The Report Card on Growth Differentiation Factor 15
Consistent Marks But Not Yet Ready for Promotion

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In the present era that includes multiple potential treatment strategies for patients with acute and chronic coronary artery disease (CAD), a primary goal is to match the intensity of therapy with an individual patient’s risk for an adverse outcome. To accomplish this goal, improved risk stratification algorithms are needed. Among the potential strategies to improve risk assessment, measurement of circulating biomarkers offers several advantages, including wide availability and the potential to serially assess evolving pathophysiology. Of the many biomarkers studied for this purpose, however, only a few have demonstrated clear clinical utility.

Cardiac troponins I and T are well-established biomarkers of myocardial necrosis and have been validated for risk stratification in patients with acute coronary syndromes (ACS). Most (but not all) studies have concluded that higher risk patients identified on the basis of troponin elevation derive greater relative and absolute benefit from more intensive ACS therapies.1–3 Higher levels of the neurohormones brain natriuretic peptide (BNP) and N-terminal pro-BNP have also been consistently demonstrated to associate with increased risk of mortality and heart failure in patients with ACS and chronic CAD, but studies to date have shown disappointing results regarding a link to treatment outcomes.4–6 In this issue of Circulation: Cardiovascular Genetics, Kempf et al7 report the prognostic impact of a very interesting novel biomarker, growth differentiation factor 15 (GDF-15), in patients with both stable angina pectoris and ACS, providing an excellent framework to explore the performance criteria that should be used to assess the potential clinical utility of a novel marker.

Determining a biomarker’s clinical utility involves multiple steps, including assessment of pre- and postanalytical factors affecting sample measurement, the contribution of new information from the biomarker, and the ability of the biomarker to improve patient management and/or outcomes.8 With regard to new information contributed by the biomarker, publications evaluating novel biomarkers have traditionally focused on statistical measures of association, such as adjusted hazard ratios or relative risks, to describe the relationship between increasing or decreasing levels of the novel marker and cardiovascular events. Though important to demonstrate, independent associations may provide a misleadingly optimistic assessment of clinical utility. For example, in a large study of 19 circulating markers and incident CAD, although multiple independent associations were found for many of the biomarkers, none improved risk prediction beyond standard risk factors, as assessed by improvement in the c-statistic (a measure of discrimination analogous to the area under the receiver operating characteristic curve [AUC]).9 However, whereas measures of association may yield an overly optimistic picture, measures of discrimination may be too pessimistic with regard to assessing new risk predictors.10

To address limitations of standard statistical performance metrics, several additional performance criteria have been recently advocated as important tools to assess the clinical performance of new biomarkers11,12:

1. Global model fit (Akaike and Bayes information criterion);
2. Discrimination (Integrated Discrimination Index);
3. Calibration (Hosmer-Lemeshow test); and
4. Reclassification (Net Reclassification Index).

These performance metrics, particularly measures of calibration and reclassification, although certainly not perfect, seem to more directly address the clinical utility of a novel marker. As such, it will become increasingly important for articles assessing the clinical impact of novel biomarkers to report a comprehensive statistical evaluation using the metrics above.11 In contrast, reporting requirements may be lower when the goal of a study is scientific discovery rather than clinical utility: a novel biomarker may be relevant from a pathophysiological perspective without meeting the more rigorous criteria required to demonstrate clinical value. Readers are referred to an excellent “Clinician’s Guide” by McGeechan et al.,12 describing the comprehensive assessment of risk prediction models.

The statistical metrics described earlier can be used to assess the incremental risk prediction information provided by a novel marker beyond a reference model. Selecting an appropriate reference model is extremely important for making conclusions about added clinical utility. For example, in patients with ACS, validated prediction tools such as the TIMI, GRACE, and PURSUIT risk scores accurately identify high-risk patients that may benefit from more intensive therapies.13–15 However, studies of novel markers in patients with ACS rarely use these risk scores as the reference model,
more commonly using less well-validated reference models and thus providing potentially incomplete information as to the clinical utility of the novel marker under investigation.

**GDF-15**

GDF-15, a member of the transforming growth factor-β superfamily, is expressed only at low levels in normal tissue, except for placenta. However, in stress states, including myocardial ischemia and reperfusion, expression and secretion of the mature circulating GDF-15 protein are markedly increased.

**Does GDF-15 Add New and Clinically Important Information Regarding Risk?**

In this issue of *Circulation: Genetics*, Kempf et al report an independent association between increasing levels of GDF-15 and coronary heart disease mortality among 1352 patients with stable angina and evidence of CAD at angiography. The addition of GDF-15 to a model consisting of age, gender, body mass index, hypertension, diabetes, smoking, lipid parameters, CAD severity, history of myocardial infarction and renal function improved discrimination of coronary heart disease deaths, as measured by the AUC. In the ACS subgroup (n=877), a similar independent association between GDF-15 and coronary heart disease mortality was seen, but there was no significant improvement in the AUC, probably because discrimination of the reference model for coronary heart disease mortality was better in the ACS subgroup (AUC=0.82) than the stable angina subgroup (AUC=0.74). GDF-15 levels were not independently associated with nonfatal myocardial infarction in either subgroup.

These findings from the AtheroGene registry provide further validation of associations between high GDF-15 levels and mortality that have been reported across a broad spectrum of cardiovascular disease states. Because most of the research to date has been performed by the investigators who made the initial discoveries linking GDF-15 to cardiovascular disease, it will be important for the findings to be validated by other independent research groups. Moreover, the current study is the first to report whether GDF-15 improves discrimination for cardiovascular events beyond traditional risk factors, a more stringent performance metric than measures of association. Although GDF-15 improved the AUC for mortality in patients with stable angina pectoris, there was no improvement in the ACS cohort despite similar total numbers of deaths. Importantly, ejection fraction was not included in the analyses of improved discrimination.

**Does Measurement of GDF-15 Guide Treatment Strategy?**

Given the limited number of studies performed on GDF-15, few data are available with regard to the therapeutic implications of elevated GDF-15 levels. In the FRISC-II trial of patients with non-ST elevation ACS, randomization to an invasive coronary revascularization strategy was associated with reduced cardiovascular events only in the subgroup with elevated GDF-15 levels, suggesting that high GDF-15 levels may identify candidates for invasive therapy. These findings will have to be replicated in prospective studies before acceptance in clinical decision making. Moreover, measurement of GDF-15 should be performed in existing and future blood banks from randomized controlled trials testing novel treatments for CAD to explore potential interactions with therapy.

**Remaining Analytic Issues for the GDF-15 Assay**

Wollert and coworkers have previously reported GDF-15 levels in healthy subjects and identified an optimal cutoff of ≥1800 ng/L across several disease states. To date, most clinical studies of GDF-15 have been performed in a relatively homogenous population. As has been seen with BNP and high sensitivity C-reactive protein, GDF-15 levels may vary significantly and across established threshold limits by gender, ethnicity, obesity, renal function, and sex hormone status. The relationship between GDF-15 and obesity, in particular, requires further study, as the AtheroGene findings of a weak positive association contradicts prior reports of an inverse association between GDF-15 and body mass index. Furthermore, although stability has been confirmed in measurement of GDF-15 over several weeks to months using an in-house assay, extent of diurnal variation has not yet been established. Moreover, the influence of common pharmacotherapies for ACS on GDF-15 levels, including antiplatelet, antithrombin, lipid lowering, and reverse-remodeling medications, remains to be determined.

**Conclusions**

The evidence thus far has consistently shown that high levels of GDF-15 (≥1800 ng/L) associate with increased mortality in patients with ACS as well as chronic CAD, independent of troponin or BNP level. However, data are as yet insufficient to completely assess its clinical utility in improving risk prediction algorithms that have been validated in these populations. Future studies should report changes in discrimination, calibration, and reclassification when GDF-15 is added either alone or as part of a multiple marker panel to established predictors of mortality, or validated risk prediction models such as the GRACE or PURSUIT risk scores, which were specifically designed to predict mortality in patients with ACS. Once clinical utility is established, the final phases of evaluation, including assessing the impact of GDF-15 measurement on clinical outcomes and cost-effectiveness, will be required before widespread clinical acceptance.

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**References**


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