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Pharmacogenetics of β-Blockers

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Abstract

β-Blockers are an important cardiovascular drug class, recommended as first-line treatment of numerous diseases such as heart failure, hypertension, and angina, as well as treatment after myocardial infarction. However, responses to a β-blocker are variable among patients. Results of numerous studies now suggest that genetic polymorphisms may contribute to variability in responses to β-blockers. This review summarizes the pharmacogenetic data for β-blockers in patients with various diseases and discusses the potential implications of β-blocker pharmacogenetics in clinical practice.

Keywords

pharmacogenetics; β-blockers; hypertension; heart failure; atenolol; metoprolol; β_1-adrenergic receptor gene; ADRB1; cytochrome P450 2D6 gene; CYP2D6

Excessive activation of the adrenergic nervous system contributes to the pathophysiology or symptoms of many cardiovascular diseases. β-Blockers are competitive antagonists at the β-adrenergic receptors, thereby modulating activities in this pathway.[1] β-Blockers are among the most widely prescribed of all drug classes, with more than 120 million prescriptions in the United States in 2004, and atenolol was the fourth most commonly prescribed of all drugs, with 42 million prescriptions in the same year.[2] Currently, 17 β-blockers have been approved by the U.S. Food and Drug Administration (Table 1). Although most of their pharmacologic effects are attributed to their ability to block β-adrenergic receptors, there are many differences among the agents. For example, some are relatively selective for the β_1-adrenergic receptors, whereas others are nonselective. Further, some have ancillary properties in addition to their β-blocking effects, such as intrinsic sympathomimetic activity, α-adrenergic–receptor blockade, and direct vasodilating effects. There is also variability in the pharmacokinetic properties of the various β-blockers. However, all β-blockers antagonize the β_1-adrenergic receptor, and this effect is believed to be responsible for most of the therapeutic benefit associated with β-blocker therapy.

β-Blockers are recommended as a first-line agent for various diseases, including heart failure, hypertension, and angina, as well as after myocardial infarction.[3-6] However, β-blocker therapy often produces variable responses among patients.[7, 8] Genetic differences may contribute to this variability in responses 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 those who are at high risk for adverse events from the drug.

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In this review, the pharmacogenetics literature on β-blockers are summarized and the potential clinical implications of these data are discussed. Studies were identified in the MEDLINE database from 1966–July 2006 by combining the following Medical Subject Heading search terms: genetic polymorphism, single nucleotide polymorphism, pharmacogenetics, adrenergic β antagonists, as well as individual β-blocker names. We also reviewed the references of all identified articles.

Minor allele frequencies and the functional consequences of the major polymorphisms discussed in this review are summarized in Table 2.[9-12]

Blood Pressure and Antihypertensive Responses

The original indication for β-blockers was hypertension, and β-blockers remain among the most commonly prescribed antihypertensives. However, response to these drugs is highly variable whereby 30−60% of patients with hypertension who are treated with β-blocker monotherapy will fail to achieve adequate blood pressure control.[7, 8] This variability may be accounted for, in part, by genetic polymorphisms. Table 3 summarizes data from pharmacogenetic studies on blood pressure responses to β-blockers.[13-24] In particular, various polymorphisms in the genes involved in sympathetic and renin-angiotensin-aldosterone systems (RAAS) have been explored for the variability. Ser49Gly and Arg389Gly, two common single nucleotide polymorphisms (SNPs) in the β_1-adrenergic receptor gene (*ADRB1*), have been most extensively studied. In vitro studies showed that the serine-to-glycine change at codon 49 increased agonist-promoted receptor down-regulation and that receptors containing Arg389 had higher basal and isoproterenol-stimulated receptor activities (Table 2).[9, 10] Because β_1-adrenergic receptors containing Ser49 and/or Arg389 have higher activity, one might expect that patients carrying Ser49 and/or Arg389 would have a better response to β-blocker therapy.

Data from several studies suggest that blood pressure responses to β-blocker therapy may differ by *ADRB1* genotypes. In a study from our laboratory, homozygosity for Arg389 was significantly associated with about 3-fold greater daytime diastolic blood pressure changes after a minimum of 4 weeks of treatment with a stable dose of metoprolol in 40 patients with hypertension ($p=0.0018$).[13] Of note, no difference was seen in S-metoprolol area under the plasma concentration–time curve between Arg389Arg and Gly389 carriers, suggesting the finding was not due to differences in an individual's pharmacokinetics, but due to differences in pharmacodynamics. In addition, the response was significantly associated with *ADRB1* haplotype: Ser49Arg389/Ser49Arg389 had the greatest daytime reduction in diastolic blood pressure. Based on these findings, a statistical model was developed to predict treatment blood pressure (BP): Treated BP (mm Hg) = 18.82 + (0.79 × baseline daytime diastolic BP) − 8.3 (if Arg389Arg) − 5.1 (if Ser49Ser).[13] The Ser49Arg389/Ser49Arg389 haplotype was also identified as a predictor for a good systolic blood pressure response to metoprolol in 61 Chinese patients with hypertension, suggesting its predictability across races.[14] Consistent with the previous study, this study also found that Arg389Arg was significantly associated with a greater decrease in both systolic and diastolic blood pressure compared with Arg389Gly and Gly389Gly. In healthy volunteers, Arg389Arg had significantly greater reduction in systolic blood pressure than Gly389Gly after 1 day of metoprolol treatment.[15] Again, plasma concentrations 3 hours after metoprolol were not significantly different between Arg389Arg and Gly389Gly, suggesting differences in response were not due to variability in metoprolol pharmacokinetics.

Association of *ADRB1* polymorphisms with blood pressure responses to the other β-blockers has not been well established. Although, compared with Gly carriers, Arg389Arg was associated with a significantly larger decrease in resting systolic blood pressure and mean

arterial blood pressure with atenolol treatment in healthy volunteers,[16] blood pressure responses to atenolol in patients with hypertension have not been associated with the *ADRB1* SNPs.[17, 18] Bisoprolol has also been investigated but was not associated with the *ADRB1* SNPs.[17]

The discrepancy of the findings between metoprolol and atenolol or bisoprolol may be multifactorial. Whether there are differences in the pharmacogenetic associations for these drugs is not clear. However, it would be somewhat surprising to see differences given the similarities in their pharmacology. Probably a more likely explanation in the case of the discrepancies for the *ADRB1* studies is differences in study design and in the care with which the blood pressure data were collected. Specifically, the studies with positive associations were all prospectively conducted to test pharmacogenetic hypotheses, whereas most of the negative studies were pharmacogenetic associations that were tested on existing databases (Table 3). Since retrospective studies, such as database analyses, are more likely confounded and biased,[25] caution should be exercised in interpreting results of retrospective analyses. In addition, most of the negative studies did not account for the β-blocker pharmacokinetics, an important source of confounding. Finally, how the phenotype (blood pressure data) was determined is also important. Given the minute-to-minute variability in blood pressure, failure to collect blood pressure data in a very controlled or precise fashion (e.g., by ambulatory blood pressure monitoring) may lead to a variability in the blood pressure data that is too great to discern any impact of genetics on the blood pressure response to β-blockers. Also, differences in obtaining blood pressure data may have caused differences in observations on effects of *ADRB1* genotypes on systolic and diastolic blood pressure among the studies.

Data on the association between *ADRB1* polymorphism and blood pressure response to a β-blocker may also help explain the underlying physiologic mechanism for the differences in blood pressure response to a β-blocker between Caucasians and African-Americans. Compared with African-Americans, Caucasians have a higher frequency of Arg389Arg genotype (53% vs 34% in African-Americans) in the *ADRB1* gene. Also, Arg389Arg has been identified as a predictor of good response to metoprolol. Therefore, the genotype frequency difference between the two races may play a role in causing response differences to β-blocker therapy. This will be confirmed by prospective studies powered to evaluate the relative influence of *ADRB1* polymorphisms on clinical responses to β-blockers in both African-Americans and Caucasians.

Other genes involved in regulation of various cardiovascular systems such as β_2-adrenergic receptor gene (*ADRB2*), G protein β3 subunit gene (*GNB3),* and G protein α subunit gene (*GNAS*) have been tested for their association with β-blocker response. However, none of these have reported positive associations in more than one study. Specifically, *ADRB2* has been tested in two studies, but neither showed this gene to be associated with response.[19, 20] Only one study each has reported on the association of SNPs in *GNB3* and *GNAS* with blood pressure response to β blockers, respectively.[20, 21] However, given the small sample sizes and positive association in a subgroup in the studies, further studies are needed to confirm the findings.

The SNPs in the genes in RAAS have also been studied.[22, 23] However, only two SNPs (A-6G and Met235Thr alleles in angiotensinogen gene [*AGT*]) out of 30 SNPs in seven genes were significantly associated with systolic blood pressure responses.[23] Of the 10 SNPs in lipid metabolism genes, only one SNP (16730C>T) in the low-density lipoprotein receptor (*LDLR*) gene was found to be associated with greater systolic blood pressure reduction after atenolol treatment.[24] Physiologic implications of the findings are not clear at present.

Replication of positive associations in a second, independent cohort is an essential criterion for having confidence that a noted genetic association might be real. Among the studies focused

on blood pressure response to β-blockers, only the SNPs in the *ADRB1* gene meet this test. Although not all studies testing this gene have shown associations with blood pressure response, four different studies from four different laboratories have shown such associations. More important, the direction of the association was the same in all studies, namely, Arg389 homozygotes had the greatest blood pressure lowering, and the Ser49Arg389 haplotype was associated with the best response. Also note that these associations are consistent with the previous in vitro study data, which suggested that the Ser49 and Arg389 forms of the receptor would lead to higher levels of receptor activation and to better response to β-blocker therapy. Thus, it is also possible that in the future a patient's *ADRB1* genotype may be used to predict blood pressure response to a β-blocker by using a statistical model such as the one previously proposed.[13] If this could be validated prospectively, then the current empiric selection process for antihypertensive drugs could become more objective and individualized. Further studies are required for the genes that have had single studies with a positive association, but at present the data are strongest for the potential role of *ADRB1* on blood pressure response to β-blockers.

Heart Rate Response

Heart rate is controlled by the sympathetic and parasympathetic nervous systems, with stimulation of cardiac β-adrenergic receptors (notably β_1-adrenergic receptors) leading to increases in heart rate, counterbalanced by the parasympathetic nervous system to decrease heart rate. In fact, the negative chronotropic response on exercise heart rate is considered the gold standard for assessing the degree of β_1-adrenergic–receptor blockade.[2] As such, numerous studies have tested changes in resting heart rate and exercise heart rate before and after a β-blocker relative to *ADRB1* genotypes (Table 4).[15, 16, 18, 21, 26] In healthy volunteers, metoprolol treatment was associated with greater reduction in both resting and exercise heart rates in Arg389Arg compared with that in Gly389Gly,[15] whereas atenolol was not.[16] Of note, the heart rate was corrected for plasma metoprolol concentrations in the former study.[15] In hypertension, neither Ser49Gly nor Arg389Gly was associated with heart rate changes after atenolol, bisoprolol, or metoprolol treatment,[18, 21, 26] even after the heart rates were adjusted for by S-metoprolol concentrations. Thus, among five studies testing for an association with the negative chronotropic response, only one healthy volunteer study, which enrolled only Arg389Arg and Gly389Gly homozygotes, showed an effect of this polymorphism on response. Therefore, the data suggest that the *ADRB1* SNPs (particularly codon 389) are not associated with heart rate response to β-blockers. To our knowledge, there have been no studies specifically targeted at an angina population. However, given that the primary benefit of β-blockers in angina is through their negative chronotropic effects, it is unlikely that the *ADRB1* genes would be strongly associated with β-blocker efficacy in angina.

Other Outcomes in Hypertension

Table 5 summarizes β-blocker pharmacogenetic association studies that evaluated responses other than blood pressure and heart rate in hypertension.[27-32] Left ventricular hypertrophy, myocardial stiffness, and progression of atherosclerosis, all of which are well-known predictors of cardiovascular morbidity and mortality in hypertension, were studied. As shown in Table 5, despite numerous genes and SNPs being tested, only three have shown positive associations, and in each case the associations appeared to be modest. Further, no SNPs have been replicated for association in a second population. All of these studies were in relatively small samples and of inadequate duration to observe the full benefits of β-blockers on the given phenotype. Thus, larger and longer studies are needed to better elucidate the role of genetics in these β-blocker response phenotypes.

Heart Failure

Heart failure is characterized by activation of the sympathetic nervous system and RAAS.[33] β-Blockers have been shown to improve morbidity and prolong survival in patients with heart failure.[5] However, prognosis of heart failure varies, suggesting interindividual variability in response to the current drug therapy among patients. Most β-blocker pharmacogenetics studies in heart failure have focused on the β-adrenergic receptor genes (Table 6).[34-43]

Despite their well-documented benefits, there is substantial evidence that β-blocker dosages often are not optimally titrated, in part because of concerns about decompensation during titration. One study testing the relationship between initial tolerability to metoprolol controlled release–extended release (CR/XL) found that Arg389 homozygotes better tolerated the initiation of a β-blocker, as indicated by less need for increased diuretic doses during the titration period.[34] The *ADRB1* polymorphisms were associated with initial tolerability, with haplotype being most informative. Specifically, 52% of patients who were Ser49Ser and Arg389Gly required an increase in diuretics, whereas none of the patients who were Ser49Gly and Arg389Arg required an increased diuretic dose during titration. Patients with other genotype combinations required increased diuretic doses, at rates that were 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.

Left ventricular ejection fraction (LVEF) is considered a good surrogate marker for predicting the adverse outcomes in systolic heart failure, with the degree of improvement in LVEF typically being strongly associated with survival benefit.[44] As such, several studies have tested the pharmacogenetic associations between the β-adrenergic receptor genes and improvement in LVEF, with somewhat mixed results. Two studies showed significant associations between *ADRB1* genotype and LVEF, with Arg389 homozygotes demonstrating the greatest improvement in LVEF.[35, 36] However, two other studies showed no association between this gene and LVEF improvement.[37, 38] One study testing the role of *ADRB2* and LVEF response to carvedilol found that those who were Gln27 homozygotes had a significantly lower proportion of good responders (i.e., those with improvement in LVEF) compared with those who were Glu27 carriers,[39] although another study did not find this gene to be associated with change in LVEF.[37] Thus, at present it is not possible to draw clear conclusions about the relationship between change in LVEF and β-adrenergic receptor genotype.

Association of Arg389Gly with clinically more important adverse outcomes such as death or hospitalization due to heart failure exacerbation has also been examined. Bucindolol is an investigational and nonselective β-blocker. In the β-Blocker Evaluation of Survival Trial (BEST), bucindolol did not provide overall survival benefit compared with placebo.[45] In a post hoc analysis, however, Arg389Arg was significantly associated with fewer adverse outcomes in patients receiving bucindolol versus placebo (hazard ratio 0.66), whereas those who were Gly389 carriers did not obtain such benefit from the drug.[38] The study results suggested that pharmacogenetics studies might help select the patients who will be more responsive to the drug. In addition, the genotype associated with survival benefit from bucindolol is the same genotype associated with improved LVEF in some studies. In the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF), there was no association between *ADRB1* genotype and outcomes (death and hospitalization). As such, some have concluded the lack of a pharmacogenetic effect for β-blockers with these important outcomes.[46] However, the MERIT-HF genetic substudy treated those who received metoprolol CR/XL and the placebo as a same group in the analysis and simply compared outcomes between genotype groups, irrespective of their treatment assignment. This makes it hard to evaluate the genetic association of the outcomes relative to β-blocker therapy.

The interaction between genes and either β-blocker therapy or dose has also been studied. The angiotensin-converting enzyme gene (*ACE*) contains an insertion (I)/deletion (D) polymorphism, of which D/D has been associated with elevated plasma ACE level,[12] and higher rates of the adverse outcomes in heart failure. However, this deleterious effect of D/D was not seen in patients with systolic heart failure who received a β-blocker at baseline.[40, 41] In idiopathic dilated cardiomyopathy, the *ADRB1* Gly49 carrier state was suggested as a predictor of adverse outcomes in patients who received a low dose of β-blocker (≤ 50% of target dose).[42] However, the carrier state was not associated with adverse outcomes in those who were received high doses of a β-blocker.[42] Thus, these studies suggest that certain genotypes may be at increased risk of adverse outcomes and that β-blockers may attenuate the risk associated with that genotype. In this scenario, it is not possible to discern a pharmacogenetic effect if all or most subjects are treated with optimal β-blocker doses.

β-Blocker therapy has also been shown to improve morbidity and mortality in patients who survive acute coronary syndromes (ACS).[4, 5] One group of authors followed 735 patients with ACS for survival for 3 years, of whom 597 were receiving a β-blocker when they were discharged.[43] In this study, the common SNPs in *ADRB1* were not associated with the outcome, independent of whether patients were receiving a β-blocker or not. However, among patients who were receiving a β-blocker, those homozygous for both Arg16 and Gln27 in *ADRB2* had a significantly higher 3-year mortality rate than patients with Gly16Gly/Glu27Glu or the other diplotypes (20%, 6%, and 11%, respectively, p=0.002), suggesting that additional therapy and/or monitoring is required for this risk group.

Noncardiovascular Diseases

Table 7 summarizes studies of β-blockers for noncardiovascular diseases.[47-49] Most of these focus on topical β-blockers, commonly used to modulate intraocular pressure (IOP) in patients with glaucoma.[50] Interindividual variability has been shown to exist in IOP responses to β-blockers, leading to the interest in pharmaco-genetic studies.[51] In 48 healthy volunteers, Arg389Arg in *ADRB1* was associated with higher baseline IOP and greater reduction in IOP after topical betaxolol therapy for 3−6 weeks compared with that in Gly389 carriers.[47] However, *ADRB2* genotypes were not associated with IOP and systemic hemodynamic responses to a single dose of ocular timolol in 89 healthy volunteers.[48] Ser49Ser in *ADRB1* and 393T>C in *GNAS1* were associated with higher systolic and diastolic blood pressure, compared with Gly49 carriers, after 4 weeks of therapy with topical timolol in a group of 19 patients with glaucoma and 18 healthy volunteers.[49] Although these studies were quite small and mostly conducted in healthy volunteers, they suggest that further pharmacogenetic studies of β-blockers in patients with glaucoma are warranted.

β-Blocker Responses and *CYP2D6* Gene Polymorphism

Differences in drug metabolism can cause variability in pharmacokinetics, which may produce variable responses. Many of the β-blockers are substrates for the cytochrome P450 (CYP) 2D6 enzyme, including metoprolol, carvedilol, propranolol, labetalol, and timolol.[52] Among the β-blockers, metoprolol is most highly dependent on the CYP2D6 enzyme, with 70−80% of its metabolism through this pathway. The *CYP2D6* gene is highly polymorphic with about 80 alleles reported.[53] Patients are commonly classified as ultraextensive metabolizers, extensive metabolizers, intermediate metabolizers, or poor metabolizers based on the number of copies of functional *CYP2D6* alleles. The well-known influence of *CYP2D6* genotype on metoprolol pharmacokinetics[54-56] has led to obvious questions about the effect of these kinetic differences on adverse effects or efficacy. These studies are summarized in Table 8,[34, 57-59] which highlights that despite the dramatic effects of *CYP2D6* genotype on pharmacokinetics, this does not appear to translate into differences in efficacy or adverse effects.

In a case-control study, adverse events associated with metoprolol therapy were 4.9−5.2-fold more likely to occur in poor metabolizers than in non–poor metabolizers ($p<0.0001$).[57] However, it was a retrospective study with a small sample size. Prospective studies with larger samples did not confirm these results. Specifically, although the expected effects of *CYP2D6* genotype on pharmacokinetics of metoprolol were observed, rates of efficacy or adverse effects were not significantly different between the poor metabolizer and non–poor metabolizer groups.[34, 58, 59] This was perhaps most surprising in patients with heart failure, in whom therapy must be started at very low doses (concentrations). However, even in this population, *CYP2D6* genotype was not associated with poor tolerability to metoprolol CR/XL on initiation of therapy.[32] Although no studies have compared adverse-event rate or efficacy of metoprolol between ultraextensive and extensive metabolizers, it is unlikely that there would be differences in the adverse-event rate between the two groups. It is possible that ultraextensive metabolizers would require higher doses to achieve β-blockade, but this would be easy to detect and address clinically (without genotyping) since resting heart rate is a sensitive marker for the degree of β-blockade.

Thus, the studies suggest *CYP2D6* genotype influences neither efficacy nor toxicity with metoprolol. Since the other β-blockers are much less reliant on CYP2D6 than metoprolol, it is also likely that their efficacy and toxicity will not be significantly influenced by *CYP2D6* genotype. Thus, despite the clinical availability of *CYP2D6* genotyping, data suggest such genotyping would be of little clinical benefit.

Discussion of the β-Blocker Pharmacogenetics Literature

We have summarized the current β-blocker pharmacogenetics literature. Perhaps not surprising is that most of the studies focus on the primary target for the β-blockers, the *ADRB1* gene. Within this gene, Arg389Gly is particularly interesting. Specifically, the Arg389 homozygous genotype has been associated in numerous settings with better response to β-blockers, including hypertension (blood pressure lowering), heart failure (tolerability to β-blocker initiation, LVEF improvement, survival), and glaucoma (IOP lowering). Although not all studies showed a positive association, the positive ones are always in the same direction (e.g., Arg389Arg is a predictor of better response). However, the direction of the association with many other widely studied polymorphisms in pharmacogenetics, such as *ACE* I/D and the common *ADRB2* SNPs has not been consistent, even in studies showing a significant association. The findings relative to the codon 389 polymorphism are also biologically supported by the results from the functional studies.[10] As such, the *ADRB1* codon 389 polymorphism represents a starting point from which β-blocker therapy might be individualized in the future.

Among the other genes that have been studied, results have been less consistent, with either nonreplication in a second cohort or testing in only a single study to date. Nonetheless, some of these represent interesting findings that warrant replication. Perhaps most notable in this group are the data suggesting that patients with ACS who are homozygous for both Arg16Gly and Gln27Glu in *ADRB2* were found to have higher risk for adverse outcomes even while receiving a β-blocker.[45]

Many factors may have played a role in producing the conflicting data summarized in the various tables. Statistical factors such as small sample size, post hoc database analysis, and uncorrected multiple comparisons may have caused discrepancies. Various nonstatistical factors including differences in study design and population, pharmacologic properties of the drugs, inaccurate measurement of the phenotype, and lack of pharmacokinetic assessment may also have contributed. Future pharmacogenetic studies should take these factors into consideration and aim to minimize such factors in the study design.

Potential Clinical Implications of β-Blocker Pharmacogenetics

One of the goals of pharmacogenetics research is to provide clinicians with a tool with which to individualize therapy based on a person's genetic make-up. Although the data for β-blockers are not yet to that point, one can envision that such tools might be available in the near future (i.e., 5−10 yrs), particularly for diseases like hypertension or glaucoma. Specifically, the data on the *ADRB1* gene are relatively strong, and if they can be shown to be predictive prospectively, it might be translated to practice. A similar approach could work in glaucoma, if similar data could be accrued. Use of pharmacogenetic data in patients with heart failure or after ACS might be further in the future since the primary goal of therapy in these settings is event reduction. This requires large clinical trials, for which there are likely to be few, if any, with β-blockers. Alternatively, such data will have to come from existing clinical trial data that have yet to be analyzed for pharmacogenetics, or from observational cohorts with strong prescription drug use data (which are available through some group health organizations). Nonetheless, heart failure and after an ACS are settings where pharmacogenetics could provide greater benefit, since the response (i.e., prevention of death, stroke, and myocardial infarction) cannot be measured in an individual patient. Specifically, if a patient is unlikely to benefit from β-blocker therapy based on their genotype, then they could avoid exposure to the drug, as well as the atten-dant risks, and perhaps receive an alternative therapy that would be beneficial. However, this level of evidence will be difficult to accrue and, therefore, is less likely to be available in the near term.

Conclusion

The β-blocker pharmacogenetics literature provides hope for the potential clinical utilization of genetic information to individualize β-blocker therapy. Although the *ADRB1* gene is considered to hold great hope for providing part of the genetic picture as it relates to variable drug response, identification of additional genes that also contribute to response variability will be important. This will help explain a sufficient degree of the variable responses to a β-blocker in order to be useful clinically.

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References

1. Reiter MJ. Cardiovascular drug class specificity: β-blockers. Prog Cardiovasc Dis 2004;47:11–33. [PubMed: 15517513]
2. Zaugg, AM. Pressure. The IMS Health Report. IMS Health Incorporated; Norwalk, CT: 2005.
3. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289:2560–72. [PubMed: 12748199]
4. Pfeffer MA, Braunwald E, Moye LA, et al. the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. N Engl J Med 1992;327:669–77. [PubMed: 1386652]
5. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure). J Am Coll Cardiol 2001;38:2101–13. [PubMed: 11738322]
6. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/

American Heart Association task force on practice guidelines (committee on the management of patients with chronic stable angina). J Am Coll Cardiol 2003;41:159–68. [PubMed: 12570960]

7. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. II. Results of long-term therapy. JAMA 1982;248:2004–11. [PubMed: 6750167]
8. Materson BJ, Reda DJ, Cushman WC, et al. the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. N Engl J Med 1993;328:914–21. [PubMed: 8446138]
9. Rathz DA, Brown KM, Kramer LA, et al. Amino acid 49 polymorphisms of the human β_1-adrenergic receptor affect agonist-promoted trafficking. J Cardiovasc Pharmacol 2002;39:155–60. [PubMed: 11791000]
10. Mason DA, Moore JD, Green SA, et al. A gain-of-function polymorphism in a G-protein coupling domain of the human β_1-adrenergic receptor. J Biol Chem 1999;274:12670–4. [PubMed: 10212248]
11. Green SA, Turki J, Innis M, et al. Amino-terminal polymorphisms of the human β_2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry 1994;33:9414–19. [PubMed: 7915137]
12. Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I–converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 1990;86:1343–6. [PubMed: 1976655]
13. Johnson JA, Zineh I, Puckett BJ, et al. β_1-Adrenergic receptor polymorphisms and antihypertensive response to metoprolol. Clin Pharmacol Ther 2003;74:44–52. [PubMed: 12844134]
14. Liu J, Liu ZQ, Yu BN, et al. β_1-Adrenergic receptor polymorphisms influence the response to metoprolol monotherapy in patients with essential hypertension. Clin Pharmacol Ther 2006;80:23–32. [PubMed: 16815314]
15. Liu J, Liu ZQ, Tan ZR, et al. Gly389Arg polymorphism of β_1-adrenergic receptor is associated with the cardiovascular response to metoprolol. Clin Pharmacol Ther 2003;74:372–9. [PubMed: 14534524]
16. Sofowora GG, Dishy V, Muszkat M, et al. A common β_1-adrenergic receptor polymorphism (Arg389Gly) affects blood pressure response to β-blockade. Clin Pharmacol Ther 2003;73:366–71. [PubMed: 12709726]
17. O'Shaughnessy KM, Fu B, Dickerson C, et al. The gain-of-function G389R variant of the β_1-adrenoceptor does not influence blood pressure or heart rate response to β-blockade in hypertensive subjects. Clin Sci (Lond) 2000;99:233–8. [PubMed: 11787477]
18. Karlsson J, Lind L, Hallberg P, et al. β_1-Adrenergic receptor gene polymorphisms and response to β_1-adrenergic receptor blockade in patients with essential hypertension. Clin Cardiol 2004;27:347–50. [PubMed: 15237695]
19. Jia H, Sharma P, Hopper R, et al. β_2-Adrenoceptor gene polymorphisms and blood pressure variations in East Anglian caucasians. J Hypertens 2000;18:687–93. [PubMed: 10872552]
20. Filigheddu F, Reid JE, Troffa C, et al. Genetic polymorphisms of the β-adrenergic system: association with essential hypertension and response to β-blockade. Pharmacogenomics J 2004;4:154–60. [PubMed: 15069461]
21. Jia H, Hingorani AD, Sharma P, et al. Association of the G(s)alpha gene with essential hypertension and response to β-blockade. Hypertension 1999;34:8–14. [PubMed: 10406816]
22. Kurland L, Melhus H, Karlsson J, et al. Aldosterone synthase (CYP11B2)–344 C/T polymorphism is related to antihypertensive response: result from the Swedish irbesartan left ventricular hypertrophy investigation versus atenolol (SILVHIA) trial. Am J Hypertens 2002;15:389–93. [PubMed: 12022239]
23. Kurland L, Liljedahl U, Karlsson J, et al. Angiotensinogen gene polymorphisms: relationship to blood pressure response to antihypertensive treatment. Results from the Swedish irbesartan left ventricular hypertrophy investigation versus atenolol (SILVHIA) trial. Am J Hypertens 2004;17:8–13. [PubMed: 14700505]
24. Liljedahl, U.; Lind, L.; Kurland, L., et al. Single nucleotide polymorphisms in the apolipoprotein B and low-density lipoprotein receptor genes affect response to antihypertensive treatment [online

exclusive article].; BMC Cardiovasc Disord. 2004. p. 16Available from http://www.biomedcentral.com/1471-2261/4/16

25. Piantadosi, S. Clinical trials: a methodological perspective. Vol. 2nd ed.. John Wiley & Sons; Hoboken, NJ: 2005.
26. Beitelshees AL, Zineh I, Yarandi HN, et al. Influence of phenotype and pharmacokinetics on β-blocker drug target pharmacogenetics. Pharmacogenomics J 2006;6:174–8. [PubMed: 16402084]
27. Liljedahl U, Kahan T, Malmqvist K, et al. Single nucleotide polymorphisms predict the change in left ventricular mass in response to antihypertensive treatment. J Hypertens 2004;22:2321–8. [PubMed: 15614026]
28. Kurland L, Melhus H, Karlsson J, et al. Polymorphisms in the angiotensinogen and angiotensin II type 1 receptor gene are related to change in left ventricular mass during antihypertensive treatment: results from the Swedish irbesartan left ventricular hypertrophy investigation versus atenolol (SILVHIA) trial. J Hypertens 2002;20:657–63. [PubMed: 11910301]
29. Hallberg, P.; Lind, L.; Michaelsson, K., et al. Adipocyte-derived leucine aminopeptidase genotype and response to antihypertensive therapy [online exclusive article].; BMC Cardiovasc Disord. 2003. p. 11Available from http://www. biomedcentral.com/1471-2261/3/11
30. Hallberg P, Lind L, Billberger K, et al. Transforming growth factor β_1 genotype and change in left ventricular mass during antihypertensive treatment: results from the Swedish irbesartan left ventricular hypertrophy investigation versus atenolol (SILVHIA) trial. Clin Cardiol 2004;27:169–73. [PubMed: 15049387]
31. Bozec E, Fassot C, Tropeano AI, et al. Angiotensinogen gene M235T polymorphism and reduction in wall thickness in response to antihypertensive treatment. Clin Sci (Lond) 2003;105:637–44. [PubMed: 12911327]
32. Diez J, Laviades C, Orbe J, et al. The A1166C polymorphism of the AT1 receptor gene is associated with collagen type I synthesis and myocardial stiffness in hypertensives. J Hypertens 2003;21:2085–92. [PubMed: 14597852]
33. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007–18. [PubMed: 12748317]
34. Terra SG, Pauly DF, Lee CR, et al. β-Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. Clin Pharmacol Ther 2005;77:127–37. [PubMed: 15735607]
35. Terra SG, Hamilton KK, Pauly DF, et al. β_1-Adrenergic receptor polymorphisms and left ventricular remodeling changes in response to β-blocker therapy. Pharmacogenet Genomics 2005;15:227–34. [PubMed: 15864115]
36. Mialet Perez J, Rathz DA, Petrashevskaya NN, et al. β_1-Adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. Nat Med 2003;9:1300–5. [PubMed: 14502278]
37. de Groote P, Helbecque N, Lamblin N, et al. Association between β_1- and β_2-adrenergic receptor gene polymorphisms and the response to β-blockade in patients with stable congestive heart failure. Pharmacogenet Genomics 2005;15:137–42. [PubMed: 15861037]
38. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, et al. A polymorphism within a conserved β_1-adrenergic receptor motif alters cardiac function and β-blocker response in human heart failure. Proc Natl Acad Sci USA 2006;103:11288–93. [PubMed: 16844790]
39. Kaye DM, Smirk B, Williams C, et al. β-Adrenoceptor genotype influences the response to carvedilol in patients with congestive heart failure. Pharmacogenetics 2003;13:379–82. [PubMed: 12835612]
40. McNamara DM, Holubkov R, Janosko K, et al. Pharmaco-genetic interactions between β-blocker therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. Circulation 2001;103:1644–8. [PubMed: 11273991]
41. de Groote P, Helbecque N, Lamblin N, et al. β-Adrenergic receptor blockade and the angiotensin-converting enzyme deletion polymorphism in patients with chronic heart failure. Eur J Heart Fail 2004;6:17–21. [PubMed: 15012914]
42. Magnusson Y, Levin MC, Eggertsen R, et al. Ser49Gly of β_1-adrenergic receptor is associated with effective β-blocker dose in dilated cardiomyopathy. Clin Pharmacol Ther 2005;78:221–31. [PubMed: 16153393]

43. Lanfear DE, Jones PG, Marsh S, et al. β_2-Adrenergic receptor genotype and survival among patients receiving β-blocker therapy after an acute coronary syndrome. JAMA 2005;294:1526–33. [PubMed: 16189366]
44. Curtis JP, Sokol SI, Wang Y, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 2003;42:736–42. [PubMed: 12932612]
45. β-Blocker Evaluation of Survival Trial Investigator. A trial of the β-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659–67. [PubMed: 11386264]
46. White HL, de Boer RA, Maqbool A, et al. An evaluation of the β_1-adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study. Eur J Heart Fail 2003;5:463–8. [PubMed: 12921807]
47. Schwartz SG, Puckett BJ, Allen RC, et al. β_1-Adrenergic receptor polymorphisms and clinical efficacy of betaxolol hydrochloride in normal volunteers. Ophthalmology 2005;112:2131–6. [PubMed: 16325708]
48. Fuchsjager-Mayrl G, Markovic O, Losert D, et al. Polymorphism of the β_2-adrenoceptor and IOP lowering potency of topical timolol in healthy subjects. Mol Vis 2005;11:811–15. [PubMed: 16205624]
49. Nieminen T, Uusitalo H, Maenpaa 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;61:811–19. [PubMed: 16315032]
50. Alward WL. Medical management of glaucoma. N Engl J Med 1998;339:1298–307. [PubMed: 9791148]
51. Zimmerman TJ, Boger WP III. The β-adrenergic blocking agents and the treatment of glaucoma. Surv Ophthalmol 1979;23:347–62. [PubMed: 37605]
52. Brodde OE, Kroemer HK. Drug-drug interactions of βadrenoceptor blockers. Arzneimittelforschung 2003;53:814–22. [PubMed: 14732961]
53. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol 2004;369:23–37. [PubMed: 14618296]
54. Rau T, Heide R, Bergmann K, et al. Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. Pharmacogenetics 2002;12:465–72. [PubMed: 12172215]
55. Taguchi M, Nozawa T, Mizumaki K, et al. Nonlinear mixed effects model analysis of the pharmacokinetics of metoprolol in routinely treated Japanese patients. Biol Pharm Bull 2004;27:1642–8. [PubMed: 15467211]
56. Nozawa T, Taguchi M, Tahara K, et al. Influence of CYP2D6 genotype on metoprolol plasma concentration and β-adrenergic inhibition during long-term treatment: a comparison with bisoprolol. J Cardiovasc Pharmacol 2005;46:713–20. [PubMed: 16220080]
57. Wuttke H, Rau T, Heide R, et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. Clin Pharmacol Ther 2002;72:429–37. [PubMed: 12386645]
58. Zineh I, Beitelshees AL, Gaedigk A, et al. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. Clin Pharmacol Ther 2004;76:536–44. [PubMed: 15592325]
59. Fux R, Morike K, Prohmer AM, et al. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. Clin Pharmacol Ther 2005;78:378–87. [PubMed: 16198657]

Table 1
Characteristics of β-Blockers Approved in the United States

β-Receptor Property, Agent	Intrinsic Sympathomimetic Activity	Dosage Forms Available	Major Elimination Route	Data Available on Pharmacogenetics
β_1-Selective antagonist				
Acebutolol	Yes	Oral	Liver	No
Atenolol	No	Oral	Kidney	Yes
Betaxolol[a]	No	Oral, ophthalmic	Liver, kidney	Yes
Bisoprolol	No	Oral	Liver, kidney	Yes
Esmolol	No	Intravenous	Liver, kidney	No
Metoprolol	No	Oral, intravenous	Liver	Yes
Nonselective antagonist				
Carteolol	Yes	Oral,[b] ophthalmic	Kidney	No
Levobunolol	No	Ophthalmic	Liver	No
Metipranolol	No	Ophthalmic	Liver, kidney	No
Nadolol	No	Oral	Kidney	No
Penbutolol	Yes	Oral	Liver	No
Pindolol	Yes	Oral	Kidney	No
Propranolol	No	Oral, intravenous	Liver	Yes
Sotalol	No	Oral	Kidney	No
Timolol	No	Oral, ophthalmic	Liver	Yes
Combined α_1 and β-antagonist				
Carvedilol	No	Oral	Liver	Yes
Labetalol	No	Oral, intravenous	Liver	No

[a] L-isomer is no longer approved in the United States.

[b] Oral dosage form is no longer available in the United States.

Table 2

Summary of Minor Allele Frequency and Functional Consequences of the Important Genetic Polymorphisms

Gene	Polymorphism	Minor Allele	Frequency of Minor Allele by Race	Functional Consequences
ADRB1	Ser49Gly[9]	Gly	Caucasians 12−16% African-Americans 23−28% Hispanics 20−21% Asians 14%	Gly49 allele has greater agonist-promoted receptor downregulation
	Arg389Gly[10]	Gly	Caucasians 24−34% African-Americans 39−46% Hispanics 31−33% Asians 20−30%	Arg389 allele has higher basal and agonist-simulated adenylyl cyclase activity
ADRB2	Gly16Arg[11]	Arg	Caucasians 39% African-Americans 49% Asians 51%	Gly16 allele has greater agonist-promoted downregulation
	Gln27Glu[11]	Glu	Caucasians 25% African Americans 19% Asians 9%	Glu27 allele is resistant to receptor downregulation
ACE	I/D[12]	I[a]	Caucasians 40−48% African-Americans 37−43% Asians 58−70%	D allele is associated with higher plasma ACE level

ADRB1 = β_1-adrenergic receptor gene; Ser = serine; Gly = glycine; Arg = arginine; *ADRB2* = β_2-adrenergic receptor gene; Gln = glutamine; Glu = glutamate; *ACE* = angiotensin-converting enzyme gene; I = insertion; D = deletion.

[a] Insertion allele is a major allele in Asians.

Table 3

Summary of Pharmacogenetics Studies on Blood Pressure Responses to β-Blockers

Study Type[a]	Study Population	β-Blocker	No. of Subjects	Duration	Gene	Single Nucleotide Polymorphisms	Outcomes	Results	p Value
Prospective[13]	Hypertension	Metoprolol	40	≥ 4 wks	*ADRB1*	Arg389Gly Ser49Gly	ΔDBP	Arg389Arg greater reduction in daytime DBP than Gly carriers: 13.3 ± 8.4% vs 4.5 ± 8.2%	0.0018
								Ser49Arg389/Ser49Arg389 diplotype had greatest daytime ΔDBP: 14.7-mm Hg decrease vs 8.8- and 5.9-mm Hg decrease in other diplotypes	0.0006
Prospective[14]	Hypertension (Chinese)	Metoprolol	61	4 wks	*ADRB1*	Arg389Gly Ser49Gly	ΔMAP, ΔSBP, ΔDBP	Arg389Arg greatest reduction in SBP and DBP compared with Arg389Gly and Gly389Gly: SBP: 10.4 ± 4.0%, 2.8 ± 4.7%, and 1.1 ± 1.5%, respectively; DBP: 6.1 ± 4.3%, 2.2 ± 4.2%, and 0.9 ± 4.0%, respectively	<0.001
								Ser49Arg389/Ser49Arg389 haplotype had greatest ΔSBP (12.0 ± 3.8% decrease)	<0.001
Prospective[15]	Healthy volunteers	Metoprolol (25, 50, or 75 mg q8h)	16	1 day	*ADRB1*	Arg389Gly	ΔSBP, ΔDBP	Arg389Arg greater reduction in SBP than Gly389Gly:	0.011
								75 mg/day: 5.9 ± 0.7% vs 4.6 ± 0.5%;	
								150 mg/day: 9.2 ± 1.0% vs 6.0 ± 0.8%;	
								225 mg/day: 11.6 ± 1.2% vs 9.9 ± 0.9%	
Prospective[16]	Healthy volunteers	Atenolol	34	1 dose	*ADRB1*	Arg389Gly	ΔMAP, ΔSBP, ΔDBP	Arg389Arg greater reduction in SBP and MAP than Gly carriers:	
								SBP 8.7 ± 1.3 vs 0.2 ± 1.7 mm Hg	<.001
								MAP 7.2 ± 1.0 vs 2.0 ± 1.7 mm Hg	0.009
Retrospective[17]	Hypertension	Atenolol	92	4 wks	*ADRB1*	Arg389Gly	ΔSBP, ΔDBP	No associations	NS
		Bisoprolol	55						
Retrospective[10]	Hypertension with LVH	Atenolol	52	12 wks	*ADRB1*	Arg389Gly Ser49Gly	ΔSBP, ΔDBP	No associations	NS
Retrospective[19]	Hypertension	Various	144	4 wks	*ADRB2*	Arg16Gly Gln27Glu	ΔSBP, ΔDBP	No associations	NS

Study Type[a]	Study Population	β-Blocker	No. of Subjects	Duration	Gene	Single Nucleotide Polymorphisms	Outcomes	Results	p Value
Retrospective[20]	Hypertension	Atenolol	270	4, 8 wks	4 genes	6 SNPs	ΔMAP, ΔSBP, ΔDBP	Female C825C in *GNB3* had greater reductions in SBP, DBP, and MAP than T carriers:	
								SBP 32.9 ± 19.3 vs 16.4 ± 18.8 mm Hg;	<0.001
								DBP 22.9 ± 12.2 vs 14.8 ± 11.7 mm Hg;	<0.001
								MAP 26.3 ± 13.7 vs 15.3 ± 13.4 mm Hg	0.001
								No association with the other SNPs	
Retrospective[21]	Hypertension	Various	114	4 wks	*GNAS*	Exon 5 FokI+/−	ΔMAP, ΔSBP, ΔDBP	FokI+ more common in the good responders than the poor responders: 62.5% vs 41.7%	0.02
Retrospective[22]	Hypertension	Atenolol	43	12 wks	*CYP11B2*	−344C>T	ΔSBP, ΔDBP	No associations	NS
Retrospective[23]	Hypertension	Atenolol	49	12 wks	7 genes	30 SNPs	ΔSBP, ΔDBP	Greater SBP reduction in *AGT* Thr235 or *AGT* A-6 carriers than Met235Met or *AGT* G-6G (no average values were given in the study report)	≤0.03
								No association with the other SNPs	
Retrospective[24]	Hypertension	Atenolol	49	12 wks	7 genes	10 SNPs	ΔSBP, ΔDBP	On average, 14-mm Hg SBP reduction in C16730C carriers in *LDLR*	0.006
								No association with the other SNPs	

SNPs = single nucleotide polymorphisms; *ADRB1* = β_1-adrenergic receptor gene; Arg = arginine; Gly = glycine; Ser = serine; Δ = change between before and after treatment; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; SBP = systolic blood pressure; NS = not statistically significant; LVH = left ventricular hypertrophy; *ADRB2* = β_2-adrenergic receptor gene; Glu = glutamate; Gln = glutamine; C = cytosine; T = thymidine; Thr = threonine; *GNAS* = Gs protein α subunit gene; *CYP11B2* = cytochrome P450 11B2 isozyme gene; *AGT* = angiotensinogen gene; *LDLR* = low-density lipoprotein receptor gene.

[a]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; retrospective studies were conducted on an existing data set.

Table 4

Summary of Pharmacogenetics Studies on Heart Rate Responses to β-Blockers

Study Type[a]	Study Population	β-Blocker	No. of Subjects	Duration	Gene	Single Nucleotide Polymorphisms	Outcomes	Results	p Value
Prospective[15]	Healthy volunteers	Metoprolol (25, 50, or 75 mg q8h)	16	1 day	*ADRB1*	Arg389Gly	ΔRHR, ΔEHR	Arg389Arg had greater reduction in RHR and EHR than Gly389Gly:	
								RHR at 75 mg/day: 6.3 ± 0.8% vs 4.1 ± 0.7%, 150 mg/day: 10.1 ± 1.0% vs 6.2 ± 1.1%, 225 mg/day: 14.4 ± 1.4% vs 10.9 ± 1.3%	0.008
								EHR at 75 mg/day: 8.9 ± 0.5% vs 6.6 ± 0.7%, 150 mg/day: 14.0 ± 0.9% vs 11.7 ± 1.0%, 225 mg/day: 20.1 ± 1.5% vs 16.4 ± 1.3%	0.017
Prospective[16]	Healthy volunteers	Atenolol	34	1 dose	*ADRB1*	Arg389Gly	ΔRHR, ΔEHR	No associations	NS
Retrospective[18]	Hypertension	Atenolol	92	4 wks	*ADRB1*	Arg389Gly	ΔRHR	No associations with ΔRHR	NS
		Bisoprolol	55						
Retrospective[21]	Hypertension	Atenolol	52	12 wks	*ADRB1*	Arg389Gly	ΔRHR	No associations with ΔRHR	NS
Prospective[26]	Hypertension	Metoprolol	54	≥ 4 wks	*ADRB1*	Ser49Gly	ΔRHR, ΔEHR	No associations	NS
						Arg389Gly			

ADRB1 = β_1-adrenergic receptor gene; Arg = arginine; Gly = glycine; Ser = serine; Δ = change between before and after treatment; RHR = resting heart rate; EHR = exercise heart rate; NS = not statistically significant.

[a]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; retrospective studies were conducted on an existing data set.

Table 5

Summary of Pharmacogenetics Studies on Other Hypertension-Related Responses to β-Blockers

Study Population	β-Blocker	No. of Patients	Duration	Gene	Single Nucleotide Polymorphisms	Outcomes	Results	p Value
Hypertension[27]	Atenolol	49	12 wks	25 genes	74 SNPs	ΔLVMI	*ADRA2A* 1817 GG had reduction in LVMI of 4 ± 18 g/m^2 compared with increases in LVMI with G1817A and A1817A: 20 ± 21 and 13 ± 26 g/m^2, respectively	0.03
Hypertension[28]	Atenolol	43	12 wks	5 genes	5 SNPs	ΔLVMI	No associations	NS
Hypertension[29]	Atenolol	47	48 wks	*ALAP*	1583A>G	ΔLVMI	No associations	NS
Hypertension[30]	Atenolol	47	48 wks	*TGFB1*	+915G>C	ΔLVMI	No associations	NS
Hypertension[31]	Celiprolol	26	20 wks	*AGT*	Met235Thr	ΔCarotid IMT	Thr235Thr had greater reduction than Thr235Met: 21 ± 15% vs 8 ± 16%, compared with increase of 3 ± 16% with Met235Met	<0.01
Hypertension[32]	Atenolol	70	≥ 1 yr	*AGTR1*	1166A>C	PIP, K_{LV}	No associations	NS

SNPs = single nucleotide polymorphisms; Δ = change between before and after treatment; LVMI = left ventricular mass index; *ADRA2A* = α_{2A}-adrenergic receptor; NS = not statistically significant; *ALAP* = adipocyte-derived leucine aminopeptidase; A = adenine; C = cytosine; G = guanine; T = thymidine; Met = methionine; Thr = threonine; *TGFB1* = transforming growth factor β_1; *AGT* = angiotensinogen; *AGTR1* = angiotensin II type I receptor; PIP = procollagen type I; K_{LV} = left ventricular chamber stiffness.

Table 6

Summary of Pharmacogenetics Studies on Responses to β-Blockers in Heart Failure

Study Type[a]	Study Population	β-Blocker	No. of Patients	Duration	Gene	Polymorphisms	Outcomes	Results	p Value
Prospective[34]	Systolic HF	Metoprolol CR/XL	61	> 5 mo	*ADRB1*	2 SNPs	Tolerability, % of patients to reach target dose	Gly389 carriers required more HF drugs than Arg389Arg (48% vs 14%)	0.006
					ADRB2	3 SNPs			
					GNAS1	1 SNP		Ser49Ser needed more HF drugs than Gly49 carriers (41% vs 11%)	0.03
								No associations with *ADRB2* and *GNAS1*	NS
Prospective[35]	Systolic HF	Metoprolol CR/XL	54	> 5 mo	*ADRB1*	Arg389Gly	ΔLVEF, ΔLVESD, ΔLVEDD	Arg389Arg had greater improvement in LVEF than Gly carriers (from 23 ± 5% to 29 ± 10% vs from 22 ± 9% to 23 ± 11%)	0.008
						Ser49Gly			
								LVEDD changed with metoprolol CR/XL in Gly49 carriers vs Ser49Ser (from 65 ± 13 to 63 ± 12 mm vs from 61 ± 9 to 63 ± 9 mm)	0.003
Retrospective[36]	Systolic HF	Carvedilol	224	> 6 mo	*ADRB1*	Arg389Gly	ΔLVEF	Arg389Arg had greater improvement in LVEF than Gly carriers: 8.7 ± 1.1% vs 0.93 ± 1.7%	0.02
Prospective[37]	Systolic HF	Bisoprolol	199	3 mo	*ADRB1*	2 SNPs	ΔLVEF	No associations	NS
		Carvedilol			*ADRB2*	3 SNPs			
Prospective[38]	Systolic HF	Bucindolol	1040	Median 2 yrs	*ADRB1*	Arg389Gly	Death, hospitalization	Arg389Arg had greater reduction in outcomes in bucindolol group than in placebo group (HR 0.66)	0.004
								No drug benefit in Gly carriers	
Retrospective[39]	Systolic HF	Carvedilol	80	4 mo	*ADRB2*	2SNPs	ΔLVEF	Glu27 carriers had more good responders than Gln27Gln (63% vs 26%)	0.003

Study Type[a]	Study Population	β-Blocker	No. of Patients	Duration	Gene	Polymorphisms	Outcomes	Results	p Value
Retrospective[40]	Systolic HF	Various	328	Median 21 mo	*ACE*	Intron 16	Death, HT	D allele associated with higher risk for outcomes than I/I homozygotes (HR 1.80)	0.04
						I/D		No association in patients receiving a β-blocker	
Retrospective[41]	Systolic HF	Bisoprolol	199	Median 31 mo	*ACE*	Intron 16	Death, HT	No association	NS
		Carvedilol				I/D			
Retrospective[42]	Dilated cardiomyopathy	Various	375	37−60 mo	*ADRB1*	Ser49Gly	Death, HT	Among patients taking a β-blocker, Gly49 carrier was associated with longer survival rate than Ser49Ser (HR 0.24, 95% CI 0.07 −0.80)	0.014
						Arg389Gly		Among patients taking a high-dose β-blocker, no genetic association was detected	NS
Retrospective[43]	Previous ACS	Various	735	3 yrs	*ADRB1*	2 SNPs	Death	Among those taking a β-blocker, patients homozygous for Arg16 and Gln27 in *ADRB2* had a higher 3-year death rate: Arg16Arg/ Gln27Gln27: 20% Heterozygote for codons 16 and 27: 11% Gly16Gly/Glu27Glu: 6%	0.002
					ADRB2	2 SNPs			

HF = heart failure; CR/XL = controlled release–extended release; *ADRB1* = β_1-adrenergic receptor gene; *ADRB2* = β_2-adrenergic receptor gene; *GNAS* = Gs protein α subunit gene; SNPs = single nucleotide polymorphisms; Arg = arginine; Gly = glycine; Ser = serine; NS = not statistically significant; Δ = change between before and after treatment; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; *ACE* = angiotensin-converting enzyme gene; HT = heart transplantation; I/D = insertion/deletion; HR = hazard ratio; CI = confidence interval; ACS = acute coronary syndrome; Glu = glutamate; Gln = glutamine.

[a]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; retrospective studies were conducted on an existing data set.

Table 7

Summary of Pharmacogenetics Studies on β-Blockers in Indications Other Than Cardiovascular Diseases

Indication	Study Population	No. of Subjects	Study Drug	Duration	Gene	Single Nucleotide Polymorphisms	Outcomes	Results	p Value
Glaucoma[47]	Healthy volunteers	48	Betaxolol	3–6 wks	*ADRB1*	Ser49Gly	ΔIOP	Arg389Arg in *ADRB1* was associated with higher baseline IOP than Gly389 carriers: 15.8 ± 2.4 vs 13.7 ± 2.9 mm Hg	0.009
						Arg389Gly			
								Greater reduction in IOP in Arg389Arg compared with Gly389 carriers: 3.4 vs 1.5 mm Hg	0.0009
Glaucoma[48]	Healthy volunteers	89	Timolol	6 wks	*ADRB2*	Gly16Arg	ΔIOP	No association	NS
						Gln27Glu			
Glaucoma[49]	Healthy volunteers	18	Timolol	4 wks	*ADRB1*	2 SNPs	ΔSBP	Ser49Ser had higher SBP and DBP than Gly49 carriers (BP values not reported)	0.03 (SBP)
					GNAS1	1 SNP	ΔDBP		<0.01 (DBP)
	Patients with glaucoma	19						Greater reduction in DBP from rest to exercise in C393C in *GNAS1* (BP values not reported)	<0.01

SNPs = single nucleotide polymorphisms; *ADRB1* = β_1-adrenergic receptor gene; *ADRB2* = β_2-adrenergic receptor gene; *GNAS1* = Gs protein α subunit gene; Ser = serine; Arg = arginine; Gly = glycine; Glu = glutamate; Gln = glutamine; NS = not statistically significant; Δ = change between before and after treatment; IOP = intraocular pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; BP = blood pressure.

Table 8

Summary of Pharmacogenetics Studies on Responses to Metoprolol in Relation to *CYP2D6* Genotypes

Study Type	No. of Subjects	Metoprolol Indication	Duration	Outcomes	Results	p Value
Case-control[57]	24	Various	Various	Metoprolol-associated ADR	ADR 4.9−5.2-fold higher in PM vs non-PM	<0.0001
Prospective cohort[34]	61	Heart failure	> 5 mo	Tolerability (ADR during titration)	No association	NS
Prospective cohort[58]	50	Hypertension	4 wks	General and dose-limiting ADR	No association	NS
Prospective cohort[59]	121	Various	6 wks	Metoprolol-associated ADR	No association	NS

CYP2D6 = cytochrome P450 2D6; ADR = adverse drug reactions; PM = poor metabolizers; NS = not statistically significant.