Are Multiple Biomarker Testing Strategies Ready for Prime Time in Heart Failure?

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In patients with heart failure, the promise that biomarkers may provide has been extensively explored. Although brain natriuretic peptide (BNP) had been proposed as a potential tool for screening patients with left ventricular systolic dysfunction, subsequent studies suggested that the biomarker had little benefit in this context.1 Indeed, the utility of BNP is perhaps most valuable when used in the more restricted and specific diagnostic context of the dyspneic patient without a clear-cut diagnosis.2 The potential utility of biomarkers for heart failure has been explored to a greater degree in the context of prognosis.3–5 However, the utility of any biomarker should be demonstrated to be incrementally better when compared to optimal clinical prediction models and other potential candidate biomarkers.6 Prior studies evaluating the prognostic utility of biomarkers in heart failure were often limited in this context.

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In this issue of Circulation: Heart Failure, Dunlay et al7 have published the results of a study from the Mayo Clinic examining multiple biomarkers when used for prognostication of community patients with heart failure. Three currently available biomarkers, including C-reactive protein (CRP), troponin T, and BNP were examined in comparison with a clinical model for mortality risk. The combination of biomarkers, and in particular CRP and BNP, increased significantly the discrimination of the model for prediction of 1-year mortality risk, suggesting the exciting possibility that this combination of biomarkers may be clinically useful to guide prognosis and therapy.

However, although a biomarker may seem prognostically important in a statistical model, demonstrating that it can impact on and guide therapy is a quantum jump. Indeed, recent studies suggest that a biomarker-guided strategy may not differ when compared head to head with best clinical decision making. In the multicenter Trial of Intensified Versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure, BNP-guided therapy of heart failure was compared with symptom-guided therapy in a randomized controlled trial in 499 patients with heart failure and reduced left ventricular ejection fraction (≤45%).8 Heart failure therapy guided by N-terminal BNP resulted in similar overall rates of hospitalization-free survival and quality of life compared with symptom-guided treatment.8 In 612 patients presenting to the emergency department, a randomized trial comparing the use of BNP with usual care found that routine BNP-guided management had no effects on the clinical outcomes or use of health services.9 Similar findings were observed in the recently published Rapid Emergency Department Heart Failure Outpatients Trial.10 Why might it be that biomarkers that have been demonstrated to be significant statistically in a predictive model no longer demonstrate an effect in randomized trials comparing it with symptom guided or usual clinical care? One factor that likely plays a role is that it may be very difficult for any biomarker or clinical prediction model to improve on the diagnostic acumen of experienced clinicians who are able to see the patient in a wholistic context and use additional information that may not be included in various prediction models. A biomarker is one of many pieces of information that clinicians have access to in the context of a clinical encounter, and the incremental knowledge from that single piece of information may be greatly outweighed by additional information available from the patient’s history, physical examination, and other laboratory tests.11 The most useful biomarkers are likely to be those which provide very unique information with very high sensitivity and specificity, relative to other prognostic indicators available to the clinician.

Recently published studies have compared the clinical covariates in the Framingham cardiovascular disease risk prediction model with an extensive array of multiple biomarkers for the prediction of future cardiovascular disease risk. In the first of these studies, a panel of 10 biomarkers was examined including highly anticipated potential candidates including CRP, BNP, N-terminal proatrial natriuretic peptide, aldosterone, renin, fibrinogen, d-dimer, plasminogen-activator inhibitor type 1, homocysteine, and the urinary albumin-to-creatinine ratio.12 However, this extensive panel of biomarkers added only modestly to the discriminative ability beyond that of a clinical model alone.12 In another biomarker study, which examined CRP, cystatin C, lipoprotein-associated phospholipase 2, midregional proadrenomedullin, midregional proatrial natriuretic peptide, and N-terminal pro-BNP, the 2 biomarkers that remained predictive of cardiovascular events were CRP and N-terminal pro-BNP.13 However, again, these biomarkers had little additional incremental value when compared with well-established cardiovascular risk factors, and there was negligible net reclassifi-
cuation improvement with the addition of multiple biomarkers.\(^{13}\)

Dunlay et al have completed the important initial step of documenting an incremental effect of multiple biomarkers in a community-based cohort of patients with heart failure. However, further studies are needed to determine the mechanisms by which these biomarkers are associated with prognosis. Biomarkers are often bystanders that indicate the occurrence of a potential dysregulatory process and are not necessarily bioactive targets for future therapies. As such, an examination of causal pathways may identify alternate associations, which are simpler and less costly to measure. For example, CRP may be a marker of systemic inflammation, suggesting the co-occurrence of an inflammatory process such as pneumonia or sepsis. In the latter cases, other nonspecific markers of inflammation such as the white blood cell count or the presence of fever may also be indicators of the same underlying process as CRP. Tropinin elevation may be an indication of myocardial ischemia, which has been demonstrated to be associated with increased mortality in patients with heart failure.\(^{14}\) However, there may be other clues to the presence of ischemia in these patients provided by the presence of electrocardiographic abnormalities. It is also notable that all the biomarkers tested in this study were increased in patients who were hospitalized inpatients. However, given that the prognosis of those who are hospitalized with heart failure is much worse than ambulatory outpatients with more stable heart failure, it is likely that the optimal management strategy and utility of biomarkers will likely need to be customized to the setting in which they are being managed.\(^{15,16}\)

Despite the extensive prior literature on cardiovascular biomarkers, several important questions remain unanswered in the context of heart failure care. To what extent do CRP and BNP impact on therapy and what should be done about patients with high values of these biomarkers? Should such patients be treated more intensively and if so, what form of therapeutic regimen should they receive? If patients with higher levels of biomarkers are to be treated more intensively, do these biomarkers change when therapeutic end points are attained? Are they useful as disease surveillance biomarkers in the same way that tumor biomarkers may provide information regarding recurrent disease among patients with malignancies? These questions require rigorous evaluation and may require randomized controlled trials of different therapeutic strategies before a policy of broad use of these biomarkers can be widely recommended for routine clinical use.

**Disclosures**

Dr Lee is a Clinician-Scientist of the Canadian Institutes of Health Research. Dr Tu is a Canada Research Chair in Health Services Research and a Career Investigator of the Heart and Stroke Foundation of Ontario.

**References**


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