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Heart Failure Pharmacogenetics: Past, Present and Future

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Abstract

Heart failure is an increasingly common disease associated with significant morbidity and mortality in the aging population. Recent advances in heart failure pharmacotherapy have established a number of agents as beneficial to disease progression and outcomes. However, current consensus guideline recommended pharmacotherapy may not represent an optimal treatment strategy in all heart failure patients. Specifically, individuals with genetic variation in regions central to mediation of beneficial response to standard heart failure agents may not receive optimal benefit from these drugs. Additionally, targeted approaches in Phase III clinical trials that select patients for inclusion based on the genotype most likely to respond might advance the currently stalled drug development pipeline in heart failure. This article reviews the literature in heart failure pharmacogenetics to date, opportunities for discovery in recent and upcoming clinical trials, as well as future directions in this field.

Keywords

heart failure; pharmacogenetics; left ventricular ejection fraction; β -blocker; ACE inhibitor; mortality

Introduction

Heart failure is the most common cause of hospitalization in individuals over age 65, and affects approximately 5 million Americans. Between the late 1980's and 2000, there were marked advances in heart failure pharmacotherapy, with angiotensin converting enzyme (ACE) inhibitors, β -blockers, aldosterone antagonists and the combination of hydralazine/nitrates all being documented to reduce mortality in heart failure. Since then ACE inhibitors (or angiotensin receptor blockers (ARBs)) and β -blockers have become standard therapy in nearly all patients with systolic heart failure, with aldosterone antagonists and hydralazine/nitrate being recommended in selected patients.¹ Numerous other promising drug classes have been studied over the last 15 years, but none have been able to document efficacy in the background of these standard therapies.

Pharmacogenetics/pharmacogenomics is a field that aims to identify the genetic predictors of response to drug therapy, with the potential of leading to genetically-targeted therapies, or advancing our understanding of the mechanisms of benefit. A number of pharmacogenetic investigations have been conducted in heart failure, with the majority to date focused on β -

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blockers. Herein we provide a summary of the literature, particularly the recent advances in the field, discuss the future of heart failure pharmacogenomics, and highlight how use of pharmacogenomics data might be a tool for identifying patient groups in whom to target novel drug therapy development.

Heart Failure Pharmacogenetics to Date

β -blocker Pharmacogenetics

The vast majority of pharmacogenetic literature in heart failure to date addresses genetic associations with response/outcomes with β -blocker therapy. The pharmacologic action of β -blockers is derived from competitive inhibition of sympathomimetic neurotransmitters at β -adrenergic receptors. The use of β -blockers in heart failure has demonstrated beneficial effects on both survival and disease progression, and is considered mandatory therapy in patients with systolic heart failure who lack contraindications.^{1–4}

β -adrenergic receptors are G-protein coupled receptors expressed in the heart at a concentration ratio of 70:30 β_1 to β_2 .⁵ The β_1 -adrenergic receptor is the primary subtype present on cardiomyocytes and is largely responsible for acute increases in cardiac performance seen with adrenergic activation.⁵ As shown in Figure 1, the β_1 -adrenergic receptor couples to the stimulatory G-protein (G_s) and is subject to downregulation in response to elevated norepinephrine concentrations. G_s activation initiates a signaling cascade with subsequent activation of adenylyl cyclase, increase in cAMP and activation of protein kinase A (PKA). PKA targets a number of downstream effectors within the cardiomyocyte that facilitate both inotropic and chronotropic actions. The less commonly expressed β_2 -receptor activates both the inhibitory G-protein (G_i) and G_s and is not sensitive to agonist mediated downregulation. Activation of G_i is associated with signals mediating cell survival, countering apoptosis induced by G_s activation.⁶

Genetic association of β -adrenergic receptor SNPs with β -blocker induced left ventricular functional improvements

ADRB1—The gene encoding the β_1 -adrenergic receptor, *ADRB1*, contains two common nonsynonymous single nucleotide polymorphisms (SNPs). An arginine to glycine switch at codon 389 of *ADRB1* (Arg389Gly) is located proximal to the cytoplasmic tail of the β_1 -adrenergic receptor, a region identified as important for receptor coupling to the G_s -protein. Based on functional data supporting increased receptor activation for the Arg389 form of the receptor, it was predicted that Arg389 allele carriers would derive greater benefit from β -blocker pharmacotherapy.^{7–9}

Studies testing this hypothesis in heart failure fall into two categories; those focusing on prognostic indicators such as left ventricular ejection fraction (LVEF), and those centered on outcomes such as death or cardiac transplantation. Results of these studies are summarized in Table 1.

A retrospective analysis of 224 carvedilol treated heart failure subjects showed greater improvement in LVEF with Arg389Arg homozygotes and Arg389Gly heterozygotes compared to subjects homozygous for the Gly389Gly genotype ($8.7 \pm 1.1\%$ vs. $7.0 \pm 1.5\%$ vs. $0.93 \pm 1.7\%$, respectively; $p < 0.02$).⁹ A separate cohort of 135 carvedilol treated patients showed Arg389Arg subjects had significantly greater improvement in LVEF compared to Gly389 carriers (Arg389Arg 18.8%; Arg389Gly 9.4%; Gly389Gly 6.0%; $p < 0.001$).¹⁰ Another smaller study of 54 metoprolol treated patients also found a consistent association, showing Arg389Arg subjects to have a significant improvement in LVEF ($p = 0.008$), whereas Gly389 carriers experienced no significant change in LVEF ($p = 0.45$).¹¹

In contrast to these findings, several studies have not observed greater LVEF improvements in Arg389Arg patients. A prospective cohort study of 199 subjects treated with 3 months of maximally tolerated doses of bisoprolol or carvedilol saw no associations with change in LVEF and β -adrenergic receptor polymorphisms.¹² Another study of carvedilol in 183 subjects did not find a significant association between LVEF and *ADRB1* codon 389, although increase in LVEF after treatment tended to be greater in Arg389Arg and Arg389Gly carriers compared to Gly389Gly homozygotes.¹³ Similarly, no significant changes in LVEF by *ADRB1* codon 389 genotype were observed among bucindolol treated β -Blocker Evaluation of Survival Trial (BEST) participants.¹⁴

Overall, several but not all studies show a significant association between *ADRB1* genotype and improvement in LVEF. However, in all studies with a positive association, the Arg389Arg homozygotes always have the most favorable response.

ADRB2—*ADRB2* is an intronless gene encoding the β_2 -adrenergic receptor. The Arg16Gly polymorphism has been associated with enhanced agonist promoted downregulation while β_2 -adrenergic receptors containing the Gln27Glu substitution were found to be resistant to downregulation.^{15, 16} The Gln27Glu polymorphism has been associated with change in LVEF in independent carvedilol treated heart failure cohorts.^{17, 18} Published in 2010, Metra, et al. showed Glu27Glu homozygous subjects treated with carvedilol experienced greater increase in LVEF compared to Gln27 carriers.¹³ A previous assessment in 80 subjects receiving carvedilol for at least 4 months found Glu27 allele prevalence was significantly greater among good responders to carvedilol versus poor responders to therapy.¹⁸ A good response in this study was identified as an absolute improvement of at least 10% in LVEF or 5% in left ventricular fractional shortening (LVFS). Finally, a small cohort study of 33 subjects showed Glu27 carriers had a significant improvement in LVEF, whereas Gln27Gln homozygotes did not.¹⁷ Despite small sample sizes, the significant beneficial effects of the Glu27 allele on LVEF response to carvedilol therapy has been replicated, in differing degrees, within three independent cohorts. Overall, the data suggest a possible role for both *ADRB1* and *ADRB2* nonsynonymous polymorphisms in the improvement in LVEF with β -blocker therapy.

Genetic association of β -adrenergic receptor SNPs with heart failure outcomes relative to β -blocker therapy

ADRB1—Class III/IV heart failure *ADRB1* Arg389Arg homozygous BEST participants treated with bucindolol experienced a 38% reduction in mortality compared to placebo (HR, 0.62; 95% CI, 0.40–0.96; $p = 0.03$).¹⁴ With the same comparison, however, Gly389 carriers did not show evidence of clinical response to bucindolol compared to placebo (HR, 0.90; 95% CI, 0.62–1.30; $p = 0.57$).¹⁴ The effect on hospitalization was consistent with these data, as Arg389Arg homozygotes had a decrease in hospitalizations with bucindolol compared to placebo (HR, 0.64; 95% CI, 0.46–0.88; $p = 0.006$) and Gly389 carriers again showed no benefit with bucindolol over placebo (HR, 0.86; 95% CI, 0.64–1.15; $p = 0.30$).¹⁴ In a cohort study of 201 Brazilian heart failure patients, Arg389 carriers had higher incidence of non-sustained ventricular tachycardia and worse heart failure survival than Gly389Gly homozygotes.¹⁹ This risk, however, was mitigated by high-dose β -blocker therapy, a finding that could be viewed as consistent with the BEST data, where the Arg389 is associated with greater treatment benefits from β -blocker therapy.¹⁹

In contrast to the above studies, several cohort studies did not find a significant association between genotype and treatment-related outcomes. Published in 2009, the largest prospective cohort study evaluating pharmacogenetic effects on heart failure outcomes in 2,460 patients found an increased mortality risk associated with Caucasian Gly389 allele

carriers not treated with β -blocker, although there was no significant difference in outcomes by genotype among β -blocker-treated patients.²⁰ The lack of a genetic association with outcomes among β -blocker treated subjects was also documented in an earlier cohort study, where Sehnert, et al. found no significant effect on transplant-free survival among β -blocker treated patients for polymorphisms within the adrenergic receptors.²¹ A genetic substudy of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) including 600 trial subjects randomized to metoprolol CR/XL or placebo also showed no association between *ADRB1* codon 389 genotype and clinical outcomes for the entire cohort.²² Notably, this analysis was not separated by treatment group, and a pharmacogenetic association with clinical outcomes would therefore be difficult to assess.

Most of the outcomes studies focused on *ADRB1* Arg389Gly, but one cohort study also evaluated the codon49 polymorphism. Found in the extracellular N-terminal region of the receptor, the serine to glycine switch at codon 49 of the β_1 -adrenergic receptor has been associated with Gly49 having increased agonist promoted down-regulation when compared to the more common Ser49 allele.²³ *ADRB1* Gly49 carriers receiving low-dose (less than 50% of full dose) β -blocker therapy had significantly lower 5-year mortality (RR, 0.24; 95% CI, 0.07–0.80; $p = 0.02$) compared to Ser49Ser patients.²⁴ Among those patients receiving high-dose therapy (greater than 50% of full dose), the 5-year mortality risk was not different by codon 49 genotype (RR, 0.27; 95% CI, 0.04–2.04; $p = 0.20$), suggesting great benefit among Ser49Ser with high versus low/no dose β -blocker.²⁴

While the data on Arg389Gly may seem conflicting, they may not be as conflicting as they appear. Specifically, BEST and the Brazilian cohort showed significant differences in outcomes when patients with a single genotype were compared relative to treatment vs. placebo (or no/low dose β -blocker). These analysis approaches allowed for the assessment of treatment benefit by genotype, and both suggested that the Arg389 genotypes accrued significant benefits from β -blocker therapy while Gly389Gly did not. In contrast, the other two cohort studies compared outcomes across genotype among patients treated with a β -blocker and were not able to observe a genetic association. While both are legitimate approaches to analysis, they address slightly different questions and one possible explanation for the apparent discrepancies is that the *ADRB1* genotype influences outcomes, and treatment with a β -blocker minimizes the risk of the genotype, thus resulting in no differences across genotypes among treated patients. Several other lines of evidence, discussed below, support this hypothesis. It is also possible that randomized controlled trials represent a superior mechanism for testing such hypotheses, as compared to cohort studies. Differences in the ancillary pharmacological properties of the β -blockers may also contribute.

The α_2 c-adrenergic receptor, *ADRA2C*

As highlighted in Figure 1, the α_2 c-adrenergic receptor (*ADRA2C*) is present on prejunctional sympathetic nerve terminals and is responsible for the release of norepinephrine, for which β -adrenergic receptors are the target. A four amino acid deletion polymorphism (Del322-325) in *ADRA2C*, disproportionately represented in the African American population, leads to a loss of receptor autoinhibition and with higher baseline adrenergic drive.^{25, 26} A synergistic effect between α_2 c Del322-325 and β_1 Arg389 receptor variants has also been shown to increase risk of heart failure in African Americans.²⁷ These data make this polymorphism particularly interesting as it relates to β -blocker pharmacogenetics. Published in 2010, BEST bucindolol treated *ADRA2C* Del322-325 carriers had a 3-fold greater decrease in norepinephrine concentrations at 3 months compared to subjects without the Del genotype.²⁸ Additionally, bucindolol therapy did not provide a survival benefit to *ADRA2C* Del322-325 carriers ($p = 0.80$), whereas those

subjects with the wild-type α_2c -receptor had a 30% mortality reduction with bucindolol vs. placebo ($p = 0.025$).²⁸ Within the BEST heart failure cohort, it is hypothesized that the norepinephrine lowering (sympatholytic) properties of bucindolol are enhanced by loss of function in prejunctional α_2c Del322-325 receptors.

An exaggerated decrease in norepinephrine in response to bucindolol therapy has been associated with a negative effect on mortality.¹⁴ As bucindolol is the only β -blocker with sympatholytic properties, a similar pharmacogenetic interaction would presumably not be replicated in the study of a different β -blocker that lacked this ancillary property.

This polymorphism was also evaluated in an earlier study of 54 metoprolol CR/XL treated heart failure patients.²⁹ Determinants of LVEF improvement included Del322-325 carrier status in addition to the Arg389Arg genotype. Patients with both Arg389Arg/Del322-325 carrier genotypes showed the largest increase in LVEF with metoprolol CR/XL therapy (whereas the opposite genotype group, Gly389-carrier/Ins/Ins, exhibited no improvement in LVEF).²⁹ In contrast to the BEST data, this study suggested Del322-325 carriers derive greater benefit from the β -blocker, this is consistent with the physiological and disease risk data described above, where Del322-325 increases norepinephrine release and Arg389Arg has a greater response to norepinephrine. Thus, it is not surprising that for β -blockers that lack sympatholytic properties (i.e. all the marketed β -blockers), it is possible that Del322-325 carriers might derive greater benefit as they likely have a greater baseline adrenergic activation.

G-protein coupled receptor kinase 5, *GRK5*

The G-protein coupled receptor kinase 5 (*GRK5*, *GRK5*) found in the heart facilitates the uncoupling and desensitization of ligand-occupied β -adrenergic receptors (Figure 1). A glutamine to leucine switch at codon 41 is the only polymorphism found in the coding region of *GRK5*. Transgenic mouse models have shown the Leu41-*GRK5* facilitates greater agonist-promoted desensitization of β -adrenergic receptors compared to the Gln41 genotype.³⁰ The data suggest the Leu41 genotype is a gain-of-function mutation that provides an effect similar to that of an endogenous β -blocker.³⁰ The *GRK5* Leu41 variant is enriched in populations of African descent and cohort study of 375 African-Americans with heart failure showed β -blocker naïve *GRK5* Leu41 carriers had significantly longer transplantation-free survival compared to β -blocker naïve *GRK5* Gln41 homozygotes. β -blocker treated *GRK5*-Gln41 homozygotes demonstrated longer transplantation-free survival times than those with the same genotype whom were β -blocker naïve (HR, 0.22; 95% CI, 0.12–0.40; $p < 0.001$). However, Leu41 carriers derived no benefit from treatment with β -blocker (HR, 0.78; 95% CI, 0.35–1.7; $p = 0.53$).³⁰

A second, larger prospective cohort study was published in 2009 evaluating heart failure outcomes in 2,460 patients relative to *GRK5* genotype at codon 41. Consistent with the previous *GRK5* study, Leu41 carrier status was associated with longer survival and a significant decrease in mortality following age and sex adjustment in African Americans not treated with β -blocker compared to Gln41Gln homozygotes (HR, 0.325; 95% CI, 0.133–0.796; $p = 0.01$). Also consistent with the previous study, Gln41Gln patients derived substantial survival benefit from treatment with β -blocker (when compared against untreated patients).

Clinical implications of the β -blocker pharmacogenetic data to date

Several studies suggest that the *ADRB1* polymorphisms, particularly Arg389Gly may influence response to β -blocker therapy; either improvement in LVEF or long-term outcomes, where Arg389Arg homozygous patients appear to derive the greatest benefits.

Two studies also showed associations with the *ADRA2C* Ins322-325Del polymorphism, and although directionally different in their associations, the findings are potentially explained by the differing pharmacology of the two drugs studied (bucindolol and metoprolol). Finally, two studies have suggested that the beneficial effects of β -blocker therapy primarily reside in those who are *GRK5* Gln41Gln homozygotes. Collectively, these data suggest that genetic polymorphisms in genes encoding the adrenergic receptors and their regulatory proteins may influence response to therapy. In most cases, these effects were most evident when comparisons were made between treated versus untreated patients with a given genotype.

Can these data be used clinically? Although they suggest some patients are probably deriving minimal benefit from β -blocker treatment, they are not sufficiently strong to warrant withholding a β -blocker, given the place of β -blockers in therapy in the consensus guidelines. They may however provide insights into data suggesting that African Americans garner fewer benefits from β -blockers than whites. Specifically, *ADRB1* Gly389, *ADRA2C* 322-325Del and *GRK5* Leu41 are all more common in African Americans than whites, and the data suggest that each of these might be the alleles associated with a less favorable response to β -blockade.

Among the drugs discussed in these pharmacogenetic studies, the one that is not approved for use is bucindolol. Of note, in 2008, ARCA Biopharma made a new drug application to the Food and Drug Administration (FDA) for approval of bucindolol in heart failure, with therapy recommended based on *ADRB1* genotype. In 2009 the FDA completed review of the new drug application and denied approval based on the BEST data; requesting that the company undertake a controlled clinical trial. In 2010 ARCA and the FDA reached agreement on the design of a 3,200 patient safety and efficacy trial in heart failure patients whose genotype suggest a favorable response to bucindolol. Specifically, the trial will be a superiority trial against metoprolol CR/XL in patients who are *ADRB1* Arg389Arg and is expected to launch in late 2011.³¹ If successful, this would represent the first example of genetically-guided drug development in cardiovascular disease.

RAAS-inhibitor Pharmacogenetics

ACE—There exists relatively little pharmacogenetic data related to heart failure progression and outcomes in response to inhibitors of the renin-angiotensin-aldosterone system (RAAS).³² ACE-inhibitors compete for the angiotensin I binding site of the angiotensin I converting enzyme (ACE, *ACE*) and decrease the production of angiotensin II, a potent vasoconstrictor. Numerous association studies have been performed relative to the presence or absence of a 287 base pair insertion/deletion (I/D) polymorphism in the *ACE* gene. The D allele has been associated with higher levels of circulating plasma ACE in an additive manner, where I/D individuals have ACE levels intermediate to that of I/I or D/D homozygotes.^{33, 34} The *ACE* I/D is the only renin angiotensin system polymorphism for which sufficient data exists to suggest a potential role in heart failure therapies.

McNamara and colleagues published an association study on the *ACE* I/D on the endpoint of death or heart transplantation in a prospective cohort of 479 heart failure subjects. Subjects were categorized on the basis of ACE inhibitor therapy at study entry, into low dose ($\leq 50\%$ of target dose of ACE inhibitor, $n = 227$) or standard (high) dose ($>50\%$, $n = 201$). Furthermore, only 42% of this cohort received β -blocker therapy at study entry. For the entire cohort, the D allele was associated with poorer transplant-free survival, and the greatest risk was seen in those subjects homozygous for the *ACE* D/D genotype. The adverse effect of the *ACE* D allele was more evident among those subjects not receiving β -blocker therapy at study entry. However, in subjects receiving β -blocker therapy, there was no association with *ACE* genotype on outcomes. Considering low- versus high-dose ACE

inhibitor therapy, the adverse effect of the D allele was principally evident in the low-dose group, and diminished in the high-dose group. Repeat analysis in those subjects on low-dose ACE inhibitor therapy and not receiving β -blocker at study entry showed the adverse effect of the *ACE* D allele on outcomes was greatly increased.³⁵ Overall these data suggest the increased risk associated with the D allele was reduced by neurohormonal blockade provided with standard heart failure therapies.

Two other studies have evaluated the role of the *ACE* I/D genotype relative to aldosterone escape and spironolactone therapy. A study evaluating aldosterone escape found the prevalence of *ACE* D/D genotype was greater among those subjects with aldosterone greater than the laboratory reference (> 42 nmol/L) compared to those that had aldosterone levels within the reference range (62% vs. 24%, $p = 0.005$).³⁶ Another small study of spironolactone treated patients found that after 12 months, a significant improvement in LVEF was only observed in *ACE* I/I and I/D subjects, whereas the change observed among *ACE* D/D homozygotes was not significant.³⁷ The results are in contrast to the previous report of a higher prevalence of the *ACE* D/D genotype in patients with aldosterone escape, as it was expected that those subjects with a greater RAAS activation at baseline would experience an enhanced benefit with an aldosterone antagonist.

In summary, the *ACE* D allele associated with higher circulating levels of ACE has also been associated with poorer transplant-free survival, imparting a risk that is substantially reduced with standard heart failure therapies. Additionally, the *ACE* D/D genotype has demonstrated greater prevalence among subjects with “aldosterone escape”, although this genotype has not been associated with beneficial LVEF response to spironolactone treatment.

Heart Failure Pharmacogenetics to Date

The pharmacogenetic studies to date in heart failure highlight the potential role of genetic polymorphisms in influencing the interpatient variability in response to heart failure pharmacotherapy; particularly the β -blockers. Collectively the studies discussed here suggest there are perhaps genotypes that place patients at risk for poor outcomes with heart failure and that specific drugs may ameliorate this risk. This was suggested in studies evaluating the influence of *ADRB1*, *ADRB2*, *ADRA2C*, *GRK5* and *ACE*, where in most cases genetic associations were not evident in patients treated with high dose (i.e. $> 50\%$ recommended) β -blocker or ACE inhibitor but were evident when treated patients were compared against those who were untreated, on placebo, or on low dose. This has implications for future pharmacogenetic studies, and interpretation of the existing literature. Specifically, if the heart failure treatment ameliorates the risk of a genotype, this greater benefit in a genetic group will not be evident if all the patients in the analyses are treated. Thus, the best data for furthering our understanding of the genetic determinants of drug response will likely come from randomized controlled trials.

The Future of Heart Failure Pharmacogenetics

The field of heart failure pharmacogenomics is relatively young, as the earliest association reported in this review was published on the *ACE* I/D polymorphism in 2001. There will be no more large, placebo-controlled randomized trials of β -blockers or ACE inhibitors in heart failure and most of the trials that defined the role of ACE inhibitors and β -blockers in heart failure were conducted before the benefit of collecting genetic material for future analyses was commonly realized. Thus most of the evidence to date for β -blockers and ACE inhibitors draws upon small, prospective cohort studies. Some of the cohort data were collected before all patients were treated with β -blockers and ACE inhibitors, thus contrasts between treated and untreated patients were possible. Moving forward, such studies will be more difficult as contemporary patients are nearly all treated with an ACE inhibitor (or

ARB) and a β -blocker. Thus the ability to extend our understanding of β -blocker and ACE inhibitor pharmacogenetics may be limited.

There remain some randomized controlled trials for which genetic samples are available and more work could be done. Specifically genetic data were available for 600 participants of MERIT-HF, from which the one study was published evaluating outcomes relative to *ADRB1* Arg389Gly genotype in the entire cohort, not independent of treatment. Analyses that compared outcomes by treatment, within genotype, from the MERIT-HF data would be particularly informative. Genetic analyses of 3,239 patients enrolled in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program were published in abstract form in 2008.³⁸ Subjects were genotyped for 165 tag SNPs in 14 candidate genes that included *ACE*, *ADRB1*, *ADRB2*, and *ADRA2C*. Following multiple comparison adjustment for the analyses of cardiovascular death and heart failure hospitalization or death, no individual SNP was significant at $p < 0.05$. These findings have yet to be formally published or validated.³⁸ Genetic samples were also collected in the African American Heart Failure Trial (A-HeFT), and an abstract was published indicating a lack of association between the *ACE* D allele and LVEF in this population, but again these data have never been published in full.³⁹

Several clinical trials are currently ongoing that might provide additional insights into genetic determinants of response. A Pharmacogenomic Study of Candesartan in Heart Failure (ClinicalTrials.gov identifier: NCT00400582) is an open-label candesartan study, and will evaluate the impact of genetic variations on the response to candesartan in an estimated 300 heart failure patients already treated with an ACE inhibitor.⁴⁰

The Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function (TOPCAT, ClinicalTrials.gov identifier: NCT00094302) study will evaluate effectiveness of an aldosterone antagonist, spironolactone, in reducing all-cause mortality in heart failure patients with preserved systolic function.⁴¹ This randomized, placebo-controlled trial with an estimated enrollment of 3,515 subjects will assess the primary outcome measures of aborted cardiac arrest and composite of hospitalization for the management of heart failure. Secondary outcome measures include all cause mortality, composite cardiovascular mortality or cardiovascular related hospitalization, hospitalization for the management of heart failure incidence rate, and sudden death or aborted cardiac arrest. TOPCAT will provide an excellent opportunity to evaluate the pharmacogenetic effects of polymorphisms within RAAS genes in a large heart failure population with outcomes data. These ongoing studies may provide insights into the subgroups of patients who derive the greatest benefit from these therapeutic approaches.

Replication of genetic associations is one of the greatest challenges in pharmacogenetics, including in heart failure, because in most scenarios there is not an identical (or even similar) study population/clinical trial population in which to replicate the findings. Thus it is essential that the available data are used to their greatest potential and that future clinical trials collect genetic samples so that such analyses can be undertaken.

Potential for pharmacogenetics in development of novel heart failure therapies

Perhaps the greatest potential for heart failure pharmacogenetics lies in development of novel therapeutic approaches. If one considers ACE inhibitors and ARBs to be similar, no new drug classes have been shown to have survival benefits in heart failure since the publication of the RALES trial documenting benefits of spironolactone in 1999. In the interim period, a number of drug classes have failed in late drug development for heart

failure, including vasopeptidase inhibitors, endothelin blockers, TNF receptor blockers, among others. The challenge for novel therapies in this population is to provide incremental benefit above the stable background therapies with established, demonstrable benefits on survival. Many believe the failure of these promising drug classes indicates that in a substantial portion of the heart failure population, the current standard therapies represent the optimal benefit that can be obtained from pharmacotherapy. If this is correct, continued drug development in the broad population is not likely to be fruitful. However, there almost certainly exist subpopulations of heart failure patients who are not obtaining optimal benefit from the current standard therapies, who might benefit from additional pharmacological approaches. The challenge is identifying that subgroup. The data presented herein suggest genetics may represent a tool for identifying responsive subgroups in Phase 2 trials, followed by Phase 3 trials that enroll only the genetic group predicted to achieve the greatest benefit. This approach is currently being undertaken in the development of bucindolol.

Overall, the future of heart failure pharmacogenetics as an approach for improving heart failure pharmacotherapy and/or our understanding of pharmacotherapy is promising. There is still significant headway to be made in improving mortality and clinical outcomes within this population. Pharmacogenetics appears to represent an important tool for accomplishing this goal.

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Figure 1.

Schematic of adrenergic receptor (AR) signaling in the heart. For clarity, only the classic signal transduction pathways are shown, but there are other events from adrenergic signaling that occur through G-protein and non-G- protein interactions. The dual coupling of β_2 -AR to G_s and G_i is shown in the myocytes but not in the presynaptic neuron. AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; GRK, G-protein-coupled receptor kinase; IP3, inositol triphosphate; PLC, phospholipase C; EPI, epinephrine; NE, norepinephrine. Permission pending on reprint from Johnson JA, Liggett SB.

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Table 1

Summary of heart failure pharmacogenetic associations

SNP	Reference allele/Function	Pharmacogenetic Associations	
<i>ADRB1</i> Arg389Gly	Reference: Arg389	Prognostic indicators	Outcomes
	Increased receptor activation of adenylyl cyclase with Arg389 allele ⁷⁻⁹	Greater LVEF improvement in Arg389Arg homozygotes among carvedilol and metoprolol treated subjects ⁹⁻¹¹ Trend toward increase in LVEF with carvedilol treated Arg389 carriers ¹³ No association with LVEF and Arg389Gly in bisoprolol or carvedilol treated patients ¹² No changes in LVEF by codon 389 among bucindolol treated patients ¹⁴	Arg389Arg – reduced mortality with bucindolol compared to placebo, no clinical response among Gly389 carriers ¹⁴ ly389 – decreased risk of NSVT, improved survival ¹⁹ No association with outcome among subjects receiving β -blocker ²⁰ No effect on transplant-free survival for polymorphisms of adrenergic receptors ²¹ No association with outcomes for metoprolol CR/XL or placebo randomized patients ²² Gly389 – increased mortality risk in Caucasians not receiving β -blocker ²⁰ Gly389 carriers –higher 5-year mortality risk compared to Arg389Arg in subjects receiving low-dose β -blocker ²⁴
<i>ADRB1</i> Ser49Gly	Reference: Ser49	Prognostic indicators	Outcomes
	Gly49 - increased agonist promoted down-regulation and adrenergic coupling, more sensitive to inhibition ²³	Decreased LVEDD in Gly49 carriers ¹¹ Ser49Gly + Arg389Arg diplotype - decrease in LVEDD ¹¹ Ser49Ser + Arg389Gly diplotype - increase in LVEDD ¹¹	Gly49 - carriers on low-dose β -blocker, lower 5-year mortality, no association among those receiving high-dose β -blocker ²⁴
<i>ADRB2</i> Gly16Arg	Reference: Gly16	Outcomes	
	Conflicting data regarding agonist mediated downregulation ^{15, 16, 42, 43}	Two copies of Arg16Gln27 haplotype associated with increased risk for death or heart transplantation ⁴⁴	
<i>ADRB2</i> Gln27Glu	Reference: Gln27	Prognostic indicators	
	Glu27 – resistance to downregulation in vitro ^{15, 16} Glu27Glu – enhanced vasodilation in response to agonist in vivo ⁴²	Glu27Glu - greater increase in LVEF compared to Gln27 carriers in response to carvedilol ¹³ Glu27 carriers - improvement in LVEF, not seen in Gln27 ¹⁷ Glu27 - allele prevalence greater among “good responders” to carvedilol ¹⁸	
<i>ADRA2C</i> Del322-325	Reference: Ins322-325	Prognostic indicators	Outcomes
	Loss of α_2c receptor autoinhibition of norepinephrine release ^{25, 26}	Del322-325 carriers – 3-fold greater decrease in NE ²⁸ Del322-325 carriers – greater negative and chronotropic response to metoprolol CR/XL ²⁹ Synergistic effect between Arg389Arg/ Del322-325 carrier genotypes had largest increase in LVEF ²⁹	Del322-325 carriers – no survival benefit with bucindolol therapy, wild-type had 30% reduced incidence of mortality ²⁸
<i>GRK5</i> Gln41Leu	Reference: Gln41	Outcomes	
	Leu41 – gain-of-function, greater agonist-promoted desensitization of β -adrenergic receptors ³⁰	Leu41 β -blocker naïve – longer transplantation-free survival in African Americans, no difference in treated subjects ³⁰ Leu41 – longer survival in β -blocker untreated African Americans ²⁰	
<i>ACE</i> I/D	Reference: D	Prognostic indicators	Outcomes
	Increased plasma levels of ACE associated with the D allele ^{33, 34}	D/D – greater prevalence among subjects with “aldosterone escape” ³⁶	D allele associated with poorer transplant- free survival,

SNP	Reference allele/Function	Pharmacogenetic Associations	
		D/D – nonsignificant change in LVEF after spironolactone treatment ³⁷	exaggerated with low-dose ACE inhibitor and no β -blocker ³⁵

Abbreviations: LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia