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Progress toward genetic tailoring of heart failure therapy

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Abstract

Heart failure (HF) is a modern epidemic and a heterogeneous disorder with many therapeutic options. While the average response to each individual treatment is favorable, significant interindividual variation exists in the response to HF therapeutics. As a result, the optimal regimen for an individual patient or subgroup of patients is elusive, with current treatment being mainly empirical. Pharmacogenetic customization of HF therapy may provide an important opportunity to improve the treatment of HF. Common genetic variations exist in genes related to most classes of HF drugs, many of which have known functional consequences for or established relationships with drug response. This review summarizes the current understanding of the pharmacogenetics of HF therapeutics, including angiotensin-converting enzyme inhibitors and β-blockers, and focuses on recent advances and medium-term expectations for the field.

Keywords

Aldosterone antagonist; angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; β-blocker; heart failure; personalized medicine; pharmacogenetics

Introduction

Heart failure (HF) is a modern epidemic and an increasing public health concern. As mortality from coronary artery disease and stroke decline, the prevalence of HF increases, with approximately 5 million individuals affected and more than 500,000 new cases annually in the US. HF is lethal, with 1-year mortality rate estimates ranging from 25 to 45% [1,2]. The management of HF is also costly because of the chronic, progressive nature and frequent exacerbations of the disease, resulting in 3.4 million hospital visits in 2006 in the US [2]. Furthermore, with an incidence of approximately 10% in patients over 65 years of age and an aging population, this disease is likely to increase in importance [2].

HF is a heterogeneous disorder arising from a variety of etiologies that result in inadequate cardiac performance. After an initial (and potentially ongoing) insult, the disease is characterized by cascades of adverse physiological responses that lead to vasoconstriction, fluid retention and further compromise of cardiac function. These sympotoms are often accompanied by adverse cardiac remodeling and dilation, with reduced ejection fraction, although half of all patients with HF maintain an ejection fraction that is almost normal [3]. Maladaptive physiological responses in HF are well described, including the upregulation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, as well

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as other responses that are less understood, such as the involvement of inflammatory and apoptotic pathways in this disease [1,4–6].

Treatment strategies that are proven to reduce mortality are limited to use in patients with HF with reduced ejection fraction; therefore, this review focuses mainly on this patient group. Most therapeutic agents with established benefit act by interrupting the neurohormonal pathways discussed previously (ie, RAAS and the sympathetic nervous system), such as β-blockers (BBs), angiotensin-converting enzyme (ACE) inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) and aldosterone antagonists [7]. However, other therapies such as hydralazine-isosorbide dinitrate (HN) combination therapy have mechanisms of action that are less understood. Other important drugs that are commonly used in HF include drugs targeting disease symptoms, such as diuretics and digoxin, or complications, such as warfarin.

As the number of drug classes that are indicated for use in HF has increased (currently at least seven drug classes), it has become more difficult to determine whether each additional therapy has incremental benefit that outweighs the added risks and cost for specific individuals or subgroups of patients. While the average population response to HF therapeutics is favorable, significant interindividual variation exists in the response (Figure 1). This variability should not be surprising given the diverse etiologies and genetic backgrounds upon which the HF phenotype can occur. Common genetic variation exists in genes related to most classes of HF drugs, and many of these variants have known functional consequences. As more is understood about the interplay of drugs and genes, genetic sequence variants may help to explain some of the variation in patient responses, and therefore may help physicians to provide more rational, efficient and targeted treatments for HF [8].

This review discusses the current understanding of the pharmacogenetics of HF therapies, focusing on recent advances and expectations for the near future. Therapies discussed include ACE-Is, ARBs, aldosterone receptor antagonists, BBs, natriuretic peptides (NPs), HN, diuretics and warfarin. These examples vary in terms of the amount of data available and, therefore, are illustrative of the range of advances in studying pharmacogenetics from an early stage of understanding (eg, HN) to more advanced stages (eg, warfarin). A better understanding of the pharmacogenetics of HF therapies, its advances and limitations, and how this field is advancing toward clinical use is important to optimize how physicians incorporate this emerging clinical science.

Antagonizing the renin-angiotensin-aldosterone system

Inhibition of the RAAS is a major focus of therapy in HF. There have been a large number of pharmacogenetic studies related to agents targeting the RAAS. The most interesting genetic variants and associated phenotypes for response to HF therapy, categorized by relevant therapeutic agent, are summarized in Table 1.

Angiotensin-converting enzyme inhibitors

Treatment with an ACE-I is a cornerstone of HF therapy, and is recommended to all patients with HF without contraindication [7]. ACE-Is have demonstrated survival benefit in multiple randomized clinical trials for HF with reduced ejection fraction [9]. These agents block the production of angiotensin II by antagonizing ACE (encoded by the *ACE* gene), reducing the adverse effects of angiotensin II, including vasoconstriction, aldosterone production and ventricular remodeling [5].

Many studies have been conducted to identify pharmacogenetic interactions of ACE-I, but a clear understanding of these interactions remains elusive [10–19]. One polymorphism that has been studied extensively is a 287-bp insertion/deletion (I/D) in intron 16 of the *ACE* gene (rs4646994). While one study suggested that the *ACE* I/D genotype affects ACE-I efficacy in heart failure [14], this variant remains of uncertain importance, and has been reviewed elsewhere recently (see references [20,21]). In terms of adverse drug effects, a polymorphism in the gene encoding the neurokinin-2 receptor (*TACR2*) has been associated with ACE-I-induced cough, a frequent side effect that often leads to discontinuation of the drug [22]. A large, ongoing clinical trial, the PERindopril GENEtic association study (PERGENE), may provide new insights into ACE-I pharmacogenetics [23]. This cohort trial aims to genotype polymorphisms from 11 candidate genes in patients (n = 12,218) treated with ACE-Is for stable coronary artery disease. Although HF is not an endpoint of this study, new pharmacogenetic interactions that can be tested in patients with HF may be identified.

Angiotensin receptor blockers

Clinically, ARBs are primarily useful in HF as a substitute for ACE-Is and have been demonstrated to have comparable survival benefit in this setting [24,25]. ARBs inhibit the binding of angiotensin II to its primary receptor, angiotensin receptor type 1, which is encoded by *AGTR1*. While there are relatively few studies of ARB pharmacogenetics specifically in patients with HF, several studies in hypertension have been conducted and many of the response phenotypes (eg, blood pressure lowering and reversal of hypertrophy) are relevant for HF. One study revealed significantly faster reduction of left ventricular hypertrophy after the initiation of ARB therapy in *ACE* D-allele carriers [26]. Another study examining the efficacy of ARBs as add-on therapy to ACE-Is demonstrated that carriers of the C-allele at the *AGTR1* A1166C polymorphism (rs5186), which is located in a microRNA binding site in the 3′ untranslated region [27], had greater blood pressure and N-terminal proB-type NP (NT-proBNP) responses to treatment [28]. The study was provocative, but was underpowered, necessitating validation studies before further inferences can be made. Additional *AGTR1* variants may also be related to blood pressure reductions resulting from ARB treatment. A small study of irbesartan in patients with hypertension identified a significant relationship between irbesartan concentration and *AGTR1* genotype for blood pressure reduction. The associated SNP is in the promoter of *AGTR1* (rs1492078) [29], suggesting a potential role via transcriptional regulation. ARBs are metabolized via the cytochrome P450 (CYP) enzymes, and genetic variations in CYP enzymes have been implicated in affecting the response to some ARBs [30]. Specifically, the *CYP2C9*2* variant was demonstrated to increase the blood pressure reduction observed with irbesartan in patients with hypertension [31], with some evidence for an impact on losartan efficacy [32–34].

Aldosterone receptor antagonists

Aldosterone receptor antagonists have demonstrated reductions in mortality in two clinical trials: one in patients with severe HF [35] and one in patients with HF after acute myocardial infarction [36]. Thus, these agents are Class I indicated in suitable patients [7]. Pharmacogenetic data for the effect of aldosterone antagonists is limited, but one small study has investigated the pharmacogenetics of these agents in patients with HF [37]. Patients receiving standard HF therapy (n = 93) were randomly assigned to receive spironolactone or placebo. Among patients receiving spironolactone, only *ACE I/D* insertion carriers had significant improvement in ejection fraction, compared with baseline values. Conversely, when comparing changes in ejection fraction between the spironolactone and placebo groups, *ACE* D/D homozygotes trended toward a stronger effect (3.0 in D/D vs 1.7;

p = not significant) [37]. Additional studies to further elucidate the role of pharmacogenetics in response to aldosterone receptor antagonists are needed.

β-adrenergic antagonists

BBs have been demonstrated to reduce HF mortality in multiple randomized clinical trials and are recommended for the treatment of all patients with HF without contraindications [7]. BBs antagonize the β-adrenergic receptors (β-ARs), a family of GPCRs that increase heart rate and cardiac contractility, and stimulate renin release in the kidneys. Despite the efficacy of these compounds in clinical trials, response to BBs varies significantly, with inconsistent recovery of ejection fraction, and many patients continuing to experience disease progression [38]. These agents also have potential adverse effects, particularly during dose titration, such as reduced contractility, bradycardia and the potential to cause or worsen HF exacerbations [39]. Increasing evidence suggests that genetic factors may explain some of this variability. The pharmacogenetic factors associated with BBs have been reviewed in detail elsewhere (see reference [40]), and the discussion in this review summarizes the key points and focuses on current and future directions. The key genetic variants relevant to BB therapy, their molecular phenotypes and the associated clinical phenotypes are summarized in Table 2.

Adrenergic receptor polymorphisms

The adrenergic receptor genes are highly polymorphic, and many of the variants have functional consequences. Much attention has focused on *ADRB1* and *ADRB2*, which encode the β-AR1 and β-AR2, respectively; these receptors are the molecular targets for BBs. The variants in these genes and their functional consequences have been well researched (see references [41,42]). Variants in both *ADRB1* and *ADRB2* have been associated with improvements in ejection fraction with BB treatment [43,44]. Subsequently, several large cohort studies have been conducted to examine the relationship between β-AR polymorphisms, mortality rates and treatment with carvedilol or metoprolol in patients with HF [45–47]; one study has been conducted in patients with acute coronary syndrome [46]. These studies have revealed varying results, with two studies indicating an important association for the *ADRB2* haplotype, but not *ADRB1* variants [45,46], one indicating that the *ADRB1* $Arg^{389}Gly$ variant is significant, but not the *ADRB2* variants [47], and two studies demonstrating no significant association with any of these variants [48,49]. Taken together, these data do not support a definitive conclusion. It is important to note that all of these studies are limited because they included few or no patients who were BB naive, making inference as to the effects of the drug more difficult.

Conversely, the randomized, controlled β-blocker Evaluation of Survival Trial (BEST) investigated the effects of bucindolol (ARCA biopharma Inc) [50]. The clinical trial was terminated prematurely, failed to meet its primary endpoint and demonstrated little overall benefit with bucindolol therapy, in contrast with other published trials of BB therapy in HF. Subsequent pharmacogenetic analyses of these data revealed that there was enhanced benefit for bucindolol among *ADRB1* Arg^{389} homozygotes [51]. Following the discovery of this pharmacogenetic association, the developers of bucindolol submitted an NDA to the FDA for bucindolol to be used in conjunction with a genetic test for the *ADRB1* $Arg^{389}Gly$ genotype; bucindolol would have been the first genetic-guided therapy to be approved for HF. Recently, the FDA review panel examined this issue, but did not recommend approval [52]. While clinical use of pharmacogenetics to guide BB therapy awaits further data, the experience with bucindolol is indicative of how close pharmacogenetics may be to being applied in the clinic for HF.

α-AR variants may also have an impact on the response to BB therapy. *ADRA2C* encodes the α_{2c}-AR, which regulates presynaptic norepinephrine release. Another substudy of the BEST trial examined the effects of a frame-shift mutation caused by a 12-nucleotide deletion in exon 1 of *ADRA2C* (rs61767072) [53]. A previous analysis suggested that patients with a strong sympatholytic response to bucindolol were at an increased risk of adverse events, indicating that changes in the ability of *ADRA2C* to regulate sympathetic activity might be involved [54]. While no difference in sympathetic activity by genotype was observed in the placebo group, patients with the *ADRA2C* deletion demonstrated a greater sympatholytic response than wild-type homozygotes to bucindolol treatment; only wild-type homozygotes exhibited reductions in mortality and in need for transplantation with bucindolol treatment [53].

Within the adrenergic system, some important multilocus or epigenetic effects have recently been discovered. Pharmacogenetic analysis of a large cohort of patients with hypertension demonstrated that the *ADRB1* Ser^{49}/Arg^{389} haplotype was associated with increased mortality at baseline and significant improvement with atenolol therapy, but no response to treatment with verapamil [55]. However, allelic associations were not tested, making the contribution of each allele and the extent of any interaction unclear. The *ADRB1* Arg^{389} allele may also interact with polymorphisms in *ADRA2C*. Kardia *et al* recently identified significant gene-gene interactions between *ADRB1* and *ADRA2C* [56], confirming results from a previous study demonstrating that Arg^{389} homozygotes carrying a deletion in *ADRA2C* experienced the greatest improvement in left ventricle ejection fraction (LVEF) with BB treatment [57].

Other associated genes

Downstream of the gene encodingβ-AR, polymorphisms in proteins related to signal transduction may also affect individual response to BBs. For example, G-protein receptor kinase 5 (GRK5) phosphorylates β-ARs in the myocardium, resulting in uncoupling of the receptor from adenyl cyclase [58]. A non-synonymous $Glu^{41}Leu$ substitution in the *GRK5* gene identified by Liggett *et al* results in enhanced uncoupling *in vitro* and in animal models [59]. A pharmacogenetic interaction between the $Gln^{41}Leu$ polymorphism and BB use was also identified in humans. In a prospective cohort of African American patients (n = 375), the authors also showed that Leu^{41} carriers had better survival than Gln^{41} homozygotes in the absence of BB therapy, while there was no difference between genotype groups when treated with BB, indicating selective benefit of BB for Gln homozygotes [59]. These findings were confirmed by Cresci *et al* in African Americans; however, no association was observed in Caucasians, in whom the variant is approximately one-tenth as frequent compared with African Americans [47].

Given the far-ranging effects of manipulating the adrenergic system, polymorphisms in even more distantly associated genes or pathways may impact variability in response to BB. For example, one of the early associations of the *ACE* I/D polymorphism was BB response [60], although this finding has not been confirmed by further studies [61]. More recently, a study of patients (n = 309) with idiopathic dilated cardiomyopathy from the BEST trial was conducted examining the polymorphisms in the gene encoding endothelin 1 (*EDN1*), based upon previous research demonstrating decreases in endothelin levels with bucindolol treatment [62]. A pharmacogenetic interaction was identified between bucindolol treatment and *EDN1* genotype. Two SNPs, rs5370 and rs2071942 (loci are in linkage disequilibrium (LD)), were associated with the rate of HF hospitalization and all-cause mortality in bucindolol-treated patients, but not in the placebo group [63].

β-blocker metabolism

Polymorphisms affecting drug metabolism may also be important in BB selection and dosing. CYP2D6 metabolizes metoprolol and, to a lesser extent, carvedilol. A study by Bijl *et al* determined that CYP2D6*4 homozygotes (ie, poor metabolizers) had significantly lower heart rate and diastolic blood pressure with metoprolol treatment than either CYP2D6*1 homozygotes (ie, extensive metabolizers) or heterozygotes (ie, intermediate metabolizers) [64]. No differences were observed by genotype in patients treated with atenolol. In patients with HF receiving metoprolol, a small study by Sharp *et al* demonstrated that the *CYP2D6* genotype influenced metoprolol blood concentration significantly, but had no effect on metoprolol dosing or clinical outcomes [65]. However, the study was underpowered with respect to poor metabolizers (n = 3), suggesting that further research is required [65].

Other agents of interest in heart failure

Natriuretic peptide system

The importance of the NP system in cardiovascular homeostasis and HF has been recognized increasingly [66]. The NP system is understood to be an important counter-regulatory system that reduces blood pressure and has general salutary effects in HF. There are three naturally occurring NPs: atrial NP (ANP); B-type NP (BNP); and C-type NP (CNP). BNP has applications in HF diagnosis and prognosis, but this molecule and the other NPs are also useful as therapeutics. Recombinant BNP (ie, nesiritide) and ANP (ie, carperitide) have been approved for the treatment of HF in the US and Japan, respectively, and other ‘designer’ peptides are being investigated [67,68].

Improved targeting of NP therapies is highly desirable because these compounds are currently expensive, parenteral and associated with adverse effects despite being efficacious. Pharmacogenetics may help to improve targeting, as substantial evidence suggests the importance of genetic variation in the NP system (reviewed in reference [66]). An analysis from the Framingham Study identified three SNPs in *NPPA* and *NPPB* that were significantly associated with both circulating NP levels and blood pressure [69]. From a strictly pharmacogenetic perspective, there have been limited published studies related to NPs and HF, but ongoing studies promise important results within the next few years. An NIH-funded pharmacogenetic assessment of the effect of recombinant BNP in patients with HF, measuring pharmacokinetic (ie, drug levels and elimination) and pharmacodynamic (ie, serum and urine cyclic guanosine monophosphate) endpoints, is ongoing. In addition, an ongoing, large (n = 7000), randomized clinical trial of BNP in acutely decompensated HF (ASCEND-HF) is also collecting genetic samples and should have adequate power to investigate the effects of drug and genotype interactions on important clinical outcomes such as dyspnea and clinical events (ie, death or hospitalization) [70].

Isosorbide-dinitrate/hydralazine

Combination therapy with HN is, to our knowledge, the first drug that is approved and marketed based on race, having been tested for the treatment of HF in self-identified African-Americans. This therapy has resulted in many interesting questions regarding medical care, race and genetics. Racial differences in response to HN treatment were first identified in a post-hoc analysis of the V-HeFT-II trial that compared HN with enalapril in patients with HF [71]. As a result, the benefit of HN in addition to standard therapy (ie, BBs and ACE-Is) was then tested in self-identified African-Americans in the African-American Heart Failure Trial (AA-HeFT) [72]. The randomized trial demonstrated a 40% reduction in the relative risk for death, leading to FDA approval of the drug. This approach highlights the question of whether it is desirable to use race to assign medical therapy, and underscores the

need to better understand the genetic and biological differences that belie such race-based differences in efficacy. Race is a social construct that is at best an approximate proxy for biological differences, and includes several other components such as shared cultural and environmental factors that must be separated from genetic/biological factors. Pharmacogenetics may be able to more precisely identify the genetic differences in such cases, and may nullify the motivation to use race as a classifier for medical treatment. Thus, it is a high research priority to identify the genetic underpinnings of race-based difference in drug efficacy, such as those observed with HN.

With respect to HN therapy, the genetic determinants of response remain an active area of investigation, but some data indicate that polymorphisms in the gene *NOS3*, encoding endothelial nitric oxide synthase, may contribute to the race-specific benefit. Because HN is thought to act as a nitric oxide donor, individuals with lower *NOS3* activity might be expected to benefit more from HN therapy. A substudy of the AA-HeFT trial identified three *NOS3* polymorphisms with significant differences in frequency in African-Americans and Caucasians [73]. A pharmacogenetic interaction was identified between a non-synonymous polymorphism (rs1799983) that results in an $Asp^{298}Glu$ mutation. Glu^{298} homozygotes benefited significantly from HN treatment, whereas Asp^{298} carriers did not [73]. However, because this effect was mostly in quality-of-life scores and given the limited sample size (n = 352), this study should be interpreted as hypothesis-generating.

Diuretics

Diuretics are recommended in patients with HF who have evidence of fluid retention [7]. Several classes of diuretics are administered; however, loop diuretics are the most frequently used agents. Although there are relatively few pharmacogenetic studies examining diuretics, some results relevant to HF exist.

Specific to diuretic therapy in HF, a small study examining the interaction of polymorphisms in *CYP2C9* and *SLCO1B1* (solute carrier organic anion transporter family, member 1B1) genes and torsemide, a long-acting loop diuretic used in patients with HF, demonstrated that CYP2C9*3 and *SLCO1B1* C521T (rs4149056) had a significant effect on the plasma concentration and half-life of torsemide [74]. Other diuretic classes have also been investigated. For example, Lynch *et al* studied two SNPs in the *NPPA*/*NPPB* gene regions, rs5063 and rs5065, in patients (approximate n = 38,000) in a subgroup of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [75]. In patients carrying at least one C-allele at rs5065, treatment with chlorthalidone resulted in a significantly lower incidence of coronary heart disease, stroke and combined cardiovascular disease, as well as significantly lower all-cause mortality, when compared with amplodipine treatment; these effects appeared to be independent of changes in blood pressure.

Warfarin

Anticoagulation therapy with warfarin is commonly indicated in patients with HF because of comorbid conditions that result in an increased risk of thromboembolism, such as atrial fibrillation or severely impaired left ventricular function. Warfarin acts by binding to the vitamin K 2,3-epoxide reductase complex (VKORC1), the enzyme responsible for reducing vitamin K to its active form [76]. Warfarin is primarily metabolized to its inactive form by CYP2C9 [77]. By interfering with vitamin K recycling, warfarin prevents the vitamin K-dependent carboxylation of the clotting Factors II, VII, IX and X, thus exerting its anticoagulant effect [78]. Warfarin is one of the best understood examples of the role of pharmacogenetic interactions, with excellent reviews recently published on this topic [79,80]. The two key genes in warfarin pharmacogenetics *VKORC1* and *CYP2C9* account

for approximately 40% of variation in warfarin dosing (Figure 2) [81]. Several developments that are illustrative of the advancement of pharmacogenetics in HF are discussed in this section.

The use of pharmacogenetics to determine the dosing of warfarin is at advanced stages of development, serving as a good example to illustrate the requirements for bringing pharmacogenetics to the clinic, including practical genotype-based dosing guide and randomized interventional pharmacogenetic trials Warfarin is one of the only drugs to have been investigated for pharmacogenetic interactions using a genome-wide approach. Two studies by Cooper *et al* [82] and Takeuchi *et al* [83] examined patients (n = 379 and 1053, respectively) beginning warfarin therapy. While neither study identified any new associations, the feasibility of a genome-wide approach was confirmed, as were the effects from *VKORC1* and *CYP2C9* variants.. Genetically driven dosing algorithms have been derived and published for warfarin [84,85]. In addition, a large, NIH-sponsored interventional trial (Clarification of Optimal Anticoagulation through Genetics [COAG]) is ongoing to assess the benefit of genotyping prior to the initiation of treatment on warfarin dosing and on adverse effects. The COAG trial is expected to be completed in 2012 (ClinicalTrials.gov identifier: NCT00839657).

Warfarin also serves as a good test case for examining the cost-effectiveness of genetic testing prior to drug initiation. Although genotyping can help guide warfarin dosing [86–88], it has not been demonstrated adequately that genotyping helps to avoid adverse effects. A recent meta-analysis did not find sufficient evidence to support the use of genetic information for warfarin dosing [89]. Another study suggested that there was a 10% chance that genotype-guided warfarin dosing would be cost-effective, even with fairly optimistic assumptions for genotyping cost and processing time [90]. However, with the results of studies such as the COAG trial or with future advances in genotyping technologies, genotyping may become an important clinical strategy for determining warfarin dose.

Conclusion

HF should be considered a prime target for pharmacogenetics and personalized medicine given the great burden of disease and multiplicity of therapeutic options. Research progress in pharmacogenetics is broadly accelerating as a result of improving research technologies with lower costs, larger study cohorts, and increased awareness and acceptance in the wider medical community. Cardiovascular therapies are no exception to the increase in interest in pharmacogenetics, as illustrated by the examples described in this review, such as BBs and warfarin, which are at an advanced stage. However, even in these advanced cases, as well as in newer examples such as NPs, much research remains before clinical pharmacogenetics will be commonplace. First, and most importantly, is the need for emphasis to be placed on investigating the clinical implementation of genetically guided therapy. Warfarin is an instructive example, demonstrating that the creation of usable pharmacogenetic tools rely not only on associating a genotype with a drug-response phenotype, but also requires creating usable decision guidelines, establishing superiority to empirical therapy and demonstrating cost-effectiveness. These requirements necessitate more interventional pharmacogenetic studies (ie, assigning patients to genetic-based therapy compared with empirical therapy) to meet this goal. The second main challenge is to apply pharmacogenetics earlier in the drug development process such that future clinical applications of PGs do not require as long to develop as the current generation. If early-phase trials included broad genotyping and association to surrogate endpoints, phase III pivotal trials could simultaneously include candidate gene studies, greatly accelerating progress toward clinically useful genetic markers and genetically guided therapy. While there has been relatively slow clinical adaptation of pharmacogenetic findings thus far, this

situation is changing, and is likely to accelerate. If successful, pharmacogenetics will define a new era of advancement, producing many new tools to improve the treatment of patients using genetics.

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•• of outstanding interest

• of special interest

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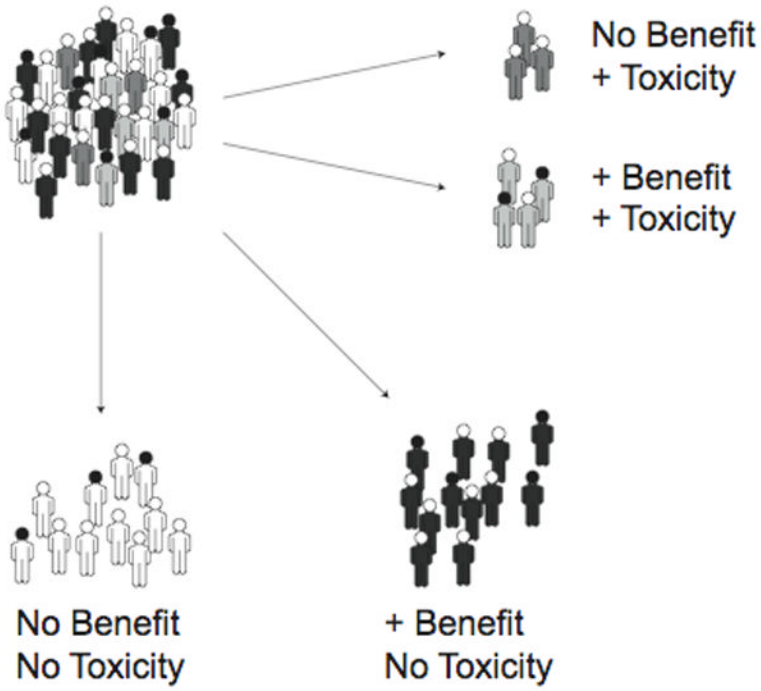

Figure 1. Variation in drug response within a disease population

The different coloring of figures represents underlying genetic heterogeneity between individuals with the same medical diagnosis. Pharmacogenomics seeks to understand this heterogeneity, use it to have better estimates of the risks and benefits of medical intervention, and then utilize it to provide improved care for individual patients.

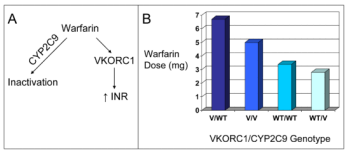

Figure 2. Pharmacogenetic influences on warfarin dosing

(**A**) The warfarin drug pathway. (**B**) The average maintenance dose of warfarin is dependent on ***VKORC1*** (vitamin K 2,3-epoxide reductase complex) and ***CYP2C9*** (cytochrome P450 family 2 subfamily C polypeptide 9) genotypes (data from reference [81]).
INR international normalized ratio**, V** variant, **WT** wild-type

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Table 1

Summary of variants with pharmacogenetic interactions for RAAS-modulating agents in HF.

Drug	Gene	Polymorphism	rs number	Molecular phenotype	Clinical phenotype	Reference
ACE inhibitors	*ACE*	Intron 16 I/D	rs4646994	Increased ACE level associated with D-allele	D-allele homozygotes with HF had lower event-free survival on low-dose ACE inhibitor therapy.	[14,91]
	TACR2	$Gly^{231}Glu$		Coding SNP of unknown function	In patients (n = 91) receiving ACE inhibitor therapy, only Gly^{231} carriers developed chronic cough.	[22]
Angiotensin receptor blockers	*ACE*	Intron 16 I/D	rs4646994	Increased ACE level associated with D-allele	Faster reduction of LVH in D-allele carriers with angiotensin receptor blocker therapy.	[26,91]
	AGTR1	A1166C	rs5186	3′ Untranslated region SNP located in a microRNA binding site	C-allele carriers had better BP and NT-proBNP responses with the addition of candesartan to treatment including an ACE inhibitor.	[27,28]
	AGTR1	A-480G	rs1492078	Located 5′ to gene in the promoter region	A significant interaction between irbesartan treatment and BP reduction was observed.	[29]
	CYP2C9	$Arg^{144}Cys$ (CYP2C9* 2)	rs1799853	Reduced catalytic capacity for certain angiotensin receptor blockers compared with *CYP2C9*1*	*CYP2C9*2* genotype increased BP response to irbesartan treatment.	[30,31]
Aldosterone antagonists	*ACE*	Intron 16 I/D	rs4646994	Increased ACE level associated with D-allele	Among patients with HF, only carriers of the I-allele demonstrated improvements in EF, EDV and ESV with spironolactone treatment.	[37,91]

ACE Angiotensin 1-converting enzyme, ***AGTR1*** angiotensin II receptor type 1, **BP** blood pressure, ***CYP2C9*** cytochrome P450 family 2 subfamily C polypeptide 9, **EDV** end diastolic volume, **EF** ejection fraction, **ESV** end systolic volume, **HF** heart failure, **I/D** insertion/deletion, **LVH** left ventricular hypertrophy, **NT-proBNP** N-terminal proB-type natriuretic peptide, **RAAS** renin-angiotensin-aldosterone system, ***TACR2*** tachykinin receptor 2

Table 2

Summary of variants with pharmacogenetic interactions for β-blocker therapy in heart failure.

Gene	Polymorphism/mutation	rs number	Molecular phenotype	Clinical phenotype	Reference
ADRB1	$Arg^{389}Gly$	rs1801253	Arg^{389} demonstrated differential effects on adenylyl levels in normal and heart failure tissues.	Increased survival or LVEF β-blocker response with $Arg^{389}Arg$. Gly^{389} associated with greater survival response in a separate study. Possibly involved in gene-gene interactions.	[44,47,51,56,57,92–94]
	$Ser^{49}Gly$	rs1801252	Gly^{49} allele leads to greater receptor downregulation on stimulation.	Lower 5-year mortality in Gly^{49} carriers on low-dose β-blockers, but no difference with high-doses.	[95,96]
ADRB2	$Glu^{27}Gln$	rs1042714	Glu^{27} allele has decreased receptor downregulation.	Glu^{27} allele associated with better response to carvedilol.	[43,97]
	$Gly^{16}Arg$	rs1042713	Gly^{16} allele has greater receptor downregulation with receptor stimulation.	Increased risk of death or transplantation detected for Arg^{16}/Gln^{27} double homozygotes.	[45,97]
ADRA2C	Exon 1 I/D	rs61767072	D-allele results in loss of autoinhibition.	Arg^{389} homozygotes carrying D-allele exhibited greatest LVEF improvements on β-blocker therapy. In bucindolol-treated patients, only WT-homozygotes exhibited reductions in mortality and transplantation.	[53,57,98,99]
ACE	Intron 16 I/D	rs4646994	Increased ACE level associated with D-allele.	D-allele associated with risk of death or transplantation in patients not receiving β-blockers.	[56,83]
EDN1	rs5370 rs2071942	rs5370 rs2071942	SNPs of unknown functionality in tight LD.	Study of placebo- and bucindolol- treated patients (n = 159 and 150, respectively) demonstrated significant interaction between treatment and genotype at both loci.	[59]
GRK5	$Gln^{41}Leu$	rs17098707	Leu^{41} enhances β-adrenoreceptor desensitization.	Leu^{41} leads to increased survival in African American patients in the absence of β-blockers.	[47,55]

ACE angiotensin 1-converting enzyme, ***ADRA2C*** adrenergic receptor α 2c, ***ADRB1*** adrenergic receptor β 1, ***ADRB2*** adrenergic receptor β 2, ***EDN1*** endothelin 1, ***GRK5*** G-protein coupled receptor kinase 5, **I/D** insertion/deletion, **LVEF** left ventricular ejection fraction, **WT** wild-type