Published in final edited form as:
Curr Heart Fail Rep. 2012 March ; 9(1): 23–32. doi:10.1007/s11897-011-0076-2.

Pharmacogenetics in Chronic Heart Failure: New Developments and Current Challenges

Jasmine A. Talameh, PharmD and
University of North Carolina at Chapel Hill, UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, Institute for Pharmacogenomics and Individualized Therapy, 120 Mason Farm Road Campus Box #7361 Chapel Hill, NC 27599, Phone: 919-966-5904, Fax: 919-966-5863, jtalameh@unc.edu

David Lanfear, MD, MS, FACC
Senior Staff, Advanced Heart Failure and Cardiac Transplantation, Research Scientist, Center for Health Services Research, Assistant Professor, Wayne State University, Henry Ford Hospital, 2799 W. Grand Boulevard Detroit, MI 48202, Phone: 313-916-6375, Fax: 313-916-8799, dlanfea1@hfhs.org

Abstract

The individual patient responses to chronic heart failure (HF) pharmacotherapies are highly variable. This variability cannot be entirely explained by clinical characteristics, and genetic variation may play a role. Therefore the purpose of this review is to 1) summarize the background pharmacogenetic literature for major HF pharmacotherapy classes (i.e. beta-blockers, angiotensin converting enzyme inhibitors, digoxin, and loop diuretics), 2) evaluate recent advances in the HF pharmacogenetic literature in the context of previous findings, and 3) discuss the challenges and conclusions for HF pharmacogenetic data and its clinical application.

Keywords

pharmacogenetics; pharmacogenomics; personalized medicine; heart failure; polymorphism; beta-blocker; angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; aldosterone antagonist; loop diuretic; digoxin; hydralazine isosorbide dinitrate

Introduction

Large clinical trials demonstrate, on average, that pharmacotherapy significantly decreases morbidity and/or mortality due to heart failure (HF). However, the individual patient responses to HF pharmacotherapies are highly variable. For example, long-term treatment with angiotensin converting enzyme (ACE) inhibitors fails to suppress angiotensin II in as many as 15% of HF patients, and aldosterone in 38% [1]. Long-term optimal dosing of beta blockers fails to improve left ventricular ejection fraction (LVEF) >5% in as many as 43% of HF patients [2]. The maintenance dose of loop diuretics can range from no diuretic at all to >400mg furosemide equivalents [3]. Even when dosed according to age, sex, weight, renal function, and concomitant pharmacotherapy, the serum concentration of digoxin can range from 0.5ng/mL to >2.0ng/mL [4].

This wide variability in response to HF pharmacotherapies is not entirely explained by clinical characteristics, which is evident in large clinical trials where there is a similar

Correspondence to: David Lanfear.

response among most clinical sub-groups [5,6]. Genetic variation may additionally contribute to differences in drug response, the study of which is referred to as "pharmacogenetics" or "pharmacogenomics" [7]. Pharmacogenetics has proven successful in other therapeutic areas [8], but whether it can be used to improve the application of pharmacotherapies for HF remains unproven. Therefore the purpose of this review is to 1) succinctly summarize the background pharmacogenetic literature for major classes of HF pharmacotherapy, 2) critically evaluate the most current HF pharmacogenetic literature in this context, and 3) discuss the conclusions and remaining challenges to clinical application of pharmacogenetics in HF.

Beta-Blocker Pharmacogenetics: Background (Literature prior to 2010)

Compared to any other class of HF pharmacotherapy, HF pharmacogenetic studies have focused on beta blockers (BBs) much more than any other. Twenty-five studies were published between 2000 and 2009. Much BB pharmacogenetic data comes from small (n<400) observational cohorts of HF patients with systolic dysfunction. These studies are heterogeneous in many aspects (e.g. design, size, endpoint, patient population, specific BB, and the genetic variants tested), making definitive conclusions difficult. A list of genetic variants associated with BB (and other HF pharmacotherapies) response is displayed in Table 1, and the major findings are discussed herein.

Type 1 β-adrenergic receptor

Stimulation of the cardiac β-adrenergic receptors results in increased heart rate and contractility. The type 1 β-adrenergic receptor (*ADRB1*) is the primary target of cardiac BBs and has been the focus of the majority of BB pharmacogenetic literature. A non-synonymous variant in this gene, Arg389Gly, has been the most-studied (Table 1). This variant is common in the general population, with racial differences in its frequency (Table 2). Functionally, Arg389 has greater basal and agonist-stimulated activity compared to Gly389 [9]. Since Gly389 generally results in less *ADRB1* sympathetic stimulation, it is raises the question of whether this variant is protective in BB-naïve HF patients, and that patients with Arg389 would receive greater benefit from BBs.

Consistent in the literature, patients possessing the Arg allele have greater LVEF improvement in response to BBs than those possessing Gly389. This comes from several prospective and retrospective studies totaling 569 patients with a variety of HF etiologies, ethnicities, and BBs [10-13]. There is also evidence to support the influence of Arg389Gly on the survival benefit from BBs. The most convincing is a large (n=1040) pharmacogenetic sub-study [14] of the Beta-Blocker Evaluation of Survival Trial (BEST) [15]. Patients homozygous for Arg389 had a statistically significant improvement in survival with bucindolol compared to placebo (HR=0.62; p=0.03), whereas Gly389 carriers did not (HR=0.90; p=0.57). It is argued whether the results for bucindolol can be applied to other BBs because of its unique pharmacologic properties [16]. While these results were replicated in a prospective, observational study of 201 HF patients treated with metoprolol or carvedilol [17], other larger cohort studies have not found this association [18]. A pharmacogenetic sub-study of MERIT-HF [5] also did not find an association of Arg389Gly with survival benefit regardless of treatment (metoprolol CR/XL or placebo) [19]. However this last study did not test BB effect within genotype groups (as was done in BEST), which may help explain the discordant results.

Type 2 β-adrenergic receptor

Although not the primary target of BBs, the type 2 β-adrenergic receptor (*ADRB2*) is present in myocardium, can mediate inotropic response, and while ADRB1 is down-regulated the

expression of ADRB2 is unchanged in the failing heart [20]. The most-studied variant in ADRB2 is Gln27Glu. Functionally, Glu27-containing *ADRB2* is resistant to agonist-promoted desensitization compared to Gln27 [21,22]. This suggests that Gln27 genotype is associated with less sympathetic output relative to Glu27, but the clinical pharmacogenetic literature is inconsistent. Several small studies showed a favorable LVEF response for patients carrying Glu27 compared to patients homozygous for Gln27 [23-25]. However, four other small studies failed to show a significant association [11,12,26,27]. Although, these included β1-selective BBs, which might limit the ability to detect an interaction with *ADRB2* variants. In terms of survival benefit, one study showed a survival difference by genotype among BB-treated HF patients [28], but several large cohort studies have not demonstrated an association [18,26,29]. Notably, the majority of patients in these studies were treated with BB, limiting the ability to examine true pharmacogenetic interactions.

Adrenergic receptor alpha-2C

The alpha-2C (*ADRA2C*) adrenergic receptor is presynaptic, auto-inhibiting norepinephrine release. A deletion variant in *ADRA2C*, causing a loss of amino acids 322-325, results in the loss of normal auto-inhibitory function and increased norepinephrine [30]. A potential interaction between *ADRB1* Arg389, the *ADRA2C* deletion, and BB response was prospectively studied in 54 HF patients with systolic dysfunction [31]. The deletion-carriers had a greater improvement in LVEF compared to insertion homozygotes (+6% versus +1%; p=0.045). Synergy between the *ADRB1* and *ADRA2C* variants was supported by the magnitude of results. No association was found in 80 IDC patients [27], but synergy with *ADRB1* Arg389 was not tested.

G-protein coupled receptor kinase 5

The function of the G-protein receptor kinases (GRK) is to desensitize ligand-occupied G-protein coupled receptors such as β-adrenergic receptors [32]. *GRK5* is abundant in the heart and a Gln41Leu variant in this gene has been studied *in vitro*, with the Leu41 version more effectively desensitizing agonist-stimulated responses compared to Gln41 [33]. Because the Gln41 subtype should have more active β-adrenergic receptors, it has been proposed that Leu41 is protective in BB-naïve HF patients, but these patients may be less responsive to BB.

In an observational study of 375 African-Americans with HF, only patients homozygous for Gln41 had significantly improved transplant-free survival with BB (HR=0.22; p<0.001) [33]. There was no difference in outcome for patients carrying Leu41 with or without BB (HR=0.78; p=0.53). Similar results were found in another study featuring 711 African-American HF patients [34]. Among all of the African-American patients, the BB treatment effect did not reach statistical significance (HR=0.698; p =0.1). However in a genetic sub-group of *ADRB1* Gly389 homozygous/*GRK5* Gln41 homozygous African-Americans, BBs were associated with marked mortality benefit (HR=0.385; p=0.012). Interestingly, when the African-Americans and Caucasians were matched by *ADRB1* and *GRK5* genotypes and BB treatment their survival times were similar. This suggests that genetic variants, rather than race, are the major factor contributing to the apparent differences in BB treatment effect between Caucasians and African-Americans.

Beta Blocker Pharmacogenetics: Recent Advances (Publication Year ≥2010)

As evidenced by the heterogeneous and observational nature of the background HF BB pharmacogenetic literature, this field is still in an early stage. The four most recent HF BB

pharmacogenetic studies support previous insights, but they also demonstrate some unexpected results.

A small but intriguing study in 93 HF patients [35] studied a panel of both pharmacokinetic and pharmacodynamic genetic variants relevant to BBs (*ADRB1*[Arg389Gly], *CYP2D6*, and *UGT1A1*) and assessed them using a multidimensional BB response criteria. *CYP2D6* and *UGT1A1* are highly polymorphic metabolic enzymes for which carvedilol is a substrate, and metoprolol is mainly metabolized by CYP2D6. They defined BB response as meeting at least three out of five criteria: the 1) duration and 2) tolerability of dose titration, 3) an increase in NYHA functional class, 4) LVEF, or 5) 6-minute walk distance. There was no association between the panel of genetic variants and their BB response criterion, but there was a weak relationship between carvedilol dose and Arg389Gly status (p=0.012). Gly389 patients reached higher doses, perhaps indicating greater BB responsiveness in those with Arg389.

A recent prospective study of 183 patients with HF and three previously studied genetic variants (*ADRB1*[Arg389Gly] and *ADRB2*[Arg16Gly and Gln27Glu]) [25] had findings consistent with the background BB pharmacogenetic literature. The increase in LVEF after carvedilol tended to be greater in *ADRB1* Arg389 homozygous (+7.8±7.6%) and heterozygous patients (+9.0±11.4%) compared to those homozygous for Gly389 (+4.1±7.6%) (p=0.0847). Subjects homozygous for *ADRB2* Glu27 showed a greater increase in the LVEF (+13.0 ±12.2%), compared to both heterozygous (+7.1 ±8.1%) and Gln27 homozygous patients (+8.3 ±11.4%) (p=0.022). In multivariable analysis, cause of HF, systolic blood pressure, dose of carvedilol, and Gln27Glu genotype were significant correlates of LVEF improvement after carvedilol treatment. Notably, the *ADRB1* Arg389Gly genotype was not independently informative in this dataset.

The *ADRA2C* insertion/deletion was tested in the genetic sub-study of BEST (n=1040) [36]. In contrast to previous data, which indicated that the *ADRA2C* deletion was associated with improved LVEF response after BB, this large and adequately powered study found no differential effect on LVEF by *ADRA2C* genotype. Interestingly, interaction with *ADRB1* Arg389Gly was not tested. Even more surprising was that this study found that the insertion allele, and not the deletion, was associated with enhanced survival benefit from BB. For the all-cause mortality end point, bucindolol produced a strong tendency toward significance (p=0.025) for a reduction in mortality by 30% in the insertion homozygotes, while there was a non-significant (p=0.79) 9% increase in mortality in the bucindolol-treated deletion-carriers. There are several possible explanations for the discrepancy in results; the previous small studies could be false positive associations, or this could be a bucindolol-specific interaction.

A recent retrospective study of 586 HF patients examined differential pharmacogenetic interactions between carvedilol and metoprolol [37]. The investigators combined two genotypes, *ADRB1* Arg389-homozygous and *ADRB2* Gln27-carrier, and compared these patients to all others in terms of time-to-death from any cause. They found a significant interaction between genotype group and carvedilol treatment (p=0.003), but no interaction with metoprolol (p=0.61). In patients treated with carvedilol, survival was lower for Arg389/Gln27 group than the remaining patients (HR=2.30). Because two different variants defined these groups and the fact that one is associated with favorable BB response while the other is not, these results are difficult to put in context of the existing literature. Another concern is that there may have been negative results for metoprolol because the genotype groups were partly defined by an *ADRB2* genotype, and metoprolol is β1-specific.

Overall these more recent results, like the pre-existing BB pharmacogenetic literature, are provocative but require validation in large, prospective clinical trials of genetic-guided BB therapy. There is sufficient evidence to support this approach, for bucindolol as well as the currently approved agents such as metoprolol and carvedilol, and this represents the most pressing challenge for BB pharmacogenetics in HF. Other areas that remain unclear are whether additional yet unidentified genes should be the focus of future research, whether other genes are relevant to BB effectiveness, and the interaction of race with genetics. The current candidate gene list revolves strictly around the receptor, and whether other genetic loci may directly modify response or interact with the current candidates is unknown. As pointed out above, all of the current candidate variants have frequencies that differ significantly by ancestry (Table 2), which raises the issue of both genetic and non-genetic confounding factors. Therefore additional investigation is required for confidence in these associations and the potential application to non-Caucasian populations.

ACE Inhibitor Pharmacogenetics: Background (Literature prior to 2010)

Our extensive searches reveal only six pharmacogenetic studies of ACE inhibitors in HF patients from 1998 to 2008. Like the BB literature, most of the ACE inhibitor pharmacogenetic literature in HF patients comes from small observational studies (n<200) that are heterogeneous in design. Not surprisingly, the literature has focused on the gene encoding the target of these agents, *ACE*. A 287 base pair insertion/deletion in intron 16 of *ACE* accounts for half of the variance in serum ACE levels [38]. The deletion results in significantly higher ACE levels [38]; therefore it was postulated that HF patients possessing the deletion would require a higher dose of ACE inhibitor to achieve the same inhibition. Most of the clinical pharmacogenetic studies are consistent with the functional effects, with respect to mean arterial pressure [39], aldosterone escape [40], serum ACE activity [41], and survival [42], but the association with LVEF is less clear [43,44].

In 107 idiopathic dilated cardiomyopathy patients receiving 2.5 years of ACE inhibitor therapy [43], the LVEF improvement was similar among *ACE* genotypes, but another study of 168 HF patients with systolic dysfunction [44] found that deletion-carriers had a greater LVEF improvement after ACE inhibitor (deletion-carriers LVEF +8.8 %; insertion homozygotes -1.73%; p=0.01). The discordance in results may be due to population-specific effects. In contrast, the relationship between the ACE variant and survival benefit from ACE inhibitors appears more clear based on the largest ACE inhibitor pharmacogenetic study in HF patients (n=479) [42]. There was a dose-dependent relationship between the ACE insertion/deletion and transplant-free survival. After a median follow-up of 33 months, patients on low-dose ACE inhibitors (≤50% of target dose) had poorer transplant-free survival associated with the deletion allele (RR for deletion homozygotes=2.07;p=0.03), and this was exaggerated in patients who were also not receiving a BB. However high-dose ACE inhibitor (>50% of target dose), with or without concomitant BB, eliminated the adverse effect of the ACE deletion. Although the deletion was associated with poorer transplant-free survival, it seemed that deletion homozygotes benefitted the most from ACE inhibitor and BB therapy.

ACE Inhibitor Pharmacogenetics: Recent Advances (Publication Year ≥2010)

There is little ACE inhibitor pharmacogenetic literature recently, with only one study published [45] within the last 2 years. This study is consistent with the previous findings on survival, and extends this to HF patients with preserved LVEF. This study enrolled 285 HF patients followed for ~7 years for all-cause mortality [45]. The deletion allele was associated with higher mortality in patients not receiving an ACE inhibitor (HR=2.23; p=0.008), but

this impact was reduced among patients receiving an ACE inhibitor (HR=1.64; p=0.20). Acknowledging the limitation that the ACE pharmacogenetic literature comes entirely from observational cohorts, the sum of these data suggest that HF patients that are deletion-carriers may need higher dose ACE inhibition to achieve similar outcomes compared to insertion homozygotes. While at this point it seems unlikely that renewed interest will come to ACE inhibitor pharmacogenetics, a variety of intriguing points remain such as whether other genes are important, whether adverse events (e.g. angioedema and hyperkalemia) can be predicted based on genetics, or whether genetics can help guide combinations of therapies (e.g. BB +ACE inhibition vs. BB alone vs. ACE inhibition alone).

Pharmacogenetics of Loop Diuretics: Background (Literature prior to 2010)

There have been six studies investigating the association between genetic variation and loop diuretic response published from 2004 to 2008. Five of the studies were performed in healthy volunteers (HV), and one small study included patients with HF. Collectively, these studies demonstrated that genetic variants involved in the metabolism (*CYP2C9*), uptake (*SLC22A11* and *SLCO1B1*), and action (*SLC12A3, SCNN1B*, and *SCNN1G*) of the loop diuretics can influence their pharmacokinetics and pharmacodynamics.

In 10mg torsemide single dose HV studies, the decreased function CYP2C9*3 allele had significant effects on torsemide pharmacokinetics and modest effects on pharmacodynamics [46]. The total oral clearance of torsemide was about 3-fold lower in CYP2C9 *3/*3 subjects compared to *1/*1 subjects. Sodium and chloride excretion were ~25% higher in carriers of one CYP2C9*3 allele after torsemide administration [46]. HVs homozygous for the two most frequent haplotypes of *SLC22A11* (gene encoding the organic anion transporter 4 [OAT4]) had an 80% difference in the renal clearance of torsemide [47], and HVs homozygous for 521T, heterozygous, and homozygous for 521C in *SLCO1B1* (gene encoding the organic anion transporting polypeptide 1B1 [OATP1B1]) had torsemide oral clearances estimated as 62, 46, and 41mL/min, respectively ($p<0.001$) [48]. Taken together, variants in CYP2C9, OATP1B1, OAT1, and OAT4 explain nearly 50% of torsemide pharmacokinetic variation [49].

Three renal sodium reuptake transporters are the primary targets of the loop diuretics: NKCC2 (gene: *SLC12A1*), NCC (gene: *SLC12A3*), and ENaC (genes: *SCNN1A, SCNN1B*, and *SCNN1G*) [50]. A three-period crossover study was performed in 97 HVs using single oral doses of bumetanide (2mg), furosemide (80mg), and torsemide (10mg) to evaluate the influence of variation in these on diuretic response [50]. There were three significant associations with the 24-hour excretion, and this was consistent among the three loop diuretics: 1) Subjects homozygous for Ala264 in *SLC12A3* excreted an average 32% more chloride and 42% more potassium compared to those homozygous for Gly264. 2) Subjects homozygous for the most frequent haplotype in *SCNN1B* excreted 24% more volume, 13% more sodium, and 13% more chloride compared to subjects without the most frequent haplotype. 3) Subjects homozygous for G4 at a synonymous C4G substitution in *SCNN1G* excreted 23% less volume and 24% less calcium compared to subjects homozygous for the C4 allele.

The loop diuretic pharmacogenetic data discussed to this point involves single-dose studies performed in HVs, but the data in HF patients receiving steady-state dosing appears consistent with the HVs. In a small, open-label pharmacokinetic study of 24 patients receiving stable doses of 10mg daily torsemide (n=18 with arterial hypertension and n=6 with HF) [51], the primary endpoint was area under the plasma concentration-time curve during the 24-hour dosing interval at steady state ($AUC_{24,ss}$). *CYP2C9* genotype, *SLCO1B1* genotype, and gender independently predicted $AUC_{24,ss}$. Similar to HVs, HF patients with

the CYP2C9 *1/*3 genotype had a mean $AUC_{24,ss}$ 46% greater than those with the *1/*1. Patients heterozygous for T521C in *SLCO1B1* had a 38% increase in $AUC_{24,ss}$ compared to patients homozygous for 521T (no 521C homozygotes found).

Pharmacogenetics of Loop Diuretics: Recent Advances (Publication Year ≥2010)

Despite the interesting associations above, whether these differences in pharmacokinetic parameters across genotypes translate into clinically meaningful differences in drug effectiveness in patients with HF remains unknown. One recent study attempted to answer this question. This was a randomized, single-blind, three-arm, triple-crossover study in 95 HVs [52] who received a single oral dose of bumetanide (2mg), furosemide (80mg), and torsemide (10mg) at 2 weeks intervals. Together, eight genetic variants had an impact of 20, 15, 10, and 23% on the variation in the urinary excretion of sodium, volume, potassium, and calcium. Thus, genetic variation seems to importantly impact not only pharmacokinetics of loop diuretics but also their clinical effect. The incorporation of genetic data may help in determining diuretic dosing, though the clinical situation where this would be necessary is not obvious. Important questions which remain to be addressed are whether genetic variation can predict worsening renal function associated with chronic diuretic therapy, or even the risk of recurrent hospitalization.

Digoxin Pharmacogenetics: Background (Literature prior to 2010)

Digoxin is a narrow therapeutic index drug with recommended serum digoxin concentration (SDC) being 0.7-0.9 ng/mL [53]. The pharmacokinetics, and therefore SDC, may be affected by genetic variation. Indeed, a study in monozygotic and dizygotic twins estimated the genetic component contributing to digoxin AUC_{0-12} to be 89% [54]. The seminal paper investigating the influence of genetic variation on digoxin pharmacokinetics was published in 2000 [55], and it has been followed by 12 more studies with inconsistent results.

The majority of the digoxin pharmacogenetic literature has focused on a common C3435T variant in *ABCB1* (Table 2). *ABCB1* encodes for P-glycoprotein (P-gp), an efflux protein for which digoxin is a substrate. In the seminal paper, subjects homozygous for 3435T (n=5) had >2-fold lower expression of P-gp in the duodenum compared to subjects homozygous for 3435C (n=6; p=0.056). As would be expected, subjects homozygous for 3435T had 38% higher SDC than subjects homozygous for 3435C (p=0.006). Acknowledging this small sample size, these results have been consistent with six subsequent studies in HVs [56-61], as well as a population-based study of 195 “digoxin-users” (HF status not reported) [62]. Despite this seemingly consistent line of evidence, some contrasting data has arisen. Another study of 39 HF patients found no difference in steady-state SDC among C3435T genotypes, which was consistent with another study in 50 HVs [63] as well as a meta-analysis [64]. Unfortunately, this small HF study did not control for differences in renal function, which can vary widely among patients with HF.

Overall the preponderance of evidence favors an impact of genetic variation on digoxin pharmacokinetics. Despite this, whether the difference in digoxin pharmacokinetics by C3435T genotypes is clinically meaningful in patients with HF is not established. Adding to this complexity is that the association of the C3435T genotype with digoxin pharmacokinetics may depend on ethnicity. Two studies in Japanese subjects found a reverse association, in which the 3435C genotype had higher SDC [65,66].

Digoxin Pharmacogenetics: Recent Advances (Publication Year ≥2010)

Only a single study, with a unique post-mortem SDC study design (n=112), was identified in our searches regarding digoxin pharmacogenetics in the past 2 years. This study's results are consistent with the notion that *ABCB1* 3435T confers higher SDC [67], but adds to the existing data by suggesting that the interactions with C3435T may be gender-specific. There was a relationship between the frequency of 3435T allele and post-mortem SDC, but surprisingly the results were driven by females. If true, this relationship could help explain previous data demonstrating higher mortality in women treated with digoxin versus placebo due to differences in SDC between women and men [68]. Validation of this finding in adequately sized, prospective, gender-specific cohorts is needed. If validated, one could envision using genotype to identify patients at higher risk of toxicity who should not receive digoxin, receive reduced dosing, or more intense drug level monitoring.

Future Challenges

While there are many gaps in the HF pharmacogenetic knowledge base, limiting its current clinical application, we have already learned a great deal from the relatively modest body of HF pharmacogenetic literature. For example, while genetic variant functional/mechanistic effects need to be demonstrated to truly establish causation, this is not sufficient as these associations do not always translate into clinical effects. Another important insight is that there can be synergy/interaction between multiple genetic variants as is the case for *ADRB1* Arg389Gly and *ADRA2C* insertion/deletion with LVEF response to BBs. Even more daunting is the complexity and specificity of some pharmacogenetic associations. HF pharmacogenetic associations may be race-specific (e.g. *GRK5* Gln41Leu and BB response in African-Americans), dose-specific (e.g. *ACE* insertion/deletion and low- and high-dose ACE inhibitors), gender-specific (e.g. *ABCB1* C3435T and SDC in women), and drug-specific (e.g. *ADRB1/ADRB2* and response to carvedilol but not metoprolol).

Despite the fact that pharmacogenetics has been in existence for decades, the number of studies on HF therapies are still relatively small and we are yet in the early stages of this part of the field. This foundation has yielded the important insights above and also provided numerous improvements in approach both in terms of genotyping and analysis. This has set the stage for accelerated advances moving forward. At this point, some of the key knowledge gaps include: 1) Lack of foundational pharmacogenetic data regarding angiotensin receptor blockers, aldosterone antagonists, and hydralazine/isosorbide dinitrate; 2) Investigation into acute or intravenous HF pharmacotherapies; 3) Better understanding of multi-variant / multi-drug combinations on pharmacogenetics. Most importantly, what is broadly needed in order to make real progress are prospective intervention clinical trials where a genetic-guided approach is compared to empiric therapy. These are required to validate proposed associations and establish that a specific response to the genetic information can improve treatment outcomes. Because HF is a fatal and common disease requiring polypharmacy, any information (even genetic) that could improve HF pharmacotherapies would give profound patient and public health benefit.

Annotated References

(* of importance; * * of outstanding importance)

1. MacFadyen RJ, Lee AF, Morton JJ, et al. How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? Heart. 1999; 82(1): 57–61. [PubMed: 10377310]

2. Chen L, Meyers D, Javorsky G, et al. Arg389Gly-beta1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart

failure after chronic treatment with carvedilol. Pharmacogenet Genomics. 2007; 17(11):941–949. [PubMed: 18075464]

3. Mielniczuk LM, Tsang SW, Desai AS, et al. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail. 2008; 14(5):388–393. [PubMed: 18514930]
4. Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003; 289(7):871–878. [PubMed: 12588271]
5. MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999; 353(9169): 2001–2007. [PubMed: 10376614]
6. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991; 325(5):293–302. [PubMed: 2057034]
7. Lanfear DE, McLeod HL. Pharmacogenetics: using DNA to optimize drug therapy. Am Fam Physician. 2007; 76(8):1179–1182. [PubMed: 17990842]
8. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med. 2011; 364(12):1144–1153. [PubMed: 21428770]
9. Mason DA, Moore JD, Green SA, et al. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. J Biol Chem. 1999; 274(18):12670–12674. [PubMed: 10212248]
10. Mialet Perez J, Rathz DA, et al. Beta 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. Nat Med. 2003; 9(10):1300–1305. [PubMed: 14502278]
11. Terra SG, Hamilton KK, Pauly DF, et al. Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker therapy. Pharmacogenet Genomics. 2005; 15(4):227–234. [PubMed: 15864115]
12. Chen L, Meyers D, Javorsky G, et al. Arg389Gly-beta1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart failure after chronic treatment with carvedilol. Pharmacogenet Genomics. 2007; 17(11):941–949. [PubMed: 18075464]
13. Luo M, Bi Y, Xu YX. Effects of metoprolol on beta1 adrenergic receptor polymorphism and receptor density in urban Chinese patients with heart failure. Chin Med J (Engl). 2007; 120(19): 1720–1723. [PubMed: 17935678]

14* *. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. Proc Natl Acad Sci U S A. 2006; 103(30):11288–11293. This paper used transfected cells, genotyped human nonfailing and failing ventricles, and a sub-study of a clinical trial to evaluate variants in ADRB1. They found that only HF patients who were homozygous for Arg389 had survival benefit from bucindolol compared to placebo. [PubMed: 16844790]

15. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001; 344(22):1659–1667. [PubMed: 11386264]
16. Bristow MR, Krause-Steinrauf H, Nuzzo R, et al. Effect of baseline or changes in adrenergic activity on clinical outcomes in the beta-blocker evaluation of survival trial. Circulation. 2004; 110(11):1437–1442. [PubMed: 15337700]
17. Biolo A, Clausell N, Santos KG, et al. Impact of beta1-adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol. 2008; 102(6):726–732. [PubMed: 18773997]

18*. Sehnert AJ, Daniels SE, Elashoff M, et al. Lack of association between adrenergic receptor genotypes and survival in heart failure patients treated with carvedilol or metoprolol. J Am Coll Cardiol. 2008; 52(8):644–651. This was a large observational cohort that found in mostly treated HF patients, there was no association of common variants in adrenergic receptors with survival. [PubMed: 18702968]

19. White HL, de Boer RA, Maqbool A, et al. An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study. Eur J Heart Fail. 2003; 5(4):463–468. [PubMed: 12921807]

20. Bristow MR, Ginsburg R, Umans V, et al. Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. Circ Res. 1986; 59(3):297–309. [PubMed: 2876788]

21. Green SA, Turki J, Innis M, et al. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry. 1994; 33(32):9414–9419. [PubMed: 7915137]

22. Green SA, Turki J, Bejarano P, et al. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. Am J Respir Cell Mol Biol. 1995; 13(1):25–33. [PubMed: 7598936]

23. Kaye DM, Smirk B, Williams C, et al. Beta-adrenoceptor genotype influences the response to carvedilol in patients with congestive heart failure. Pharmacogenetics. 2003; 13(7):379–382. [PubMed: 12835612]

24. Troncoso R, Moraga F, Chiong M, et al. Gln(27)-->Glubeta(2)-adrenergic receptor polymorphism in heart failure patients: differential clinical and oxidative response to carvedilol. Basic Clin Pharmacol Toxicol. 2009; 104(5):374–378. [PubMed: 19422106]

25. Metra M, Covolo L, Pezzali N, et al. Role of beta-adrenergic receptor gene polymorphisms in the long-term effects of beta-blockade with carvedilol in patients with chronic heart failure. Cardiovasc Drugs Ther. 2010; 24(1):49–60. [PubMed: 20352314]

26. de Groote P, Helbecque N, Lamblin N, et al. Association between beta-1 and beta-2 adrenergic receptor gene polymorphisms and the response to beta-blockade in patients with stable congestive heart failure. Pharmacogenet Genomics. 2005; 15(3):137–142. [PubMed: 15861037]

27. Nonen S, Okamoto H, Fujio Y, et al. Polymorphisms of norepinephrine transporter and adrenergic receptor alpha1D are associated with the response to beta-blockers in dilated cardiomyopathy. Pharmacogenomics J. 2008; 8(1):78–84. [PubMed: 17404580]

28. Shin J, Lobmeyer MT, Gong Y, et al. Relation of beta(2)-adrenoceptor haplotype to risk of death and heart transplantation in patients with heart failure. Am J Cardiol. 2007; 99(2):250–255. [PubMed: 17223428]

29. Liggett SB, Wagoner LE, Craft LL, et al. The Ile164 beta2-adrenergic receptor polymorphism adversely affects the outcome of congestive heart failure. J Clin Invest. 1998; 102(8):1534–1539. [PubMed: 9788966]

30. Neumeister A, Charney DS, Belfer I, et al. Sympathoneural and adrenomedullary functional effects of alpha2C-adrenoreceptor gene polymorphism in healthy humans. Pharmacogenet Genomics. 2005; 15(3):143–149. [PubMed: 15861038]

31* *. Bristow MR, Murphy GA, Krause-Steinrauf H, et al. An alpha2C-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the beta-blocker bucindolol in chronic heart failure. Circ Heart Fail. 2010; 3(1):21–28. This was a large (n = 1040) pharmacogenetic sub-study of the BEST trial. They found bucindolol lowered cardiovascular mortality in ADRA2C insertion homozygotes but not deletion carriers. [PubMed: 19880803]

32*. Lobmeyer MT, Gong Y, Terra SG, et al. Synergistic polymorphisms of beta1 and alpha2C-adrenergic receptors and the influence on left ventricular ejection fraction response to beta-blocker therapy in heart failure. Pharmacogenet Genomics. 2007; 17(4):277–282. This paper demonstrated synergy between genetic variants and LVEF response to BBs in patients with HF. [PubMed: 17496726]

33. Kohout TA, Lefkowitz RJ. Regulation of G protein-coupled receptor kinases and arrestins during receptor desensitization. Mol Pharmacol. 2003; 63(1):9–18. [PubMed: 12488531]

34* *. Liggett SB, Cresci S, Kelly RJ, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. Nat Med. 2008; 14(5):510–517. This paper consisted of *in vitro*, case-control, and prospective observational studies. They found no difference in transplant-free survival in GRK5 Leu41-carriers regardless of BB treatment status.

Also, BB-naïve Leu41-carriers had longer transplant-free survival than BB-naïve Gln41 homozygotes. [PubMed: 18425130]

35* *. Cresci S, Kelly RJ, Cappola TP, et al. Clinical and genetic modifiers of long-term survival in heart failure. J Am Coll Cardiol. 2009; 54(5):432–444. This was a large (n = 2,460) pharmacogenetic study of ADRB1 Arg389Gly and GRK5 Gln41Leu. They found that these genetic variants, rather than race, are the major contributors to the difference in BB treatment effect in African-Americans and Caucasians. [PubMed: 19628119]

36*. Baudhuin LM, Miller WL, Train L, et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure. Am J Cardiol. 2010; 106(3):402–408. This recent study found that common variants in ADRB1, CYP2D6, and UGT1A1 were not associated with a clinical response to metoprolol or carvedilol therapy, but variants in ADRB1 and CYP2D6, alone and in haplotype, were significantly associated with the dose of carvedilol. [PubMed: 20643254]

37*. Petersen M, Andersen JT, Hjelvang BR, et al. Association of beta-adrenergic receptor polymorphisms and mortality in carvedilol-treated chronic heart-failure patients. Br J Clin Pharmacol. 2011; 71(4):556–565. This recent study demonstrates that there may be differential pharmacogenetic interaction depending on specific BB, as there was a significant interaction with carvedilol and not metoprolol. [PubMed: 21395649]

38. Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990; 86(4):1343–1346. [PubMed: 1976655]

39. O'Toole L, Stewart M, Padfield P, et al. Effect of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene on response to angiotensin-converting enzyme inhibitors in patients with heart failure. J Cardiovasc Pharmacol. 1998; 32(6):988–994. [PubMed: 9869506]

40. Cicoira M, Zanolla L, Rossi A, et al. Failure of aldosterone suppression despite angiotensin-converting enzyme (ACE) inhibitor administration in chronic heart failure is associated with ACE DD genotype. J Am Coll Cardiol. 2001; 37(7):1808–1812. [PubMed: 11401115]

41. Tang WH, Vagelos RH, Yee YG, et al. Impact of angiotensin-converting enzyme gene polymorphism on neurohormonal responses to high- versus low-dose enalapril in advanced heart failure. Am Heart J. 2004; 148(5):889–894. [PubMed: 15523323]

42*. McNamara DM, Holubkov R, Postava L, et al. Pharmacogenetic interactions between angiotensin-converting enzyme inhibitor therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. J Am Coll Cardiol. 2004; 44(10):2019–2026. This paper demonstrates dose-dependent *ACE* insertion/deletion association with transplant-free survival. The adverse effect of the deletion is exaggerated in patients not receiving BB, and that the adverse effects are eliminated with high-dose ACE inhibitor. [PubMed: 15542286]

43. Tiago AD, Badenhorst D, Skudicky D, et al. An aldosterone synthase gene variant is associated with improvement in left ventricular ejection fraction in dilated cardiomyopathy. Cardiovasc Res. 2002; 54(3):584–589. [PubMed: 12031704]

44. Cuoco MA, Pereira AC, Mota Gde F, et al. Genetic polymorphism, medical therapy and sequential cardiac function in patients with heart failure. Arq Bras Cardiol. 2008; 90(4):252–256. [PubMed: 18516385]

45*. Wu CK, Luo JL, Tsai CT, et al. Demonstrating the pharmacogenetic effects of angiotensin-converting enzyme inhibitors on long-term prognosis of diastolic heart failure. Pharmacogenomics J. 2010; 10(1):46–53. This paper extends the pharmacogenetic interaction between the *ACE* insertion/deletion and ACE inhibitors to HF patients with preserved LVEF. [PubMed: 19752885]

46. Vormfelde SV, Engelhardt S, Zirk A, et al. CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. Clin Pharmacol Ther. 2004; 76(6):557–566. [PubMed: 15592327]

47. Vormfelde SV, Schirmer M, Hagos Y, et al. Torsemide renal clearance and genetic variation in luminal and basolateral organic anion transporters. Br J Clin Pharmacol. 2006; 62(3):323–335. [PubMed: 16934049]

48. Vormfelde SV, Toliat MR, Schirmer M, et al. The polymorphisms Asn130Asp and Val174Ala in OATP1B1 and the CYP2C9 allele *3 independently affect torsemide pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008; 83(6):815–817. [PubMed: 18043684]
49. Vormfelde SV, Toliat MR, Schirmer M, et al. The polymorphisms Asn130Asp and Val174Ala in OATP1B1 and the CYP2C9 allele *3 independently affect torsemide pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008; 83(6):815–817. [PubMed: 18043684]
50. Vormfelde SV, Sehrt D, Toliat MR, et al. Genetic variation in the renal sodium transporters NKCC2, NCC, and ENaC in relation to the effects of loop diuretic drugs. Clin Pharmacol Ther. 2007; 82(3):300–309. [PubMed: 17460608]
51. Werner D, Werner U, Meybaum A, et al. Determinants of steady-state torasemide pharmacokinetics: impact of pharmacogenetic factors, gender and angiotensin II receptor blockers. Clin Pharmacokinet. 2008; 47(5):323–332. [PubMed: 18399713]
52*. Vormfelde SV, Brockmoller J. The genetics of loop diuretic effects. Pharmacogenomics J. 2010 [Epub ahead of print]. This paper demonstrates that genetic variation seems to be a stronger predictor of the loop diuretic drug response than pharmacokinetic variation.
53. Heart Failure Society of America. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010; 16(6):e1–194. [PubMed: 20610207]
54. Birkenfeld AL, Jordan J, Hofmann U, et al. Genetic influences on the pharmacokinetics of orally and intravenously administered digoxin as exhibited by monozygotic twins. Clin Pharmacol Ther. 2009; 86(6):605–608. [PubMed: 19776737]
55* *. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A. 2000; 97(7):3473–3478. This is the seminal paper describing the association between the *ABCB1* C3435T variant and P-glycoprotein expression and serum digoxin concentration. [PubMed: 10716719]
56. Johne A, Kopke K, Gerloff T, et al. Modulation of steady-state kinetics of digoxin by haplotypes of the P-glycoprotein MDR1 gene. Clin Pharmacol Ther. 2002; 72(5):584–594. [PubMed: 12426522]
57. Kurata Y, Ieiri I, Kimura M, et al. Role of human MDR1 gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. Clin Pharmacol Ther. 2002; 72(2):209–219. [PubMed: 12189368]
58. Verstuyft C, Schwab M, Schaeffeler E, et al. Digoxin pharmacokinetics and MDR1 genetic polymorphisms. Eur J Clin Pharmacol. 2003; 58(12):809–812. [PubMed: 12698307]
59. Comets E, Verstuyft C, Lavielle M, et al. Modelling the influence of MDR1 polymorphism on digoxin pharmacokinetic parameters. Eur J Clin Pharmacol. 2007; 63(5):437–449. [PubMed: 17404720]
60. Larsen UL, Hyldahl Olesen L, Guldborg Nyvold C, et al. Human intestinal P-glycoprotein activity estimated by the model substrate digoxin. Scand J Clin Lab Invest. 2007; 67(2):123–134. [PubMed: 17365992]
61. Xu P, Jiang ZP, Zhang BK, et al. Impact of MDR1 haplotypes derived from C1236T, G2677T/A and C3435T on the pharmacokinetics of single-dose oral digoxin in healthy Chinese volunteers. Pharmacology. 2008; 82(3):221–227. [PubMed: 18810246]
62*. Aarnoudse AJ, Dieleman JP, Visser LE, et al. Common ATP-binding cassette B1 variants are associated with increased digoxin serum concentration. Pharmacogenet Genomics. 2008; 18(4): 299–305. This paper extended the digoxin pharmacogenetic findings from single-dose healthy volunteer studies to a population of steady-state digoxin-using patients. They found that the common *ABCB1* C1236T, G2677T, and C3435T variants and the associated TTT haplotype were associated with higher SDC. [PubMed: 18334914]
63. Gerloff T, Schaefer M, Johne A, et al. MDR1 genotypes do not influence the absorption of a single oral dose of 1 mg digoxin in healthy white males. Br J Clin Pharmacol. 2002; 54(6):610–616. [PubMed: 12492608]
64. Chowbay B, Li H, David M, et al. Meta-analysis of the influence of MDR1 C3435T polymorphism on digoxin pharmacokinetics and MDR1 gene expression. Br J Clin Pharmacol. 2005; 60(2):159–171. [PubMed: 16042669]

65. Horinouchi M, Sakaeda T, Nakamura T, et al. Significant genetic linkage of MDR1 polymorphisms at positions 3435 and 2677: functional relevance to pharmacokinetics of digoxin. Pharm Res. 2002; 19(10):1581–1585. [PubMed: 12425480]

66. Sakaeda T, Nakamura T, Horinouchi M, et al. MDR1 genotype-related pharmacokinetics of digoxin after single oral administration in healthy Japanese subjects. Pharm Res. 2001; 18(10): 1400–1404. [PubMed: 11697464]

67*. Neuvonen AM, Palo JU, Sajantila A. Post-mortem ABCB1 genotyping reveals an elevated toxicity for female digoxin users. Int J Legal Med. 2011; 125(2):265–269. This recent paper demonstrates that the pharmacogenetic interaction between *ABCB1* C3435T and digoxin may be gender-specific. [PubMed: 21311904]

68. Adams KF Jr, Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol. 2005; 46(3):497–504. [PubMed: 16053964]

69*. McNamara DM, Holubkov R, Janosko K, et al. Pharmacogenetic interactions between beta-blocker therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. Circulation. 2001; 103(12):1644–1648. This was the first paper to report a pharmacogenetic interaction between the *ACE* insertion/deletion variant and BB survival benefit in patients with HF. [PubMed: 11273991]

70. Borjesson M, Magnusson Y, Hjalmarson A, et al. A novel polymorphism in the gene coding for the beta(1)-adrenergic receptor associated with survival in patients with heart failure. Eur Heart J. 2000; 21(22):1853–1858. [PubMed: 11052857]

71. Terra SG, Pauly DF, Lee CR, et al. beta-Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. Clin Pharmacol Ther. 2005; 77(3):127–137. [PubMed: 15735607]

72. Magnusson Y, Levin MC, Eggertsen R, et al. Ser49Gly of beta1-adrenergic receptor is associated with effective beta-blocker dose in dilated cardiomyopathy. Clin Pharmacol Ther. 2005; 78(3): 221–231. [PubMed: 16153393]

73. Muthumala A, Drenos F, Elliott PM, et al. Role of beta adrenergic receptor polymorphisms in heart failure: systematic review and meta-analysis. Eur J Heart Fail. 2008; 10(1):3–13. [PubMed: 18158268]

74. Littlejohn MD, Palmer BR, Richards AM, et al. Ile164 variant of beta2-adrenoceptor does not influence outcome in heart failure but may interact with beta blocker treatment. Eur J Heart Fail. 2008; 10(1):55–59. [PubMed: 18068431]

75. Taylor MR, Slavov D, Humphrey K, et al. Pharmacogenetic effect of an endothelin-1 haplotype on response to bucindolol therapy in chronic heart failure. Pharmacogenet Genomics. 2009; 19(1):35–43. [PubMed: 18953265]

76. Cicoira M, Rossi A, Bonapace S, et al. Effects of ACE gene insertion/deletion polymorphism on response to spironolactone in patients with chronic heart failure. Am J Med. 2004; 116(10):657–661. [PubMed: 15121491]

77. de Denus S, Zakrzewski-Jakubiak M, Dube MP, et al. Effects of AGTR1 A1166C gene polymorphism in patients with heart failure treated with candesartan. Ann Pharmacother. 2008; 42(7):925–932. [PubMed: 18594050]

78. McNamara DM, Tam SW, Sabolinski ML, et al. Aldosterone synthase promoter polymorphism predicts outcome in African Americans with heart failure: results from the A-HeFT Trial. J Am Coll Cardiol. 2006; 48(6):1277–1282. [PubMed: 16979018]

79. McNamara DM, Tam SW, Sabolinski ML, et al. Endothelial nitric oxide synthase (NOS3) polymorphisms in African Americans with heart failure: results from the A-HeFT trial. J Card Fail. 2009; 15(3):191–198. [PubMed: 19327620]

Table 1

Genetic variants associated with HF pharmacotherapy response

GENE	VARIANT	rsID	BENEFICIAL ALLELE	REFERENCES
BETA BLOCKERS				
ACE	Ins/Del	rs1799752	Del	[42, 69]
ADRA1D	T1848A	rs2236554	A	[27]
	A1905G	rs709024	G	[27]
ADRA2C	Ins/Del	rs61767072	Ins	[36]
			Del	[31]
ADRB1	Ser49Gly	rs1801252	Gly	[11, 13, 70-72]
	Arg389Gly	rs1801253	Arg	[2, 10, 11, 13, 14, 17, 25, 31, 35, 37, 71-73]
			Gly	[37]
ADRB2	Gln27Glu	rs1042714	Glu	[23-25, 37]
	Thr164Ile	rs1800888	Thr	[74]
EDN1	G/A (IVS)-4	rs2071942	G	[75]
	Lys198Asn	rs5370	Lys	[75]
GRK5	Gln41Leu	rs17098707	Gln	[33, 34]
NET	T-182C	rs2242446	T	[27]
ACE INHIBITORS				
ACE	Ins/Del	rs1799752	Ins	[39-42, 45]
AGTR1	A1166C	rs5186	A	[45]
CYP11B2	T-344C	rs1799998	C	[43]
ALDOSTERONE ANTAGONISTS				
ACE	Ins/Del	rs1799752	Ins	[76]
ANGIOTENSIN RECEPTOR BLOCKERS				
AGTR1	A1166C	rs5186	C	[77]
HYDRALAZINE/ISOSORBIDE DINITRATE				
CYP11B2	T-344C	rs1799998	C	[78]
NOS3	Glu298Asp	rs1799983	Glu	[79]
***LOOP DIURETICS**				
ACE	Ins/Del	rs1799752	Del	[52]
ADD1	Gly460Trp	rs4961	Trp	[52]
ANP	Val32Met	rs5063	Val	[52]
	Ter152Arg	rs5065	Arg	[52]
CYP2C9	CYP2C9*1/*2/*3	n/a	*3	[46]
GNB3	C825T	rs5443	C	[52]
SCNN1B	Most frequent haplotype vs. others	n/a	Most frequent haplotype	[50]
SCNN1G	C4G	rs5723	C	[50]
SLC12A3	Gly264Ala	rs1529927	Ala	[50]

* Data from healthy volunteers

ACE = angiotensin converting enzyme, ADD1 = alpha adducin 1, ADRA1D = alpha-1d adrenergic receptor, ADRA2C = alpha-2c adrenergic receptor, ADRB1 = beta-1 adrenergic receptor, ADRB2 = beta-2 adrenergic receptor, AGTR1 = angiotensin II receptor type 1, Arg = arginine, ANP = atrial natriuretic peptide precursor, Asn = asparagine, CYP11B2 = cytochrome P450 family 11 subfamily B polypeptide 2, CYP2C9 = cytochrome P450 family 2 subfamily C polypeptide 9, Del = deletion, EDN1 = endothelin-1, Gln = glutamine, Glu = glutamic acid, Gly = glycine, GNB3 = guanine nucleotide binding protein beta polypeptide 3, GRK5 = G-protein coupled receptor kinase 5, Ile = isoleucine, Ins = insertion, IVS = intervening sequence, Leu = leucine, Lys = lysine, Met = methionine, NET = norepinephrine transporter, NOS3 = nitric oxide synthase 3, SCNN1B = sodium channel nonvoltage-gated 1 beta, SCNN1G = sodium channel nonvoltage-gated 1 gamma, Ser = serine, SLC12A3 = solute carrier family 12 member 3, Ter = termination, Thr = threonine, Trp = tryptophan, Val = valine

Table 2

Frequencies of genetic variants associated with HF pharmacotherapy response

GENE	VARIANT	rsID	MINOR ALLELE	CAUCASIAN	AFRICAN-AMERICANS
ABCB1	C3435T	rs1045642	C	45%	87% (Africans)
ACE	Ins/Del Intron 16	rs1799752	Ins	44%	43%
ADD1	Gly460Trp	rs4961	Trp	17%	11%
ADRA1D	T1848A	rs2236554	A	46%	12% (Africans)
	A1905G	rs709024	A	38%	70% (Africans)
ADRA2C	Ins/Del 322-325	rs61767072	Del	4%	43%
ADRB1	Ser49Gly	rs1801252	Gly	17%	25%
	Arg389Gly	rs1801253	Gly	27%	38%
ADRB2	Gly16Arg	rs1042713	Arg	40%	50% (Africans)
	Gln27Glu	rs1042714	Glu	42%	20%
	Thr164Ile	rs1800888	Ile	2%	<2% (Africans)
AGTR1	A1166C	rs5186	C	25%	5%
ANP	Val32Met	rs5063	Met	4%	2%
	Ter152Arg	rs5065	Ter	14%	43% (Africans)
CYP11B2	T-344C	rs1799998	C	43%	30%
CYP2C9	*2	N/A	N/A	14%	<1%
	*3	N/A	N/A	11%	<1%
EDN1	G/A (IVS)-4	rs2071942	A	29%	17% (Africans)
	Lys198Asn	rs5370	Asn	30%	17%
GNB3	C825T	rs5443	T	39%	91% (Africans)
GRK5	Gln41Leu	rs17098707	Leu	2%	24%
NET	T-182C	rs2242446	C	25%	15% (Africans)
NOS3	Glu298Asp	rs1799983	Asp	22%	7% (Africans)
SCNN1B	Most frequent haplotype	N/A	n/a	65%	n/a
SCNN1G	C4G	rs5723	G	28%	24% (Africans)
SLC12A3	Gly264Ala	rs1529927	Ala	8%	<1% (Africans)