

Review Article

Biomarker-Guided Therapies in Heart Failure: A Forum for Unified Strategies

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ABSTRACT

The complexity of standard medical treatment for heart failure is growing, and such therapy typically involves 5 or more different medications. Given these pressures, there is increasing interest in harnessing cardiovascular biomarkers for clinical application to more effectively guide diagnosis, risk stratification, and therapy. It may be possible to realize an era of personalized medicine for heart failure treatment in which therapy is optimized and costs are controlled. The direct mechanistic coupling of biologic processes and therapies achieved in cancer treatment remains elusive in heart failure. Recent clinical trials and meta-analyses of biomarkers in heart failure have produced conflicting evidence. In this article, which comprises a summary of discussions from the Global Cardiovascular Clinical Trialists Forum held in Paris, France, we offer a brief overview of the background and rationale for biomarker testing in heart failure, describe opportunities and challenges from a regulatory perspective, and summarize current positions from government agencies in the United States and European Union. (*J Cardiac Fail* 2013;19:592–599)

Key Words: Pharmacogenetics, biologic markers, clinical trials, cardiovascular diseases.

Personalized medicine is the practice of obtaining non-obvious information, such as biomarkers, from an individual patient for the purpose of guiding therapeutic decisions tailored to that patient's needs. In the field of

oncology, biomarker testing is used to identify treatments for highly specific molecular targets to match effective therapies to specific populations, thereby improving tolerance to treatments with toxicity profiles that would be unacceptable in an unselected population.^{1–3} The clinical utility of biomarkers in the arena of cardiology is less clear, due in part to the fact that usual practice groups together several pathways leading to heart failure (HF) as well as the corresponding selection of therapies.

In addition, the heterogeneity of HF compared with a given type of cancer adds a complicating factor. Oncotype diagnostic assays use multimarker profiling to assess therapeutic options in oncology. Most of these profile somatic alterations (eg, estrogen receptor or HERG2 status in tumor cells) that are usually related to tumor cell mutations. In cardiology, however, genetic variants likely to influence therapeutic decisions are typically germline and as such only indirectly modify disease prognosis or response to therapy. Historical and biologic factors affecting the focus of research to date may also explain the relatively more thorough investigation of biomarkers in oncology. For instance, estrogen receptor status in breast cancer directly

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dictates treatment with tamoxifen, thus mechanistically linking the marker to a biologic process and treatment⁴—a success that has not yet been achieved in HF.

However, there are numerous reasons for exploring the use of biomarkers to guide therapy in HF, including challenges in optimizing therapy and utility for risk stratification and prognosis.⁵ In the present article, which includes a summary of discussions from the Global Cardiovascular Clinical Trialists Forum in Paris, France, we provide a brief overview of current evidence regarding biomarker-guided therapy and diagnosis and elucidate some of the challenges, opportunities, and rationales for future research in biomarker-guided therapy in HF. We focus primarily on circulating biomarkers and pharmacogenetics. Finally, we survey the current regulatory framework in this arena.

Rationales for the Use of Biomarkers in Heart Failure

Approximately 5.1 million people ≥ 20 years old in the USA live with chronic HF. An estimated 670,000 new cases are diagnosed annually among USA adults ≥ 45 years old, and HF causes or contributes to almost 300,000 deaths each year.⁶ Various demographic trends, including the aging of the population and greater likelihood of survival after acute myocardial infarction, suggest that the prevalence of HF will likely continue to increase; indeed, the American Heart Association estimates that by 2030, HF prevalence will increase by 25% over 2013 estimates.⁶ Although there have been significant advances in the treatment of HF, morbidity and mortality remain high. Pharmacologic regimens have become increasingly complex, and standard therapy now often consists of multiple drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, diuretics, digoxin, and, in African-American patients, hydralazine–isosorbide dinitrate). The economic impact is significant as well: Costs of HF hospitalizations amount to \sim \$29 billion/year in the USA alone.⁶

Heterogeneity in response to therapies warrants further research to identify biomarkers that can not only stratify risk but also identify the underlying disease process that may be targeted by specific therapies. Recognizing the heterogeneity of HF and dissecting it into different therapeutic groups would improve the targeting of interventions, which in turn could improve response rates and avoid adverse effects in patients unlikely to benefit. Studies have demonstrated the need to target specific phenotypes based on this heterogeneity.⁷ Better, more precise targeting of therapies could allow the focused use of those drugs most likely to be effective and safe in a given individual, thereby potentially enhancing compliance, improving outcomes, and lowering the cost of medical care.

Several small studies and a recent meta-analysis suggest better clinical outcomes with a biomarker-guided approach using natriuretic peptides.⁸ However, recent European Society of Cardiology (ESC)⁹ and American Heart Association/

American College of Cardiology guidelines¹⁰ for HF conclude that there is insufficient evidence to recommend biomarker-guided therapy in the management of HF patients. Therefore, in contrast to oncology, biomarker approaches are not yet routinely used in the management of HF.

Overview of Biomarker-Guided Approaches in Heart Failure

Biomarker testing in HF has typically sought to identify patients who may be being treated in suboptimal fashion rather than those who need a specific drug or device therapy. There are essentially 4 different kinds of biomarkers: prognostic, predictive, theranostic, and surrogate, as described in Table 1. A distinction between prognostic and predictive markers is worth noting: A marker is considered to be predictive if it shows differential benefit of a particular therapy based on marker status (eg, only patients with a given marker will respond well to a specific therapy); prognostic markers provide information about an outcome in the absence of therapy or portend an outcome different from that experienced by patients without the marker, regardless of therapy.^{11–13} Prognostic markers, therefore, are affected similarly under treatment: the higher (or lower) the marker, the better the outcome regardless of treatment; such markers may be used for risk stratification. Theranostic markers, which modify treatment effect in terms of relative risk, include a range of approaches, such as pretreatment identification of patient subgroups likely to respond to therapy or at higher risk of drug side effects, or monitoring of drug efficacy and safety once treatment begins. Predictive markers, however, have a significant interaction with a specific treatment. For example, those with high values of a predictive marker may have a better outcome with treatment than those with low values.

Statistical Considerations: Effect Models

An effect model describes the relationship between the risk with treatment (R_t) as a function (f) of the risk without treatment (R_c , for the risk in the control group of a randomized trial): $R_t = f(R_c)$. Prognostic markers modify the position of the patients on the untreated risk axis (R_c), whereas theranostic markers alter the prediction of treated risk (R_t) through the f function (Fig. 1).¹⁴ Building the complete effect model through the identification of relevant biomarkers and their role is an essential step toward the practice of personalized medicine. Cox and logistic models are examples that can be used for this purpose.

The reduction of risks of stroke and myocardial infarction by aspirin therapy in the context of primary prevention illustrates the modification of the effect model according to sex.¹⁵ Myocardial infarction is reduced in men (relative risk [RR] 0.68, 95% confidence interval [CI] 0.54–0.86) but not in women (RR 0.99, 95% CI 0.83–1.19). Risk of stroke, however, is reduced in women (RR 0.81, 95% CI 0.69–0.96) but increased in men (RR 1.13, 95% CI

Table 1. Biomarker Types

Type	Description	Examples in Cardiovascular Disease
Prognostic markers	Measure increased risk of events	Age Natriuretic peptides LVEF Troponin Gal-3 ST2 GDF-15 HDL/LDL cholesterol QSOX1
Predictive markers	Used to make treatment decisions	VKORC1 (warfarin) CYP2C9 (warfarin) CYP2C19 (clopidogrel) QRS duration (ICDs)
Theranostic markers	Modify treatment effect in terms of relative risk	LVEF (preserved vs reduced) Heart rate (ivabradine) LBBB (CRT)
Surrogate markers	Part of the mechanism of action of the treatment, and where utility resides in guiding therapy during follow-up	Blood pressure LDL cholesterol Serum creatinine Hemoglobin A1c

CYP2C9, Cytochrome P450 2C9; CYP2C19, Cytochrome P450 2C19; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; HDL, high-density lipoprotein; ICD, implantable cardioverter/defibrillator; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; QSOX1, quiescin-Q6.

0.96–1.33). Thus, sex plays the role of theranostic marker for the benefit of aspirin, depending on the outcome considered.

Pharmacogenetics in Heart Failure

Beta-blockers are a cornerstone of chronic HF therapy.¹⁶ However, they may be poorly tolerated or less effective in some patients, making this a logical possibility for a genetically guided approach. The β 1-adrenergic receptor (AR) position 389 Arg/Gly polymorphism has been widely examined. Most studies have been small and characterized by a number of limitations, and they have reported conflicting results regarding effects on disease risk, disease progression, and response to treatment.^{17–21}

Two large phase III randomized trials of beta-blockers in HF—the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF)²² and the Beta-Blocker Evaluation of Survival Trial (BEST)¹⁸—included DNA substudies that examined this polymorphism. In MERIT-HF, no effect of the polymorphism was observed

on the combined end point of time to all-cause mortality or HF hospitalization in either the placebo or the metoprolol succinate groups. In contrast, BEST showed a substantial effect of the polymorphism on response to treatment with bucindolol, likely owing to a pharmacologic interaction with the effects of bucindolol, with no effect on HF or arrhythmia end points observed in the placebo group.¹⁸

More recent studies have shown no difference in outcomes by genotype in patients treated with metoprolol or carvedilol.²¹ The basis for the apparent interaction of the β 1 389 Arg/Gly polymorphism with bucindolol, which is not found with carvedilol or metoprolol, likely resides in the unique pharmacologic properties of bucindolol,^{16–18} but further studies are needed to elucidate this issue.

Polymorphisms in the renin-angiotensin-aldosterone system (RAAS) have also been examined,^{23,24} and explorations aimed at identifying treatment selection and dosing with these genetic variations are in process.^{25–27}

Other areas of nonpharmacologic investigation include pharmacogenetic associations with response to exercise,²⁸

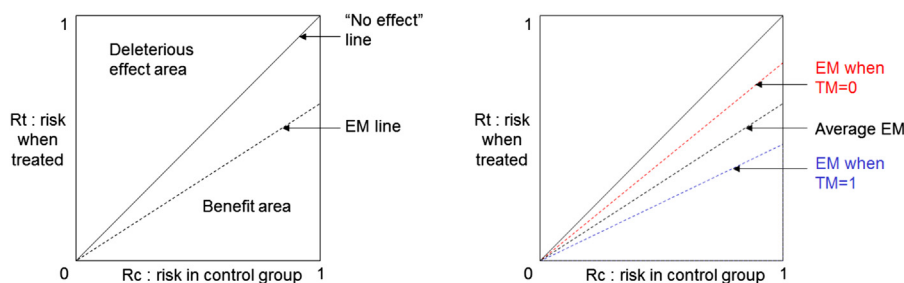


Fig. 1. Among possible models, the multiplicative effect model (EM) assumes that relative risk ($RR = R_t/R_c$) associated with treatment is constant whatever the baseline risk; the “ f ” function is the multiplication by RR ; theranostic markers (TMs) may be associated with different RR .¹⁴

as well as implantable cardiac defibrillators²⁹ and biventricular pacing in HF. However, the clinical utility of pharmacogenetic testing in cardiovascular patients remains challenging, as demonstrated by antiplatelet agents.³⁰ Fundamental questions remain about genotyping and the utility in modifying antiplatelet therapy on the basis of such testing.³¹

Research efforts are currently evaluating many other potential pharmacogenetic targets, including the α_2c -adrenergic receptor,³² endothelial nitric oxide synthase,³³ G-protein β_3 subunit,³⁴ acetylcholine receptor M2 gene,³⁵ G-protein-coupled receptor kinase variants,³⁶ and Corin polymorphisms.³⁷ Although research is progressing rapidly, further studies are necessary to establish genetic testing for targeting efficacy or safety with HF therapies.

Natriuretic Peptides

Among the available biomarkers in HF, natriuretic peptides (NPs) (both B-type NP [BNP] and the amino-terminal [NT-proBNP]) have accumulated the most evidence linking them to outcomes, although their optimal clinical application remains uncertain. Studies show that NT-proBNP levels on hospital admission predict long-term mortality and that patients whose NP levels decrease during acute hospitalization have a better prognosis than those whose levels do not change.³⁸

Following a small pilot study published in 2000,³⁹ a series of randomized trials, all of them relatively small and most single-blinded, examined the use of NP-guided therapy in patients with HF. They included the STARS-BNP,⁴⁰ TIME-CHF,⁴¹ SIGNAL HF,⁴² and PRIMA trials⁴³; the Vienna study⁴⁴; the BATTLESCARRED,⁴⁵ PROTECT,⁴⁶ UP-STEP,⁴⁷ and STARBRITE⁴⁸ studies; and a small ($n = 60$) trial by Anguita et al.⁴⁹ Primary results from these studies were published from 2007 to 2011. With the exceptions of SIGNAL HF and Anguita et al, the study comparisons showed an advantage for BNP-guided therapy over the comparator arm. In addition, the 2009 meta-analysis by Felker et al,⁸ which focused on findings reported from the Troughton et al,³⁹ STARBRITE, STARS-BNP, BATTLESCARRED, TIME-CHF, and PRIMA studies, found that the use of NP measurements as a guide for the titration of therapy in HF was associated with a $\sim 30\%$ reduction in mortality.⁸ However, the confidence intervals for the hazard ratios reported in the meta-analysis were in some cases wide, and most crossed the line of no effect (Fig. 2).⁸

As Felker et al noted, a clear indication for the role of NP-guided therapy in HF still awaits definitive elucidation in an adequately powered randomized trial.⁸ One such study is currently under way: the Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment (GUIDE-IT) randomized trial (ClinicalTrials.gov identifier NCT01685840), which opened to patient enrollment in December 2012 and is expected to include $\sim 1,100$ participants. In addition, midregional pro-A-type NP (MR-proANP) has recently emerged as a biomarker with prognostic potential in early trials.⁵⁰

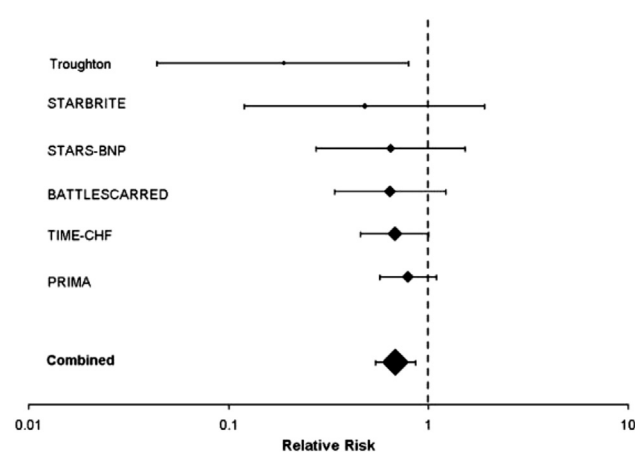


Fig. 2. Forest plot of all-cause mortality among patients with heart failure randomized to biomarker-guided therapy versus control. Reprinted from *Am Heart J*, 158, Felker GM, Hasselblad V, Hernandez AF, O'Connor CM, Biomarker guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials, 422-30, 2009, with permission from Elsevier.

Other Biomarkers in Heart Failure

A number of other biomarkers have been associated with an increased risk of poor outcomes in patients with HF, including ST2, galectin-3, growth differentiation factor-15, c-reactive protein, neutrophil gelatinase-associated lipocalin, copeptin, malondialdehyde, and others,⁵¹⁻⁵⁹ but none has an established indication for risk stratification in current HF guidelines. More recently, mass spectrometry assays applied to protein-based biomarker discovery have yielded a new potential diagnostic biomarker for acute decompensated HF: the quiescin-Q6 (QSOX1) protein.⁶⁰ Some studies have shown that some of these biomarkers might be used to guide therapy, although no prospective studies have been performed to test this strategy.⁶¹⁻⁶⁴

In recent years, it has become evident that alterations in gene and protein expression underlie the disease process and determine its progression as well as outcomes. The use of “omics”-based biomarker approaches offers the opportunity to predict the disease phenotype, develop companion diagnostics, and make specific treatment decisions. In HF, several omics-based biomarkers have been identified and show promise for patient stratification and guided therapy. These include genomics, transcriptional profiling (especially microRNAomics), proteomics, and metabolomics. Rather than a single approach, the integration of genomic, proteomic, and patient characteristics (phenotype) into a single model may be the first step toward better models for predicting response to therapy and outcomes, ie, “personalized medicine.”

Better biomarkers are urgently needed to improve screening, diagnosis, and monitoring of diseases; for guiding molecularly targeted therapy; and for monitoring therapeutic response, especially in syndromes such as HF that are clinically and pathophysiologically heterogeneous and frequently associated with multiple comorbid conditions.

Interpreting Findings in Biomarker Research: Issues to Consider

There are a number of issues to consider when interpreting the data. The first is the concept of regression to the mean, which is evident in biomarker-guided investigations in which the largest studies have been neutral or negative. However, results from a meta-analysis of biomarker-guided therapies in HF still indicated an overall benefit.⁸ These contradictory findings—which may themselves possibly arise from a variety of causes, including publication and/or reporting bias—highlight the unmet need for a robustly powered study that can definitively determine whether guiding therapy based on serial measurement of NPs improves outcomes in HF.

Second, it has been suggested that younger patients in these trials may experience greater benefit than older patients,^{41,65} further underscoring the need for evaluation in a large sufficiently powered trial. Critics of biomarker-guided approaches argue that providers should titrate drugs and use evidence-based therapies regardless of BNP values. Although data suggest that there is room for improvement in maximizing evidence-based therapies,^{66,67} a growing body of evidence supports biomarkers as surrogates, though this remains to be validated.

Finally, there is concern that the results have been unpredictable.^{68,69} One possible explanation might be that in biomarker-guided studies, it is assumed that the patients with the highest levels of a biomarker are likely to benefit more than those with lower levels. Several studies suggest that this might not be true, and that in fact those with higher biomarker levels could be too sick to benefit from therapy and those with lower levels are more able to benefit.⁶⁸ Therefore, developing biomarker-guided therapies requires careful consideration of what patients to target, whether the target goals are correct (using absolute values versus percentage reductions), and a number of issues relating to trial design.

In addition, challenges exist surrounding the validation of biomarkers for use in clinical practice, including: discrimination (the ability to separate low- and high-risk individuals) and calibration (the ability to accurately predict the level of risk) for a prognostic marker; reproducibility of the interaction between treatment effect and level of a predictive marker (are the ratios between hazard ratios, odds ratios, or relative risks in the presence or absence of the biomarker reproducible between studies?); and prediction (does the level of surrogate on treatment predict the clinical benefit?) and capture

(does the level of surrogate on treatment explain the observed clinical benefit?) as essential properties for surrogate markers. Table 2 summarizes a series of key steps in validating candidate biomarkers for use in clinical practice.⁷⁰

Approvability of Biomarker-Guided Therapy

A number of regulatory issues must be considered in the context of studies of biomarker-guided therapy. In particular, the generalizability of the findings is of critical importance. What were the inclusion and exclusion criteria of the population studied? Are there cultural patterns to care that preclude the use of biomarkers?

Other key issues are the risk of treatment and the need to adjust doses. This is relevant when the treatment involves exposure-based dosing, where there is an expectation of a link between exposure and outcome. For example, there is no utility in testing renin levels to adjust or administer RAAS inhibitors. Why consider testing when patients should be treated anyway? To return to our contrasting example of oncology, in the arena of cancer therapy, decisions largely depend on a risk-benefit balance for choosing treatment options. Because agents are typically highly toxic, such an approach becomes valuable in the decision matrix. In cardiology, treatments are generally safer, and the weight of evidence supports the risk-benefit ratio in favor of benefit. Additionally, biomarkers most commonly used in oncology are products of the primary cause of the disease (ie, tumor cells), rather than indirect downstream modulators as is typically the case with cardiovascular markers.

Finally, safety issues should be addressed. First, can the marker allow risk to be avoided? Or, in other words, can it identify patients in whom the treatment should not be used or identify who should titrate to higher doses or those who may be more sensitive? Second, when guiding therapy with markers, is there a risk that aggressive adjustment of indicated therapies may cause harm? Furthermore, the ability to select optimal therapeutic agents for a given patients could improve adherence to medication and expose patients to smaller numbers of drugs. A number of new trials and initiatives will provide important information on these questions.

Funding Opportunities: United States and European Union

The National Heart, Lung, and Blood Institute (NHLBI) and the EU Research and Innovation Directorate General

Table 2. Phases of Evaluation of a Novel Risk Marker

1. Proof of concept: Do novel marker levels differ between subjects with and without outcome?
2. Prospective validation: Does the novel marker predict development of future outcomes in a prospective cohort or nested case-cohort/case-cohort study?
3. Incremental value: Does the novel marker add predictive information to established standard risk markers?
4. Clinical utility: Does the novel risk marker change predicted risk sufficiently to change recommended 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?

Reproduced with permission from Hlatky et al.⁷⁰ Reprinted from *Circulation*, 119, Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association, 2408-16, 2009, with permission from Wolters Kluwer Health.

representatives presented goals and visions regarding personalized medicine. Notably, the alignment of these agencies is encouraging and may provide a framework for global collaborative efforts. The EU Framework Programme for Research and Technological Development has devoted a great portion of available funding to research in health initiatives.⁷¹ Personalized medicine is one area identified as a priority for funding research, which would include the creation of networks among academic institutions, industry, regulatory agencies, patient representatives, and other stakeholders. Examples include the European Commission Seventh Framework Programme for Research (FP7) and projects such as Biostat-CHF (www.biostat-CHF.eu) and Heart Omics in Ageing (HOMAGE).⁷²

To identify bottlenecks in progress and propose solutions for future activities, a number of workshops were organized, and a Personalized Medicine Conference was convened in May 2011.⁷³ Challenges identified included: 1) generating knowledge and developing the right tools; 2) translation to clinical applications; 3) breaking down barriers and speaking the same language; and 4) economic impact, with a need for studies and standard methodologies. The “time for action” in personalized medicine comes in the context of defining a common strategic framework for research and innovation activities: Horizon 2020.⁷⁴

The NHLBI vision of the development of personalized medicine is remarkably similar. The NHLBI Strategic Plan includes a mandate to develop personalized preventive and therapeutic regimens for cardiovascular conditions and lung and blood diseases.⁷⁵ Funded programs include research initiatives in systems biology, genomics, fundamental discoveries, and clinical applications. The nongovernmental Foundation for the National Institutes of Health supports the Biomarkers Consortium, a public-private partnership with multiple industry sponsors. The Consortium is designed to model biomarkers of atherosclerosis in an effort to facilitate development of new drugs that may have incremental therapeutic benefit in the era of widespread statin use. This type of a collaborative approach might also be applied in integrating biomarker data in HF. The NHLBI hosted working groups on personalized medicine and cardiovascular pharmacogenomics in 2011.^{76,77} Participants recommended the inclusion of DNA collections in NHLBI-funded clinical trials, as is being done in the Heart Failure Clinical Research Network. Finally, dissemination and sharing of existing data, as is done for genetic data in the National Institutes of Health—funded Database of Genotypes and Phenotypes (dbGaP)⁷⁸ remain a crucial foundation for advancing our understanding of the personalized approach.

Conclusion

Research evaluating personalized medicine through multi-marker profiling in HF is proceeding, but a number of challenges remain despite the potential benefits. There are still questions regarding the level of evidence needed to support product approval and labeling. Government agencies are

encouraging and supportive, and understand the need for innovative treatment approaches. High annual mortality, high morbidity, and heterogeneity of response to treatment underscore the need for predictability of response in this patient population. Although biomarker testing is not routinely being used to guide therapy in HF, we believe this treatment approach is not too distant. Certainly the data are supportive, but further research is warranted to strengthen the approach.

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