Pharmacogenetics in Heart Failure Trials

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KEYWORDS

• Pharmacogenetics • Adrenergic receptors • Heart failure
• Clinical trials

Personalized medicine is a growing theme in clinical trials and research initiatives, stimulated by a variety of factors including funding opportunities supported by government agencies, a need for novel therapeutic approaches, and a growing body of literature linking genetic variation to clinical outcomes. Personalized medicine is fundamentally about obtaining information from an individual's genome and using it to make therapeutic decisions tailored to the individual. A natural starting point for personalized medicine is pharmacogenetics: using genetic information to predict an individual's response to therapy, both in terms of efficacy and safety.

In oncology, the therapeutic index of anti-cancer agents can, in some settings, be improved by pharmacogenetic targeting.[1–5] In human immunodeficiency virus, pharmacogenetic markers can be used to predict drug safety.[6] As knowledge of appropriate use and clinical usefulness of companion genetic testing matures, pharmacogenetic strategies can be incorporated into therapeutic guidelines.

In cardiology, genetic variations have been associated with hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), where genetic variants can help identify patients more likely to experience adverse effects.[7] Variations in cytochrome P450 genes may alter an individual's ability to metabolize drugs. In cardiology, this is highly relevant to anticoagulant and antithrombotic therapies, and may increase bleeding risk in certain patients. In August 2007, the US Food and Drug Administration approved revision of warfarin labeling to include genetic testing,[8] because 2 genetic variants predict response to therapy.[9] The VKORC1 allele predicts sensitivity to warfarin, and the cytochrome P450 2C9 gene variant predicts drug metabolism. Genetic variation has also been linked to clinical outcomes, such as the increased risk of ventricular arrhythmias and sudden cardiac death in patients with a β2 adrenergic receptor (AR) polymorphism.[10] Advances in technology and the ability to perform genome-wide association studies (GWAS) have increased our knowledge base and, in a short time, these studies have identified genetic determinants of disease risk in several therapeutic areas, including diabetes,[11–14] hyperlipidemia,[15–17] and atherosclerosis.[18,19]

HEART FAILURE

Heart failure is a major and growing public health problem, with more than 5 million people in the United States living with chronic heart failure, 550,000 new cases diagnosed each year, and approximately 300,000 deaths caused by heart failure.[20] A variety of demographic trends, including the aging of the population and greater survival after acute myocardial infarction, suggest that the prevalence of heart failure is likely to continue increasing.[21] Although there have been significant advances in the treatment of heart failure, there is a substantial need for greater targeting of heart failure therapy. Morbidity and mortality from heart failure remain high despite the improvements in therapy. Pharmacologic regimens have become increasingly complex, and standard heart failure therapy now frequently consists of 5 or more drugs. The economic impact of chronic heart failure

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hospitalizations is approximately $35 billion annually in the United States alone. Greater targeting of therapy would allow the focused use of drugs most likely to be efficacious and safe in individual patients, potentially enhancing compliance and improving outcomes.

PHARMACOGENETICS IN HEART FAILURE TRIALS

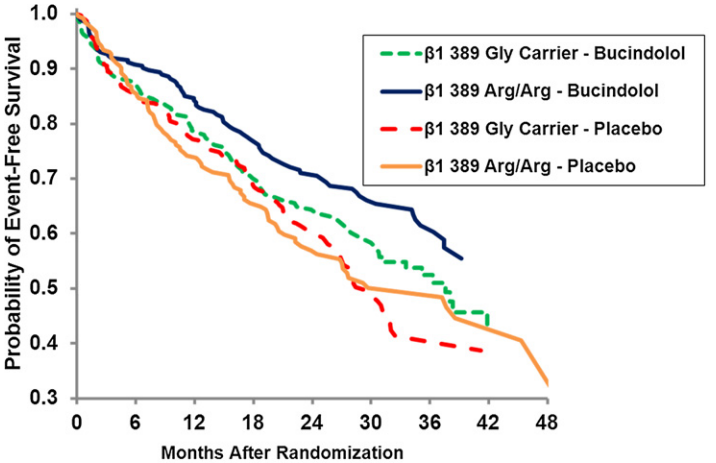
Polymorphisms of the β-ARs

β-blockers are one of the cornerstones of chronic heart failure therapy, with substantial impact on mortality and morbidity. However, β-blocker therapy is not efficacious, or is poorly tolerated, in some patients with heart failure, making this a logical possibility for genetically targeted therapy. The β1-AR position 389 Arg/Gly polymorphism, caused by a nucleotide 1165 C (Arg) to G (Gly) transversion, has been widely studied. The β1 389 Arg/Gly polymorphism alters signaling in multiple models, and may affect the β-blocker therapeutic response in heart failure.[22]

Studies have suggested that the β1 389 AR Arg/Gly polymorphism may have an impact on left ventricular ejection fraction improvement (LVEF) with β-blocker therapy,[23–27] but these studies have had several limitations and are not conclusive for clinical usefulness. Many smaller studies have examined this polymorphism, with conflicting results regarding the impact on disease risk, progression, and response to treatment.[28–30]

Two large (phase III) randomized, placebo-controlled heart failure trials with β-blockers, MERIT-HF, and the β-Blocker Evaluation of Survival Trial (BEST), included DNA substudies. The β1 389 Arg/Gly polymorphism was evaluated in both studies. The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) contained a 600-patient substudy testing the hypothesis that the β1 389 AR Arg/Gly polymorphism influenced the outcome of heart failure, or conferred a differential response to treatment with Metoprolol CR/XL.[31] Based on previous studies, the MERIT-HF substudy hypothesized that patients with the β1-389 AR Gly variant would have better outcomes, as measured by mortality and hospitalization. The investigators further hypothesized that patients with the β1-389 AR Arg allele would show a greater response to treatment with β-blockade. In this study, no effect of the polymorphism was observed in either a morbidity/mortality benefit or a response to metoprolol treatment.

In contrast, BEST showed a significant impact of the β1 389 AR Arg/Gly polymorphism on response to treatment with the β-blocker bucindolol. BEST contained a 1040-patient DNA substudy, evaluating improvement in morbidity/mortality by β1 AR genotype.[22] Patients who were β1 389 AR Arg homozygotes had significant improvements in cause-specific and all-cause morbidity and mortality compared with patients who were β1 389 AR Gly carriers. **Fig. 1** gives Kaplan-Meier curves for bucindolol or placebo in the β1 Arg/Arg or Gly carrier genotypes for the combined endpoint of all-cause mortality or heart failure hospitalization. For patients with the Arg/Arg genotype, there is a substantial (33%, hazard ratio



Subpop	Group 1 Event Rate	Group 2 Event Rate	HR and CI	*P* value
Bucindolol Treatment	Arg/Arg 87/257 (34%)	Gly Carrier 105/258 (41%)	0.77 (0.57 – 1.03)	.08
Placebo Treatment	Arg/Arg 102/236 (43%)	Gly Carrier 131/289 (45%)	0.99 (0.76 – 1.30)	.95
Arg/Arg Genotype	Bucindolol 87/259 (34%)	Placebo 102/236 (43%)	0.67 (0.50 – 0.89)	.005
Gly Carrier Genotype	Bucindolol 105/258 (41%)	Placebo 131/289 (45%)	0.86 (0.66 – 1.11)	.24

Fig. 1. All-cause mortality/heart failure hospitalization, BEST Trial DNA substudy.