822, which increased with the addition of GDF-15 to 0.839. The base model within Dallas Heart Study has very good discriminatory capability - comparatively, the Framingham Risk

Score c-statistic is approximately 0.75 (13). 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 resultant high c-statistic, further increases would be very difficult to achieve (14). Whether a statistically significant but modest improvement in the c-statistic of 0.017 with the addition of GDF-15 is clinically meaningful is thus less clear.

Due to the limitations in the c-statistic, newer metrics have been proposed (14), and include the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI) metrics. The NRI summarizes individuals that were correctly reclassified (up-classifying those with events and down-classifying 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 (< 10%), intermediate (10-19%), and high risk (20% or greater) individuals according to the Adult Treatment Panel III guidelines (15). The category-free NRI is an extension of the category-based NRI to outcomes for which risk categories are not well-defined, such as mortality (16). It is important to note that results of the category-based and category-free NRI 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. In comparison, the category-free NRI in the older individuals in the Rancho Bernardo Study was 0.30 (4). The maximum category-free NRI is 2.0 (100% of events are moved up in risk + 100% of non-events are moved down) (16). Importantly, the category-free NRI captures all changes in predicted risk, even very small ones that are unlikely to be of clinical significance. Thus, moving the predicted risk of an individual with a future event from 5% to 5.1% would be counted the same as moving them from 5% to 20%, even though the latter is much more meaningful. The metric may be recalculated using different requirements for defining a change in risk, e.g. 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 multi-marker approach, which may overcome the shortcomings of a single biomarker.

Lastly, assuming that the addition of GDF-15 results in 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 toxic gases. If the canary died, the workers would know to leave the mine. Whether GDF-15 measurement may be useful as a proverbial canary by changing clinical decisions, or whether it serves merely as a harbinger of poor outcome without specific therapeutic implications, is unclear. Though a higher risk of coronary heart disease might prompt aggressive risk factor modification, a higher predicted risk of overall mortality may not directly translate into changes in therapy. This may be particularly true if the cause of higher mortality is cancer or another type of non-cardiovascular 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 levels in the general population

remains unclear. Future studies elucidating underlying biological pathways may help to identify specific therapies that are useful in people with elevated GDF-15 concentrations.

Acknowledgments

Dr. Ho is supported by an American Heart Association Clinical Research Program award. Dr. Wang is supported by NIH R01-HL086875, R01-HL102780, R01-DK081572, R01-HL098283, and R01-HL083197.

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. [PubMed: 13751193]
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. [PubMed: 19364974]
3. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation. 2007; 115:949–52. [PubMed: 17325253]
4. 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. [PubMed: 21536998]
5. 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. [PubMed: 19561023]
6. 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-beta superfamily. Proc Natl Acad Sci. 1997; 94:11514–9. [PubMed: 9326641]
7. 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. [PubMed: 16397142]
8. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res. 2006; 98:351–60. [PubMed: 16397141]
9. 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. [PubMed: 21516086]
10. Taddei S, Virdis A. Growth differentiation factor-15 and cardiovascular dysfunction and disease: Malefactor or innocent bystander? Eur Heart J. 2010; 31:1168–71. [PubMed: 20299701]
11. Xu X, Li Z, Gao W. Growth differentiation factor 15 in cardiovascular diseases: From bench to bedside. Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals. 2011
12. 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. [PubMed: 20578239]
13. Wilson PW. Prediction of cardiovascular disease events. Cardiol Clin. 2011; 29:1–13. [PubMed: 21257097]
14. 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. [PubMed: 17569110]
15. 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. [PubMed: 11368702]

16. 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. [PubMed: 21204120]