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Charting a Roadmap for Heart Failure Biomarker Studies

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Heart failure is a syndrome with a pathophysiological basis that can be traced to dysfunction in several interconnected molecular pathways. Identification of biomarkers of heart failure that allow measurement of the disease on a molecular level has resulted in enthusiasm for their use in prognostication and selection of appropriate therapies. However, despite considerable amounts of information available on numerous biomarkers, inconsistent research methodologies and lack of clinical correlations have made bench-to-bedside translations rare and left the literature with countless publications of varied quality. There is a need for a systematic and collaborative approach aimed at definitively studying the clinical benefits of novel biomarkers. In this review, on the basis of input from academia, industry, and governmental agencies, we propose a systematized approach based on adherence to specific quality measures for studies looking to augment current prediction model or use biomarkers to tailor therapeutics. We suggest that study quality, rather than results, should determine publication and propose a system for grading biomarker studies. We outline the need for collaboration between clinical investigators and statisticians to introduce more advanced statistical methodologies into the field of biomarkers that would allow for data from a large number of variables to be distilled into clinically actionable information. Lastly, we propose the creation of a heart failure biomarker consortium that would allow for a comprehensive list of biomarkers to be concomitantly analyzed in a pooled sample of randomized clinical trials and hypotheses to be generated for testing in biomarker-guided trials. Such a consortium could collaborate in sharing samples to identify biomarkers, undertake meta-analyses on completed trials, and spearhead clinical trials to test the clinical utility of new biomarkers. (J Am Coll Cardiol HF 2014;■:■–■) © 2014 by the American College of Cardiology Foundation

"Out of clutter, find simplicity. From discord, find harmony."
Albert Einstein (1)

Heart failure is among the leading causes of death and disability worldwide (2). Among the challenges in treating this patient population are inadequacies in prediction of disease severity, with a resultant mismatch between risk stratification and intensity of therapy (3). Identification of biomarkers that allow measurement of the disease on a molecular level has resulted in considerable enthusiasm for their use in prognostication and selection of appropriate therapies (4–6). Illustrating this point, a PubMed search of the phrase "biomarkers in heart failure" resulted in close to 6,500

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Abbreviations and acronyms

AUC = area under the receiver-operating characteristic curve

BNP = B-type natriuretic peptide

hsCRP = high-sensitivity C-reactive protein

IDI = integrated discrimination improvement

NRI = net reclassification improvement

ROC = receiver-operating characteristic

publications over the last decade (Fig. 1) (5). Reasons for this include high-throughput molecular biology techniques that allow increased availability of point-of-care, rapid-turnaround biomarker testing, and reductions in costs of analysis (7).

Nonetheless, the current state of biomarker research in heart failure is one of exponential gains in information that have far exceeded the ability to contextualize findings: more "interesting data" than "clinically actionable information". As a result, despite considerable amounts of information available on numerous biomarkers, inconsistent research methodologies, insufficient study size, and lack of clinical correlations have made bench-to-bedside translations rare, leaving the literature with numerous publications of varied quality. This has led to slow adoption of established biomarkers, debates about the utility of biomarkers in standard clinical care, and delays in approval by regulatory agencies for clinical use (8,9). For example, the clinical efficacy of natriuretic peptide–guided therapy in heart failure remains unclear, despite 12 studies over the last decade that included >2,500 patients; fortunately, a multicenter trial is currently underway (GUIDE-IT [Guiding Evidence Based Therapy Using Biomarker Intensified Treatment]; NCT01685840) to provide clearer recommendations (10). Furthermore, considering the large number of biomarkers discussed in the literature, it is worth noting that beyond the natriuretic peptides, only galectin-3 and serum ST2 (sST2) are cleared by the Food and Drug Administration (FDA) for use as aids in assessing prognosis in heart failure. Even so, the appropriate clinical use of these 2 novel biomarkers is unclear due to a shortage of well-designed studies informing their proper clinical use, accompanied by a large number of studies repeatedly depicting their prognostic value.

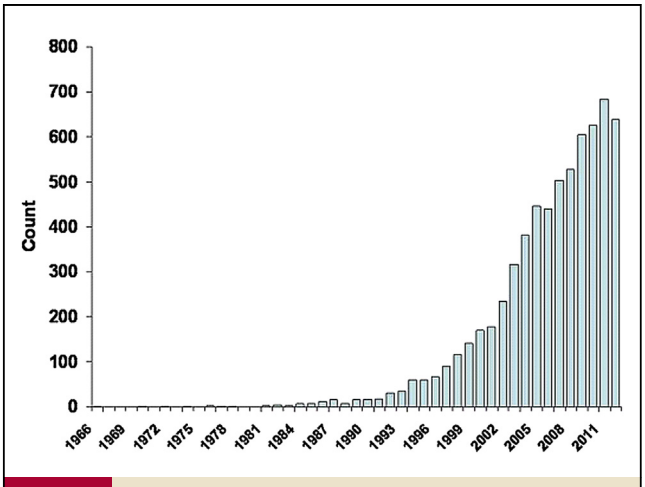

Figure 1 Publications Involving Heart Failure Biomarkers

The number of publications involving heart failure biomarkers has dramatically increased over the last decade. This has likely resulted from high-throughput molecular biology techniques that allow increased availability of rapid-turnaround biomarker testing and reductions in costs of analysis. The majority of these studies report associations between novel biomarkers and prognosis from heart failure.

This paper describes unanswered questions in the field of heart failure biomarkers and recommends a roadmap for further studies that will provide more definitive answers about the clinical role of biomarkers in diagnosis, prognosis, and treatment of heart failure. It is based on discussions among cardiologists, epidemiologists, clinical trialists, statisticians, journal editors, and regulatory agency representatives at the ninth annual Global Cardio Vascular Clinical Trialists Forum (CVCT) in Paris, France.

What Qualifies as a Useful Heart Failure Biomarker?

In theory, a biomarker can be any measurement made on a biological system. In practice, however, biomarkers in heart failure typically refer to substances measured in the blood other than commonly used laboratory tests and imaging studies (6).

To understand the added clinical utility of biomarkers in heart failure, criteria have been previously recommended by van Kimmenade and Januzzi (Table 1) (5,11). When biomarkers are considered for clinical use (together with other clinical parameters and cardiac tests), currently only the natriuretic peptides meet the proposed standards. The majority of the remaining emerging biomarkers remain entangled in debates as to whether they provide any incremental value over established clinical measurements.

We argue that instead of the current piecemeal approach in which biomarkers are evaluated with a variety of statistical approaches with or without comparisons with other markers, there is a need for standardized methodologies for clinical assessment of biomarkers in heart failure. Presently, the vast majority of biomarker publications in heart failure are related to prognosis, and considerable opportunities exist for harmonization of research methods for these studies. Although demonstration of prognostic value is of importance, modification of therapeutics based on biomarker values in a time-sensitive and cost-effective manner that improves patient outcomes is the *sine qua non* of a useful biomarker. Unfortunately, studies attempting to address these questions are scarce.

Biomarkers for Diagnosis

To date, heart failure biomarkers have had their greatest impact in the realm of disease diagnosis. Prior to the widespread use of natriuretic peptides for this purpose, clinicians relied on data from subjective variables such as clinical symptoms and physical examination findings to