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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Manuscript received February 20, 2013; revised manuscript received May 16, 2013; revised manuscript accepted May 20, 2013.

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See page 597 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2013.05.012

dictates treatment with tamoxifen, thus mechanistically linking the marker to a biologic process and treatment[4]—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 ∼$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 guidelines[10] 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 (Rt) as a function (f) of the risk without treatment (Rc, for the risk in the control group of a randomized trial): $Rt = f(Rc)$. Prognostic markers modify the position of the patients on the untreated risk axis (Rc), whereas theranostic markers alter the prediction of treated risk (Rt) 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