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Clinical Adoption of Prognostic Biomarkers: The Case for Heart Failure

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Abstract The recent explosion of scientific knowledge and technological progress has led to the discovery of a large array of circulating molecules commonly referred to as biomarkers. Biomarkers in heart failure (HF) research have been used to provide pathophysiologic insights, aid in establishing the diagnosis, refine prognosis, guide management, and target treatment. However, beyond diagnostic applications of natriuretic peptides, there are currently few widely recognized applications for biomarkers in HF. This represents a remarkable discordance considering the number of molecules that have been shown to correlate with outcomes, refine risk prediction, or track disease severity in HF in the past decade. In this article, we use a broad framework proposed for cardiovascular risk markers to summarize the current state of biomarker development for patients with HF. We use this framework to identify the challenges of biomarker adoption for risk prediction, disease management, and treatment selection for HF and suggest considerations for future research. (Prog Cardiovasc Dis 2012;55:3-13)

Keywords: Heart failure; Biomarkers; Risk prediction; Prognosis

Basic science discoveries and technological progress have introduced a large array of circulating molecules—commonly referred to as biomarkers—in clinical cardiovascular research, including heart failure (HF) research. Publications related to biomarker research in HF have been exponentially proliferating over the last decade (Fig 1). However, the penetration of biomarkers in HF clinical practice has been limited to mostly diagnostic uses of B-type natriuretic peptide (BNP) or its precursor fragment, N-terminal pro-BNP (NT-proBNP).[1] Although the definition of a biomarker is not necessarily confined to circulating molecules, we will use the term *biomarker* to refer to circulating biomarkers beyond routine laboratory tests in this article. Circulating biomarkers include a wide array of molecules, from traditional protein-based markers to newer omics markers and micro-RNAs. Examples of protein markers include hormones and prohormones with vasoactive properties such as natriuretic peptides, endothelin, mid-regional-pro-adrenomedullin, and C-terminal provasopressin (copeptin); structural proteins such as troponins; and various proteins with enzymatic activities such as myeloperoxidase and galectin 3. On the other hand, transcriptomic, proteomic, and metabolomic markers generate "signatures" (patterns of expression) through the simultaneous measurement of multiple RNAs, proteins, or metabolites with high-throughput methods—an approach that contrasts the traditional single concentration value of a circulating marker.[2] Omics approaches, however, are still in an early discovery stage at this point. In this article, therefore, we will focus on protein-based markers.

Biomarkers in HF research have been primarily used to (*a*) identify pathophysiologic perturbations that either precede HF or result as downstream consequences of HF and the altered physiology of target organs in HF; (*b*) aid in diagnosis, differential diagnosis, and classification of clinical HF; (*c*) guide therapy and aid in patient management; and (*d*) refine risk stratification. However, beyond certain applications of BNP and NT-proBNP, there are currently no

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Abbreviations and Acronyms

AHF = acute heart failure

BNP = B-type natriuretic peptide

CRT = cardiac resynchronization therapy

HF = heart failure

HFPEF = heart failure with preserved ejection fraction

ICD = implantable cardioverter defibrillators

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-BNP

other uses for biomarkers in HF endorsed by national or international guidelines.[3] In the case of prognostic applications of biomarkers, this discrepancy is especially striking. In the past decade, a large number of molecules have been shown to correlate with or refine prognosis in HF, both in unselected populations and more targetedsubgroups (eg, patients with HF and reduced or preserved ejection fraction exclusively, advanced HF, stable chronic HF, or acute HF). Yet, no marker has entered the clinical arena as a tool for decision making. In the heart of this paradox lies (*a*) the lack of a unified framework for the development of biomarkers in HF and (*b*) the disconnection between projected risks, identification of underlying biology, and therapeutic decisions in HF. In this article, we summarize the current status of biomarker development for patients with a known HF diagnosis (ie, postdiagnostic applications) using a general framework proposed for cardiovascular biomarkers. We use this framework to identify the challenges of biomarker adoption for risk prediction, disease management, and treatment selection in HF.

Framework for the development of new biomarkers in heart failure

The plethora of biomarkers in cardiovascular disease has necessitated a framework for the evaluation of emerging biomarkers in the context of clinical applications. Building on the original "benchmark criteria" for cardiovascular biomarkers initially proposed by Morrow and de Lemos in 2007,[4] Maisel[5] has recently proposed a revision to reflect the specific needs of the patients with HF and incorporate the possibilities of biomarker-guided targeted therapy and "biomonitoring" (Table 1). Similar principles have been endorsed by laboratory societies.[3]

To enter prospective clinical evaluation and "benchmarked" against current standards, a marker has to go through a certain development cycle. The American Heart Association released a statement in 2009, reviewing concepts of risk evaluation and proposing standards for the critical appraisal of risk assessment in general and with emerging markers in specific.[6] The proposed model for development of cardiovascular biomarkers resembles that of a new drug or device. Briefly, the following phases of development have been proposed:

1. *Proof of concept:* Do marker levels differ between subjects with and without outcome?
2. *Prospective validation:* Does the marker predict development of future outcomes in a prospective cohort or nested case-cohort/case-cohort study?
3. *Incremental value:* Does the marker add predictive information to established risk markers?
4. *Clinical utility:* Does the risk marker change predicted risk sufficiently to change therapy?
5. *Clinical outcomes:* Does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?
6. *Cost-effectiveness:* Does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?

Building on this broad framework, we propose an adaptation to the case of HF risk assessment and disease management applications (Fig 2). We use this framework to (*a*) assess the current status of development of biomarkers in HF and (*b*) identify the "roadblocks" in

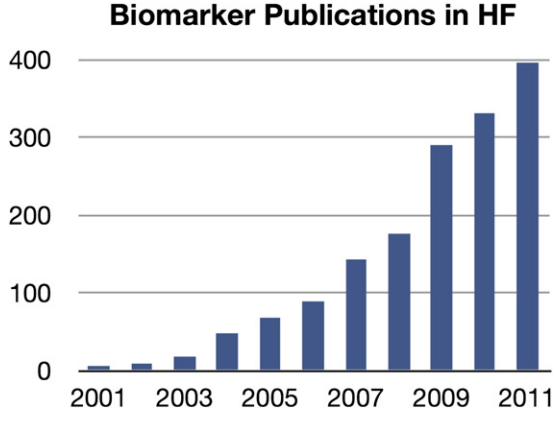

Fig 1. Number of articles including the terms "biomarker" and "heart failure" 2001 to 2011. Source: Web of Science SM. Accessed March 31, 2012.

Table 1
Characteristics of the ideal biomarker

Morrow and de Lemos (2007)	Maisel (2011)
Sensitive and specific	Either highly sensitive (for diagnostic purposes) or highly specific (for assessment of treatment effects)
Reflects disease severity	Reflects abnormal physiology
Correlates with prognosis	Clinically actionable risk stratification more desirable
Aids in clinical decision making	Serves as the basis for targeted therapy
Level decreases with effective therapy	Effective surrogate for biomonitoring

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