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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 research have been used to provide pathophysiological 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 heart failure. 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 heart failure 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 heart failure patients. We utilize this framework to identify the challenges of biomarker adoption for risk prediction, disease management, and treatment selection for heart failure and suggest considerations for future research.

Introduction

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 (Figure 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 pro-hormones with vasoactive properties like natriuretic peptides, endothelin, mid-regional-proadrenomedullin, and C-terminal pro-vasopressin (copeptin); structural proteins like troponins; and various proteins with enzymatic activities like 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.

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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 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 targeted subgroups (e.g. 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 (i.e., post-diagnostic applications) using a general framework proposed for cardiovascular biomarkers. We utilize 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 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).⁵ 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 (AHA) 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 (Figure 2). We utilize this framework to

(a) assess the current status of development of biomarkers in HF and (b) identify the “roadblocks” in the translation of “statistical” evidence into clinical applications. We also discuss current and emerging possibilities for biomarker uses specific to patients with HF outside this broad development framework, including “biomonitoring” and therapy “tailoring”.

Current Status of Heart Failure Biomarker Development

Recently, van Kimmenade and Januzzi have summarized the various domains of established and developing protein-based biomarkers in HF using a pathophysiologic classification.⁷ Realizing that several markers contribute to multiple pathways, we follow this classification in Table 2 to summarize the current development status of these markers. Similar to development of new drugs or devices, there are several steps in the process for an investigational biomarker to become a clinical tool for disease management. These steps start with demonstrating the association of biomarker levels with the outcome of interest (in the case of HF, association with mortality alone or in combination with hospitalizations) and culminate in prospective testing to evaluate usefulness as a disease management tool – preferably in randomized trials. In Table 2, we use the AHA phases above, adapted now for HF research purposes as outlined in Figure 2, as an approximation to describe the current development stage of biomarkers that have been evaluated in patients with HF. This table does not intend to provide an exhaustive list of current evidence of biomarkers in HF but rather to serve as a snapshot of current status of development to facilitate further discussion. It is evident from Table 2 that only natriuretic peptides have gone through the entire spectrum of development.

Interestingly, the overwhelming number of biomarkers become stagnant at “phase 3”, i.e. demonstrating that they possess incremental predictive information over established risk markers. In principle, this should be the “rate-limiting” step and phase 3 “clearance” should be the signal to move forward with testing in clinical scenarios. In other words, if an investigational biomarker added prognostic information that cannot be obtained with clinical means or clinically available biomarkers, this should have accelerated clinical evaluation of the biomarkers in prospective studies. In fact, a number of biomarkers have been demonstrated to reclassify risk for future events among patients with HF (“phase 4”), which implies even stronger, clinically relevant prognostic value – albeit change in therapeutic approach based on risk of future events would only be applicable to stage D HF patients at this point because this is the only group where decisions for advanced therapies (left ventricular assist device [LVAD] implantation or heart transplantation) are depending upon absolute 1-year mortality risk. However, the paucity of biomarkers that have actually entered the advanced phases (5 to 6) of development or are under active investigation underscores the difficulties with biomarker development in HF. Beyond practical issues (time to enter clinical trials and complete, commercially available method, unit cost of measurement etc.), which definitely play a role in the transformation of an investigational biomarker into a clinical tool, there are also issues with the framework of development per se in HF.

Prognostic Biomarkers in Heart Failure: Building Consistent Evidence

The key to consistent (and comparable) evidence, with the ultimate goal to promote introduction of a new biomarker into practice, is reasonably consistent definitions of the population and the outcome of interest. For HF, these definitions have been drifting over time with little consistency even among contemporary studies.

Population Heterogeneity

Early work on biomarkers focused on stable outpatients with systolic HF.^{8–10} As the importance of HF with preserved ejection fraction (HFPEF) became apparent, prospective studies either enrolled patients without a left ventricular ejection fraction (LVEF) criterion^{11,12} or primarily focused on HFPEF.^{13,14} However, the profile of younger patients with systolic HF is quite different from that of older patients with HFPEF. The latter population carries a high comorbidity burden responsible for a large proportion of adverse events.¹⁵ Thus, not only the pathophysiology of HFPEF may favor different biomarkers as prognostic tools, but also the sources of adverse events are diverse and alter the prognostic value of HF-related biomarkers in this population.¹⁶ Although the definition of “systolic” vs. “diastolic” HF bears some arbitrariness, it is nevertheless important to differentiate these populations to set clinically relevant expectations when evaluating a biomarker as a risk stratification tool. Similarly, it is unlikely that a biomarker would bear the same prognostic value in the setting of acute heart failure (AHF), a highly dynamic state¹⁷ with mortality and readmission exceeding 30% at 30 days,¹⁸ and in stable patients in an office setting.

Outcome Definition

For cardiovascular risk assessment in the general adult population, the definition of outcome (i.e., incident cardiovascular events) has seen only minimal variability in the last two decades. In contrast, the outcome of interest in HF has varied from mortality alone to all-possible combinations of all-cause or cardiovascular mortality plus all-cause, cardiovascular-specific, or HF-specific (re) hospitalizations, and emergency department visits.^{19,20} This reflects both the focus on hospitalizations as a quality metric and also the need to increase the number of events for statistical power in prospective studies. However, hospitalization risk in HF patients is not entirely attributable to the underlying biology and state of HF. First, a substantial proportion – if not the majority – of hospitalizations in patients with HF, especially in older adults with a substantial comorbidity burden, are not directly related to HF, regardless of left ventricular ejection fraction (LVEF).¹⁵ Second, non-biological factors substantially affect risk for hospitalization,^{21–23} highlighting the complexity of modeling and intervening on HF hospitalizations. As a result, biological markers (clinical, imaging, or circulating) and biology-based models perform only modestly for HF hospitalization risk prediction.²⁴

Time Frame

The issues with population and outcome definitions are compounded by the variability of the time frame for the outcome of interest. With the exception of studies looking at 1-year mortality in advanced systolic (stage D) HF – with the aim of patient selection for left ventricular device (LVAD) implantation and/or listing for transplantation – the time frame for evaluation of biomarkers as risk predictors in other HF populations has ranged from a few days to several years. In fact, the time frame has been variable even for AHF patients, ranging from 30 days to 180 days and beyond. The 180-day measurement is a more biologically plausible cut-off point, as risk from the acute incident tends to tail off after that point.

The Fallacy of “Incremental Value”

Currently, most investigational markers in cardiovascular medicine that target risk prediction undergo the scrutiny of demonstrating risk reclassification value – a concept that goes beyond an independent P value for prediction of outcomes or increment in C statistic.²⁵ We expand on the risk reclassification in the next subheading. Because reclassification by definition requires a clinical risk prediction model as a yardstick to examine the added value of the new biomarker, the bar is invariably set high. The clinical risk prediction model in

these cases usually includes a large set of established risk factors and markers. Alternatively, the baseline model can be an established risk score (e.g. Framingham Risk Score). Therefore, for a biomarker to demonstrate strong risk reclassification properties for the outcome of interest, a truly independent and incremental association with the outcome is required. These statistical properties are usually driven by the ability of the marker to express the activity of a pathophysiological pathway that is difficult to assess with standard clinical means. Natriuretic peptides are a prime example where the information added by the biomarker is incremental enough to impact clinical decisions. This incremental value has its roots in the modest performance of current clinical means to assess ventricular overload and myocardial stress. Similarly, troponins reflect myocyte damage that is not associated with symptoms, ECG changes, or other routine laboratory tests and therefore the information offered by troponin levels represents truly incremental information. As expected, these markers have shown strong reclassification properties.^{12,26,27}

Before the era of risk reclassification, however, the incremental predictive value of a biomarker, and its independent association with risk, was judged on the basis of its statistical properties in models including other, arbitrarily selected clinical risk factors. In principle, any marker that is part of a pathophysiological pathway can potentially be associated with the outcome if the clinical model is reduced to a few adjustment variables, outcome is adapted to increase power, or follow-up is extended long enough for events to accumulate. For example, in HF, it is plausible that the concentration of a marker reflecting myocardial stress and overload (e.g. natriuretic peptides), ongoing myocardial damage (e.g. troponins), neurohormonal activity (e.g. copeptin), or renal tubular damage (e.g. neutrophil gelatinase-associated lipocalin) will parallel the severity of disease. Such a marker is expected to be associated with subsequent hospitalizations or mortality when used as the sole predictor in a model. The question is whether the addition of this marker to clinical information or routine laboratory tests (e.g. serum sodium or creatinine) modifies the risk profile of the patient in a clinically meaningful way. Inadequate clinical information on HF severity in the prediction model increases the chances of a biomarker to show “independent” value. Similarly, minor independent value (a marginal hazard ratio for clinical events) can be augmented with inclusion of additional events in the outcome (such as hospitalizations, emergency department visits, unplanned office visits etc.), or extending the follow-up time until an adequate number of event accumulates to reach statistical significance.

Most observational studies in HF focused on biomarkers demonstrate some independent association with some outcome, also reflecting publication bias. However, the variability of the clinical adjustment models in these studies, including those described in Table 2, is remarkable. The clinical model has ranged from no variables (after stepwise elimination of other risk factors) to a data-driven set of risk factors (i.e., a model derived after stepwise regression in the data at hand) or a clinically-driven, literature-based clinical model (i.e., a model that includes clinical factors previously reported in the literature or a previously validated score like the Seattle Heart Failure Score). The smaller the study the higher the chance that the stepwise model will include few predictors! On the other hand, there is considerable variability in clinically-driven adjustment models also, ranging from an elementary set of known risk factors in HF (e.g. age, LVEF, NYHA class) to a comprehensive set of variables or an established model in the case of advanced systolic HF (the Seattle Heart Failure Score or the Heart Failure Survival Score). This variability reflects the lack of a standard set of risk factors for each HF subpopulation of interest (stage C vs. stage D HF, acute vs. chronic HF, preserved vs. reduced HF etc.). As a result, several biomarkers reported to have an “independent” association with outcomes will eventually fail to show meaningful risk refinement properties in rigorous prospective studies exactly because of the arbitrary definition of the “incremental value” – and this drawback extends to the reclassification properties discussed below.

Risk Reclassification: The Crossroads Between Statistical and Clinical Significance

Briefly, risk reclassification implies a change in the projected risk to the right direction with the use of the new marker as compared to the projected risk with the baseline, usually clinical model. This is accomplished when the biomarker-added model assigns higher risk to a substantial proportion of patients who eventually develop the event of interest and, conversely, lower risk to a substantial proportion of patients who do not develop the event. This is best clinically interpretable when the patient appropriately moves “up” or “down” on a scale of widely acceptable risk categories. For example, let us consider the case of coronary calcium score by computed tomography and general cardiovascular disease risk. Appropriate “upwards” risk classification implies that a high calcium score adequately increases projected risk to place a patient who eventually develops an event (in a prospective study) to a higher risk category (e.g. >20% 10-year risk) at baseline compared to the category (e.g. 10–20% 10-year risk) assigned by the Framingham Risk Score alone. A low calcium score would have to lower risk enough to place a patient without an event to a lower risk category (e.g. <10% 10-year risk in this example) - appropriate “downwards” risk classification.²⁵

These statistical measures simultaneously highlight all the limitations in the development of HF biomarkers for prognostic purposes. In Table 3, we have summarized recent biomarker studies assessing reclassification in HF patients. Since the initial publication by Pencina *et al*,²⁵ risk reclassification has been adopted as the “holy grail” of clinical relevance for prognostic markers in cardiovascular medicine. However, meaningful reclassification requires initial meaningful classification. This translates into useful absolute risk categories at a reasonable horizon. In contrast to cardiovascular risk prediction, where 10-year risk categories (e.g. <6%, 6% to 20% and >20% – alternatively with further classification of intermediate risk to 6% to 10% and 11% to 20%) are widely accepted as the standard for risk classification, there is no such a scheme in patients with stage C HF for outcomes such as mortality or mortality plus admission. Reclassification measures that are not dependent on risk categories are statistically possible,²⁵ but have been met with less enthusiasm by clinical audiences, partly because these measures are not directly interpretable. The other issue is the need for a widely accepted “base” clinical model, which the biomarker-added model needs to be compared against. For cardiovascular risk prediction, a new biomarker is traditionally compared against a set of clinical predictors usually in the form of a score, e.g. the Framingham Risk Score, before being tested in phase 5 or 6 studies. The only application where risk scores have found their place in HF is selection of stage D patients for advanced therapies.²⁸ As evident from Table 3, the “base” model varies widely between studies, precluding building of consistent evidence.

Risk Classification and Clinical Decision Making in Heart Failure

For stable, eligible patients with stage D HF, decisions for LVAD implantation and/or listing for heart transplantation may be facilitated by 1-year mortality projections with multifactorial risk assessment tools.²⁸ Therefore, prognosis refinement with biomarkers could impact decision making in this group. In fact, although biomarker-added models have not been endorsed for decisions in these patients, studies have suggested that biomarkers can meaningfully reclassify risk in these patients.²⁶ However, for patients with stage C HF, either with reduced (“systolic”) or preserved LVEF (“diastolic”), no decisions depend upon complex risk projections. For example, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) are recommended on the basis of LVEF alone¹ or a combination of LVEF, QRS duration, and symptoms,²⁹ respectively. Without doubt, both LVEF and QRS duration are markers of risk in their own right; however, there is wide

variation of risk within the groups with low LVEF or prolonged QRS. Of note, preliminary data suggest that biomarkers may aid in predicting risk of sudden cardiac death, and thus ICD benefit,³⁰ or response to CRT.³¹ However, the integration of biomarkers for ICD or CRT implantation decisions is still in its infancy.

For patients with HFPEF, the value of risk classification is even more nebulous. These patients are older and have a higher comorbidity burden that alters the association between HF status and outcome. For example, among the highly selected patients of I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Trial), 40% of deaths were non-cardiac.³² This issue is even more pronounced when it comes to hospitalization risk, which is heavily influenced by non-cardiac conditions. Most importantly, there are no effective therapies specifically for HFPEF to date.³³ Thus, it is difficult to argue for the use of biomarkers in terms of clinical decision-making in this group. Of note, in a post-hoc analysis of I-PRESERVE, irbesartan appeared to benefit those with low NT-proBNP.³⁴ Albeit this analysis should be interpreted with caution, it highlights the challenges associated with risk assessment in HFPEF.

Baseline vs. Serial Biomarker Measurements for Risk Assessment

Beyond serial measurements of BNP or NT-proBNP for HF status monitoring purposes, several other biomarkers have been evaluated in serial determinations as risk prediction tools. Cardiac troponins have been extensively studied both in acute^{35–37} and chronic^{38,39} HF. Despite the potential of serial measurements to provide useful insights, especially in AHF, the issues in terms of a development framework are compounded with serial determinations. For example, in patients with AHF, troponins have been measured in 6-hourly to daily intervals after admission and several days afterwards.^{35–37} From a practical perspective, it is unlikely that such frequent determinations can be clinically implemented. Therefore, appropriate frequency and timing for these measurements suitable for the setting (acute vs. chronic) is of key importance. However, serial measurements are currently under intense investigation and these results are best interpreted from a discovery perspective at this point.

Biomarkers for Heart Failure Management

There are three main uses of biomarkers in the management of HF. First, biomarkers can be used as risk stratification tools as discussed above. Second, biomarkers can be used as “biomonitoring” tools with serial determinations to guide treatment intensity and facilitate decisions for management. In this respect, natriuretic peptide-guided therapy has been already tested extensively in clinical trials. The evidence however has been inconsistent thus far.⁴⁰ A pooled-data meta-analysis in 2009 showed a significant mortality advantage for biomarker-guided therapy (hazard ratio was 0.69, 95% CI 0.55 to 0.86) compared to standard care.⁴¹ However, in TIME-CHF (The Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure), a natriuretic-peptide-guided approach reduced HF admissions in patients under age 75, but had no effect in those over age 75, highlighting the population and outcome issues discussed. Hence, whether a biomarker-guided strategy is useful for all patients and especially those with HFPEF remains unclear and needs further evaluation. Finally, the cost-effectiveness of biomarkers as biomonitoring tools is currently limited to analyses from studies with natriuretic peptides.^{42,43}

Biomarkers as Therapeutic Targets for HF Treatment

Perhaps the most intriguing potential of biomarkers in HF is patient selection for specific therapies based on underlying pathophysiology as determined by biomarkers. Several post-

hoc analyses from clinical trials have shown that certain therapies benefit a specific subset of patients characterized by elevated levels of a relevant biomarker. For example, in a post-hoc analysis from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure), rosuvastatin treatment was associated with better outcomes only in patients with C-reactive protein levels ≥ 2.0 mg/L.⁴⁴ Similarly, in RALES (Randomized Aldactone Evaluation Study), the benefit from spironolactone was associated with higher levels of collagen synthesis markers.⁴⁵ A number of ongoing studies are evaluating this concept.⁴⁶

Future Directions

For biomarkers to become useful for risk stratification, a consensus is needed on a standardized framework for population and outcome definitions, and a finite time horizon. Modeling of outcomes should be adapted to reflect the characteristics of the HF population of interest. On top of standard HF characteristics, a comorbidity score would be important to consider. Clinical application of risk stratification for decision-making has persistent challenges before entering mainstream HF practice. Approaches that use biomarkers to tailor treatment to the specific patients and the underlying pathophysiology are more likely to enter practice in the near term. As a token to this trend, several ongoing trials are testing this approach, whereas no trial is currently addressing the issue of differential treatment based on projected risks.

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ABBREVIATIONS

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
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-BNP

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Figure 1. Number of articles including the terms “biomarker*” and “heart failure” 2001–2011. Source: Web of Science SM. Accessed March 31, 2012.

Figure 2. Framework and areas of uncertainty in the development of biomarkers in heart failure. Stages adapted from Hlatky MA et al, *Circulation* 2009;119:2408-2416.

Table 1

Characteristics of the Ideal Biomarker

Morrow and deLemos (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”

Adapted from Maisel A, *J Am Coll Cardiol* 2011;58:1890-1892, with permission.

Table 2

Development Stages of the Various Biomarker Domains in Heart Failure

Domain	Biomarkers	Development Phase	Studies
Inflammation			
	C-reactive protein	4	Ky et al ²⁶
	TNF- α and receptors	3	Rauchhaus et al ⁴⁷
	Interleukins	3	Subramanian et al ⁴⁸ Ma et al ⁴⁹
	Lp-PLA2	3	Gerber et al ⁵⁰
	YKL-40	3	Bilim et al ⁵¹
	sTWEAK	3	Chorianopoulos et al ⁵²
	Midkine	3	Kitahara et al ⁵³
	Pentraxin 3	3	Suzuki et al ⁵⁴ Kotooka et al ⁵⁵
	CA-125	3	Monteiro et al ⁵⁶
	S100A8/A9 complex	3	Ma et al ⁴⁹
	Osteoprotegerin	3	Ueland et al ⁵⁷ Røysland et al ⁵⁸
	Adiponectin	3	Kistorp et al ⁵⁹
Oxidative Stress			
	Myeloperoxidase	3, 4	Tang et al ⁶⁰ Ky et al ²⁶
	Oxidized LDL	3	Tsutsui et al ⁶¹
ECM Remodeling			
	Matrix Metalloproteinases	3	Radauceanu et al ⁶² Lopez-Andrès et al ⁶³
	Tissue Inhibitors of Metalloproteinases	3	Frantz et al ⁶⁴ Bhalla et al ⁶⁵
	Pro-collagen	3	Zannad et al ⁴⁵ Lopez-Andrès et al ⁶³ Radauceanu et al ⁶²
	Galectin-3	3	Lok et al ⁶⁶ Shah et al ⁶⁷ Lopez-Andrès et al ⁶³
Neurohormones			
	Norepinephrine	3	Conn et al ⁸ Latini et al ⁶⁸
	Renin, Aldosterone	2, 3	Conn et al ⁸ Pacher et al ⁹ Latini et al ⁶⁸
	Copeptin (C-terminal provasopressin)	3, 4	Alehagen et al ¹⁴ Peacock et al ⁶⁹ Tentzeris et al ¹² Masson et al ⁷⁰
	Endothelins	2, 3	Adlbrecht et al ⁷¹ Masson et al ⁷⁰ Latini et al ⁶⁸
	Chromogranin A	2	Røsjø et al ⁷²
	MR-proADM	3	Masson et al ⁷⁰ Peacock et al ^{69,71}
	MR-proANP	3	Masson et al ⁷⁰ Maisel et al ⁷³
Myocyte injury - apoptosis			
	Troponins	4	Dunlay et al ¹¹ Pascual-Figal et al ⁷⁴ Tentzeris et al ¹² Ky et al ²⁶
	H-FABP	3	Arimoto et al ⁷⁵
	sTRAIL	3	Niessner et al ⁷⁶

Domain	Biomarkers	Development Phase	Studies
Myocyte stress			
	Natriuretic peptides	5, 6	Felker et al ⁴¹ Eurlings et al ⁷⁷ Adlbrecht et al ⁷⁸
	Soluble ST2	4	Pascual-Figal et al ⁷⁴ Bayes-Genis et al ⁷⁹ Ky et al ⁸⁰
	Growth-differentiation factor 15	3	Kempf et al ⁸¹ Anand et al ⁸²
	Neuregulin 1	3	Ky et al ⁸³
Renal involvement			
	Cystatin C	3	Manzano-Fernández et al ⁸⁴
	β -trace protein	3	Manzano-Fernández et al ⁸⁴
	NGAL	3	Damman et al ⁸⁵ Maisel et al ⁸⁶

H-FABP: Heart-type fatty acid binding protein; Lp-PLA2: Lipoprotein-associated phospholipase A2; MR-proADM: Mid-regional pro-adrenomedullin; MR-proANP: midregional pro-atrial natriuretic peptide; NGAL: Neutrophil gelatinase-associated lipocalin; sTRAIL: soluble tumor necrosis factor-related apoptosis-inducing ligand; sTWEAK: soluble tumor necrosis factor-like weak inducer of apoptosis

Table 3
Studies Evaluating the Risk Reclassification Properties of Biomarkers in Patients with Heart Failure

Study	Biomarkers	HFREF vs. HFPEF	Acute vs. Chronic	Outcomes	Time Frame	Comparison Model
Dunlay et al ¹¹	hs-CRP, BNP, cTnT	Mixed	Mixed	Mortality	1 year	Data driven
Masson et al ⁷⁰	MR-proANP, MR-proADM, CT-proET-1, Copeptin	Mixed	Chronic	Mortality, Mortality plus cardiovascular admission	Not predefined (median, 3.9 years)	Literature based
Ky et al ⁸⁰	Soluble ST2, NT-proBNP	Mixed	Chronic	Mortality plus heart transplantation	Not predefined (median, 2.8 years)	Seattle Heart Failure Model
Tenzeris et al ¹²	Copeptin, hs-cTnT	Mixed	Chronic	Mortality plus heart failure admission	Not predefined (median, 3.6 years)	Clinical plus NT-proBNP
Maisel et al ⁸⁶	Neutrophil gelatinase-associated lipocalin	Mixed	Acute	Mortality plus heart failure readmission	30 days	BNP
Manzano-Fernández et al ⁸⁴	β -trace protein, cystatin C	Mixed	Acute	Mortality plus heart failure readmission	Not predefined (median, 1.4 years)	Data driven
Pascual-Figal et al ⁷⁴	Soluble ST2, NT-proBNP, hs-cTnT	Mixed	Acute	Mortality	Not predefined (median, 2.0 years)	Data driven
Ky et al ²⁶	hs-CRP, MPO, BNP, sFMT-1, cTnI, Soluble ST2, creatinine, uric acid	Mixed	Chronic	Mortality plus heart transplantation plus LVAD implantation	Not predefined (median, 2.5 years)	Seattle Heart Failure Model
Bayes-Genis et al ⁷⁹	Soluble ST2, NT-proBNP	Mixed	Chronic	Mortality	Not predefined (median, 2.8 years)	Literature based

BNP: B-type natriuretic peptide; CRP: C-reactive protein; cTnI: cardiac troponin I; cTnT: cardiac troponin T; CT-proET-1: C-terminal pro-endothelin-1; hs: high-sensitivity; MPO: myeloperoxidase; MR-proADM: mid-regional pro-adrenomedullin; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide