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β-Blocker pharmacogenetics in heart failure

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Abstract

β-Blockers (metoprolol, bisoprolol, and carvedilol) are a cornerstone of heart failure (HF) treatment. However, it is well recognized that responses to a β-blocker are variable among patients with HF. Numerous studies now suggest that genetic polymorphisms may contribute to variability in responses to a β-blocker, including left ventricular ejection fraction improvement, survival, and hospitalization due to HF exacerbation. This review summarizes the pharmacogenetic data for β-blockers in patients with HF and discusses the potential implications of β-blocker pharmacogenetics for HF patients.

Keywords

Pharmacogenetics; β-Blockers; Heart failure; Metoprolol; *ADRB1*; *ADRB2*

Introduction

Heart failure (HF) is characterized by neurohormonal activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system in response to a drop in cardiac output [1]. Excessive activation of these systems results in hemodynamic alterations such as systemic vasoconstriction and increases in sodium/water retention, and ventricular remodeling, the latter of which is primarily responsible for the progressive nature of the disease.

It was in the 1980s that the important role of neurohormonal activation in HF was first documented [2], with evidence supporting the role of β-blockers emerging in the 1990s [3]. Historically, β-blockers were contraindicated in patients with HF due to their negative inotropic effect. However, as the neurohormonal paradigm of HF was appreciated, there was increasing interest in the β-blockers. β-Blockers are competitive antagonists at the β-adrenergic receptors (β-AR), thereby reducing the level of SNS activation [4]. From mid-1990s to early 2000s, several landmark studies demonstrated that the β-blockers metoprolol, bisoprolol, and carvedilol reduce morbidity and mortality compared to placebo, when added to standard background therapy that included angiotensin–converting enzyme (ACE) inhibitor therapy (Table 1). Based on these trial data, these β-blockers are recommended by the consensus HF management guidelines as essential therapy for patients who have systolic HF and lack contraindications to β-blocker therapy [8].

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However, not all β-blockers have shown beneficial effects in HF patients [8]. In addition, there is variability in responses to β-blockers among HF patients. β-Blocker therapy requires a careful monitoring and slow dose titration to minimize adverse events from the drug [9]. Despite careful titration, approximately 25% of patients require discontinuation of therapy due to intolerance to the drug [10]. Additionally, morbidity and mortality rates in symptomatic HF patients remain high [11], therefore, identifying causes of response variability to β-blockers may help optimize β-blocker therapy and HF regimens. Genetic differences may contribute to this variability in response to β-blockers. Pharmacogenetics is the study of genetic contributions to variable drug response, with the clinical potential to optimize therapy by identifying (predicting) the patients who will respond well (or poorly) to a given drug or are at high risk for adverse events from the drug.

The purpose of this review is to summarize the β-blocker pharmacogenetics literature in HF and to discuss the potential clinical implications of these data. Studies were identified in the Medline database from 1966 to January 2007 by combining MeSH search terms ‘heart failure, congestive, genetic polymorphism, ‘single nucleotide polymorphism,’ ‘pharmacogenetics,’ ‘adrenergic beta antagonists’ as well as individual β-blocker used for HF. We also checked the references of all identified papers. Only studies that tested pharmacogenetic hypotheses on β-blockers in HF or provided analyses data in a subgroup of patients who were on β-blockers were included in this review.

Genetic polymorphisms of β-AR

The pharmacological effects of β-blockers derive from their ability to antagonize the β-ARs. Thus, the genes for these receptors have been a primary focus in β-blocker pharmacogenetic studies. In the cardiovascular system, there are two β-ARs that β-blockers can antagonize: β_1-AR and β_2-AR, both of which are members of the G-protein coupled receptors superfamily. The β_1-AR gene (*ADRB1*), consisting of 2,860 bp, is located in chromosome 10q24–26. It encodes a 51.3 kDa protein, with 477 amino acid residues. β_1-ARs are primarily found in the heart, controlling contractility, and heart rate. β_1-ARs are also expressed in kidney, vasculature, and adipose tissues. β_2-ARs are more widely distributed including expression in the heart, vasculature, respiratory smooth muscle, kidney, adipose tissue and brain, among others. The gene consists of one exon with 2,033 bp located at chromosome 5q31–q32. The receptors play an important role in the regulation of a variety of the systems such as cardiac, vascular, respiratory, and endocrine systems. β-Blockers used for the treatment of HF possess different receptor specificity: Metoprolol and bisoprolol are β_1-selective, while carvedilol is a non-selective β-blocker with additional antagonist effects at the α_1-AR (Table 2).

There are 13 validated SNPs in the *ADRB1*, which have been reported to the National Center for Biotechnology Information Single Nucleotide Polymorphism database (dbSNP). An additional six validated SNPs located near the *ADBR1* gene region are also found in dbSNP. Of these SNPs, two polymorphisms have been extensively studied both in vitro and in vivo: Ser49Gly (nt 34552562 A>G on NT_030059, rs1801252) and Arg389Gly (nt 34553582 C>G on NT_030059, rs1801253). The Ser49Gly polymorphism is located in the N-terminus and the Arg389Gly polymorphism is located in a putative G-protein binding. The functional changes these polymorphisms cause are summarized in Table 3. Interestingly, a recent report using fluorescent resonance energy transfer (FRET)-based approach compared β_1-AR binding affinity of the three β-blockers (bisoprolol, metoprolol, and carvedilol) between Arg389 and Gly389 receptors [28]. Although Gly-389-β_1-AR showed a comparable degree of inhibitory effects by the antagonists on its activation and cAMP production, carvedilol had significantly higher degree of inhibitory effects than the other two β-blockers in Arg-389-β_1-AR. These data suggest that effects of β-blockers may differ by β_1-AR 389 allele.

Of the 13 validated SNPs in the *ADRB2* gene and 15 additional validated SNPs in the region close to the gene that have been reported to dbSNP (accessed on March 15, 2007), two polymorphisms have been widely investigated both in vivo and in vitro. The Gly16Arg (nt 9369376 G>A on NT 029289, rs1042713) and the Gln27Glu (nt 9369409 C>G on NT_29289, rs1042714) polymorphisms, both of which are located in the extracelluar portion of N-terminus, did not influence the receptors' ability to couple to G-protein and to activate adenylyl cyclase [24]. Rather, the polymorphisms altered the extent to which the receptors underwent down-regulation (Table 3). In an in vivo study with healthy volunteers, the Arg16 and the Gln27 alleles have been associated with increased desensitization mediated by isoproterenol infusion [29]. Receptor expression and functions by common haplotypes of β_2-AR have also been studied [30]. Of the 11 haplotypes constructed from 13 SNPs in the 5′ untranslated region and the coding sequence, there were two haplotypes that represented over 80 and 30% of the observed haplotypes in Caucasians and African-Americans, respectively. In an HEK293 cell transfection experiment, the amount of β_2-AR and its mRNA were significantly different between the two haplotypes [30].

In an in vitro experiment with ventricle tissues isolated from patients with HF, β_1-Arg-389 homozygote had 4.3-fold greater contractility than β_1-Gly-389 carrier upon agonist stimulation [31]. In failing hearts, the ratio of the amount between β_1-AR and β_2-AR is reduced due to down-regulation of β_1-AR compared to that in normal hearts [32]. In addition, there is evidence that β_2-AR plays an important role in regulation of contractility and apoptosis induced by activation of β_1-AR in failing hearts [33]. However, it is not currently clear whether *ADRB2* genotype/haplotype influences regulation of contractility and apoptosis in failing hearts and how it differs by *ADRB1* genotype.

β-Blockers pharmacogenetics in HF

Genetic associations with β-blocker-induced changes in left ventricular ejection fraction

Left ventricular ejection fraction (LVEF) is regarded as a surrogate marker to predict the adverse outcomes in systolic HF [34]. The degree of improvement in LVEF is well correlated with survival of the patients in HF [34]. As such, many studies have looked at associations of genetic polymorphisms of β-AR genes with improvement in LVEF after a β-blocker (Table 4). However, the results have been somewhat inconclusive. Two studies (one with metoprolol succinate and the other with carvedilol) reported significant associations between *ADRB1* genotype and LVEF, with patients homozygous for Arg389 demonstrating the greatest improvement in LVEF [23,35] Conversely, two other studies (one with carvedilol or bisoprolol, the other with bucindolol) found no such association [31,36]. These mixed results may have arisen from many factors such as use of different β-blockers, duration of therapy, characteristics of the study population, among others.

Two studies evaluated the association of *ADRB2* genotype and LVEF response to carvedilol [36,37]. Again, the results are mixed: one found that compared to Glu27 carriers, Gln27 homozygotes had significantly lower proportion of good responders defined as LVEF improvement by 10% in 3 months (63vs. 26%, $P = 0.003$) [37]. However, a study where response to either bisoprolol or carvedilol was assessed did not observe the same association [36]. A possible explanation for this is that bisoprolol, used by 65% of subjects in this study, is β_1-AR selective, and so *ADRB2* SNPs might be expected to have a less important role for this drug. Therefore, it is not possible to draw clear conclusions about the relationship among change in LVEF and β_1-AR and β_2-AR genotype at present.

The α2c-adrenergic receptor (α2c-AR) is an autoreceptor regulating presynaptic norepinephrine release. The gene (*ADRA2C*) located at chromosome 8p21-p11.2 has a 12-nucleotide deletion polymorphism which results in loss of four consecutive amino acid residues

at 322–325 [26]. The deletion allele has been shown to reduce the auto-inhibitory function of the receptor [26]. This insertion/deletion and the *ADRB1* Arg89Gly polymorphisms have been shown to synergistically increased the risk for HF in African-Americans in a case control study [39]. One study tested whether the *ADRA2C* and *ADRB1* polymorphisms synergistically influenced the LVEF response to metoprolol in 54 HF patients [38]. In this study, patients with *ADRB1* Arg389Arg and *ADRA2C* deletion carriers had the greatest improvement of LVEF (12 vs. 0–2% in others). However, large studies are needed to determine the effects of the two polymorphisms on clinical outcomes in HF patients.

Genetic associations with clinical outcomes during β-blocker therapy in randomized controlled trials

ADRB1 genotype may be a prognostic factor for adverse clinical outcomes, such as death and hospitalization in HF [31]. Bucindolol is an investigational non-selective β-blocker, which in the BEST trial did not show overall survival benefit versus placebo, although most secondary endpoints showed significant benefit from bucindolol [8]. In a post hoc analysis, *ADRB1* Arg389Arg was significantly associated with fewer adverse outcomes in patients receiving bucindolol versus placebo [hazard ratio (HR) = 0.66, 95% CI 0.50–0.88] [31]. Interestingly, the benefit of bucindolol was not observed in Gly389 carriers. Additionally, the genotype associated with survival benefit from bucindolol is the same genotype associated with improved LVEF in some studies. MERIT-HF is the other large clinical trial that has reported genetic results [5]. In examining the relationship between the *ADRB1* genotype and the trial outcomes (death and hospitalization), they found no significant association [40]. However, this analysis has been criticized because it combined treatment (metoprolol CR/XR) and placebo groups as one group and tested the association between outcomes and genotype. This analysis approach makes it difficult to assess the pharmacogenetic associations with adverse outcomes. It is similarly difficult to assess the effect of the polymorphism on the natural history of the disease, which would have been possible through consideration of the placebo-only patients. Thus, the data from this study are probably not informative regarding the role of the *ADRB1* polymorphism and outcomes with metoprolol therapy.

Genetic associations with clinical outcomes during β-blocker therapy in retrospective cohort studies

Given that data from randomized-controlled trials are limited, insights might also be gained from non-interventional cohort studies. These studies are summarized in Table 5. For example, data from one such analysis suggest that high dose of a β-blocker may improve the unfavorable clinical outcomes associated with an *ADRB1* genotype in HF. In a study with idiopathic dilated cardiomyopathy patients, 5-year mortality was lower in Gly49 carriers in *ADRB1* than Ser49Ser (RR = 0.24, 95% CI0.07–0.80) in patients who received a low dose of β-blocker (≤50% of target dose) [41]. In the same study, Gly389 carriers had higher 5-year mortality rate than Arg389Arg in those who were on a low dose of β-blocker (RR = 2.42, 95% CI 1.04–5.63) [41]. However, these genotypes were not associated with the adverse outcomes in those who were on high dose of a β-blocker [41].

β-Blocker therapy may also influence the risk associated with other genes in HF patients. For example, the *ACE* gene has a 287-bp insertion/deletion (I/D) polymorphism in intron 16. D/D genotype has been associated with elevated plasma ACE levels and higher rates of the adverse outcomes in HF [27,42]. In a study with systolic HF patients, McNamara et al. [42] reported that although they saw significantly higher adverse events (death or heart transplantation) in patients with the D/D genotype, the association was not detected in patients who received a β-blocker at baseline. Importantly, the result was subsequently replicated in an independent study [44].

In a recently published study, a β_2-AR haplotype (Arg16Arg26/Gln27Gln) was associated with increased risk for death or heart transplantation in 220 patients, 95 and 80% of whom were on an ACE inhibitor/angiotensin receptor blocker and a β-blocker at baseline [43]. When considered relative to β-blocker use, this association was most strongly driven by those not on a β-blocker (HR of 3.52 vs. HR of 1.55). Although these findings came from subgroup analyses, the results suggest that certain genotypes/haplotypes may be at increased risk of adverse outcomes and that β-blockers may attenuate the risk associated with that genotype/haplotype. Interestingly, these findings are consistent with those from an acute coronary syndrome population, in which the Arg16Gln27 haplotype was also associated with adverse outcomes, even among those treated with a β-blocker [45]. Collectively, these data may suggest that the Arg16Gln27 haplotype of the *ADRB2* may be a high-risk haplotype group deserving of more aggressive therapy.

Genetic associations with β-blocker tolerability in HF

Although the benefits of β-blocker therapy are well documented, it has been reported that β-blockers are often not titrated to optimal doses, in part due to concerns about decompensation during titration [2,10]. One study determined whether *ADRB1* genotypes were associated with initial tolerability of metoprolol CR/XL [46]. The study found that there were significant differences by genotype in tolerability of the initiation of β-blocker therapy, as assessed by less need for increased diuretic doses during the titration period. Specifically, Gly49 carriers showed better tolerance to β-blocker initiation than Ser49Ser. Similarly, those who were Arg389Arg tolerated β-blocker initiation the best. An analysis by *ADRB1* haplotype showed that 52% of patients who were Ser49Ser and Arg389Gly required an increase in diuretics, while none of the patients who was Ser49Gly and Arg389Arg were required to increase diuretic dose during β-blocker titration. Patients with other genotype combinations had need for diuretic dose titration that was intermediate between these two groups. If these findings were replicated, it might provide a mechanism for identifying those patients who will need careful attention and close follow up during the β-blocker titration period.

Many β-blockers including metoprolol and carvedilol are substrates for the cytochrome (CYP) P450 2D6 enzyme [12]. In particular, metoprolol is most highly dependent on CYP2D6 with 60–70% of its metabolism via this pathway, whereas 20–30% of metabolism of carvedilol is via *CYP2D6* [12]. The *CYP2D6* gene is highly polymorphic with about 80 alleles reported to date [47]. Due to the polymorphic drug metabolizing enzyme, pharmacokinetics of metoprolol vary among individuals [48,49]. This may result in variable responses to the drug, particularly at therapy initiation, given the need to initiate β-blockers at low doses. Several studies also have determined whether the pharmacokinetic differences caused by the *CYP2D6* polymorphisms are translated into variable adverse effects or efficacies in different diseases [46,50–52]. In HF, only one study has tested this question [46]. In this study, *CYP2D6* genotype was not associated with tolerability to metoprolol CR/XL upon initiation of therapy. Together with the study results in other diseases [51,52], it appears that *CYP2D6* genotype does not play a role in causing variability in responses (adverse or efficacious) to metoprolol. While other β-blockers have not been tested in this regard in HF, given that they are all less dependent on CYP2D6 for their metabolism than metoprolol, it seems unlikely that *CYP2D6* variability would importantly affect their efficacy or tolerability.

Summary of pharmacogenetic findings for β-blockers in HF

The majority of the β-blocker pharmacogenetic studies in HF have focused on the β_1-AR gene, the primary target for the β-blockers. Within this gene, Arg389Gly polymorphism is particularly interesting. Although LVEF response to a β-blocker with regards to the Arg389Gly polymorphism is not conclusive [23,31,35,36], it was the Arg389 homozygous genotype that has been associated with better LVEF response in the studies that reported a positive association

[23,36]. The same genotype has also been associated with better clinical outcomes (survival and hospitalization) in a sub-study from a large clinical trial [36]. Importantly, this genotype has been associated with better response to β-blockers in different settings, such as hypertension (blood pressure lowering) [53,54] and glaucoma (intraocular pressure lowering) [55]. Interestingly, while not all studies reported a positive association, studies with a positive association always showed Arg389Arg is a predictor of better response. On the other hand, the direction of the association with many other polymorphisms, such as ACE I/D and the common *ADRB2* SNPs, has not been consistent, even in studies with a significant association. Finally, the functional studies on codon 389 polymorphism in *ADBR1* support a logical biological mechanism for the clinical findings [22]. As such, the *ADRB1* codon 389 polymorphism may be a starting point for individualized β-blocker therapy in the future. Data on the other genes have not been sufficiently consistent to draw clear messages on their role. The Revpresence of mechanistic corroboration for *ADRB1* Arg389-Gly polymorphism that has been associated with clinical outcomes in patients with HF, and the lack thereof for other variants, also supports this conclusion.

Potential clinical implications of β-blocker pharmacogenetics

There are several potential clinical implications for β-blocker pharmacogenetics, based on the current literature and for the future. These are summarized below under specific categories.

Determining who receives β-blocker therapy or which β-blocker

Data from several studies suggest that there is a genotype group that responds less favorably to β-blocker therapy [43,45]. However, given the consensus-guideline driven use of β-blockers, it is hard to envision withholding β-blocker therapy based on genetic information. The level of evidence required to take such action would probably come from a randomized-controlled trial (or two) and these are not likely to be done. Thus, it is unlikely that in the future we will withhold β-blocker therapy based on genotype. However, based on results in a large clinical trial with over 1,000 patients enrolled in an adrenergic receptor polymorphism sub-study [31], a small pharmaceutical company is seeking FDA approval of bucindolol, with the therapy targeted at patients with specific genotypes. They suggest that the patients with the genotypes of interest may have better outcomes with bucindolol than the currently used β-blockers, whereas for those with alternative genotypes, the current β-blockers would be preferred. The FDA submission will be of great interest to the pharmacogenetics research community as it will represent the first request for labeling in a specific genotype group during the drug approval process, outside of cancer. FDA approval of bucindolol, with an indication in specific genetic groups, may also sound the beginning of pharmacogenetic-guided therapy in cardiovascular disease. The recent study using FRET to study receptor activation, and showing that carvedilol inhibited Arg389Arg more effectively than metoprolol or bisoprolol also lends support to the concept that certain genotypes might respond more favorably to certain drugs [28].

Identifying those perhaps not fully benefitting from therapy or given dose

Another potential application of β-blocker pharmacogenetics is identifying those patients whose genotype potentially places them at risk for responding less than optimally to a β-blocker, or for whom a low dose is insufficient. Specifically, several studies suggest that *ADRB1* Gly389 carriers might respond less favorably to β-blockers than Arg389Arg patients [23,36]. As discussed above, it is unlikely that one would withhold therapy from this former group; however, this might be a genotype group that should be targeted for more aggressive HF therapy.

Data from several studies also suggest that patients of certain genotypes may require high doses of β-blocker therapy to offset the risk associated with a given genotype [42,44]. While it is

preferable for all patients to receive target doses of β-blocker, such genetic information might provide insights into those patients in whom it is especially important for them to be on target doses. Use of genetic information for the above examples could be supported based on the current literature, and could be implemented in practice with minimal controversy.

Identifying target populations for drug development

It might be possible to use genetic information to identify high-risk populations, whom might be best suited for new drug development. In the past decade, there have been numerous HF drugs that failed to show efficacy in late Phase III clinical trials, at a point when the pharmaceutical company has invested hundreds of millions in the drug. These include endothelin blockers, vasopeptidase inhibitors, phosphodiesterase inhibitors, and TNF receptor blockers. As a result of these failures, pharmaceutical industry is now much less interested in developing new drugs for HF. Given that most of the studies did not pre-select patients for risk or poor outcomes with current therapy, it is not surprising that they were unable to show benefit in addition to standard therapy of an ACE inhibitor, β-blocker, diuretic, and often digoxin. However, it is quite likely that some of the drugs that made it this far in the drug development process would be of benefit in a subset of the HF population. Thus, if genetic data could be utilized to identify a high-risk population to enroll in the study, efficacy might be more easily documented. Based on the current data, the best candidate in this category is the *ADRB2* Arg16Gln27 haplotype. Two different studies (one in HF and one in post-acute coronary syndrome patients) have shown that carriers of this haplotype are at increased risk of adverse outcomes, even in the face of treatment with standard drug therapy [43,45].

The approach of utilizing genetic information to target patients for inclusion of Phase II or, more likely, Phase III clinical trials has been advocated as an approach that might substantially reduce the drug development cost, and salvage drugs that might not otherwise be able to meet the efficacy standards of the FDA. The pharmaceutical industry, however, has generally been unenthusiastic about this approach, since it would segment the market for their drug. However, HF seems to be a perfect case where there are examples of drugs that might be salvaged through a pharmacogenetic-driven drug development approach.

In conclusion, the data on β-blocker pharmacogenetics provide evidence for the influence of genetic variability in drug response, and provide insights into the potential role of using genetic information to improve drug therapy outcomes. Based on the literature to date, it seems that HF may represent one of the first areas where genetic information is used to guide therapy, particularly as it relates to β-blockers, and those who may require additional therapy due to predicted sub-optimal response to β-blockade.

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Table 1

Important β-blocker clinical trials in HF patients

Trial name	Treatments	Population	*N*	Primary outcomes	Findings	*P*-value for PO	References
COPERNICUS	Carvedilol versus placebo	Severe HF	2,289	Death	Carvedilol ↓risk of PO by 35%, and ↓risk of death or hospitalization by 24%	0.0014	[2]
CIBIS-II	Bisoprolol versus Placebo	NYHA III–IV	2,647	All-cause mortality	Bisoprolol ↓risk of PO by 34%	<0.0001	[3]
MERIT-HF	Metoprolol CR/XL versus Placebo	NYHA II–IV	3,991	Composite of death and hospitalization	Metoprolol ↓risk of PO by 19%, and ↓ risk of death or heart transplantation by 32%	<0.001	[5]
COMET	Carvedilol versus Metoprolol CR/XL	NYHA II–IV	3,029	All-cause mortality	Carvedilol ↓risk of PO by 17%	0.0017	[6]
BEST	Bucindolol versus Placebo	NYHA III–IV	2,708	All-cause mortality	Early termination of the trial due to no significant difference between the treatments. However, CV death rate was lower in bucindolol group than placebo (HR, 0.86; 95% CI 0.74–0.99)	ns	[7]

COPERNICUS, The Carvedilol Prospective Randomized Cumulative Survival; CIBIS-II, The Cardiac Insufficiency Bisoprolol Study II; MERIT-HF, The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; COMET, Carvedilol or Metoprolol European Trial; BEST, The Beta-blocker Evaluation of Survival Trial; CR/XL, controlled release/extended release; HF, heart failure; NYHA, New York Heart Association functional class; *N*, sample size; ↓, decreased; PO, primary outcomes; CV, cardiovascular; ns, not significant

Table 2

β-blockers studied for the treatment of HF

Name	β-blocking property	α_1-blocking property	Elimination route[a]	References
Carvedilol	Nonselective	Yes	Oral bioavailability: About 25–35%	[4,12–15]
			Both CYP2D6 and CYP2C9 are major metabolizing enzymes	
			CYP2D6 is responsible for 30–50% of metabolism of carvedilol	
			CYP2C9 is responsible for 5–20% of metabolism of carvedilol	
Metoprolol	β_1-selective	No	Oral bioavailability:	[4,12,16,17]
			Immediate release form: About 50%	
			Controlled release form: About 25–30%	
			CYP2D6 is a major hepatic enzyme responsible for 60–70% of metoprolol metabolism.	
Bisoprolol	β_1-selective	No	Oral bioavailability: 80–90%	[4,12,18]
			Approximately 50% of oral dose is recovered as parent drug in urine	
Bucindolol	Nonselective	Yes but weak	Oral bioavailability: About 30%	[4,12,19]
			Extensively metabolized by liver enzymes	

[a] Elimination of parent drug

CYP, cytochrome P450

Table 3

Summary of minor allele frequency and functional consequences of the important genetic polymorphisms in HF β-blocker pharmacogenetics

Gene	Polymorphism	Minor allele	MAF	Functional consequences	References
ADRB1	Ser49Gly	Gly	Caucasians (12–16%)	Gly49 allele has greater receptor down-regulation with agonist treatment	[20]
			African-Americans (23–28%)		
			Hispanics (20–21%)	Gly49-β_1-AR is more sensitive to the inhibitory effects of metoprolol than Ser49- β_1-AR	[21]
			Asians (14%)		
	Arg389Gly	Gly	Caucasians (24–34%)	Arg389 allele has higher basal and agonist-stimulated	[22]
			African-Americans (39–46%)	AC activity	
			Hispanics (31–33%)	Lower AC activity upon agonist simulation in heart samples from HF patients with Arg389 allele than with Gly389 allele	[23]
			Asians (20–30%)		
ADRB2	Gly16Arg	Arg	Caucasians (39%)	Gly16 allele has greater receptor down-regulation with agonist stimulation	[24]
			African-Americans (49%)		
			Asians (51%)		
	Gln27Glu	Glu	Caucasians (25%)	Glu27 allele is resistant to receptor down-regulation	[24]
			African-Americans (19%)		
			Asians (9%)		
	Thr164Ile	Ile	Caucasians (1–2%)	Ile164 allele causes defective coupling with G protein	[25]
			African-Americans (0%)		
			Asians (0%)		
ADRA2C	Insertion/Deletion	D	Caucasians (4%)	D allele causes loss of auto-inhibitory function of the receptor	[26]
			African-Americans (41%)		
			Asians (Unknown)		
ACE	Insertion/Deletion	I[a]	Caucasians (40–48%)	D allele is associated with higher plasma ACE level	[27]
			African-Americans (37–43%)		
			Asians (58–70%)		

[a] Insertion allele is a major allele in Asians

ADRB1, β_1-adrenergic receptor gene; *ADRB2*, β_2-adrenergic receptor gene; *ADRA2C*, α_{2C}-adrenergic receptor gene; *ACE*, angiotensin-converting enzyme gene; Arg, arginine; Gly, glycine; Ser, serine; Glu, glutamate; Gln, glutamine; Thr, threonine; Ile, isoleucine; I, insertion, D, deletion; MAF, minor allele frequency; AC, adenylyl cyclase; AR, adrenergic receptors; HF, heart failure

Table 4

β-blocker pharmacogenetic studies evaluating changes in left ventricular ejection fraction in HF

Study population	Study type	B-blocker	*N*	Duration	Gene	Polymorphism	Results	*P*-value	References
Systolic	P	Metoprolol	54	>5 months	*ADRB1*	Arg389Gly	Greater LVEF improvement in Arg389Arg than Gly carriers	0.008	[35]
HF		CR/XL				Ser49Gly	(From 23 ± 5 to 29 ± 10% vs. from 22 ± 9 to 23 ± 11%)		
Systolic	R	Carvedilol	224	>6 months	*ADRB1*	Arg389Gly	Greater LVEF improvements in Arg389Arg than Gly389Gly	0.02	[23]
HF							(8.7 ± 1.1 vs. 0.93 ± 1.7%)		
Systolic	R	Bisoprolol	199	3 months	*ADRB1*	2 SNPs	No associations	ns	[36]
HF		Carvedilol			*ADRB2*	3 SNPs			
Systolic	P	Bucindolol	1040	Median	*ADRB1*	Arg389Gly	No associations	ns	[31]
HF				2 years					
Systolic	R	Carvedilol	80	4 months	*ADRB2*	2SNPs	Glu27 carriers had more good responders than Gln27Gln	0.003	[37]
HF							(63 vs. 26%)		
Systolic	R	Metoprolol	54	>5 months	*ADRB1*	Arg389Gly	Greatest improvement in LVEF those who were *ADRB1* Arg389Arg and *ADRA2C* deletion carriers	<0.02	[38]
HF		CR/XL			*ADRA2C*	I/D 322–325	(12 vs. 0–2% in others)		

CR/XR, controlled release/extended release; *N*, sample size; SNPs, single nucleotide polymorphisms; Δ, change before and after treatment; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; ns, not significant; Arg, arginine; Gly, glycine; Ser, serine; Glu, glutamate; Gln, glutamine; C, cytosine; T, thymidine, I/D, insertion/deletion; *ADRB1*, β_1-adrenergic receptor gene; *ADRB2*, β_2-adrenergic receptor gene; *ADRA2C*, α_{2c}- adrenergic receptor gene; HF, heart failure

P, prospective study, which was designed specifically to test pharmacogenetics hypotheses, or where the primary outcome studied in the pharmacogenetic study was the primary outcome in the clinical trial

R, retrospective study, which was conducted on an existing data set

Table 5

Influence of β-blocker therapy on genetic associations in retrospective cohort studies in HF patients

Study population	β-blocker	*N*	Duration	Gene	Polymorphism	Outcomes	Results	*P*-value	References
DCM	Various	375	37–60 months	*ADRB1*	Ser49Gly Arg389Gly	Death or heart transplantation	Among patients on <50% of the target dose for the given β-blocker, Gly49 carrier was associated with the longer survival than Ser49Ser (HR = 0.24, 95% CI 0.07–0.80)	0.014 ns	[41]
							Among patients on a high dose of a β-blocker, no genetic association was detected		
Systolic	Various	328	Median	ACE	I/D	Death or heart transplantation	D allele associated with higher risk for outcomes than I/I (HR = 1.80)	0.04	[42]
HF			21 months				No association in patients on a β-blocker	ns	
Various	Various	220	Median	Seven genes	Eight polymorphisms	Death or heart transplantation	Homozygotes for both Arg16Arg and Gln27Gln in the *ADRB2* gene were associated with increased risk (HR = 1.91)	0.02	[43]
			34 months				Among patients on a β-blocker, none of the genetic polymorphisms were associated with the outcomes	ns	

HF, heart failure; DCM, dilated cardiomyopathy; *N*, sample size; ns, not significant; Arg, arginine; Gly, glycine; Ser, serine; Glu, glutamate; Gln, glutamine; I/D, insertion/deletion; ADRB1, β_1-adrenergic receptor gene; *ADRB2*, β_2-adrenergic receptor gene; *ACE*, angiotensin-converting enzyme gene; CI, confidence interval