Pharmacogenomics and the Failing Heart

Are We Waiting for Godot?*

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In Samuel Beckett’s play, Waiting for Godot, the characters wait by a country roadside for a person named Godot, who never arrives (1). Godot’s conspicuous absence throughout the play has fostered a variety of different religious, philosophical, and psychoanalytical interpretations, and has led to the use of the phrase “waiting for Godot” as an expression for waiting for someone or something that will never arrive. Over the past several years, a series of intriguing observations has arisen with regard to the role genetic variations (polymorphisms) in signaling pathways that contribute to disease progression in the failing heart (2,3). These observations have given rise to the hope that information regarding genetic polymorphisms might be harnessed to develop personalized therapeutic strategies for patients with heart failure. However, this type of genetic information has not been clinically useful thus far, insofar as many of the genetic associations that have been reported have not been independently replicated.

In this issue of the Journal, Sehnert et al. (4) report on the lack of association between adrenergic receptor genotypes and all-cause mortality and transplant-free survival in heart failure patients who were treated with 2 beta-blockers that have been shown to confer a survival benefit (metoprolol succinate and carvedilol) (5). The investigators identified 637 patients enrolled in 2 separate cardiovascular genetic registries who were discharged on beta-blockers, and a diuretic. Heart failure was defined by the presence of a left ventricular ejection fraction (LVEF) ≤40% and/or a history of heart failure at the time of heart catheterization. The investigators genotyped 5 polymorphisms in 3 genes (Table 1): the beta-1 adrenergic receptor (ADRB1) (Ser49Gly, Arg389Gly), the beta2-adrenergic receptor (ADRB2) (Gly16Arg, Gln27Glu), and a loss of function deletion mutation (α2C Del322_325) in the alpha2C-adrenergic receptor (ADRA2C). They analyzed the association of single-nucleotide polymorphisms (SNPs) and haplotypes for ADRB1, ADRB2, and ADRA2C with respect to the clinical end points of all-cause death and/or transplant-free survival. Importantly, there was no significant effect of SNPs or haplotypes of ADRB1, ADRB2, and ADRA2C genes on all-cause death or transplant-free survival in either the metoprolol-treated or carvedilol-treated heart failure patients. To address the potential significance of this study vis-à-vis the quest to develop personalized genomic strategies for treating patients with heart failure, it is useful to discuss what is known about genetic variations in adrenergic signaling and the failing heart.

Genetic variations in the adrenergic signaling pathway.

Although activation of the adrenergic activation serves to enhance and/or stabilize myocardial performance in the failing heart, excessive myocardial adrenergic signaling is frankly cardiomyopathic, and is believed to contribute to disease progression in heart failure (5). Indeed, the beneficial effects of beta-blocking agents seem to be caused by their ability to prevent the deleterious effects of catecholamines on the heart and the circulation. However, clinical studies have also shown that beta-blocker therapy often produces variable responses among patients with heart failure (6). Given the existence of genetic polymorphisms in the ADRB1, ADRB2, and ADRA2C genes (Table 1), it has been suggested that genetic variations in individuals may account for, at least in part, the variable responses to beta-blockers in heart failure patients (6). For example, beta-blockers would be expected to be more beneficial in patients carrying genotypes associated with higher, rather than lower, activity of the ADRB1 gene. As shown in Table 1, a common SNP in the ADRB1 gene, Arg389Arg, leads to enhanced ADBR1 signaling. The ADRA2C deletion mutation leads to a reduction in inhibition of norepinephrine release from the pre-synaptic nerve terminals by α2C receptors, and therefore results in increased adrenergic drive. In contrast to ADBR1 polymorphisms, the investigation of ADBR2 polymorphisms seems less consistent in heart failure, and there is less evidence of their influence on the effectiveness of beta-blockade (7).

Although a number of studies have examined the role of pharmacogenetic interactions of beta-blockers with respect to changes in LVEF and cardiac remodeling (reviewed in Shin and Johnson [6] and Muthumala et al. [7]), there are only a few studies that have examined pharmacogenetic interactions of beta-blockers in relation to clinical end...
points such as death and/or heart failure hospitalization. In a substudy of the MERIT HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure), in which 307 patients on metoprolol and 293 patients on placebo were genotyped for polymorphisms in the \(\text{ADRB1}\) gene and followed up for 12 months, there was no association between the \(\text{ADRB1}\) genotype and all-cause death and/or hospitalization \(8,9\). Although this study suggests that there is a lack of interaction between genotype and beta-blockers for clinically meaningful outcomes, it bears emphasis that this substudy compared outcomes between \(\text{ADRB1}\) genotypes irrespective of their treatment assignment, which makes it difficult to evaluate the genetic association of clinical outcomes relative to beta-blocker therapy. In contrast, the BEST (Beta-blocker Evaluation of Survival Trial) showed a significant reduction in mortality and heart failure hospitalization in bucindolol-treated versus placebo-treated heart failure patients who were homozygous for the Arg389Arg \(\text{ADRB1}\) allele \(9\). Notwithstanding the important pharmacological differences between bucindolol, used in the BEST trial, and metoprolol succinate and carvedilol, used in the registry study by Sehnert et al. \(4\), there are several significant differences between prospective clinical trials and cohort registries that are important when interpreting clinical outcomes in pharmacogenomic studies. The most obvious difference is that in prospective clinical trials the patients are randomized to control and treatment groups, are carefully clinically phenotyped at the time of entry into the study, and are then closely followed up longitudinally. In contrast, in registry studies the patients are not randomized and many details regarding clinical phenotyping and background therapies are often not available. These types of differences can lead to potential bias and/or confound the results of the study. For example, if a given SNP in the adrenergic pathway leads to hyperactivation of a beta-receptor \(\text{e.g.}, \text{389Arg389}\), and this hyper-function confers an adverse outcome that is eliminated by beta-blockers, then it is not possible to determine any effect of beta-blockade if all of the patients were receiving beta-blockers. Thus, by virtue of using modern clinical registries in which all of the heart failure patients were receiving beta-blockers, Sehnert et al. \(4\) were less likely to observe important pharmacogenetic interactions between beta-blockers and the \(\text{ADRB}\) genotype. Moreover, there was no information regarding the dose of neurohormonal antagonists that were used during the study, and/or whether these agents were up-titrated to doses that have been shown to produce clinical benefits in heart failure patients. Similarly, although it was possible to confirm that at least half of the patients were taking beta-blockers at 60 days after being registered in the study, it was not clear from the database that patients were compliant with their beta-blockers at the time of death and/or cardiac transplantation. Given that the salutary effects of beta-blockers are dose-dependent and time-dependent, it becomes difficult to draw firm conclusions regarding potential pharmacogenomic interactions and heart failure outcomes. Thus, the study by Sehnert et al. \(4\), although thoughtfully analyzed and presented, cannot be viewed as definitive with respect to the lack of association between \(\text{ADRB}\) genotypes and survival in heart failure patients treated with either carvedilol or metoprolol. That said, it may well be that analyses of SNPs will never completely predict drug responsiveness in a disease as complex as heart failure, in which case the heuristic value of the study by Sehnert et al. \(4\) is that it illustrates the importance of designing, funding, and conducting prospective genome-wide association studies that will better define the role of pharmacogenomics in patients with heart failure. . . . lest we remain waiting for Godot.

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### Table 1. Effect of Gene Polymorphisms on the Pharmacological Treatment of HF

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Functional Impact</th>
<th>Impact on Pharmacological Therapy</th>
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<tbody>
<tr>
<td>(\text{ADRB1})</td>
<td>Arg to Gly switch at codon 389 ((\text{Arg389Gly}))</td>
<td>Arg389 allele has 3\times greater adenyl cyclase activity in response to agonist than the Gly389 variant</td>
<td>Arg389Arg genotype better tolerated during the initiation of beta-blockers and had greatest improvement in LVEF with beta-blockers, and improved mortality with bucindolol in BEST</td>
</tr>
<tr>
<td>(\text{ADRB1})</td>
<td>Ser to Gly switch at codon 49 ((\text{Ser49Gly}))</td>
<td>Ser49 allele has decreased agonist-promoted down-regulation and decreased adrenergic coupling</td>
<td>Ser49G9r genotype requires higher doses of diuretics during beta-blocker up-titration</td>
</tr>
<tr>
<td>(\text{ADRB2})</td>
<td>Gly to Arg switch at codon 16 ((\text{Gly16Arg}))</td>
<td>Gly16 allele has greater agonist-promoted down-regulation</td>
<td>No reported interactions with beta-blockers</td>
</tr>
<tr>
<td>(\text{ADRB2})</td>
<td>Gin to Glu switch at codon 27 ((\text{Glu27Arg}))</td>
<td>Glu27 allele is resistant to receptor down-regulation</td>
<td>Glu27 homozygotes have improved LVEF with carvedilol compared with Glu27 carriers</td>
</tr>
<tr>
<td>(\text{ADRA2C})</td>
<td>Deletion mutation of aa 322-325 ((\text{2CDel322-325}))</td>
<td>Loss of function mutation leading to decreased NE uptake</td>
<td>Increased likelihood of developing HF in patients with the beta,AR Arg389 polymorphism; effect on drug responsiveness in HF not known</td>
</tr>
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\(\text{Arg} = \text{arginine}\); \(\text{BEST} = \text{Beta-blocker Evaluation of Survival Trial}\); \(\text{Gln} = \text{glutamine}\); \(\text{Glu} = \text{glutamic acid}\); \(\text{Gly} = \text{glycine}\); \(\text{HF} = \text{heart failure}\); \(\text{LVEF} = \text{left ventricular ejection fraction}\); \(\text{NE} = \text{norepinephrine}\); \(\text{Ser} = \text{serine}\).
REFERENCES