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Pharmacogenetic factors affecting β -blocker metabolism and response

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Abstract

Introduction: β -blockers are among the most widely prescribed of all drugs, used for treatment of a large number of cardiovascular diseases. Herein we evaluate literature pertaining to pharmacogenetics of β -blocker therapy, provide insight into the robustness of the genetic associations, and determine the appropriateness for translating these genetic associations into clinical practice.

Areas covered: A literature search was conducted using PubMed to collate evidence on associations between *CYP2D6*, *ADRB1*, *ADRB2*, and *GRK5* genetic variation and drug-response outcomes in the presence of β -blocker exposure. Pharmacokinetic, pharmacodynamic, and clinical outcomes studies were included if genotype data and β -blocker exposure were documented.

Expert opinion: Substantial data suggest that specific *ADRB1* and *GRK5* genotypes are associated with improved β -blocker efficacy and have potential for use to guide therapy decisions in the clinical setting. While the data do not justify ordering a *CYP2D6* pharmacogenetic test, if *CYP2D6* genotype is available in the electronic health record, there may be clinical utility for understanding dosing of β -blockers.

Keywords

beta-blockers; CYP2D6; beta-adrenergic receptors; pharmacogenomics; precision medicine; chronic heart failure; essential hypertension; coronary artery disease

1. Introduction

Cardiovascular disease is the leading cause of death in the United States, causing approximately 660,000 deaths annually.[1,2] Clinically, β -adrenergic receptor blockers are commonly used in cardiovascular disease, including ischemic heart disease, hypertension, cardiac arrhythmias, and heart failure.[3–5] β -blockers modulate sympathetic nervous

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Declaration of interest

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system (SNS) activation to produce their negative chronotropic, inotropic, and dromotropic effects. Despite their prevalent use, variation within genes that affect β -blocker pharmacokinetic and pharmacodynamic properties contribute to wide inter-patient variability in β -blocker response. The efforts toward precision medicine approaches present a unique opportunity to re-evaluate literature pertaining to pharmacogenomics of β -blocker therapy and determine the appropriateness for translating these genetic associations into clinical practice. The genes with the strongest evidence for associations with response to β -blocker therapy include *CYP2D6*, *ADRB1*, *ADRB2* and *GRK5*. The purpose of this expert opinion article is to describe pharmacogenetic factors affecting β -blocker metabolism and response, provide insight into the robustness of the genetic associations, and discuss clinical interpretations for potential translation of variants influencing β -blocker response into practice.

2. CYP2D6 and β -blockers

2.1 Pharmacokinetic effects

Cytochrome P450 2D6 (CYP2D6) serves an important role in the biotransformation of approximately 25% of drugs.[6] Several β -blockers are substrates for CYP2D6, including metoprolol, carvedilol, propranolol, labetalol, nebivolol, and timolol.[7–11] During the 1980s, cytochrome P450 2D6 was purified and mapped to chromosome 22q13.[12–14] Currently, *CYP2D6* genotype is utilized in clinical practice to predict CYP2D6 metabolism phenotype, which is used to facilitate prescribing recommendations for a variety of medications.[15–20] *CYP2D6* genotype is used to assign CYP2D6 phenotype, and in many cases, the CYP2D6 activity score method is used in clinical practice to translate *CYP2D6* genotype to predicted phenotype.[15–21] Currently, four phenotypes are used, with increasing metabolism potential in order from poor metabolizer (PM; no CYP2D6 activity), intermediate metabolizer (IM, approximately 25%–50% normal metabolism), normal metabolizer (NM), to ultra-rapid metabolizer (UM; increased CYP2D6 activity secondary to gene duplication).[22] While there are no Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for β -blockers, associations between genotype and β -blocker pharmacokinetics and pharmacodynamics date back to the 1980s and 1990s.

Metoprolol metabolism is mediated extensively by the cytochrome P450 system, with CYP2D6 contributing to approximately 70–80% of metoprolol's metabolism to inactive metabolites.[23] *CYP2D6* is a highly polymorphic gene, with more than 100 alleles described.[24] *CYP2D6* genotype is associated with altered metoprolol metabolism and an allele-dose response effect between *CYP2D6* genotype and plasma metoprolol concentrations has been previously described.[25–33] As the number of active *CYP2D6* alleles increases (from zero in PMs to > 2 in UMs), so does the metabolism of metoprolol. This is reflected by variability in pharmacokinetic parameters (e.g., oral clearance, area under the plasma concentration-time curve, elimination half-life) based on *CYP2D6* genotype.[29–31,33,34] A meta-analysis of metoprolol pharmacokinetics by CYP2D6 phenotype demonstrated an approximate 6-fold decrease in metoprolol oral clearance in CYP2D6 PMs compared with NMs.[35] Metoprolol oral clearance was 1.5-fold lower in IMs and 2.6-fold higher in UMs compared with NMs.[35]

There is the largest body of literature on the impact of CYP2D6 phenotype on metoprolol pharmacokinetics because it is the most commonly prescribed of the β -blockers that are CYP2D6 substrates, and because CYP2D6 contributes more to the metabolism of metoprolol than the other β -blockers. However, the literature clearly documents the role of CYP2D6 on the pharmacokinetics of carvedilol, propranolol, nebivolol, and timolol.[36–49] Carvedilol also exhibits stereoselective metabolism, with CYP2D6 PMs demonstrating decreased clearance of R-carvedilol compared with CYP2D6 NMs.[50] Similar to metoprolol, there is a linear relationship between the CYP2D6 activity score and carvedilol clearance.[34,51–53] Regarding nebivolol, plasma concentrations, area under the plasma concentration-time curve, and clearance were consistently different between NMs and PMs.[43–49] Of the β -blockers discussed, labetalol has the weakest literature base.[36] Other commonly used β -blockers not subject to metabolism via *CYP2D6* include: acebutolol, atenolol, betaxolol, bisoprolol, and nadolol.

2.2 Pharmacodynamic Effects

CYP2D6 genotype is associated with altered HR response to β -blocker therapy, [25,27,30,31,54] and one study showed CYP2D6 phenotype was one of the most significant predictors of variability in HR response to metoprolol.[54] Of note, HR response, in the presence of β -blocker therapy, is a surrogate measure of the degree of β 1-adrenergic receptor blockade. Therefore, due to variability in CYP2D6 activity, the β -blockade and HR response can vary by dose. At equal doses in the lower end of the dosing range (e.g. 50 to 100 mg), CYP2D6 PM and IM phenotypes are associated with greater reductions in HR after metoprolol exposure compared to NMs.[25,27,30,31,54] Additionally, among CYP2D6 IM/PMs with New York Heart Association (NYHA) class II-IV heart failure with reduced ejection fraction (HFrEF), the odds of achieving a HR $\leq$ 60 beats/min are approximately 2-fold higher than CYP2D6 NMs during dose titration.[25] Genotypes associated with reduced CYP2D6 metabolism have also been linked to increased odds of achieving a target HR of less than 70 beats/min in patients undergoing elective PCI.[55] *CYP2D6* no functional alleles (e.g., *CYP2D6**4) are also associated with lower maintenance doses of metoprolol.[56] While the relationships between *CYP2D6* genotype and metoprolol and carvedilol pharmacokinetics are similar, a pharmacodynamic relationship between *CYP2D6* and carvedilol does not appear as strong. This observation is expected given that CYP2D6 accounts for less of S-carvedilol's metabolism; S-carvedilol is primarily responsible for β -blockade.[50] Among healthy volunteers receiving carvedilol, maximum HR reduction and resting HR did not differ by CYP2D6 activity score.[34] Similar to carvedilol, variability in nebivolol pharmacokinetics does not translate to pharmacodynamic differences between PMs and NMs.[44,45,48,57,58] Given the sigmoid dose/concentration-response relationship for β -blockers, at a certain point, increasing plasma drug concentrations does not lead to increasing response.[25,59]

While the associations between *CYP2D6* genotype and HR response are consistent, the data are weaker for BP and other responses. There are fewer studies that identify a positive association between *CYP2D6* genotype and blood pressure response.[25,60] In studies that identified an association between *CYP2D6* genotype and DBP response, a difference of approximately 5 mmHg between CYP2D6 PMs and NMs has been reported.[25,60] Only

one study identified an association between *CYP2D6* genotype and SBP.[60] More consistently, negative findings for *CYP2D6* genotype and blood pressure response have been reported.[25,26,30,31,54] Overall, the evidence for metoprolol points towards no association between *CYP2D6* genotype and clinical efficacy of metoprolol as it relates to SBP and DBP response. In a post hoc pharmacogenomic sub-study of heart failure patients in MERIT-HF[61,62], *CYP2D6* genotype was also not associated with the composite clinical outcome of death and hospitalization.[25] In another study of HFrEF participants, *CYP2D6* phenotype was not associated with risk of cardiac decompensation, increased need for background HF medications, or final daily metoprolol CR/XL doses.[33] While data are limited for carvedilol, one study suggested *CYP2D6* genotype was not associated with BP response.[34]

Data also suggest a lack of association between *CYP2D6* phenotype and adverse responses to β -blockers. *CYP2D6* genotype was not associated with increased incidence of dizziness, fatigue, or absent-mindedness in healthy volunteer studies of carvedilol.[34] Data regarding adverse drug reactions with metoprolol use are more abundant. In a real-world cohort of primary care participants where metoprolol was prescribed, PM and IMs did not have a higher incidence of common metoprolol adverse drug reactions (headache, dizziness, fatigue or drowsiness, sleep disturbances, dyspnea, or cold extremities) compared with NM and UMs, however sexual dysfunction was more common in NMs and UMs compared with PM and IMs.[26] This latter finding is somewhat paradoxical since this finding is not consistent with a concentration-related adverse effect. Similarly, in a prospective, randomized clinical trial with metoprolol in hypertensives, *CYP2D6* phenotype was not associated with the incidence of metoprolol-related side effects.[54] In another clinical study of metoprolol in hypertensives, *CYP2D6* phenotype was not associated with general, or dose-limiting metoprolol-related adverse events.[63]

Collectively, the data suggest the impact of *CYP2D6* genotype/phenotype on response is more evident at lower doses, when a patient is still on the linear portion of the dose-response curve, but pharmacogenetic effects are less evident at higher doses. Overall, pharmacokinetic variability across *CYP2D6* genotypes appear to translate primarily to differences in heart rate response after β -blocker initiation, with most data suggesting that *CYP2D6* phenotype does not influence BP or other responses, including adverse responses to β -blockers. Given that β -blockers are typically initiated at a low dose, with upward titration based on response or a HR < 60 bpm, then patients who are PM or IM may achieve the target or HR response at a lower than expected dose. In the precision medicine era, *CYP2D6* genotype may be used to predict tolerable maintenance doses of metoprolol and carvedilol in patients with HFrEF.[56]

3 *ADRB1* and β -blockers

β 1-adrenergic receptors, encoded for by *ADRB1*, are G-protein coupled receptors that are primarily expressed in cardiac tissue to mediate chronotropic, dromotropic, and inotropic effects from SNS activation.[64] *ADRB1* variants are common in the overall population and exhibit differences in frequencies across ancestral populations (Table 1).[64] The two most common and well-studied *ADRB1* variants are rs1801252 (*ADRB1* 145A>G; Ser49Gly)

and rs1801253 (*ADRB1* 1165 C>G; Arg389Gly). The variant at rs1801252 results in increased agonist-promoted down-regulation, whereas the variant at rs1801253 alters G-protein coupling, decreases adenylyl cyclase activity, thus attenuating generation of cAMP (Figure 1).[59,65,66] Thus based on the functional effects for both variants, the major allele is predicted to be associated with greater agonist-mediated response. This functional basis for differences in β -blocker response has been studied extensively in healthy volunteers and patients with a variety of cardiovascular diseases.

3.1 Pharmacodynamic effects

A number of studies have addressed the associations between *ADRB1* variants and HR and BP responses, in healthy volunteers and patients with cardiovascular disease. Most studies show no association between *ADRB1* and HR response to β -blockers, while several studies show an association between the commonly studied *ADRB1* SNPs and BP response, particularly the DBP response. In healthy volunteers, up-titration of dobutamine resulted in greater increases in SBP in Arg389Arg participants compared with Gly389 carriers.[67] Consistent with greater agonist-mediated response for Arg389Arg, another study found this genotype was also associated with greater response to β -blockade. Specifically, a healthy volunteer study found Arg389Arg was associated with greater BP lowering and decreases in resting and exercise HR responses, across various metoprolol doses, compared with Gly389Gly,[68] and the association between Arg389 and improved HR response became more apparent as the metoprolol dose was increased.[68] In another healthy volunteer study, no significant differences in HR were seen between *ADRB1* Arg389Gly genotype groups.[69] A pharmacodynamic study of patients with chronic HF, initiated on β -blocker therapy with either carvedilol or bisoprolol, showed *ADRB1* genotype was not associated with changes in HR or SBP after the maximal tolerated dose was obtained.[70] Subsequent studies conducted in various patient populations did not identify associations between Arg389Gly and maximum HR reduction.[34,41,70–73] Similarly, several studies found no association between heart rate response to β -blockers and genotype at codon 49.[67,68,70,71,73–77]

Data suggest the *ADRB1* gene may be important determinant for DBP, but not SBP response to β -blocker therapy. A study of essential hypertension patients treated with metoprolol found those with Arg389Arg genotype had a 6.5 mmHg greater DBP response than Gly389 carriers.[71] These findings were corroborated in another study of participants with essential hypertension.[72] Ophthalmic timolol administration was also associated with higher systolic and diastolic arterial pressures in Ser49Ser vs. Gly49 carriers, while genotype at position 389 was not associated with BP response.[41] A study in healthy volunteers and another study in participants with hypertension and left ventricular hypertrophy produced inconsistent results with DBP.[68,75] Some data suggest that consideration of the *ADRB1* haplotypes that result from the two commonly studied variants may be more informative than individual SNPs, and thus studies of single SNPs may have resulted in inconsistent findings with pharmacodynamic parameters.[78] Specifically, multiple studies have shown the Ser49-Arg389 haplotype is associated with improved DBP lowering compared with Ser49-Gly389 haplotype in participants with essential hypertension and coronary artery

disease.[71,72,78] Regarding SBP, previous findings do not support an association with *ADRB1* genotype, with one positive and five negative association studies.[62,70–72,75,78]

Among study participants with chronic HF, *ADRB1* genotype was not associated with HR or BP responses at the end of β -blocker titration, or with the attained maintenance β -blocker dose.[33,62] Similarly, in a pharmacogenetic sub-study of MERIT-HF[61], HR reduction attained during metoprolol titration, and maintenance dose attained was not different based on codon 389 genotype.[62] In another cohort of NYHA class II to IV HFrEF participants receiving carvedilol, HR and BP responses, both at rest and during exercise, were similar between *ADRB1* genotypes at codon 389.[79] These findings were validated in a randomized trial of chronic HF participants scheduled to receive carvedilol or bisoprolol.[59] Additionally, no significant interaction between the effects of *ADRB1* and *CYP2D6* on treatment outcomes has been observed.[80]

Collectively for hemodynamic responses, the strongest data exist for an association between *ADRB1* genotype and DBP response to β -blockers, while HR and SBP responses and target dose attainment seems to be minimally affected by *ADRB1* genotype.

3.2 Coronary artery disease outcomes

Numerous lines of evidence suggest certain *ADRB1* genotypes are associated with risk for cardiovascular events, and such risk may be ameliorated with β -blocker therapy, implying certain genotypes derive greater benefit from β -blockers (Table 2; Supplementary Table 1). Clinical outcomes among a cohort of patients with coronary artery disease randomized to treatment with verapamil SR or atenolol (INVEST trial)[81] focused on *ADRB1* haplotype and found an increased risk of major adverse cardiovascular events (MACE; defined as composite of death, nonfatal myocardial infarction, and stroke) among Ser49-Arg389 carriers compared with non-carriers (HR: 1.51; 95%CI: 1.07–2.12).[78] This association was primarily driven by the risk for death among Ser49-Arg389 carriers (HR: 3.66; 95%CI: 1.68–7.99).[78] The association with cardiovascular events identified in the INVEST trial is consistent with a case-control study that reported *ADRB1* genotype at codon 389 was associated with acute myocardial infarction.[82] When the INVEST analysis was stratified by treatment allocation, Ser49-Arg389 carriers randomized to verapamil remained at increased risk for death (HR: 8.58; 95%CI: 2.06–35.8), while the haplotype's risk was reduced for Ser49-Arg389 carriers randomized to atenolol (HR: 2.31; 95%CI: 0.82–6.55; $p=0.11$). Therefore, treatment with atenolol may offset the increased risk for MACE observed with the *ADRB1* Ser49-Arg389 haplotype.[78] These data suggest Ser49-Arg389 allele carriers are likely to derive the greatest benefit from β -blocker therapy.

3.3 Chronic heart failure

Studies suggest a variety of β -blocker response phenotypes in heart failure that may vary by *ADRB1* genotype (Table 2; Supplementary Table 1). Among participants with NYHA Class II or III symptoms with HFrEF, *ADRB1* genotype was associated with increased requirements of other heart failure medications (e.g., diuretics) for worsening symptoms of heart failure during β -blocker titration.[33] Gly389 carriers were more likely than Arg389Arg participants (48 vs. 14%) to have increased requirements of heart failure

medications. Additionally, Ser49 homozygotes were more likely to require increases in heart failure medication during titration compared to Gly49 carriers (41 vs. 11%).[33] When the analysis was expanded to evaluate the risk between *ADRB1* haplotypes, approximately 50% of participants with the Ser49Ser/Arg389Gly diplotype required increases in concomitant heart failure medications during metoprolol titration. *ADRB1* genotype was not associated with metoprolol discontinuation rates, or metoprolol dose attained at the end of β -blocker titration.[33,62,83] The absence of an association between *ADRB1* genotype and attained β -blocker dose has been validated in cohorts of participants with coronary artery disease receiving atenolol, essential hypertension receiving metoprolol, and Marfan syndrome receiving atenolol.[71,73,78] Arg389 carriers with NYHA class II to III chronic HF were also more likely to utilize emergency department resources compared to non-carriers.[84]

Studies support greater benefits from β -blocker therapy among HFrEF patients with the Arg389Arg genotype compared to Gly389 carriers. Furthermore, up-titration of β -blocker dose - a key treatment paradigm for management of chronic HFrEF - appears to benefit Arg389Arg patients, but not Gly389 carriers. A study of participants with NYHA class II-IV HFrEF evaluated the impact of the *ADRB1* Arg389Gly variant on changes in left ventricular function during maintenance therapy with carvedilol. There was a trend towards improved LVEF in Arg389 carriers compared with Gly389Gly.[79] In a pharmacogenetic substudy of the HF-ACTION trial[85], a significant interaction between *ADRB1* genotype at codon 389 and β -blocker dose for all-cause mortality has been identified among study participants with HFrEF.[86] Among *ADRB1* Arg389Arg participants, low-dose β -blocker relative to high-dose β -blocker therapy, was associated with a two-fold increase in the risk for all-cause mortality.[86] This suggests the risk associated with higher adrenergic activation in Arg389Arg individuals is not sufficiently offset by low dose β -blockade. This increased risk was not observed among Gly389 carriers receiving low versus high dose β -blockers.[86] No association was observed between *ADRB1* genotype at codon 49 and β -blocker dose for all-cause mortality.[86] This is consistent with findings in numerous other settings, where the codon 49 polymorphism is less commonly associated with clinical phenotypes than the codon 389 polymorphism.

In a genetic substudy of the BEST trial,[87] a randomized, controlled trial of participants with NYHA class III to IV HFrEF, risks for all-cause mortality and hospitalization secondary to a HF exacerbation were significantly reduced in bucindolol treated participants with the Arg389Arg genotype compared with placebo. The risks for death and hospitalization were not significantly different between bucindolol and placebo arms among Gly389 carriers, implying that the benefits of bucindolol in the studied HF population are confined to those with the Arg389Arg genotype.[88] Additionally, genotype at codon 49 in this cohort was not associated with any of the various clinical phenotypes tested.[88] Similar to the associations between *ADRB1* genotype and all-cause mortality, a genetic sub-study of the same population identified a decreased risk for ventricular tachycardia or fibrillation among bucindolol treated participants with the Arg389Arg genotype compared with placebo; this risk difference was not observed for Gly389 carriers, again suggesting that phenotype risk associated with Arg389Arg can be offset with β -blocker treatment.[89] In the same trial, among those with atrial fibrillation, bucindolol therapy in Arg389Arg participants was associated with lower risk for the composite of death and heart failure hospitalization

compared with placebo.[90] The risk for the composite endpoint was not significantly different between Gly389 carriers.[90] In contrast, in the MERIT-HF genetic sub-study, participants with the Arg389Arg genotype were not at increased risk for the composite of death or hospitalization compared to Gly389 carriers; this observation also held within the placebo and metoprolol-treated arms.[62] This finding has been validated in a separate, prospective study of HFrEF participants where risk for death or heart transplantation was similar between Gly389 carriers and Arg389Arg participants on maintenance β -blocker doses.[91] While β -blocker therapy is essential to management of all patients with chronic HFrEF, *ADRB1* Arg389Arg participants appear to derive the greatest clinical benefits from β -blockade.

3.4 Marfan syndrome

ADRB1 variation also explains interindividual variability in response to atenolol among subjects with Marfan syndrome, an autosomal dominant connective tissue disorder. In a pharmacogenomic substudy of a randomized trial conducted by the Pediatric Heart Network[92], clinical response to atenolol – assessed by improvements in the aortic-root z-score – was greater among individuals with the *ADRB1* Arg389Arg genotype compared with Gly389 carriers.[73] While the larger study found no difference in the rate of aortic-root dilation between atenolol and losartan, an interaction was observed in the pharmacogenomic substudy between *ADRB1* genotype at codon 389 and drug response.[73,93] Among those with the Arg389Arg genotype, greater improvements in aortic-root z-score were noted for atenolol-treated compared with losartan-treated participants. *ADRB1* Ser49Gly was not associated with variability in treatment response to atenolol. Similar to other disease phenotypes, *ADRB1* genotype was not associated with maintenance atenolol dose at study completion.[73] Among patients with Marfan syndrome, *ADRB1* genotype has the potential to identify those likely to benefit from atenolol therapy, and potentially to identify those who should be preferentially treated with atenolol over losartan.

3.5 Ischemic stroke outcomes

While genetic differences in cardiovascular outcomes among participants with CAD and chronic HF were associated with variation at codon 389, genotype at codon 49 has been associated with MACE in participants with ischemic stroke (Supplementary Table 1). The pharmacogenomic associations between *ADRB1* genotype and clinical outcomes were assessed in data from SPS3, an international multicenter randomized controlled clinical trial that evaluated the effects of different antihypertensive and antiplatelet therapy regimens on the rate of recurrent stroke.[94] In the pharmacogenomic analysis, the cumulative incidence of MACE and ischemic stroke were higher among Gly49 allele carriers compared with Ser49Ser participants.[95] The relative risk for MACE and recurrent ischemic stroke were 1.6 and 1.8-fold higher, respectively, among Gly49 carriers compared with Ser49Ser participants.[95] Among Gly49 carriers treated with β -blockers, the relative risks for MACE and ischemic stroke further increased to 2.8 and 2.9-fold those of Ser49Ser participants.[95] Their risk for MACE and ischemic stroke was similar between Gly49 carriers and non-carriers among those not treated with β -blockers. Overall, these data suggest the association between the Gly49 allele and risk for MACE may be increased with β -blocker therapy.

3.6 Summary

In summary, a number of studies identified associations between *ADRB1* genotype and hemodynamic and clinical outcomes across various cardiovascular disease phenotypes. Regarding hemodynamic responses, the strongest data exist for an association between *ADRB1* genotype and DBP response to β -blockers. Among hypertensive patients with coronary artery disease, β -blocker therapy may offset the risk for MACE among carriers of the Ser49-Arg389 haplotype. The use of β -blockers in patients with chronic HF appears to be associated with greater improvements among those with the Arg389Arg genotype. Furthermore, a genetic substudy of the BEST trial found no difference in mortality among Gly389 carriers between β -blocker therapy and placebo. This suggests the mortality benefit in this population may be heavily driven by the benefits of neurohormonal blockade in Arg389Arg patients. Benefits from β -blocker therapy among participants with the Arg389Arg genotype also extended to populations with Marfan syndrome as greater improvements in aortic-root z-score were noted for atenolol-treated compared with losartan-treated participants. Genotype at codon 49 appears to have the greatest impact among participants with ischemic stroke. Available data suggest cardiovascular risk among Gly49 allele carriers may be increased among β -blocker treated participants. Further research is needed to validate this finding given the clinical implications for treatment of patients with small artery stroke. Collectively, studies have documented associations between *ADRB1* and metoprolol, atenolol, bucindolol, and carvedilol, implying that this is a class effect that would be evident for any drug that antagonizes the β 1-adrenergic receptor.

4. *ADRB2* and β -blockers

ADRB2 encodes the beta-2-adrenergic receptor, a G-protein-coupled adrenergic receptor. Beta-2 adrenergic receptor is expressed in cardiac myocytes, bronchial smooth muscle, and vascular smooth muscle cells. Two common *ADRB2* SNPs rs1042713 (*ADRB2* 46A>G; Arg16Gly) and rs1042714 (*ADRB2* 79C>G; Gln27Glu) lead to a change in the encoded amino acid and have been commonly studied (Table 1). The variant at rs1042713 enhances agonist-promoted down-regulation, ultimately resulting in decreased cAMP formation.[96,97] In contrast, the Glu27 variant at rs1042714 is resistant to agonist-promoted downregulation, ultimately resulting in increased cAMP formation (Figure 1).[96–98] Due to linkage disequilibrium, these two variants lead to three haplotypes. The haplotype containing the variant allele at both positions (rs1042713 and rs1042714) displays enhanced receptor downregulation.[96,97] The *ADRB2* Gly16-Glu27 haplotype and *ADRB2* genotype at codon 27 have been associated with on-treatment BP and HR.[34,78,99] Among participants from the INVEST trial, differences in DBP were < 2 mmHg between *ADRB2* haplotypes, leading study investigators to challenge the clinical significance of these statistically significant findings.[78] Additionally, *ADRB2* genotype has not been associated with maximal tolerated β -blocker dose.[33,78]

Among study participants with chronic heart failure, the associations between *ADRB2* genotype and outcomes are mixed. Among carvedilol-treated participants with NYHA class II to IV symptoms and a LVEF $\geq$ 35%, the *ADRB2* haplotype, Gly16Gly/Glu27Glu, was associated with greater improvements in LVEF, mean arterial blood pressure, and pulmonary

capillary wedge pressure when compared with Gly16Gly/Gln27Gln and Arg16Arg/Gln27Gln haplotypes.[79] Another study evaluated *ADRB2* genotype and found greater improvements in LVEF, resting HR, and the 6-min walk test among carvedilol-treated Glu27 carriers compared with non-carriers.[99] While surrogate markers appear to be associated with *ADRB2* genotype, clinical outcomes have not been consistently associated with *ADRB2* genotype.[33,78,100] In a study of participants with NYHA class II-IV chronic HF on maintenance β -blocker therapy, Gly16 carriers were not at increased risk of cardiovascular death or heart transplant when compared with Arg16Arg participants.[100] A prospective study of chronic HF participants on metoprolol CR/XL found no differences in decompensated heart failure outcomes, utilization of heart failure medications, or quality-of-life metrics between genotype groups at codon 16.[33] Among participants in INVEST with coronary artery disease and hypertension receiving atenolol, risk for MACE (death, MI, stroke) was not associated with *ADRB2* haplotype.[78] Collectively, data among participants with chronic HF and coronary artery disease suggest *ADRB2* genotype is not associated with cardiovascular events while on a background of maintenance β -blocker therapy.

5. *GRK5* and β -blockers

G protein-coupled receptor kinases (GRK) function to desensitize ligand-occupied G protein-coupled receptors, like β -adrenergic receptors, ultimately leading to receptor down-regulation.[64,101] G protein-coupled receptor kinase 5 is widely expressed in cardiac tissue.[101,102] The *GRK5* variant rs2230345 (*GRK5* 122A>T; Gln41Leu) exhibits allele frequency differences between ancestral populations, with approximately 40% of black and 2% of white patients carrying the variant allele.[101] The *GRK5* Leu41 variant encodes an increased function kinase that enhances desensitization of the β -1 adrenergic receptor *in vitro*, thus reducing receptor stimulation and cAMP generation (Figure 1).[101,103] A prospective study in patients of African ancestry with heart failure showed longer survival times were observed in *GRK5* Leu41 carriers compared with *GRK5* Gln41Gln participants, in the absence of β -blocker therapy (Supplementary Table 1).[101] Among *GRK5* Leu41 carriers, there was no benefit associated with β -blocker therapy, whereas *GRK5* Gln41Gln had significant improvements in transplant-free survival when treated with a β -blocker. Overall, *GRK5* genotype that encodes the Leu41 allele enhances β -adrenergic receptor desensitization and decreases the risk for death or heart transplant in a gene-dose dependent fashion. In the presence of β -blocker therapy, *GRK5* Gln41Gln participants experienced survival advantages similar to that of *GRK5* Leu41 carriers with no β -blocker therapy.[101] These findings were corroborated in a prospective study of participants with HFrEF, where *GRK5* Leu41 allele carriers, compared with *GRK5* Gln41Gln participants, had improved survival among blacks not treated with β -blocker therapy.[91] In contrast, there was no association between *GRK5* genotype at codon 41 and HF outcomes among β -blocker treated black participants, suggesting that β -blocker therapy nullifies the risk associated with the Gln41Gln genotype.[91] Additional studies identified the expanded protective role of the *GRK5* Leu41 allele to extend beyond patients with HF. Data from a hypertensive cohort with coronary artery disease support decreased odds of MACE (death, myocardial infarction, or stroke) among *GRK5* Leu41 carriers compared with *GRK5* Gln41Gln

participants.[104] Importantly, the effects of the *GRK5* Leu41 allele in hypertensive patients were independent of treatment, suggesting the degree of SNS activation in the underlying pathophysiology (e.g., hypertension, HFrEF) may modulate treatment response.[104] While *GRK5* Leu41 protects against adverse cardiovascular outcomes, there are no significant differences between *GRK5* Gln41Leu genotype and blood pressure response to antihypertensive medication or exercise-induced change in heart rate after atenolol administration.[103,104] Associations between *GRK5* genotype and cardiovascular outcomes have been observed with carvedilol, metoprolol, and atenolol, thus implying the effects are consistent for drugs causing β 1-adrenergic receptor blockade. Further studies are needed to elucidate the pharmacogenomic associations between *GRK5* genotype and cardiovascular outcomes.

6. Conclusion

CYP2D6, *ADRB1*, *ADRB2*, and *GRK5* have the strongest evidence for pharmacogenomic associations with β -blocker pharmacokinetic and pharmacodynamic response and clinical outcomes. Data available to-date have evaluated these pharmacogenomic associations across a range of clinical phenotypes. The effects of genetic polymorphisms in *CYP2D6* on *CYP2D6*-dependent β -blocker (i.e., metoprolol, carvedilol, propranolol, labetalol, nebivolol, and timolol) pharmacokinetics is apparent across many studies. Metoprolol is the principal β -blocker where pharmacokinetic variability translates to differences in pharmacodynamic response, likely due to its extensive reliance on *CYP2D6* for its inactivation. Despite greater AUC and decreased apparent oral clearance in *CYP2D6* PM and IMs, these pharmacokinetic differences primarily translate into differences in HR, but not other β -blocker response phenotypes. Clinically, this results in *CYP2D6* PMs and IMs experiencing greater decreases in HR with certain β -blocker doses in the lower end of the dosing range, though this may be less apparent at higher doses. Though there has been much speculation that PMs and IMs would have increased prevalence of adverse effects to β -blockers, nearly all data indicate this is not the case. Thus, *CYP2D6* pharmacogenetics have little to no impact on the efficacy or adverse effects associated with β -blockers.

ADRB1, *ADRB2*, and *GRK5* variants have been studied in patients with many cardiovascular diseases, including essential hypertension, ischemic stroke, coronary artery disease, chronic heart failure, and Marfan syndrome. *ADRB1* genotype has been associated with major cardiovascular events and other clinical phenotypes in a variety of clinical settings, including heart failure, ischemic heart disease, and stroke prevention. Among patients with coronary artery disease, β -blocker therapy ameliorates the risk for MACE among Ser49-Arg389 carriers. In patients with chronic HF and the *ADRB1* Arg389Arg genotype, the use of β -blockers also appears to reduce the risk for cardiovascular events; a finding less commonly observed for Gly389 carriers. Generally, it appears that differences in MACE and mortality by *ADRB1* genotype are mitigated in the presence of β -blocker therapy, thus highlighting the potential for preferential use of β -blocking agents in *ADRB1* Arg389Arg patients.

Regarding *ADRB2*, data among coronary artery disease and chronic HF populations receiving β -blockade are less robust compared to associations with *ADRB1*. Overall, similar

clinical outcomes have been reported between *ADRB2* genotype groups among patients receiving maintenance β -blocker therapy. In the case of *GRK5* variants, the major allele homozygous genotype (Gln41Gln) was associated with greater treatment response with β -blockers, whereas Leu41 allele carriers experienced similar cardiovascular outcomes between β -blocker treated and untreated participants. While not all β -blockers encountered in clinical practice are represented in the literature, available data for *ADRB1* and *GRK5* suggest the observed associations apply across the β -blocker medication class. This is evidenced in part by clinical findings across multiple β -blockers. Overall, use of pharmacogenomic data to guide treatment of β -blocker therapy in patients with hypertension, coronary artery disease, and heart failure has the best potential for translation into clinical practice.

7. Expert opinion

In the current precision medicine era, genes involved in β -blocker disposition and response have not yet been translated to clinical practice. Of the genes discussed in this review, only *CYP2D6* is used in clinical practice, but not in the context of β -blocker therapy. It is possible for sites that have already adopted *CYP2D6* pharmacogenetics to implement strategies for β -blocker prescribing. Of all the β -blockers, metoprolol has the greatest pharmacogenetic evidence with *CYP2D6*. Regarding clinical utility, the data do not support ordering a *CYP2D6* pharmacogenetic test for the purposes of guiding β -blocker therapy. However, if *CYP2D6* genotype data are available in the patient's electronic health record, these data may have clinical utility. Specifically, knowledge that a patient is a PM or IM may provide the prescriber with some assurance if the patient appears to be responding well to a lower than expected dose. CYP2D6 PMs may achieve goal HR reductions at lower β -blocker doses than CYP2D6 NMs, which is the response often used to indicate complete β -blockade. Similarly, CYP2D6 UMs may require increased β -blocker doses to achieve responses comparable to NMs. Additionally, patients with HFrEF and CYP2D6 IM or PM phenotypes may never reach guideline-directed doses of metoprolol yet have a sufficient degree of β -blockade to derive the expected benefits of a full dose. Clinically, HR is an excellent biomarker for the degree of β -adrenergic receptor blockade, and in most settings β -blocker therapy is started at a low dose and titrated upwards based on HR and other response.

Currently, *ADRB1* genotype is not used to guide β -blocker prescribing decisions despite its associations with major adverse cardiovascular events and mortality. Despite the absence of clinical use of these genetic data, the total number of clinical outcomes studies and consistency of the data are of similar or greater quality than many of the examples for which Clinical Pharmacogenetics Implementation Consortium Guidelines (<https://cpicpgx.org/>) exist, and thus guidelines for *ADRB1* genotype informed β -blocker therapy should be considered. Specifically, numerous studies, including in ischemic heart disease, hypertension, heart failure, stroke and Marfan Syndrome suggest better β -blocker treatment outcomes in those with the Arg389Arg genotype, often because this genotype is associated with increased risk for adverse cardiovascular outcomes, which is offset with β -blocker therapy. Most of these studies point to the Arg389Arg genotype, or the Ser49-Arg389 haplotype being associated with risk for which β -blockers largely moderate that risk.

Current evidence suggests this increased risk is ameliorated in the presence of β -blocker therapy. This highlights a gap in current clinical pharmacogenomics implementation, whereby *ADRB1* genotype could be utilized to preferentially prescribe β -blocker pharmacotherapy in patients with the *ADRB1* Arg389Arg genotype. A genotype-guided strategy for β -blockers may be viewed as less impactful in clinical practice for HFrEF and patients who are in the first few years post-myocardial infarction, where guidelines recommend that all patients receive a β -blocker. However, even in these settings, such data would highlight those for whom achievement of target HR/target doses would be most beneficial and may improve adherence if patients know they are particularly likely to obtain benefit from the β -blocker. In other settings, such as complicated hypertension, ischemic heart disease, stroke prevention, or Marfan syndrome where there might be several options, these genetic data may highlight a β -blocker as the preferred agent for individual patients.

In contrast the current data for *ADRB2* do not suggest such data are useful in the clinical setting as it relates to guiding the use of β -blocker therapy, even if the data are already available. While there are a few interesting studies, there is not sufficient consistency in the data to warrant consideration of its use in the clinical environment. While the current state of *ADRB2* pharmacogenomics does not warrant clinical implementation, the most promising data are in the setting of heart failure and future research should be conducted in cohorts of participants with heart failure with preserved ejection fraction (HFpEF).

While there are fewer studies on the impact of the *GRK5* Gln41Leu polymorphism, the existing literature are highly consistent and thus may have potential for clinical application. This polymorphism is most common in those of African ancestry, with the greatest evidence in patients with heart failure. The Leu41 allele appears to emulate the effects of β -blockade, since *GRK5* Leu41 allele carriers have better outcomes than Gln41Gln carriers, and appear to have similar cardiovascular outcomes, regardless of β -blocker utilization. In contrast those with Gln41Gln have increased risk of poor outcomes and show significant benefit with β -blocker therapy. Similar to *ADRB1*, the clinical use of these data may not seem obvious, since β -blocker therapy is recommended for all patients with HFrEF. However, in patients with Gln41Gln it may also highlight those for whom it is essential to reach the target dose and/or may improve adherence among patients if they understand their genotype is one that derives significant benefit for β -blockers.

In summary, we suggest that *CYP2D6* data may have some clinical utility for understanding dosing of commonly used β -blockers if the data are available, though the data are not sufficiently robust to warrant ordering a *CYP2D6* pharmacogenetic test. We contend there may be clinical potential to add *ADRB1* and *GRK5* to the list of genes used clinically in pharmacogenetics, while *ADRB2* does not have evidence, at least in the context of β -blockers, that would warrant its clinical use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BP	Blood pressure
CAD	coronary artery disease
cAMP	Cyclic adenosine monophosphate
CPIC	Clinical Pharmacogenetics Implementation Consortium
DBP	Diastolic BP
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
IM	CYP2D6 intermediate metabolizer
NM	CYP2D6 normal metabolizer
NYHA	New York Heart Association
PM	CYP2D6 poor metabolizer
SBP	Systolic BP
SNS	sympathetic nervous system
UM	CYP2D6 ultra-rapid metabolizer

References

Articles of special interest have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Kochanek KDMS, Xu JQ, Arias E. Deaths: Final data for 2017. National Vital Statistics Reports. 2019;68(9):1–77.
2. Murphy SLXJ, Kochanek KD, Arias E. Mortality in the United States, 2017 In: NCHS Data Brief n, editor. Hyattsville, MD: National Center for Health Statistics; 2018.
3. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2017;39(2):119–177.
4. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Journal of the American College of Cardiology. 2018;71(19):e127.

5. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Journal of the American College of Cardiology*. 2017;70(6):776. [PubMed: 28461007]
6. Eichelbaum M, Gross AS. The genetic polymorphism of debrisoquine/sparteine metabolism--clinical aspects. *Pharmacology & therapeutics*. 1990;46(3):377-94. [PubMed: 2188269]
7. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittel-Forschung*. 2003;53(12):814-22. [PubMed: 14732961]
8. Lennard MS, Silas JH, Freestone S, et al. Oxidation phenotype--a major determinant of metoprolol metabolism and response. *N Engl J Med*. 1982 12 16;307(25):1558-60. [PubMed: 7144837]
9. Lennard MS, Silas JH, Freestone S, et al. Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br J Clin Pharmacol*. 1982 8;14(2):301-3. [PubMed: 6125207] ** Original paper that identified associations between CYP2D6 phenotype and metoprolol pharmacokinetics and pharmacodynamics.
10. Lennard MS, Tucker GT, Silas JH, et al. Debrisoquine polymorphism and the metabolism and action of metoprolol, timolol, propranolol and atenolol. *Xenobiotica*. 1986 5;16(5):435-47. [PubMed: 2874665]
11. Shin J, Johnson JA. Pharmacogenetics of beta-blockers. *Pharmacotherapy*. 2007;27(6):874-887. [PubMed: 17542770]
12. Distlerath LM, Guengerich FP. Characterization of a human liver cytochrome P-450 involved in the oxidation of debrisoquine and other drugs by using antibodies raised to the analogous rat enzyme. *Proc Natl Acad Sci U S A*. 1984 12;81(23):7348-52. [PubMed: 6594694]
13. Eichelbaum M, Baur MP, Dengler HJ, et al. Chromosomal assignment of human cytochrome P-450 (debrisoquine/sparteine type) to chromosome 22. *Br J Clin Pharmacol*. 1987 4;23(4):455-8. [PubMed: 3472585]
14. Nofziger C, Turner AJ, Sangkuhl K, et al. PharmVar GeneFocus: CYP2D6. *Clinical pharmacology and therapeutics*. 2020 1;107(1):154-170. [PubMed: 31544239]
15. Bell GC, Caudle KE, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clinical pharmacology and therapeutics*. 2017 8;102(2):213-218. [PubMed: 28002639]
16. Brown JT, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. *Clinical pharmacology and therapeutics*. 2019 7;106(1):94-102. [PubMed: 30801677]
17. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clinical pharmacology and therapeutics*. 2014 4;95(4):376-82. [PubMed: 24458010]
18. Goetz MP, Sangkuhl K, Guchelaar HJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. *Clinical pharmacology and therapeutics*. 2018 5;103(5):770-777. [PubMed: 29385237]
19. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clinical pharmacology and therapeutics*. 2015 8;98(2):127-34. [PubMed: 25974703]
20. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clinical pharmacology and therapeutics*. 2017 7;102(1):37-44. [PubMed: 27997040]
21. Gaedigk A, Simon SD, Pearce RE, et al. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. *Clinical pharmacology and therapeutics*. 2008 2;83(2):234-42. [PubMed: 17971818]
22. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*. 2020 1;13(1):116-124. [PubMed: 31647186]
23. Bae SH, Lee JK, Cho DY, et al. Simultaneous determination of metoprolol and its metabolites, alpha-hydroxymetoprolol and O-desmethylnmetoprolol, in human plasma by liquid

chromatography with tandem mass spectrometry: Application to the pharmacokinetics of metoprolol associated with CYP2D6 genotypes. *Journal of separation science*. 2014 6;37(11):1256–64. [PubMed: 24648255]

24. PharmVar CYP2D6 gene page. Available from: <https://www.pharmvar.org/gene/CYP2D6>
25. Batty JA, Hall AS, White HL, et al. An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy. *Clinical pharmacology and therapeutics*. 2014 3;95(3):321–30. [PubMed: 24193112]
26. Fux R, Morike K, Prohmer AM, et al. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clinical pharmacology and therapeutics*. 2005 10;78(4):378–87. [PubMed: 16198657]
27. Goryachkina K, Burbello A, Boldueva S, et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. *Eur J Clin Pharmacol*. 2008 12;64(12):1163–73. [PubMed: 18648788]
28. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *J Clin Pharm Ther*. 2006 2;31(1):99–109. [PubMed: 16476126]
29. Jin SK, Chung HJ, Chung MW, et al. Influence of CYP2D6*10 on the pharmacokinetics of metoprolol in healthy Korean volunteers. *J Clin Pharm Ther*. 2008 10;33(5):567–73. [PubMed: 18834373]
30. Kirchheiner J, Heesch C, Bauer S, et al. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clinical pharmacology and therapeutics*. 2004 10;76(4):302–12. [PubMed: 15470329]
31. Koytchev R, Alken RG, Vlahov V, et al. Influence of the cytochrome P4502D6*4 allele on the pharmacokinetics of controlled-release metoprolol. *Eur J Clin Pharmacol*. 1998 8;54(6):469–74. [PubMed: 9776437]
32. Taguchi M, Nozawa T, Kameyama T, et al. Effect of CYP2D6*10 on pharmacokinetic variability of routinely administered metoprolol in middle-aged and elderly Japanese patients. *Eur J Clin Pharmacol*. 2003 9;59(5–6):385–8. [PubMed: 12915955]
33. 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. *Clinical pharmacology and therapeutics*. 2005 3;77(3):127–37. [PubMed: 15735607] * Clinical study that identified an association between ADRB1 genotype and increased use of medications used to control symptoms of heart failure.
34. Sehr D, Meineke I, Tzvetkov M, et al. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. *Pharmacogenomics*. 2011 6;12(6):783–95. [PubMed: 21599570]
35. Blake CM, Kharasch ED, Schwab M, et al. A meta-analysis of CYP2D6 metabolizer phenotype and metoprolol pharmacokinetics. *Clinical pharmacology and therapeutics*. 2013 9;94(3):394–9. [PubMed: 23665868] * Meta-analysis demonstrating CYP2D6 phenotype is associated with variability in metoprolol pharmacokinetics.
36. Bijl MJ, Visser LE, van Schaik RH, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clinical pharmacology and therapeutics*. 2009 1;85(1):45–50. [PubMed: 18784654]
37. Edeki TI, He H, Wood AJ. Pharmacogenetic explanation for excessive beta-blockade following timolol eye drops. Potential for oral-ophthalmic drug interaction. *Jama*. 1995 11 22–29;274(20):1611–3. [PubMed: 7474246]
38. Johnson JA, Herring VL, Wolfe MS, et al. CYP1A2 and CYP2D6 4-hydroxylate propranolol and both reactions exhibit racial differences. *J Pharmacol Exp Ther*. 2000 9;294(3):1099–105. [PubMed: 10945865]
39. Lai ML, Wang SL, Lai MD, et al. Propranolol disposition in Chinese subjects of different CYP2D6 genotypes. *Clinical pharmacology and therapeutics*. 1995 9;58(3):264–8. [PubMed: 7554699]
40. Masubuchi Y, Hosokawa S, Horie T, et al. Cytochrome P450 isozymes involved in propranolol metabolism in human liver microsomes. The role of CYP2D6 as ring-hydroxylase and CYP1A2 as N-desisopropylase. *Drug metabolism and disposition: the biological fate of chemicals*. 1994 Nov-Dec;22(6):909–15. [PubMed: 7895609]

41. Nieminen T, Uusitalo H, Maenpää J, et al. Polymorphisms of genes CYP2D6, ADRB1 and GNAS1 in pharmacokinetics and systemic effects of ophthalmic timolol. A pilot study. *Eur J Clin Pharmacol.* 2005 12;61(11):811–9. [PubMed: 16315032]
42. Sowinski KM, Burlew BS. Impact of CYP2D6 poor metabolizer phenotype on propranolol pharmacokinetics and response. *Pharmacotherapy.* 1997 Nov-Dec;17(6):1305–10. [PubMed: 9399616]
43. Briciu C, Neag M, Muntean D, et al. Phenotypic differences in nebivolol metabolism and bioavailability in healthy volunteers. *Clujul Med.* 2015;88(2):208–13. [PubMed: 26528073]
44. Briciu C, Neag M, Muntean D, et al. A pharmacokinetic drug interaction study between nebivolol and paroxetine in healthy volunteers. *J Clin Pharm Ther.* 2014 10;39(5):535–40. [PubMed: 24845234]
45. Gheldiu AM, Popa A, Neag M, et al. Assessment of a Potential Pharmacokinetic Interaction between Nebivolol and Bupropion in Healthy Volunteers. *Pharmacology.* 2016;98(3–4):190–8. [PubMed: 27300331]
46. Guo L, Wang S, Wan Z, et al. Influence of CYP2D6*5 and *10 polymorphism on the pharmacokinetics of nebivolol in healthy Chinese subjects. *J Clin Pharm Ther.* 2020 8;45(4):632–637. [PubMed: 32379356]
47. Hu X, Lan T, Dai D, et al. Evaluation of 24 CYP2D6 Variants on the Metabolism of Nebivolol In Vitro. *Drug metabolism and disposition: the biological fate of chemicals.* 2016 11;44(11):1828–1831. [PubMed: 27538917]
48. Lefebvre J, Poirier L, Poirier P, et al. The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension. *Br J Clin Pharmacol.* 2007 5;63(5):575–82. [PubMed: 17094780]
49. Vieira CP, Neves DV, Coelho EB, et al. Effect of CYP2D6 Poor Metabolizer Phenotype on Stereoselective Nebivolol Pharmacokinetics. *Drug Metab Lett.* 2018;12(1):68–70. [PubMed: 29676238]
50. Zhou HH, Wood AJ. Stereoselective disposition of carvedilol is determined by CYP2D6. *Clinical pharmacology and therapeutics.* 1995 5;57(5):518–24. [PubMed: 7768074]
51. Honda M, Ogura Y, Toyoda W, et al. Multiple regression analysis of pharmacogenetic variability of carvedilol disposition in 54 healthy Japanese volunteers. *Biol Pharm Bull.* 2006 4;29(4):772–8. [PubMed: 16595916]
52. Saito M, Kawana J, Ohno T, et al. Population pharmacokinetics of R- and S-carvedilol in Japanese patients with chronic heart failure. *Biol Pharm Bull.* 2010;33(8):1378–84. [PubMed: 20686235]
53. Takekuma Y, Takenaka T, Kiyokawa M, et al. Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. *Biol Pharm Bull.* 2007 3;30(3):537–42. [PubMed: 17329852]
54. Hamadeh IS, Langaee TY, Dwivedi R, et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. *Clinical pharmacology and therapeutics.* 2014 8;96(2):175–81. [PubMed: 24637943] * Data from this study provide evidence for similar metoprolol tolerability, despite established differences in β -blocker pharmacokinetics, between CYP2D6 phenotypes.
55. Gao X, Wang H, Chen H. Impact of CYP2D6 and ADRB1 polymorphisms on heart rate of post-PCI patients treated with metoprolol. *Pharmacogenomics.* 2017 11 2.
56. Luzum JA, Sweet KM, Binkley PF, et al. CYP2D6 Genetic Variation and Beta-Blocker Maintenance Dose in Patients with Heart Failure. *Pharmaceutical research.* 2017 8;34(8):1615–1625. [PubMed: 28181117]
57. Lindamood C, Ortiz S, Shaw A, et al. Effects of commonly administered agents and genetics on nebivolol pharmacokinetics: drug-drug interaction studies. *J Clin Pharmacol.* 2011 4;51(4):575–85. [PubMed: 20489028]
58. Bystolic (nebivolol) [package insert]. Irvine, CA: Allergan; 2017.
59. Rau T, Dungen HD, Edelmann F, et al. Impact of the beta1-adrenoceptor Arg389Gly polymorphism on heart-rate responses to bisoprolol and carvedilol in heart-failure patients. *Clinical pharmacology and therapeutics.* 2012 7;92(1):21–8. [PubMed: 22617224]

60. Yuan H, Huang Z, Yang G, et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the therapeutic effects of metoprolol. *The Journal of international medical research*. 2008 Nov-Dec;36(6):1354–62. [PubMed: 19094446]
61. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999 6 12;353(9169):2001–7. [PubMed: 10376614]
62. 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 8;5(4):463–8. [PubMed: 12921807]
63. Zineh I, Beitelshes AL, Gaedigk A, et al. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clinical pharmacology and therapeutics*. 2004 12;76(6):536–44. [PubMed: 15592325]
64. Lymperopoulos A, French F. Pharmacogenomics of Heart Failure In: Yan Q, editor. *Pharmacogenomics in Drug Discovery and Development*. New York, NY: Springer New York; 2014 p. 245–257.
65. Joseph SS, Lynham JA, Grace AA, et al. Markedly reduced effects of (–)-isoprenaline but not of (–)-CGP12177 and unchanged affinity of beta-blockers at Gly389-beta1-adrenoceptors compared to Arg389-beta1-adrenoceptors. *Br J Pharmacol*. 2004 5;142(1):51–6. [PubMed: 15037517]
66. 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 4 30;274(18):12670–4. [PubMed: 10212248] ** Foundational study identifying functional consequences of ADRB1 Arg389Gly polymorphism, whereby the Gly allele is associated with reduced coupling to Gas, and thus reduced generation of cyclic AMP.
67. La Rosee K, Huntgeburth M, Rosenkranz S, et al. The Arg389Gly beta1-adrenoceptor gene polymorphism determines contractile response to catecholamines. *Pharmacogenetics*. 2004 11;14(11):711–6. [PubMed: 15564877]
68. Liu J, Liu ZQ, Tan ZR, et al. Gly389Arg polymorphism of beta1-adrenergic receptor is associated with the cardiovascular response to metoprolol. *Clinical pharmacology and therapeutics*. 2003 10;74(4):372–9. [PubMed: 14534524]
69. Petersen M, Andersen JT, Jimenez-Solem E, et al. Effect of the Arg389Gly beta(1)-adrenoceptor polymorphism on plasma renin activity and heart rate, and the genotype-dependent response to metoprolol treatment. *Clin Exp Pharmacol Physiol*. 2012 9;39(9):779–85. [PubMed: 22703382]
70. 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 3;15(3):137–42. [PubMed: 15861037]
71. Johnson JA, Zineh I, Puckett BJ, et al. Beta 1-adrenergic receptor polymorphisms and antihypertensive response to metoprolol. *Clinical pharmacology and therapeutics*. 2003 7;74(1):44–52. [PubMed: 12844134] ** First clinical study identifying ADRB1 genotype as an important determinant of antihypertensive response to metoprolol.
72. Liu J, Liu ZQ, Yu BN, et al. beta1-Adrenergic receptor polymorphisms influence the response to metoprolol monotherapy in patients with essential hypertension. *Clinical pharmacology and therapeutics*. 2006 7;80(1):23–32. [PubMed: 16815314]
73. Van Driest SLSL, Dietz H. Impact of variants in ADRB1 and CYP2C9 on atenolol and losartan response in Marfan syndrome. Paper presented at: Pediatric Academic Societies 2017 Annual Meeting 2017;San Francisco, CA; May 6–9, 2017.** First study suggesting ADRB1 genotype might be helpful for guiding drug therapy selection in patients with Marfan syndrome.
74. Beitelshes AL, Zineh I, Yarandi HN, et al. Influence of phenotype and pharmacokinetics on beta-blocker drug target pharmacogenetics. *Pharmacogenomics J*. 2006 May-Jun;6(3):174–8. [PubMed: 16402084]
75. Karlsson J, Lind L, Hallberg P, et al. Beta1-adrenergic receptor gene polymorphisms and response to beta1-adrenergic receptor blockade in patients with essential hypertension. *Clin Cardiol*. 2004 6;27(6):347–50. [PubMed: 15237695]

76. O'Shaughnessy KM, Fu B, Dickerson C, et al. The gain-of-function G389R variant of the beta1-adrenoceptor does not influence blood pressure or heart rate response to beta-blockade in hypertensive subjects. *Clin Sci (Lond)*. 2000 9;99(3):233–8. [PubMed: 11787477]
77. Sofowora GG, Dishy V, Muszkat M, et al. A common beta1-adrenergic receptor polymorphism (Arg389Gly) affects blood pressure response to beta-blockade. *Clinical pharmacology and therapeutics*. 2003 4;73(4):366–71. [PubMed: 12709726]
78. Pacanowski MA, Gong Y, Cooper-Dehoff RM, et al. beta-adrenergic receptor gene polymorphisms and beta-blocker treatment outcomes in hypertension. *Clinical pharmacology and therapeutics*. 2008 12;84(6):715–21. [PubMed: 18615004] ** Study documenting that in patients with hypertension and ischemic heart disease, ADRB1 genotype may influence drug therapy outcomes and thus drug selection.
79. 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 2;24(1):49–60. [PubMed: 20352314]
80. Wu D, Li G, Deng M, et al. Associations between ADRB1 and CYP2D6 gene polymorphisms and the response to beta-blocker therapy in hypertension. *The Journal of international medical research*. 2015 6;43(3):424–34. [PubMed: 25823457]
81. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A Calcium Antagonist vs a Non-Calcium Antagonist Hypertension Treatment Strategy for Patients With Coronary Artery Disease The International Verapamil-Trandolapril Study (INVEST): A Randomized Controlled Trial. *JAMA*. 2003;290(21):2805–2816. [PubMed: 14657064]
82. Iwai C, Akita H, Kanazawa K, et al. Arg389Gly polymorphism of the human beta1-adrenergic receptor in patients with nonfatal acute myocardial infarction. *Am Heart J*. 2003 7;146(1):106–9. [PubMed: 12851615]
83. 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 8 1;106(3):402–8. [PubMed: 20643254]
84. Kim KM, Murray MD, Tu W, et al. Pharmacogenetics and healthcare outcomes in patients with chronic heart failure. *Eur J Clin Pharmacol*. 2012 11;68(11):1483–91. [PubMed: 22543981]
85. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *Jama*. 2009 4 8;301(14):1439–50. [PubMed: 19351941]
86. Fiuzat M, Neely ML, Starr AZ, et al. Association between adrenergic receptor genotypes and beta-blocker dose in heart failure patients: analysis from the HF-ACTION DNA substudy. *Eur J Heart Fail*. 2013 3;15(3):258–66. [PubMed: 23115322]
87. Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, et al. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001 5 31;344(22):1659–67. [PubMed: 11386264]
88. Liggett SB, Miallet-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 7 25;103(30):11288–93. [PubMed: 16844790] ** Foundational paper that identified the mortality benefit of β -blockers in participants with the ADRB1 Arg389Arg genotype.
89. Aleong RG, Sauer WH, Robertson AD, et al. Adrenergic receptor polymorphisms and prevention of ventricular arrhythmias with bucindolol in patients with chronic heart failure. *Circ Arrhythm Electrophysiol*. 2013 2;6(1):137–43. [PubMed: 23275278]
90. Kao DP, Davis G, Aleong R, et al. Effect of bucindolol on heart failure outcomes and heart rate response in patients with reduced ejection fraction heart failure and atrial fibrillation. *Eur J Heart Fail*. 2013 3;15(3):324–33. [PubMed: 23223178]
91. Cresci S, Kelly RJ, Cappola TP, et al. Clinical and genetic modifiers of long-term survival in heart failure. *J Am Coll Cardiol*. 2009 7 28;54(5):432–44. [PubMed: 19628119] * Study validating benefits of β -blockade among GRK5 Gln41Gln participants.

92. Lacro RV, Dietz HC, Wruck LM, et al. Rationale and design of a randomized clinical trial of beta-blocker therapy (atenolol) versus angiotensin II receptor blocker therapy (losartan) in individuals with Marfan syndrome. *Am Heart J*. 2007 10;154(4):624–31.
93. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med*. 2014 11 27;371(22):2061–71. [PubMed: 25405392]
94. Benavente OR, White CL, Pearce L, et al. The Secondary Prevention of Small Subcortical Strokes (SPS3) study. *Int J Stroke*. 2011 4;6(2):164–75. [PubMed: 21371282]
95. Magvanjav O, McDonough CW, Gong Y, et al. Pharmacogenetic Associations of beta1-Adrenergic Receptor Polymorphisms With Cardiovascular Outcomes in the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes). *Stroke*. 2017 5;48(5):1337–1343. [PubMed: 28351962] * Study identified an association between ADRB1 genotype and cardiovascular events among participants with a history of ischemic stroke receiving β -blocker therapy.
96. 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 7;13(1):25–33. [PubMed: 7598936]
97. 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 8 16;33(32):9414–9. [PubMed: 7915137]
98. Dishy V, Sofowora GG, Xie HG, et al. The effect of common polymorphisms of the beta2-adrenergic receptor on agonist-mediated vascular desensitization. *N Engl J Med*. 2001 10 4;345(14):1030–5. [PubMed: 11586955]
99. Troncoso R, Moraga F, Chiong M, et al. Gln(27)-->Glu(27)-adrenergic receptor polymorphism in heart failure patients: differential clinical and oxidative response to carvedilol. *Basic Clin Pharmacol Toxicol*. 2009 5;104(5):374–8. [PubMed: 19422106]
100. Huang J, Li C, Song Y, et al. ADRB2 polymorphism Arg16Gly modifies the natural outcome of heart failure and dictates therapeutic response to beta-blockers in patients with heart failure. *Cell Discov*. 2018;4:57. [PubMed: 30374408]
101. Liggett SB, Cresci S, Kelly RJ, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. *Nature medicine*. 2008 5;14(5):510–7.** Foundational study demonstrating benefits of β -blockade in GRK5 Gln41Gln participants.
102. Premont RT, Koch WJ, Inglese J, et al. Identification, purification, and characterization of GRK5, a member of the family of G protein-coupled receptor kinases. *J Biol Chem*. 1994 3 4;269(9):6832–41. [PubMed: 8120045]
103. Kurnik D, Cunningham AJ, Sofowora GG, et al. GRK5 Gln41Leu polymorphism is not associated with sensitivity to beta(1)-adrenergic blockade in humans. *Pharmacogenomics*. 2009 10;10(10):1581–7. [PubMed: 19842931]
104. Lobmeyer MT, Wang L, Zineh I, et al. Polymorphisms in genes coding for GRK2 and GRK5 and response differences in antihypertensive-treated patients. *Pharmacogenet Genomics*. 2011 1;21(1):42–9. [PubMed: 21127457]

Article highlights

- *ADRB1*, *ADRB2*, *GRK5* and *CYP2D6* have been extensively studied for their associations with efficacy, adverse effects and or clinical outcomes resulting from treatment with β -blockers. We summarize this literature and discuss the potential clinical utility of genotype-guided approaches to β -blocker treatment.
- *CYP2D6* intermediate and poor metabolizers have significantly higher plasma drug concentrations than others at an equal dose. This may result in greater heart rate response, or effective β -blockade at lower than usual doses, but otherwise *CYP2D6* genotype/phenotype has minimal clinical impact, including that it appears to have minimal to no impact on β -blocker-related adverse effects. If *CYP2D6* genotype data are already available to the prescribing clinician, they may provide clinical utility given patients who are poor or intermediate metabolizers may achieve the target HR response at a lower than expected dose. Ordering a *CYP2D6* test to guide β -blocker therapy is not recommended.
- Numerous studies suggest greater β -blocker efficacy in those with the *ADRB1* Arg389Arg genotype, including for cardiovascular outcomes, the latter of which appear to be due to higher risk for cardiovascular events in this genotype group, which is offset with β -blocker therapy.
- Similarly, *GRK5* Gln41Gln is associated with increased risk of adverse cardiovascular outcomes, which is offset by treatment with a β -blocker therapy, resulting in this genotype group being more responsive to β -blockers.
- Data generally do not suggest an important role of *ADRB2* variability influences responses to β -blockers.
- Current evidence is consistent with the potential clinical use of *ADRB1* and *GRK5* genotype to guide β -blocker therapy and development of Clinical Pharmacogenetics Implementation Consortium guidelines should be considered.

Figure 1.
Pharmacodynamic Pathways of $\beta 1$ and $\beta 2$ Receptors and Resulting cAMP Generation

Table 1.

Phenotype and Variant Allele Frequencies

	EUROPEAN	AFRICAN	ASIAN
PHENOTYPE FREQUENCIES			
CYP2D6			
PM	6	2	2
IM	38	45	29
NM	51	44	66
UM	4	4	2
VARIANT ALLELE FREQUENCIES			
<i>ADRB1</i>			
rs1801252 (Gly49)	13	16	5
rs1801253 (Gly389)	31	37	38
<i>ADRB2</i>			
rs1042713 (Gly16)	63	51	46
rs1042714 (Glu27)	42	29	12
<i>GRK5</i>			
rs2230345 (Leu41)	2	16	0

IM: intermediate metabolizer; NM: normal metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer. CYP2D6 phenotype frequencies from <https://cpicpgx.org/>. *ADRB1*, *ADRB2*, and *GRK5* variant allele frequencies from dbGaP, with the resulting encoded variant allele amino acid in parentheses.

Table 2: Evidence Table for Pharmacogenetics of Cardiovascular Outcomes with respect to *ADRB1*, *ADRB2*, and *GRK5*

Study Type ^a	Study Population	β-blocker	No. of Subjects	Duration	Gene	SNPs	Outcomes	Findings
Prospective (Pacanowski, 2008)	CAD secondary prevention	Atenolol	5895	2 years	ADRB1, ADRB2	ADRB1: rs1801252 (Ser49Gly), rs1801253 (Arg389Gly) ADRB2: rs1042713 (Gly16Arg), rs1042714 (Gln27Glu), rs1042718 (Arg175Arg)	MACE (death, MI, stroke)	Ser49-Arg389 carriers – increased MACE and death risk Death risk in Ser49-Arg389 carriers attenuated in atenolol, but not verapamil treated participants ADRB2 not associated with MACE overall or in treatment specific manner
Prospective (Fitzat, 2013)	HF+EF (LVEF < 35%; NYHA class II-IV)	Multiple	902	2.5 years	ADRB1	ADRB1: rs1801252 (Ser49Gly), rs1801253 (Arg389Gly)	All-cause death or all-cause hospitalization All-cause death	Arg389Arg – increased risk of death with low-dose β-blocker that was offset with high-dose β-blocker. β-blocker dose not associated with outcomes in Gly389 carriers Ser49Gly: no association
Prospective (White, 2003)	HF+EF (LVEF 40%; NYHA class II-IV)	Metoprolol CR/XL	600	1 year	ADRB1	ADRB1: rs1801253 (Arg389Gly)	All-cause mortality or hospitalization	ADRB1 genotype not associated with outcomes
Prospective (Liggett, 2006)	HF+EF (LVEF 35%; NYHA class III to IV)	Bucindolol	1040	3 years	ADRB1	rs1801253 (Arg389Gly)	All-cause mortality HF Exacerbations (Hospitalization because of HF)	Arg389Arg – bucindolol decreased risk for death and HF exacerbations vs. placebo Gly389 carriers – no association with mortality benefit or reduced HF exacerbations with bucindolol vs. placebo
Prospective (Magvanjav, 2017)	Small artery ischemic stroke secondary prevention	Multiple	926	4 years	ADRB1	ADRB1: rs1801252 (Ser49Gly), rs1801253 (Arg389Gly)	MACE (death, MI, stroke)	Gly49 carriers + β-blocker – increased risk for MACE vs. Ser49Ser + β-blocker Arg389Arg not associated with MACE in the presence of β-blocker therapy
Prospective (Liggett, 2008)	HF+EF (LVEF < 40%; NYHA class II-IV)	Multiple	375	2.5 years	GRK5	rs2230345 (Gln41Leu)	Death or heart transplantation	Increased risk of primary endpoint in Gln41Gln was offset by β-blocker treatment Leu41 carriers derive minimal benefit from β-blocker treatment
Prospective (Cresci, 2009)	HF+EF (LVEF < 40%)	Multiple	2451	4 years	ADRB1, GRK5	ADRB1: rs1801253 (Arg389Gly) GRK5: rs2230345 (Gln41Leu)	Death or heart transplantation	Gly389 carrier – Death or heart transplantation risk attenuated with β-blocker Among African Americans: Increased risk of primary endpoint in Gln41Gln was offset by β-blocker treatment
Prospective (Lobmeyer, 2011)	CAD	Atenolol	1258	2 years	GRK5	rs2230345 (Gln41Leu)	MACE (death, MI, stroke)	Leu41 carrier – decreased odds of MACE regardless of treatment strategy

Prospective studies were designed specifically to test pharmacogenetics hypotheses, or the primary outcome studied in the pharmacogenetic study was the primary outcome in the clinical trial.

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