

## Established and Emerging Roles of Biomarkers in Heart Failure Clinical Trials

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**Abstract**—The role of circulating biomarkers in heart failure clinical trials has evolved in recent decades. Increasing evidence behind the use of natriuretic peptides, emergence of novel biomarkers, and increased emphasis on targeting therapies toward physiological basis of disease (so-called precision medicine) have all contributed to the continued expansion of biomarker use in heart failure clinical trials. We will explore the advantages and pitfalls encountered through the use of biomarkers in clinical trials as an inclusion criterion, toxicity marker, and end point. We will also review their role in providing insights into the mechanism of action of therapeutics and guiding therapy in the management of patients with heart failure. (*Circ Heart Fail.* 2016;9:e002598. DOI: 10.1161/CIRCHEARTFAILURE.115.002528.)

**Key Words:** biomarkers ■ heart failure ■ natriuretic peptides ■ precision medicine ■ retrospective study

The use of circulating heart failure (HF) biomarkers in the design of clinical trials has seen exponential growth; starting with expansion in the clinical application of B-type natriuretic peptide (BNP) and its precursor N-terminal pro-BNP (NT-proBNP) followed by emergence of an array of novel HF biomarkers emblematic of different pathophysiological links in HF, biomarker testing in HF promises to provide better understanding of the diagnosis.<sup>1–3</sup> Such evolution in how patients with HF are evaluated may lead to a more effective synergy between developers of HF therapies, the in vitro diagnostics industry, biomarker researchers, clinical trialists, and regulatory agencies alike. Although the term biomarker may also apply to imaging markers, for the purposes of this review, we will only consider the use of circulating biomarkers.

In general, circulating biomarkers have been used in HF clinical trials as (1) an inclusion criterion to enrich the study population with higher risk subjects, (2) a measure of drug toxicity, (3) an outcome measure/end point, (4) a means to retrospectively explain efficacy of a therapeutic, and (5) a target for therapy.

Of the 1047 completed or ongoing HF trials in the past decade, 408 (39%) studies included biomarkers in the trial design (Figure 1).<sup>4</sup> Of these, 55% used a biomarker as an end point for the trial, 21% used biomarkers for inclusion or exclusion criteria, whereas 20% used biomarkers for inclusion or exclusion criteria in addition to using them as an end point. BNP and NT-proBNP were the most frequently used biomarkers (82%). Figure 2 summarizes select biomarkers representative of various pathways.

### Biomarker Use as Inclusion Criteria in HF Clinical Trials

The role of biomarkers for inclusion into clinical trials is predicated on the concept that a given elevation of a specific biomarker such as BNP or NT-proBNP may not only confirm the presence of HF but also serves to enrich the population with a specific HF phenotype with higher risk for adverse outcome. Of all the potential roles, biomarkers may play in HF trials, their use as an inclusion criterion has become standard practice across a wide range of clinical trial phases, allowing for focus on the correct patients at the correct level of risk; this in turn helps to minimize sample size, providing cost-effectiveness in trial design.

### Patient Selection

Although HF is the first and foremost a clinical diagnosis based on symptoms, signs, and imaging, the use of BNP or NT-proBNP as an adjunct to clinical diagnosis improves diagnostic accuracy above and beyond other clinical variables; conversely, a lower concentration of either peptide argues strongly against the presence of significant HF.<sup>5</sup> This role of the natriuretic peptides is possibly more important in patients with preserved left ventricular ejection fraction (EF) because the potential for misdiagnosis of HF is greater in this population leading to a dilution of observed benefits of a proposed treatment. A recent example was TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial), where study participants could be enrolled on the basis of clinical suspicion for HF, along with either an elevated BNP or NT-proBNP or recent HF hospitalization; patients

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*Circ Heart Fail* is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.115.002528

were treated with either spironolactone or placebo. Although no overall benefit was seen with spironolactone for the primary outcome, in those enrolled based on elevated natriuretic peptide, significant benefit was seen (hazard ratio, 0.65; 95% confidence interval, 0.49–0.87;  $P=0.003$ ).<sup>6</sup> Patients who were enrolled without meeting the biomarker entry requirement had a lower event rate, raising concern for potential misdiagnosis or possibly with an HF phenotype not responsive to mineralocorticoid receptor antagonist therapy. A well-adjudicated diagnosis of HF, as opposed to allowing investigators to make a diagnosis of HF based on clinical suspicion, may have been as beneficial as BNP or NT-proBNP concentrations however. Such preadjudication is challenging to accomplish, well-illustrating potential value of using the natriuretic peptides as an inclusion criteria in trials of patients with HF with preserved EF (HFpEF).

### Risk Enrichment

Beyond their value for diagnosis, elevated BNP and NT-proBNP are closely associated with high risk of adverse HF outcomes, including death and rehospitalization,<sup>7,8</sup> and this ability for risk prediction is particularly useful for enriching the study population with patients with higher event rates to minimize risk for type II error in underpowered studies (Table 1).

The value of BNP or NT-proBNP for predicting risk seems to be somewhat similar in HF patients with preserved and reduced EF, despite lower concentration for both peptides in patients with HFpEF.<sup>19</sup> For each 100 pg/mL increase of BNP, a 35% increase in the relative risk of death has been observed<sup>20</sup> and similar findings are seen with NT-proBNP.<sup>7</sup>

Choosing an appropriate biomarker threshold to identify risk is crucial when designing studies with biomarkers as an inclusion criterion and should be done by methodically balancing identification of high-risk patients (the higher the better) with the need to be inclusive of a wide range of patients to improve the generalizability of the results (the lower the better). For example in Val-HeFT (Valsartan Heart Failure Trial), higher NT-proBNP value was associated with higher risk with risk climbing above  $\approx 1000$  pg/mL.<sup>21</sup> Such

information provides an important reference point on which to choose a trial-specific biomarker cutoff value based on the trial's needs.<sup>21,22</sup> In the PARADIGM-HF trial (Prospective Angiotensin–Neprilysin Inhibition Versus Enalapril in Heart Failure), patients were required to have a BNP of at least 150 pg/mL or an NT-proBNP of  $\geq 600$  pg/mL, or if they had been hospitalized for HF within the previous 12 months, a BNP of at least 100 pg/mL or an NT-proBNP of  $\geq 400$  pg/mL with resulting high event rates, which allowed for more timely completion of this event-driven study.<sup>10</sup>

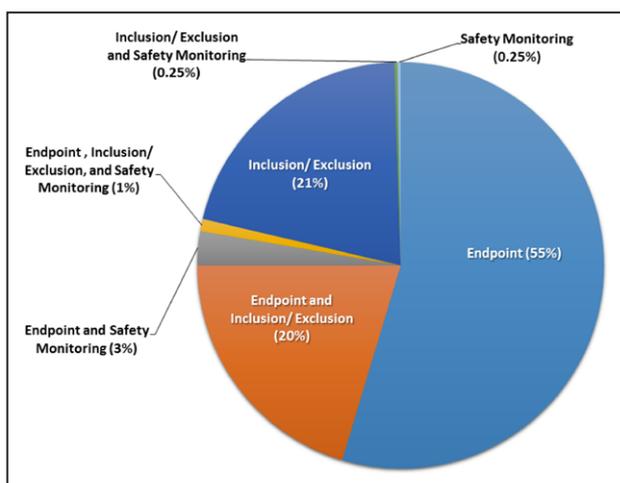
Although higher concentrations of selected predictive biomarkers may enrich a trial with study participants at high risk, it is preferable to avoid selecting a threshold biomarker concentration that leads to the enrollment of patients less likely to respond to therapy due to excessive risk. An example of this may be illustrated in a post hoc analysis of I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Trial) by Anand et al.<sup>23</sup> Patients with HFpEF and NT-proBNP concentration below the median of 339 pg/mL benefited from irbesartan in terms of the primary outcome of all-cause mortality and cardiovascular hospitalization (hazard ratio, 0.74; 95% confidence interval, 0.60–0.90;  $P=0.003$ ), all-cause mortality (hazard ratio, 0.75; 95% confidence interval, 0.56–0.99;  $P=0.046$ ), and HF composite outcome (hazard ratio, 0.57; 95% confidence interval, 0.41–0.80;  $P=0.001$ ) compared with patients with an NT-proBNP concentration above the median. This curious finding may indicate it as being too late for those with higher NT-proBNP concentrations to receive benefit from irbesartan, or it may simply reflect a spurious finding in a trial that was neutral for its primary end point. In most therapies and trials, higher risk patients tend to have the most benefit.<sup>24–27</sup>

Several emerging biomarkers might be considered eligible for the consideration of use in HF clinical trials because they provide different information than BNP or NT-proBNP. In each case, rather than more generally predicting risk, these markers might be used to specifically identify the presence of a remediable process in HF, to more precisely assist in drug development. Among these are the cardiovascular stress biomarker ST2 (reflective of vascular and myocardial remodeling), peptides such as endothelin-1 or C-terminal proavopressin (linked to pulmonary artery constriction and salt/water handling, respectively), or insulin-like growth factor-binding protein-7; this latter peptide is of interest given recent links to reduced myocardial diastolic noncompliance, suggesting a unique application to target one aspect of the pathophysiology of HFpEF.<sup>28</sup>

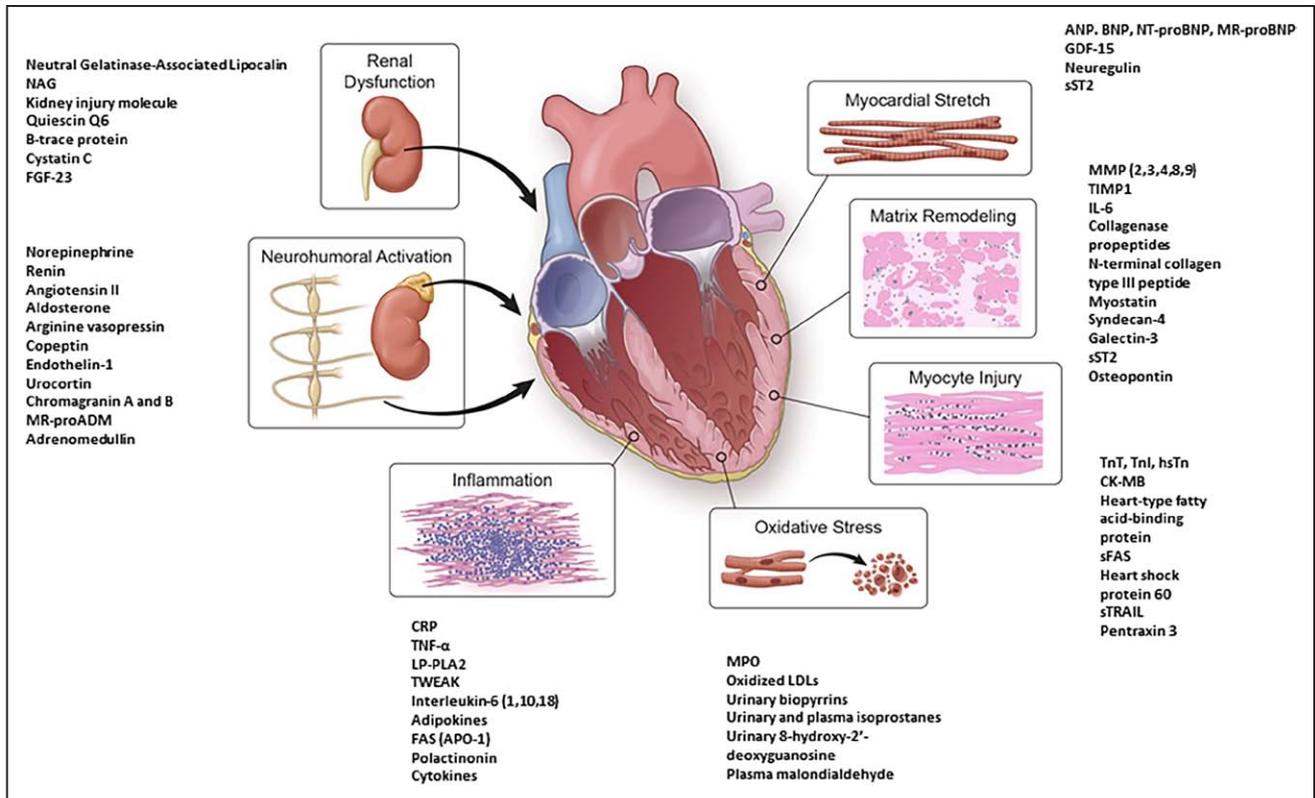
Table 2 summarizes the characteristics ideally present in a biomarker for use as an inclusion criterion for clinical trials. Natriuretic peptides, for example, seem to satisfy these characteristics; however, more data are needed on newer biomarkers relative to these characteristics.

### Biomarker Use for Toxicity Monitoring in HF Clinical Trials

During execution of clinical trials of novel therapeutics, it is important to establish reliable methods to monitor cardiac toxicity to ensure patient safety. Numerous mechanisms of cardiotoxicity in the course of drug development have been



**Figure 1.** Biomarker use in heart failure trials.<sup>4</sup> A broad range of the roles of biomarkers has been reported in trial design.



**Figure 2.** Classes of biomarkers contributing to the biomarker profile in heart failure. ANP indicates atrial natriuretic peptide; CK-MB, creatinine kinase- MB fraction; CRP, c-reactive protein; FAF, fibroblast growth factor; FAS, tumor necrosis super family member 6; GDF-15, growth differentiating factor 15; LDL, low density lipoprotein; LP-PLA2, lipo protein associated phospholipase 2; MPO, myeloperoxidase; MR-proADM, mid regional-pro adrenomedullin; NAG, N-acetyl beta-D glucosaminidase; NT-proBNP, N-terminal pro B-type natriuretic peptide; TNF- $\alpha$ , tumor necrosis factor alpha; and TWEAK, tumor necrosis factor like weak inducer of apoptosis.

described, and interest has grown in the use of biomarkers to act as an early warning system to detect toxicity. When used appropriately, biomarkers may be of particular use for identifying toxicity in dose ranging studies, thus minimizing risk before later-phase trials; in this regard, biomarker monitoring for toxicity may help to minimize cost outlays from studies failing because of risk.

When biomarkers are used to detect toxic effects of HF therapeutics, it is necessary to well establish a biological link between biomarker and therapy toxicity, and in studies of serial biomarker measurement, any risk estimated by the change in biomarker levels over time should be carefully validated, including knowledge of how much change in a biomarker is needed to predict risk.

How biomarkers may predict cardiovascular toxicity of therapeutic agents has been recently highlighted in oncology trials. Abnormal concentrations of troponins, markers of myocyte injury, are closely associated with anthracycline-induced myocyte death and cardiotoxicity, as well as trastuzumab-related loss of myocyte contractility.<sup>29,30</sup> Highly sensitive troponin (hsTn) assays, which allow for discernment of minute amounts of myocardial injury or necrosis, may be particularly useful to identify such cardiotoxicity, which in turn predicts risk for events such as HF.<sup>31</sup>

hsTn measurements might be used in HF clinical trials as a measure of toxicity of treatment modalities, although this association should be applied with caution, as multiple

explanations for release of hsTn outside of cardiotoxicity of therapeutic agents exist in the context of HF.<sup>32</sup> Furthermore, with newer agents being developed that might specifically interact with the cardiac sarcomere, link(s) between hsTn and risk might be further confounded. In the recent ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure Trial), treatment with a cardiac-specific myosin activator was associated with higher concentrations of hsTnI compared with placebo. Notably, the cohort receiving the highest dose of omecamtiv mecarbil saw greater relief from dyspnea compared with placebo (51% versus 37%,  $P=0.03$ ) and more substantial reduction in NT-proBNP, but had higher hsTnI concentrations; no adverse outcomes in relation to the mild increased level of hsTnI seen in this trial have at this time been documented.<sup>33</sup> These elevated hsTnI values might translate to future risk, although this is speculative and more data are needed.

Generally speaking, currently, there no guidelines establishing hsTn cutoffs above which concentrations would signal an abnormality.<sup>34</sup> Furthermore, numerous hsTnI assays exist, with different reference ranges; establishing cutoffs above which concentrations would signal an abnormality is a much needed exercise. To support the use of hsTn for toxicity monitoring, it is necessary to interpret any changes within the clinical context, and consider changes over time together with results of other biomarkers to best understand signals detected in the course of a study. If hsTn is used as a toxicity monitor

**Table 1. Examples of Heart Failure Trials in Which NT-proBNP or BNP Was Used As an Inclusion Criterion<sup>9</sup>**

Trial	Year	HFrEF vs HFpEF	NT-proBNP Cutoff for Inclusion (pg/mL)	BNP Cutoff for Inclusion (pg/mL)	Event Rates in Control Arm	Primary End Point
PARADIGM-HF <sup>10</sup>	2014	HFrEF	400 (HF hospitalization); 600 (no HF hospitalization)	100 (HF hospitalization); 150 (no HF hospitalization)	26.5%	Composite of death from CV causes or a first hospitalization for HF
ASTRONAUT <sup>11</sup>	2013	HFrEF	1600	400	26.5%	First occurrence of CV death or rehospitalization for HF at 6 mo after randomization
O'Connor et al <sup>12</sup>	2011	HFrEF	1000	400	10.1% (rehospitalization for HF or death from any cause at 30 days)	Change in self-reported dyspnea 6 and 24 h after study drug initiation and the composite end point of rehospitalization for HF and death from any cause during the period from randomization to day 30
BATTLESCARRED <sup>13</sup>	2009	HFrEF	400		34%	All-cause mortality and the composite of death plus hospitalization for heart failure
TIME-CHF <sup>14</sup>	2009	HFrEF	400 (patients < 75 yr) 800 (patients ≥ 75)			18-mo survival free of any hospitalization and quality of life at 18 mo
RELAX-AHF <sup>15</sup>	2014	HFrEF HFpEF	1400	350	12.64%* (HFrEF); 12.75%* (HFpEF)	Dyspnea improvement
TOPCAT <sup>6</sup>	2014	HFpEF	360	100	All: 6.6 per 100 person-years Enrollment on the basis of HF hospitalization: 6.0 per 100 person-years Enrollment based on BNP/NT-proBNP: 8.5 per 100 person-years Enrollment in Americas: 12.6 per 100 person-years Enrollment in Eastern Europe: 2.3 per 100 person-years	Composite of CV mortality, aborted cardiac arrest, or HF hospitalization
RELAX <sup>16</sup>	2013	HFpEF	400			Change in peak $\dot{V}_{O_2}$
PARAMOUNT <sup>17</sup>	2012	HFpEF	400			Change in NT-proBNP
RAAM-PEF <sup>18</sup>	2011	HFpEF		100		Change in 6MWD

ASTRONAUT indicates Aliskerin on Acute Heart Failure Outcomes; BATTLESCARRED, NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PARADIGM-HF, Prospective Angiotensin–Neprilysin Inhibition Versus Enalapril in Heart Failure; PARAMOUNT, Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; RAAM-PEF, Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction; RELAX-AHF, Relaxin in Acute Heart Failure; TIME-CHF, Therapy in Elderly Patients With Congestive Heart Failure; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. Rates of events in the placebo/control arm of such studies reflect prognostic associations with natriuretic peptide concentrations.

\*Cardiovascular death or heart failure/renal failure hospitalization through day 60.

in clinical trials without a clear understanding of how to interpret concentration changes, it might undermine an otherwise potentially useful therapy. Regulators should work hand in hand with trialists, clinicians, industry, and professional societies to create paths forward.

Ultimately, this is a reminder that the biology behind drug–biomarker interactions is not always clear, and a rise in a risk biomarker in drug-treated patients might be observed even if a drug is clinically favorable. Relative to this caveat, in PARADIGM-HF,<sup>10</sup> combined use of valsartan/sacubitril led to rise in BNP concentrations related to the effect of neprilysin inhibition.<sup>35</sup> Accordingly, uninformed interpretation of BNP

might have suggested cardiac risk related to treatment with valsartan/sacubitril. In a similar vein, other drugs may lead to BNP rise because of increase in its production; neuregulin-1 is a member of the epidermal growth factor gene family with broad effects on the cardiovascular system; infusion of neuregulin-1 in patients with HF results in vasodilation, improved hemodynamics, and lower filling pressures.<sup>36</sup> Notably, neuregulin-1 and related compounds cause physiological rise in BNP and NT-proBNP concentrations because of direct stimulation of the *BNP* gene.<sup>37</sup> Thus, in the course of drug development, good knowledge of how therapeutics affect biomarkers is crucial before markers can be used as monitors for toxicity.

**Table 2. Prerequisites for the Use of a Biomarker as a Clinical Trial Inclusion Criterion**

To be used as an inclusion criterion for a clinical trial, we suggest a biomarker possess the following characteristics:
<ul style="list-style-type: none"> <li>• It must be sensitive and specific for the clinical diagnosis of HF or identify remediable prognostic pathophysiological processes in the diagnosis. Such information should be unique and beyond that which is otherwise known using clinical means.</li> </ul>
<ul style="list-style-type: none"> <li>• Performance in patients with reduced and preserved left ventricular ejection fraction must be known.</li> </ul>
<ul style="list-style-type: none"> <li>• Validated cutoffs for use as a diagnostic or prognostic should be established.</li> </ul>
<ul style="list-style-type: none"> <li>• Risk predicted by a biomarker should be remediable, and at least some knowledge of how therapy affects concentrations of the biomarker, and the risk it predicts is a prerequisite.</li> </ul>

HF indicates heart failure.

Table 3 summarizes characteristics ideally present in a biomarker for use as a tool for toxicity monitoring. Few of the biomarkers in current use satisfy all of these criteria.

**Biomarkers as Surrogate End Points in HF Clinical Trials**

Biomarkers have been increasingly used as surrogate end points in phase II HF trials, reducing sample size and minimizing cost and the duration of the trial. Although using biomarker concentrations as an end point may speed decisions about expanding development programs and allow potentially beneficial interventions to reach patients faster, the use of biomarkers as end points for phase III is largely unexplored in cardiac trials (in contrast to oncology) and has been discouraged by regulatory authorities.<sup>38</sup>

Fleming<sup>39</sup> and Fleming and Powers<sup>40</sup> described a 4-level hierarchy for end points used in clinical trials. Level 1 is a true clinical efficacy measure (eg, death). Level 2 is a validated surrogate; that is, one whose change in response to a therapy is highly correlated with the impact on morbidity and mortality, across multiple interventions (eg, systolic blood pressure in hypertension trials). Level 3 is a nonvalidated surrogate that is thought likely to predict clinical benefit. Level 4 is a correlate that is a measure of biological activity that has not been established to correlate with outcomes. Presently, most biomarkers fall into level 3 or 4, although this is evolving. There is little solid evidence to suggest the natriuretic peptides

**Table 3. Prerequisites for the Use of a Biomarker as a Tool for Toxicity Monitoring**

To be used as a tool for monitoring toxicity, we suggest the following are needed:
<ul style="list-style-type: none"> <li>• Strong knowledge of biomarker biology to justify its use for monitoring toxicity, without risk for unexpected behavior.</li> </ul>
<ul style="list-style-type: none"> <li>• Established sampling strategies with defined cutoffs.</li> </ul>
<ul style="list-style-type: none"> <li>• Knowledge of potential adverse events linked to abnormal biomarker results, and relative and absolute risks of such events.</li> </ul>
<ul style="list-style-type: none"> <li>• Understanding of the temporal relationship between biomarker abnormalities and events.</li> </ul>

**Table 4. Prerequisites for the Use of a Biomarker as a Clinical Trial Surrogate End Point**

To be used as a surrogate end point, we suggest the following are needed:
<ul style="list-style-type: none"> <li>• A strong correlation between the impact of an intervention on the biomarker and the impact of that intervention on a clinically meaningful end point, across a variety of interventions.</li> </ul>
<ul style="list-style-type: none"> <li>• The outcome measure of interest predicted by the biomarker should be remediable through therapeutic intervention.</li> </ul>
<ul style="list-style-type: none"> <li>• Preferably, a biomarker should reflect both benefit and risk related to drug exposure.</li> </ul>
<ul style="list-style-type: none"> <li>• Sampling strategies for the measurement of the surrogate biomarker, relative to risk for outcome measure must be established, with time course between change in biomarker and substituted outcome well understood.</li> </ul>

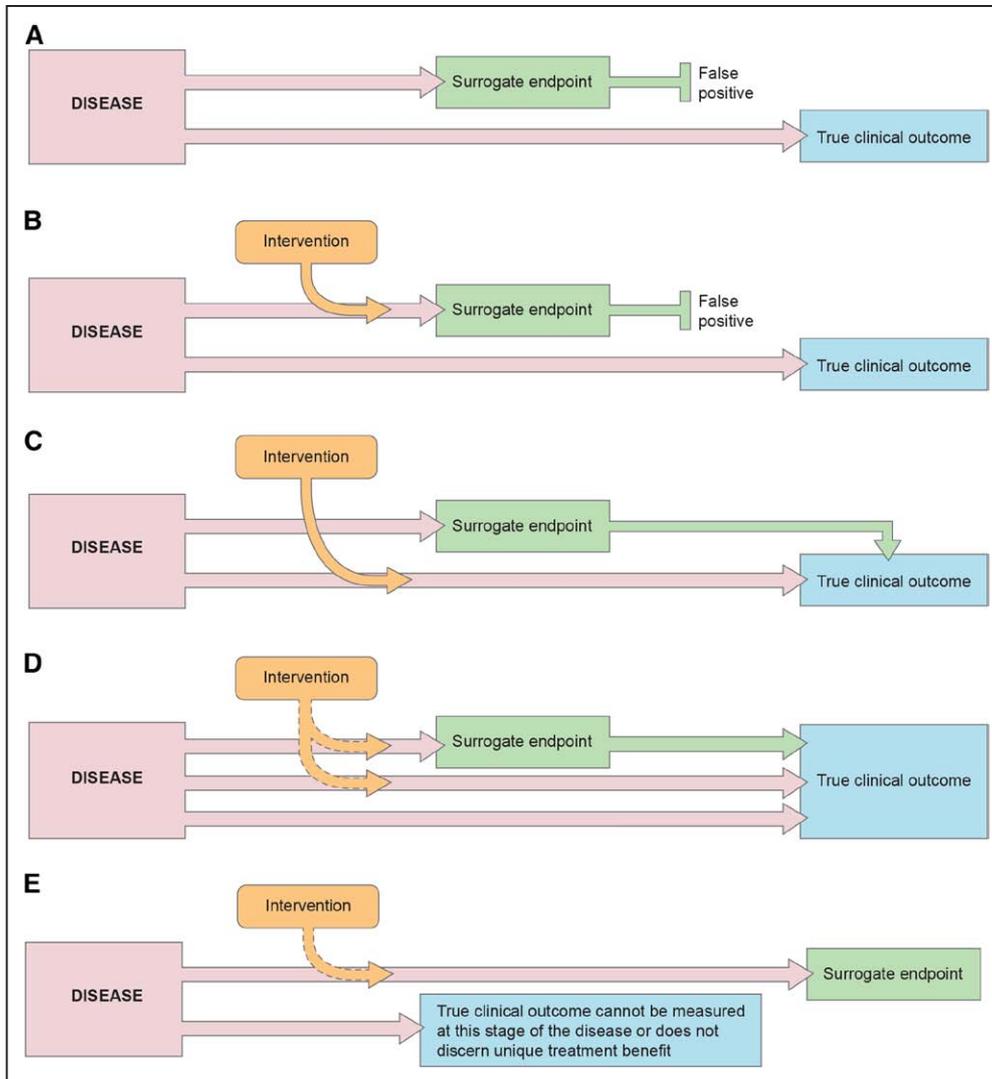
might consistently perform at level 2. Although changes in natriuretic peptide concentrations such as NT-proBNP can change in a directionally similar manner to outcomes with some therapies,<sup>10</sup> a study by Wessler et al<sup>41</sup> showed no significant correlation between therapy-induced change in BNP and NT-proBNP across numerous trials.

Similarly, in early studies, initiation of nonvasodilating β-blockers was found to increase concentrations of natriuretic peptides in some patients, while simultaneously resulting in favorable outcomes. For example, in a study of controlled release metoprolol succinate in patients with ischemic and dilated cardiomyopathy, addition of metoprolol to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers improved ventricular function,

**Table 5. Selected Post Hoc Analyses in Which Biomarkers Were Used to Predict Treatment Efficacy**

Authors	Findings	Role of Biomarker
Zannad et al <sup>51</sup>	Collagen biomarkers identified a group of patients showing greater benefit from spironolactone	Identify potential mechanism of action
Richards et al <sup>52</sup>	Baseline NT-proBNP concentrations predicted greater benefit from carvedilol	Understand benefits of a drug downstream to its mechanism of action
Cleland et al <sup>53</sup>	Lowest tertile NT-proBNP predicted benefit from rosuvastatin therapy in HFrEF	Identify a cohort of patients that derive benefit from a studied therapy
Gullestad et al <sup>54</sup>	Galectin-3 values <19.0 ng/mL may predict benefit from rosuvastatin treatment in HFrEF	Identify a cohort of patients that derive benefit from a studied therapy
Gaggini et al <sup>55</sup>	ST2 predicted benefit from high-dose β-blockade	Identify a cohort of patients that derive benefit from a studied therapy
Cao et al <sup>56</sup>	Neurotrimin may predict patients who respond to HF therapy	Identify a cohort of patients that derive benefit from a studied therapy

HF indicates heart failure; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.



**Figure 3.** Reasons why surrogate end points may fail. **A**, Change in the surrogate end point may be irrelevant to the disease process, such as failure of change in N-terminal pro B-type natriuretic peptide to predict the benefit of levosimendan.<sup>45</sup> **B**, The intervention affects the surrogate but does not affect the clinical outcome; for example, milrinone improved cardiac output and exercise tolerance but resulted in increased mortality in patients with heart failure.<sup>46</sup> **C**, Treatment effects do not affect the surrogate of the treatment, such as mineralocorticoid receptor antagonist therapy and concentrations of galectin-3.<sup>47</sup> **D**, The surrogate reflects one effect of the treatment, but there are other, more significant effects on outcome that are not captured and may be unintended, such as was seen in the Cardiac Arrhythmia Suppression Trial, where antiarrhythmic drugs lowered the burden of postmyocardial infarction ventricular arrhythmia post myocardial infarction but resulted in an increased risk of death.<sup>48</sup> **E**, The surrogate responds to therapy but does not correlate with classical clinical assessment tools because change in the surrogate may occur well before the clinical outcome might develop.<sup>40,44,49</sup>

reduced activation of the renin–angiotensin–aldosterone system, and resulted in fewer deaths; conversely, an increase in N-terminal atrial natriuretic peptide and BNP concentrations ( $P < 0.01$ ) were seen in these patients.<sup>42</sup> In another early study, Yoshizawa et al<sup>43</sup> demonstrated  $\beta$ -blocker therapy with metoprolol or carvedilol in patients with HF reduced left ventricular end-systolic and end-diastolic dimensions and improved ventricular function, but it did not change BNP concentrations at 48 weeks. Natriuretic peptides had been used as surrogate end points in these pilot trials, larger studies may not have been performed. These experiences illustrate importance of a good understanding of biomarker–drug interface, to avoid type I or II error. An in-depth explanation of why surrogate end points may fail is needed before accepting their use (Figure 3).<sup>44</sup>

These caveats notwithstanding, the importance of alternative end points to expedite drug development in HF has become increasingly recognized. The PARAMOUNT trial (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) was a phase II study comparing valsartan/sacubitril with valsartan in patients with HFpEF and utilized a primary surrogate end point of NT-proBNP reduction at 12 weeks. In this trial, valsartan/sacubitril reduced NT-proBNP to a greater extent than did valsartan after 12 weeks; this was subsequently followed by a significant reduction in left atrial volumes and dimensions at 36 weeks.<sup>17</sup> Fueled by the results of the phase II trial, a phase III trial—the Efficacy and Safety of LCZ696. PARAGON-HF (Compared With Valsartan, on Morbidity and Mortality in Heart Failure With Preserved Ejection Fraction) is now ongoing. A caveat is

**Table 6. Suggested Criteria Required to Use a Biomarker to Guide Therapy in Heart Failure Clinical Trials**

To be used as a guide for therapy, we suggest the following are needed:
<ul style="list-style-type: none"> <li>• The biomarker must be highly sensitive and specific, must be easily obtained, easy to interpret, and standardized across different clinical laboratories with a low inherent error.</li> </ul>
<ul style="list-style-type: none"> <li>• The mechanism and causes of biomarker abnormalities must be thoroughly understood and linked to clinical events.</li> </ul>
<ul style="list-style-type: none"> <li>• Risk predicted by the biomarker should be remediable.</li> </ul>
<ul style="list-style-type: none"> <li>• Treatment strategy for an abnormal concentration of the biomarker must be known.</li> </ul>
<ul style="list-style-type: none"> <li>• Biological variation of the biomarker should be established.</li> </ul>
<ul style="list-style-type: none"> <li>• There must be a specified time for when the biomarker will be remeasured in the course of treatment.</li> </ul>
<ul style="list-style-type: none"> <li>• Goal values for biomarker-guided care must be established.</li> </ul>

needed: in I-PRESERVE, there was a reduction in NT-proBNP concentrations at 6 months in the placebo and treatment arms; however, irbesartan did not improve outcomes in HFpEF.<sup>50</sup> Thus, the reduction in NT-proBNP seen in PARAMOUNT might not be accompanied by superior outcomes, but the difference in NT-proBNP reduction between arms in PARAMOUNT together with change in left atrial volume might or might not be accompanied by superior outcomes.

An additional established role of biomarkers is their use in event adjudication in HF clinical trials. In particular, the use of natriuretic peptides for HF hospitalization adjudication is critically important and follows naturally from the class I guideline recommendation about natriuretic peptide usefulness in diagnosis.

Table 4 summarizes characteristics a biomarker should possess for use as a clinical trial surrogate end point. At present, no biomarker satisfies these criteria.

### Biomarkers to Assess Subgroup Effects in HF Clinical Trials

Biomarkers can be used to gain further insights into various subgroups after trial completion, and they may help to generate hypotheses for future studies. Indeed, this is one of the most common sources of studies of biomarker testing from HF trials. Retrospective study of biomarkers in this manner may reveal insights into (1) direct mechanism of drug action, (2) benefits of a drug downstream to its mechanism of action, or (3) identification of subgroups or specific phenotypes of patients that might derive differential benefit (Table 5).

A retrospective study was performed from the blood samples from the Randomized Aldactone Evaluation Study to explore the effects of spironolactone on tissue fibrosis. Serum collagen biomarkers decreased in the spironolactone group and validated the role of an aldosterone antagonist in tissue fibrosis. In particular, elevated baseline procollagen type III aminoterminal peptide was associated with an increased risk of death and of death/hospitalization notably, benefit of spironolactone in this trial was significant only in patients with above-median baseline levels of the collagen

markers.<sup>51</sup> Nonetheless, despite the statistically strong and biologically plausible findings from a large clinical trial, selecting patients for mineralocorticoid receptor antagonist therapy by the use of baseline collagen markers has not found any traction in clinical use.

Biomarkers may also provide understanding of benefit downstream to the mechanism of action such that biomarker concentrations may be used as a barometer for improvement of HF severity. This may be the most widely used application of biomarkers in clinical trials, frequently to justify the benefit of a novel therapy. For example, Metra et al<sup>57</sup> recently showed concentrations of numerous relevant prognostic biomarkers, such as NT-proBNP, hsTnT, and cystatin C, were all more significantly reduced among patients with acutely decompensated HF treated with serelaxin, compared with patients treated with placebo. In this trial, significant reduction in each of the cardiac biomarkers (NT-proBNP and hsTnT) during the treatment phase of the trial helped to potentially understand the mechanism of serelaxin at 180 days and any potential benefit it may provide.

Although no serum biomarker is routinely used clinically or recommended by guidelines to titrate or target therapy, the possibility of tailoring HF therapy to the individual by using a biomarker profile to optimize better outcomes and minimize therapy-related adverse effects can be envisioned in the future as we search for ways to reduce costs in a society with continuously increasing healthcare costs.

### Biomarkers as a Target for Therapy in HF Clinical Trials

A final role that biomarkers may play in HF trials is as a target for therapy. The concept is based on the observation that concentrations of biomarkers such as NT-proBNP may improve after therapy initiation or intensification in HF, and when such improvements occur, they are accompanied by improved prognosis. Guided therapy is based on a foundation of standard clinical care, but with a simultaneous goal to reduce biomarker concentrations.<sup>58</sup> Adjustment of therapies in HF has traditionally been based solely on achievement of target doses of therapeutics evaluated in trials, rather than targeting an individual's response to therapy using biomarkers. Nonetheless, given the challenges of delivering high-quality HF care to all affected patients, along with the inexorably rising tide of HF diagnosis, newer approaches to objectively guide care are being explored. With recent focus on personalization of care, so-called precision medicine, it is expected such strategies will be explored in more depth.

Biomarker-guided care has been previously described in detail<sup>59</sup> and thus far solely focused on the use of BNP or NT-proBNP.<sup>60</sup> Although the natriuretic peptides are not universally available globally, the use of both BNP and NT-proBNP has risen in the past decade to the point of ubiquity. Thus, the use of BNP or NT-proBNP to guide HF care may be reasonably expected to affect a broad population, although the results of previously conducted studies have been mixed.

Pilot studies suggest that, compared with standard care, NT-proBNP-guided HF care is well tolerated, may reduce HF events,<sup>61</sup> may improve quality of life,<sup>62</sup> and may result in improved left ventricular function.<sup>63</sup> It may also be

cost-effective.<sup>14</sup> Conversely, the trial of Intensified Versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF), the largest biomarker-guided HF trial in patients with reduced EF to date, had a neutral primary outcome of hospitalization-free survival.<sup>14,58</sup> Similarly, in the BATTLESCARRED trial (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) of patients with HFpEF, the primary outcome of total mortality and death or HF hospitalization was not improved with biomarker-guided HF therapy in the group as a whole.<sup>13,58</sup> The GUIDE-IT study (Guiding Evidenced Based Therapy Using Biomarker Intensified Treatment) is a large, multicenter study, currently underway. GUIDE-IT will examine the value of NT-proBNP-guided care with a primary end point of HF hospitalization/cardiopulmonary death. This trial has an inclusion criterion of NT-proBNP >2000 pg/mL before randomization, once again emphasizing the role of NT-proBNP both as an enrichment tool for event rates but also as a target for therapy.<sup>64</sup>

In order for a biomarker to be tested for guiding care, it must possess certain requirements that unify many of the role(s) previously discussed (Table 6). To date, only the natriuretic peptides satisfy many of these criteria; we are still awaiting the results of a definitive trial to use natriuretic peptides to guide therapy.

## Conclusions

Biomarkers are increasingly accepted for use as inclusion/exclusion criteria and to enhance the risk profile of the population sample and to enrich event rates, as potential tools to monitor safety or toxicity of therapeutics, as well as to possibly provide insight into how a specific patient cohort may benefit from a therapy in post hoc analyses. With growth of so-called precision medicine in modern clinical trials of HF therapeutics, the use of biomarkers in these varied roles may possibly grow.

## Sources of Funding

Dr Ibrahim is supported by the Dennis and Marilyn Barry Fellowship in Cardiology Research. Dr Januzzi is supported, in part, by the Hutter Family Professorship.

## Disclosures

Dr Gaggin has received grant support from Roche and Portola; consulting income from Roche Diagnostics, American Regent, Boston Heart Diagnostics and Critical Diagnostics; research payments for clinical end point committees for EchoSense. Dr Konstam has received grant support from Otsuka, has served as a consultant for Merck, for Johnson & Johnson, and for Janssen, and has chaired data monitoring committees on behalf of Amgen and Novartis. Dr Januzzi has received grant support from Siemens, Singulex, and Prevencio; consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Phillips, and Novartis; and participates in clinical end point committees/data safety monitoring boards for Novartis, Amgen, Janssen, and Boehringer Ingelheim. The other author reports no conflicts.

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### Established and Emerging Roles of Biomarkers in Heart Failure Clinical Trials

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*Circ Heart Fail.* 2016;9:

doi: 10.1161/CIRCHEARTFAILURE.115.002528

*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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