

Ethnic Differences in Cardiovascular Drug Response Potential Contribution of Pharmacogenetics

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In the early 1980s, clinical differences in response to the blood pressure (BP)-lowering effects of β -blockers and, to a lesser extent, diuretics were noted between ethnic groups. The most convincing evidence at that time came from a Veterans Affairs (VA) Cooperative Trial,¹ which, along with other smaller studies, suggested that whites (those of European ancestry) had a better antihypertensive response to β -blockers than blacks (those of African ancestry), whereas blacks had a slight better response to diuretics than whites. Shortly after the first angiotensin-converting enzyme (ACE) inhibitor was approved in the mid-1980s, it was also recognized that whites responded more favorably to ACE inhibitors than did blacks. Over time, these differences in response became well accepted, such that ethnicity began to be used in helping to guide selection of antihypertensive drug therapy.^{2,3} Although the ethnic differences in response between β -blockers and ACE inhibitors in hypertension are perhaps the mostly widely recognized examples of ethnic differences in response to cardiovascular drugs, there are others.

Pharmacogenetics is a field that seeks to unravel the genetic underpinnings of variable drug responses.⁴ Given the recognized ethnic differences in drug responses and the fact that many genetic polymorphisms differ in frequency on the basis of ethnicity/ancestry, questions about whether pharmacogenetics may also lead to an understanding of the ethnic differences in drug response are not surprising. The present review will summarize the most widely recognized examples of cardiovascular drugs with differential response by ethnicity and the evidence that pharmacogenetics data may aid in our understanding of these differences. Given that there are many examples in the literature of genetic associations that are not replicated, the pharmacogenetic examples discussed herein will come from those for which there is some evidence of replication or for which there have been multiple negative findings.

In light of the socially charged issues that surround race and genetics, we will typically refer to groups either as ethnic groups (meaning groups who may have similar ancestral origins and who share certain social or cultural practices) or will refer to continental ancestry, referring to the 3 major continental populations from which the human population mainly derives (namely, European, African, and Asian ancestry).

Ethnic Differences in Response to Warfarin Therapy

Ethnic differences in the warfarin dose required for an international normalized ratio (INR) between 2 and 3 are well documented in the literature but do not appear to be widely appreciated by clinicians. For example, the anticoagulation consensus guidelines that relate specifically to warfarin do not mention the influence of ethnicity on the typical maintenance dose,⁵ a fact that may result from trials conducted predominantly in white populations. Figure 1 depicts average warfarin dose requirements for Asians, Hispanics, whites, and blacks to maintain an INR of 2 to 3.⁶ Although these data were derived from a relatively small sample, average daily doses of 3.4 mg in Asians, 5.1 mg in whites, and 6.1 mg in blacks are representative of the literature for these ethnic groups. Given that most dosing algorithms recommend initiating therapy at 5 mg daily, it is apparent from Figure 1 that this is a reasonable estimate of the starting dose in whites but likely an excessive dose in Asians and an inadequate dose in blacks. The lower dose requirement in Asians was sufficiently recognized to warrant special notation in US Food and Drug Administration (FDA)-approved labeling for warfarin, which indicates requirements for a lower dose in Asians.⁷ Although some would argue that initiation of therapy with an inappropriate dose will be corrected quickly on the basis of close monitoring of INR, data clearly suggest the risk of bleeding is highest in the first 30 days of therapy, when the appropriate dose is typically still being determined.⁸ This would suggest that more accurate initial dosing may have the potential to reduce the early risk of bleeding.

In addition to differences in dose, there are questions about whether the risks of warfarin therapy also differ by ethnicity. The large trials that established an INR range of 2 to 3 to balance the benefits (reduced thromboembolic events) with the risks (bleeding) of warfarin therapy were conducted almost exclusively in whites. Thus, it is not clear whether this is the most appropriate INR range across ethnic groups, although some data suggest it may not be in Asians. For example, in a study of 563 Taiwanese patients with mechanical valve replacements (for whom the usual INR range is 2.5 to 3.5), investigators found the risks of thromboembolism were not different for those with an INR >2 versus <2 .⁹ In

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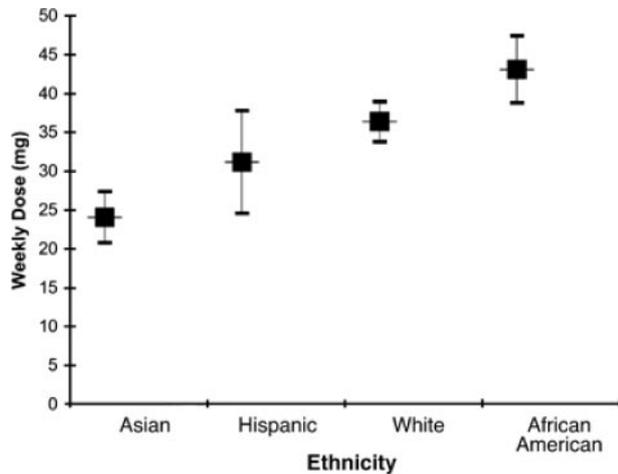


Figure 1. Average warfarin dose requirements, by ethnicity, to maintain a therapeutic INR.^{2,3} Reproduced from Dang et al,⁶ with permission from the *Annals of Pharmacotherapy*.

a study of 491 Chinese patients treated with warfarin, the INR associated with the lowest hemorrhagic and thromboembolic rate was 1.8 to 2.4.¹⁰ These data suggest Asians may have greater thromboembolic protection at lower INRs than whites. Finally, in a study of 667 Japanese nonvalvular atrial fibrillation patients studied for 1 year, INR ≥ 2.27 was associated with an OR of 4.33 (95% CI 1.30 to 14.39) for major bleeding. Furthermore, despite low-dose warfarin therapy (target INR 1.6 to 2.6), the rate of major bleeding and intracranial hemorrhage was similar to the rate observed in Western populations with full-dose anticoagulation (target INR 2 to 3) and approximately double the rate observed in Western populations for low-intensity warfarin therapy.¹¹ Combined, these data suggest that Asians might require a lower INR for protection from thromboembolism and might be at increased risk of bleeding at lower INRs.

Warfarin Pharmacogenetics

Among cardiovascular drugs, warfarin has the strongest pharmacogenetics data, which may also help explain ethnic differences in dose requirements for a stable INR. Two genes have been clearly associated with a variable warfarin dose: those encoding the major enzyme responsible for the metabolism of warfarin (cytochrome P450 2C9, *CYP2C9*) and the protein on which warfarin exerts its pharmacological effect (vitamin K epoxide reductase, *VKORC1*). The first report of genetic association with warfarin dose and *CYP2C9* genotype was in 1999,¹² and numerous studies since that time have documented this association across a variety of ethnic populations (see reviews by Wadelius and Pirmohamed¹³ and Sanderson et al¹⁴). Specifically, there are 2 polymorphisms, commonly called *CYP2C9**2 and *CYP2C9**3, both of which reduce the normal metabolic activity of the enzyme, although the *3 polymorphism does so to a greater extent than the *2 polymorphism. In a 2005 meta-analysis, which included 2775 patients and 8 different studies that related the polymorphisms to warfarin dose, the analysis suggested that carriers of at least 1 variant copy of the *2 allele required 0.85 mg less of warfarin daily (95% CI -1.11 to -0.60 mg), and those carrying at least 1 copy of the *3 allele required 1.92 mg less

Table 1. Ethnic Differences in Variant Allele Frequencies for Genes Important to Variable Warfarin Dose/Response (*CYP2C9* and *VKORC1*)

Variant	Whites	Blacks	Asians
<i>CYP2C9</i> *2	8% to 18%	Rare	Rare
<i>CYP2C9</i> *3	5% to 13%	1% to 2%	2% to 5%
Others†	Rare/absent	2% to 4%	Rare/absent
<i>VKORC1</i> variant‡	35% to 45%	8% to 10%	90% to 95%

Data derived from various sources.^{14,16–18}

†Others includes *CYP2C9**4, *5, *6, and *11.

‡The studies have included a variety of *VKORC1* SNPs, which, due to strong linkage disequilibrium, have similar or identical allele frequencies, and all show significant association with warfarin dose. Most commonly studied are 3673 G>A (also known as -1639; rs9923231), 6484 C>T (also known as 1173; rs9934438), and 6853 G>C (rs8050894). Depicted here are typical variant allele frequencies for -1639 and the SNPs in strong linkage disequilibrium with it.

of warfarin daily (95% CI -2.47 to -1.37 mg).¹⁴ Several studies have also documented that individuals with *CYP2C9* variant alleles require a longer period of time to achieve a stable dose and are at increased bleeding risk, particularly during the period of therapy initiation (ie, first 1 to 3 months).^{12,14–16} Data on the influence of *CYP2C9* variants are available from multiple populations in the United States, Europe, and Asia, and all consistently show a genetic association with *CYP2C9* polymorphisms. What differs is the frequency of the polymorphisms and thus their overall impact in that ethnic population. Table 1 depicts allele frequencies for the *CYP2C9* variant alleles and shows there are clear differences by ethnicity. Specifically, variant alleles for *CYP2C9* are much more common in whites than other groups; thus, at a population level, the impact of *CYP2C9* variants on warfarin dose is greater in whites. This may help to explain the slightly lower doses in whites versus blacks but does not explain the very low doses typically required by Asians.

Differing warfarin sensitivities by ethnicity are perhaps better explained by variant alleles in *VKORC1*. A number of different polymorphisms have been studied in this gene, and evidence currently points to a promoter polymorphism (referred to in the literature as 3673 G>A or -1639 G>A) as the most likely candidate for the functional polymorphism.^{19,20} Importantly, many different polymorphisms have been studied, and because of a high degree of linkage disequilibrium (inheritance of single-nucleotide polymorphisms [SNPs] together) between these SNPs in whites and Asians, the various SNPs tested all gave similar genetic associations. However, as with many other genes, the degree of linkage disequilibrium in *VKORC1* is lower in blacks than in other groups. In analyses in our laboratory of a variety of *VKORC1* SNPs, only 3673 and 6484 were significantly associated with warfarin dose in blacks, whereas numerous SNPs were associated with dose in whites. This is explained by high levels of linkage disequilibrium across numerous SNPs in whites but only these 2 SNPs in blacks. This emphasizes the importance of studying the functional polymorphism, because reliance on linkage disequilibrium between SNPs can be problematic across different ancestral

populations. Table 1 also provides a comparison by ethnicity for the presumed functional *VKORC1* polymorphism and reveals striking differences, such that the “variant” (ie, less common allele) in whites and blacks (with approximate frequencies of 45% and 10%, respectively) is the major allele in Asians, with a frequency of 90% to 95%.¹⁷

To date, there have been >30 studies published on the genetic association between *VKORC1* SNPs and warfarin dose, and all have shown a significant association, with the variant allele being associated with a lower warfarin dose.^{13,19–26} These studies have included numerous white populations from the United States, Europe, and Israel, along with Japanese, Chinese, Indians, and Malays. In whites, across a variety of studies, the average dose for GG homozygotes (using –1639 as the reference) was 6.1 mg daily, whereas those with a GA genotype required 4.5 mg daily, and AA homozygotes required 3.0 mg daily. Among Asians, doses for GG and GA have often not been reported separately (owing to low G allele frequency), but across studies, AA homozygotes required 2.8 mg daily, similar to the dose required by whites with the AA genotype. In the single study with a reasonably sized black cohort, daily dose requirements for GG, GA, and AA genotypes were 5.7, 4.5, and 3.1 mg, respectively, nearly identical to that in whites.²¹ Given that most blacks have the GG genotype and most Asians the AA genotype, these data suggest genetics may contribute substantially to the ethnic differences in dose.

Taken together, there is little doubt that genetic variability helps explain differences in warfarin dose requirements, particularly the *VKORC1* polymorphisms. Numerous different investigative groups have attempted to determine the amount of variability in warfarin dose that can be explained by genetic, demographic, and clinical factors. These studies suggest that between 30% and 60% of warfarin dose variability can be explained, with genetic factors responsible for explaining approximately two thirds of that variability. Clinical/demographic factors that have also been associated consistently with warfarin dose variability are age (reduced dose with increasing age), body size (increased dose with increased body size, assessed as body surface area, body mass index, or weight), and, in most studies, smoking status and interacting drugs. Given the well-known effect of high-content vitamin K foods on warfarin dose requirements, it is also possible that dietary differences between ethnic groups contribute to differences in warfarin sensitivity. It is also possible, although not tested to date, that there may be significant gene-diet interaction, particularly with *VKORC1* or other genes in the vitamin K pathway, that may also contribute to variability and might differ by ethnicity. Thus, in addition to genotype, there are a variety of other demographic, clinical, and environmental factors that may contribute to ethnic differences in warfarin dose requirements.

To advance the clinical translation of these findings, several groups have suggested warfarin dosing equations that incorporate genetic and nongenetic factors, some of which have been tested prospectively in small cohorts.^{22,18,27–29} Two studies have tested prospectively a genotype-guided versus usual-dosing control group, with 1 study considering only *CYP2C9*³⁰ and the other considering both *CYP2C9* and

VKORC1.³¹ Both studies were relatively small (≈200 subjects each) and had mixed results regarding significant differences in specified outcomes between genotype-guided versus usual-care approaches. However, these studies and others clearly support the need for an adequately powered randomized clinical trial.

One of the challenges regarding clinical use of warfarin pharmacogenetic information is the lack of availability of a dosing algorithm/equation that has relevance across various geographic and ethnic groups. On the basis of this and other issues, investigative teams with warfarin pharmacogenetics data have shared their data in a common database, with the primary goal of defining a warfarin pharmacogenetics dosing equation with validity across the globe. It is anticipated that this dosing equation will incorporate information not only on *VKORC1* and *CYP2C9* genotypes but also on various clinical and demographic factors that influence warfarin dose requirements. The group, called the International Warfarin Pharmacogenetics Consortium, comprises 21 research groups from 11 countries and 4 continents, and combined, they have contributed warfarin genotype and phenotype data on nearly 6000 individuals, with all 3 major ethnic groups well represented. After publication of the first report from this group, all data will be made publicly available on a World Wide Web site for the Pharmacogenetics and Pharmacogenomics Knowledge Base (www.pharmgkb.org). An additional aim of the International Warfarin Pharmacogenetics Consortium is to test questions relating to genetic associations and ethnicity, given that the combined group will have greater power than single-site studies to test a variety of hypotheses relating to ethnicity and warfarin pharmacogenetics.

Utilization of genetic information for warfarin dosing made headlines in both the medical and lay press in the summer of 2007 when the FDA product labeling (package insert) for warfarin was changed to include suggestions on (but not require) the use of genetic information to guide early warfarin dosing. There is great controversy about whether these data are to the point that such clinical utilization is appropriate, because there have been only 2 small randomized prospective studies testing the prospective use of genetic information to guide warfarin dosing.^{30,31} These questions will be addressed more comprehensively by a study from the National Heart, Lung, and Blood Institute, which will conduct a prospective clinical trial that tests genotype-guided warfarin dosing against usual-dose–initiation approaches. The study is intended to launch in late 2008 and last ≈18 months. This trial will not be powered to test (as a primary end point) for reductions in incidence of bleeding or prevention of thromboembolic events with the randomized dosing strategies. That the *CYP2C9* genotype is associated with bleeding risk seems clear, but it is not known whether prospective use of genetic information will reduce bleeding events. To the extent that some clinicians will judge reduced risk for bleeding to be the only meaningful end point for prospective warfarin pharmacogenetic testing, this may represent a long-term limitation of the data. Other clinicians will judge other end points to also be clinically meaningful (eg, time to stable INR or time to INR >4), and these should be well addressed by the planned trial. In the meantime, clinicians will be faced with deciding

Table 2. Pooled Estimates of Decrement in BP With Antihypertensive Drug Treatments

Drug Category	Mean BP Reduction*		White-Black Difference†
	Whites	Blacks	
Diuretics	11.5/9.1	15.0/10.7	-3.5/-1.5
CCBs	15.3/12.6	16.9/13.3	-2.4/-0.6
β -Blockers	11.7/11.3	5.9/9.5	6.0/2.9
ACE inhibitors	12.8/11.4	8.5/8.0	4.6/3.0

CCBs indicates calcium channel blockers; DBP, diastolic BP; and SBP, systolic BP.

Data derived from Brewster et al.³⁵

*Reported as SBP/DBP in mm Hg.

†White-black difference is the difference in response between groups, with negative values indicating a greater response in blacks and positive values indicating a greater response in whites.

whether and how to use genetic information with warfarin in the clinical setting. In the absence of genetic information, it seems clear that ethnicity should be considered as a factor when initial warfarin doses are selected.

Ethnic Differences in Responses to Antihypertensive Therapies

As described above, antihypertensive drugs were the first cardiovascular therapies for which there was wide recognition of clinical differences in response based on ethnicity. The Fourth Report of the Joint National Committee (JNC-IV) on the Detection, Evaluation, and Treatment of High Blood Pressure, published in 1988, was the first to recommend consideration of race/ethnicity in selection of antihypertensive therapy,³² and the 3 subsequent sets of JNC guidelines have contained similar recommendations. The most notable differences are in response to β -blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs). The widespread clinical recognition of such differences followed the 1982 VA Cooperative Study Group finding that 62% of whites and 54% of blacks achieved their BP goal with propranolol, whereas such goal was attained with hydrochlorothiazide in 55% of whites and 71% of blacks.¹ Another VA cooperative study a decade later similarly found that atenolol and captopril were less effective at BP lowering than hydrochlorothiazide and diltiazem, particularly in older blacks.^{33,34} A meta-analysis, published in 2004, evaluated 15 clinical trials published between 1984 and 1998 that reported differences in antihypertensive response between blacks and whites and that met other specified criteria.³⁵ Its analysis is summarized in Table 2 and highlights the fact that blacks generally respond more favorably to diuretics or calcium channel blockers, whereas whites tend to respond similarly to all the drug classes. In comparisons between groups, blacks respond slightly better than whites to diuretics and calcium channel blockers, whereas whites respond slightly better than blacks to ACE inhibitors and β -blockers. More recent data on lisinopril, quinapril, and losartan support the differences with ACE inhibitors and ARBs suggested by the meta-analysis.³⁶⁻³⁸

Thus, the literature suggests there are consistent, although perhaps small, differences in responses between blacks and

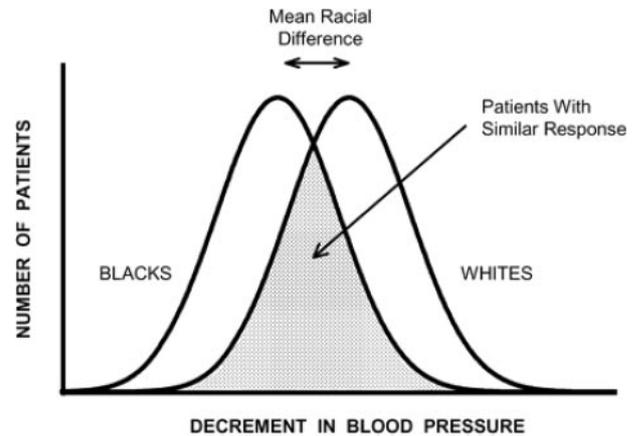


Figure 2. Representative decrement in BP among whites and blacks after administration of antihypertensive drug. Shaded area represents white and blacks who have similar responses. Differential responses are representative of those observed with ACE inhibitors, ARBs, or β -blockers. Reproduced from Sehgal,³⁹ with permission from Lippincott Williams & Wilkins. Copyright 2004, American Heart Association.

whites, particularly for ACE inhibitors, ARBs, and β -blockers. However, an important point from the meta-analysis and several other reports is that although a mean difference in response between groups exists, there is also a large degree of overlap in responses between the 2 groups, as depicted in Figure 2.³⁹ Viewed in this way, therapy decisions based on ethnicity appear less reasonable.

Perhaps the more important question is whether these arguably small differences in BP response translate into differences in outcomes. Only a few trials have addressed this question, the largest being ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial).³⁶ In the case of amlodipine versus chlorthalidone (the reference therapy), there was no difference in outcomes between blacks and nonblacks; however, for lisinopril, there were some outcomes for which there were significantly different treatment effects by ethnicity. Specifically, lisinopril (versus chlorthalidone) was associated with a significantly increased risk of stroke in blacks (relative risk 1.40), but no such effect was observed in whites (relative risk 1.00). There were also significant differences between blacks and nonblacks in the risk of combined cardiovascular disease (relative risk 1.19 in blacks versus 1.06 in nonblacks). Many have suggested that some of these differences were likely explained by the differences in BP achieved by blacks and nonblacks, although the ALLHAT analysis that controlled for BP did not suggest this to be the primary explanation.³⁶ In the INVEST trial (International Verapamil SR and Trandolapril Study), which randomized patients to a calcium channel blocker or β -blocker strategy, there were no differences in outcomes (composite of death, myocardial infarction, or stroke) by drug strategy for blacks, whites, or Hispanics.⁴⁰ In the LIFE trial (Losartan Intervention For Endpoint reduction in hypertension), losartan was superior to atenolol in nonblacks (hazard ratio 0.83, 95% CI 0.73 to 0.94), whereas it was associated with increased risk in blacks (hazard ratio 1.67, 95% CI 1.04 to 2.66).⁴¹ The African American Study of Kidney Disease and Hypertension (AASK) found that outcomes were better

or not different with ACE inhibitor versus β -blocker or calcium channel blocker therapy in blacks.^{42,43} Although this study did not provide comparisons between ethnic groups, it does suggest a lack of difference in outcomes by drug therapy in blacks. Most of the large, outcomes-driven hypertension trials do not provide insight into therapy-related differences in outcomes, either because they do not include sufficient numbers of nonwhites, or because they do not report such differences in a meaningful way in the manuscript. As such, one must conclude that on the basis of the available evidence, there are not clear differences in outcomes between blacks and whites with various antihypertensive regimens, and thus treatment decisions, as they relate to outcomes, should not be based on ethnicity.

Pharmacogenetics and Ethnic Differences in Antihypertensive Drug Responses

Overall, the literature suggests ethnic differences in the BP-lowering response to antihypertensive drugs, with less evidence for differences in outcomes. The question is whether these differences can be explained by genetic polymorphisms. The hypothesis is that a “responsive” genotype might differ in its frequency in different ethnic populations, leading to differences in response, such as is depicted in Figure 2. The more clinically relevant issue is that at present, many clinicians use ethnicity to guide selection of drug therapy. As suggested in Figure 2, a certain proportion of blacks and whites will respond well to the therapy. Even if, as suggested in Figure 2, whites are overrepresented among the “good responders,” and blacks are overrepresented among the “poor responders,” it is clear that ethnicity does not sufficiently separate those for whom a given therapy will be effective versus ineffective. The potential promise of pharmacogenetics is that it may present a more effective way of identifying responders and nonresponders, allowing clinicians to begin to move away from use of ethnicity as a method for selecting therapy. Although it appears that genetic differences are an important potential explanation for differences in response, ethnic or cultural differences can also influence response to antihypertensive medications. For example, some antihypertensive drugs are more or less effective in the presence of a high-salt diet, and dietary differences by ethnicity or geographic region are well documented. Thus, in the future, it will likely be a cadre of genetic information along with demographic and other information (eg, dietary information) considered together that might be most effective at targeting therapy, as is evident with warfarin. Whether ethnicity will be an appropriate surrogate for the cultural or dietary components or whether more refined tools to capture such information will be needed remains to be seen.

ACE Inhibitors and ARBs

The literature does not provide much insight regarding genetic polymorphisms and response. Despite the fact that there have been many studies evaluating the associations of numerous candidate genes with ACE inhibitor or ARB response, none have been consistently associated. Most studied is the *ACE* gene, and most of the studies with this gene have focused on an insertion/deletion (I/D) polymorphism,

with equivocal data. The most convincing study in this area is the pharmacogenetic substudy of ALLHAT, called GenHAT. This study tested the association of various outcomes in ALLHAT with the I/D polymorphism in 37 939 patients. No association was found between this polymorphism and BP lowering (with lisinopril or any other study drugs) nor with any of the study outcomes, either when considered in combination or stratified by drug therapy.⁴⁴ As discussed with warfarin, ethnic differences in linkage disequilibrium between blacks and whites may be diminishing the ability to document associations with this gene, because the I/D is not believed to be the functional polymorphism. Although this gene remains of interest, any polymorphism that influences the ACE inhibitor or ARB response remains to be identified.

Another gene that has been widely studied relative to the ACE inhibitor and ARB response is the gene for the angiotensin type 1 receptor, *AGTRI*. Similar to *ACE*, there have been no consistent findings with this gene, and we recently reported no association with BP response to trandolapril in whites, blacks, or Hispanics.⁴⁵ There are also clear ethnic differences in the risk for angioedema from ACE inhibitors, with blacks being at greater risk,³⁶ but there are no pharmacogenetic studies to provide insight into these differences.

β -Blockers

Unlike ACE inhibitors and ARBs, the β -blocker pharmacogenetics literature may provide some insights into ethnic differences in response. There are at least 6 papers in the literature reporting the association between BP lowering with β -blockers and 1 of 2 genetic polymorphisms in the β_1 -adrenergic receptor gene (*ADRB1*): Ser49Gly and Arg389Gly. All but 1 of the papers reported significantly greater BP lowering in the Arg389Arg individuals, with the other report showing differences that did not achieve statistical significance.⁴⁶ Studies have generally reported that alone, the Ser49Gly polymorphism does not importantly influence response, but when considered in combination with the Arg389Gly polymorphism, it may be more informative than Arg389Gly alone.^{47,48} Regarding the Arg389Gly polymorphism, there is concordance of this association in the literature. Additionally, because these have been documented as functional polymorphisms, the challenges of studying a nonfunctional polymorphism and ancestral differences in linkage disequilibrium are not believed to be an issue. Whether these polymorphisms help explain differences in β -blocker response between ethnic populations was only addressed in 1 paper, because the other studies were composed of mostly or only 1 ethnic group.⁴⁷ In multiple regression analysis of the determinants of the BP response to metoprolol, *ADRB1* genotypes were significant determinants of response, but ethnicity was not. Figure 3 depicts BP responses to metoprolol considering the Ser49Gly and Arg389Gly polymorphisms in a US-based study that included blacks and whites and a study in Chinese. As is evident from Figure 3, the 2 most responsive diplotypes (genotype combinations for the 2 polymorphisms) were consistent across the 2 studies. Of interest is that the frequency of these 2 most responsive diplotypes varies by ethnicity. Specifically, 54% of Chinese and 44% of whites but only 23% of blacks carry

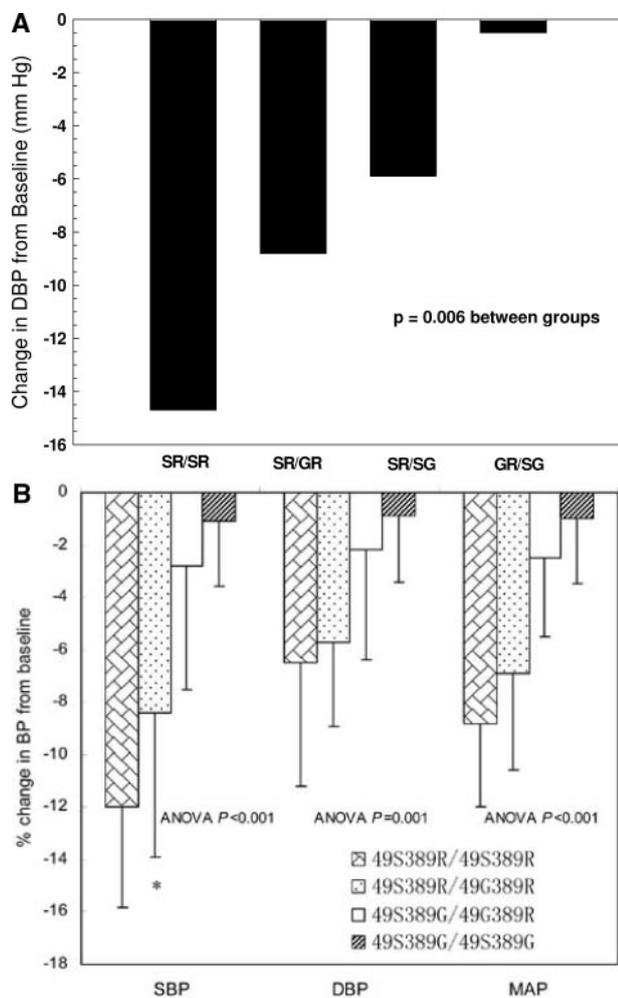


Figure 3. Antihypertensive responses to metoprolol among various *ADRB1* diplotype groups (genotype combination for Ser49Gly and Arg389Gly), among whites and blacks (A) and Chinese (B). S indicates Ser49; R, Arg389; G, Gly49 (when the first of 2 letters) or Gly389 (when the second of 2 letters); DBP, diastolic BP; SBP, systolic BP; and MAP, mean arterial pressure. Reproduced from Johnson et al⁴⁷ and Liu et al,⁴⁸ with permission.

1 of the 2 most responsive diplotypes shown in Figure 3. This is not direct evidence that this gene helps explain ethnic differences in β -blocker response, but it does provide preliminary evidence in support of such a hypothesis. The Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) Study is an ongoing National Institutes of Health-funded pharmacogenetic study of β -blocker and thiazide diuretic that is accruing a large cohort of black and white hypertensive individuals, and it should be able to address this question more directly.

Thiazide Diuretics

There are limited examples in the literature of replicated associations with the response to thiazide diuretics. The strongest example, which may also provide insight into ethnic differences in response, is a functional SNP in the G protein $\beta 3$ subunit gene (*GNB3*), which has been shown in at least 2 studies to be associated with the antihypertensive response. Although 1 study was conducted only in whites,⁴⁹ the other

Table 3. Ethnic Differences in Mortality Rates From the V-HeFT Trials*

	Blacks	Whites
V-HeFT I	n=180	n=480
I-H	9.7%	16.9%
Placebo	17.3%	18.8%
<i>P</i> (vs placebo)	0.041	0.48
V-HeFT II	n=215	n=574
I-H	12.9%	14.9%
Enalapril	12.8%	11.0%
<i>P</i> (vs enalapril)	0.95	0.02

*Data derived from Carson et al.⁵¹

included blacks and whites.⁵⁰ In the latter study, ethnicity was a significant predictor of diuretic response in univariate analysis, but when genotype was included in a multivariate analysis, genotype remained a significant predictor, whereas ethnicity did not. Thus, similar to the β -blocker data, these data suggest that genotype may be a better predictor of response than ethnicity. The contribution of dietary sodium intake and its potential ethnic differences was not addressed in the study. As with the β -blockers, these findings do not provide direct evidence that pharmacogenetics may help explain differences in response, but they are suggestive. Also as with the β -blockers, the PEAR study should provide more specific evidence in this regard. Nonetheless, studies with β -blockers and diuretics provide the conceptual framework that genetics may represent a significant (albeit not the only) factor in ethnic differences in response and, more importantly, may be superior to ethnicity in separating responders from nonresponders.

Ethnic Differences in Responses to Heart Failure Therapies

Heart failure therapies have been among the most controversial with regard to ethnic differences in response. This is largely due to the African American Heart Failure Trial (A-HeFT), which enrolled only self-declared African Americans to test the efficacy of isosorbide dinitrate-hydralazine (I-H) versus placebo and led to the eventual FDA approval of I-H for treatment of African Americans with heart failure. This represents the only FDA-approved therapy with explicit labeling for a single race/ethnicity group, and it caused great controversy about the appropriateness of clinical trials conducted exclusively in 1 race/ethnicity group and FDA labeling of drugs in a single group.

Isosorbide-Hydralazine

The A-HeFT trial was stimulated by data from the V-HeFT (Vasodilator-Heart Failure Trial) I and V-HeFT II trials, which suggested that blacks derived greater benefit from I-H than whites.⁵¹ Specifically, in V-HeFT I, I-H significantly reduced mortality compared with placebo in blacks but not whites (Table 3), although there were no statistical differences in response by ethnicity. In V-HeFT II, again, there were no significant ethnicity-by-treatment interactions, although enalapril provided significant benefit compared with

I-H in whites but not in blacks. Furthermore, mortality rates with I-H were numerically higher in whites than blacks.⁵¹ This led the investigators to conduct the A-HeFT trial, enrolling only African Americans, because the previous data suggested this group might obtain the greatest benefit.

ACE Inhibitors

Ethnic differences in response to ACE inhibitors were also suggested by the investigators reporting differences in response by ethnicity from the V-HeFT trials (Table 3).⁵¹ However, it is not clear that the data support this contention. Specifically, the report does not present statistical comparisons of mortality in enalapril-treated blacks and whites, and although mortality was numerically lower in whites than blacks, it appears unlikely this difference was statistically significant (Table 3). In a matched cohort analysis of blacks and whites from the Studies Of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials, investigators found that enalapril was associated with a significant 49% adjusted risk reduction in heart failure hospitalization in whites and a nonsignificant 14% adjusted risk reduction in blacks, for a significant treatment-by-ethnicity interaction ($P=0.005$).⁵² They did not, however, observe differences in mortality reduction between ethnic groups. In both the V-HeFT II and SOLVD analyses, whites had greater BP reduction with enalapril than blacks, which may have contributed to the observed differences in outcomes. A subsequent analysis that only involved the SOLVD Prevention Trial did not observe any differences between blacks and whites in the risk reduction associated with enalapril in progression to symptomatic heart failure.⁵³ Finally, a meta-analysis did not suggest any differences in ACE inhibitor efficacy in reducing adverse cardiovascular outcomes in heart failure between blacks and nonblacks in heart failure.⁵⁴

β -Blockers

Over a period of a couple of years, the efficacy of bisoprolol, metoprolol CR/XL, and carvedilol in heart failure were all documented.^{55–57} Thus, it came as a surprise when the large clinical trial with bucindolol (called BEST, Beta-Blocker Evaluation of Survival Trial) failed to achieve the primary end point.⁵⁸ There were 2 hypotheses put forward by the authors to explain why bucindolol failed to reduce mortality in heart failure, when other drugs had shown such benefit. Specifically, they hypothesized it might be due to differences in the patient populations for the various trials, or there were ancillary pharmacological properties of bucindolol that reduced its efficacy. Regarding the differences in study populations, the most notable difference was that BEST enrolled substantially more blacks than any other trial (ie, 23% in the bucindolol trial, <1% in the bisoprolol trial, and 5% in the metoprolol CR/XL and carvedilol trials).⁵⁹ Furthermore, in the BEST subgroup analysis, there was no benefit evident in blacks (hazard ratio 1.17, 95% CI 0.89 to 1.53), whereas there was a significant mortality reduction in nonblacks (hazard ratio 0.82, 95% CI 0.70 to 0.96). This prompted a variety of subsequent analyses to evaluate whether there was lower efficacy with β -blockers in blacks in the treatment of heart failure. A reanalysis of the carvedilol data by ethnicity

suggested no differences in outcomes, with blacks having estimates of risk reduction similar to whites.⁶⁰ Nonetheless, there were only 217 black participants in the trial, and a lack of or reduced efficacy in blacks cannot be ruled out by these analyses. Subgroup analyses of the metoprolol CR/XL data were not as convincing with regard to the lack of a difference by ethnicity.⁶¹ Although all hazard ratios in blacks were <1.0, for total mortality, the hazard ratio point estimate was 0.79 in blacks (not significant) and 0.67 in whites (significant). Similarly, for mortality plus heart failure hospitalization, the point estimate was approximately 0.98 in blacks and 0.70 in whites.^{54,61} Thus, although the authors concluded there were no differences between blacks and whites, it is not apparent this is the case. Whether the study was simply underpowered to test for ethnic differences or no such differences exist is unknown. Interestingly, the FDA package labeling for metoprolol CR/XL indicates that among the US-based participants in the metoprolol CR/XL clinical trial (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure [MERIT-HF]), no benefit was evident. Given that nearly all the blacks in MERIT-HF came from the United States,⁶¹ it is possible that reduced efficacy in this population led to the failure to observe a benefit among the US population for this trial. Thus, although there is reasonable evidence for a lack of ethnic difference in response to carvedilol, it is less clear for metoprolol CR/XL. There was also a meta-analysis that included 2 carvedilol trials, the metoprolol CR/XL trial and BEST.⁵⁴ As suggested by the previous analyses, point estimates for blacks and nonblacks were similar, except for bucindolol. In the meta-analysis that included BEST, there was significantly less relative risk reduction in blacks than whites, whereas in the meta-analysis that excluded BEST data, there was no significant difference in the relative risk reduction. However, in this meta-analysis and in 3 of the 4 trials, the risk reduction ratio (blacks/whites) was greater than 1.0, which suggests less risk reduction in blacks (albeit nonsignificant except in BEST). Given that even when combined, the other 3 trials included 82 fewer blacks than BEST, it is difficult to exclude a reduced efficacy with β -blockers in blacks. Finally, the BEST investigators conducted an analysis in which they created a subgroup in BEST that closely matched the demographics of the other trials.⁵⁹ In the BEST comparison subgroup, they showed a significant reduction in mortality (hazard ratio 0.77, 95% CI 0.65 to 0.92), which made the findings similar to the trials with the other drugs. This comparison subgroup included no blacks, which supports their initial hypothesis that differences in their study population, particularly a larger black population, may have influenced the inability to show a significant reduction in mortality with bucindolol.

Pharmacogenetics and Ethnic Differences in Responses to Heart Failure Therapies

Isosorbide-Hydralazine

If one accepts that I-H is more efficacious in blacks than whites, a potential explanation for such a finding is that there might be a “responsive” genotype that occurs exclusively or more commonly in blacks. Work is ongoing in the A-HeFT genetic substudy to address this question. However, equally

likely as a genetic or ethnic explanation for the I-H findings is that response differences highlight differences in 2 different heart failure phenotypes, which happen to differ by ethnicity. Specifically, blacks are significantly more likely to have hypertensive heart failure, whereas the underlying cause is more likely to be ischemic heart disease in whites. Thus, it is possible that blacks and whites with hypertensive heart failure would respond equally well to I-H and that ethnicity per se is not the source of response differences. It is unlikely that there will be future studies that sufficiently dissect the role of genetics versus differences in phenotype in the response differences to I-H. However, whichever of these might be the explanation, either would highlight that a proportion of whites would be expected to benefit from I-H, and a proportion of blacks would be expected to not benefit.

β -Blockers

As described, there appears to be reasonable evidence for differences in response to bucindolol between blacks and whites, and although the studies with the other β -blockers did not provide convincing evidence for differences in response, the number of blacks included was small, and such a difference cannot be excluded. As with the antihypertensive response, the pharmacogenetics data with β -blockers may be considered consistent with a potential mechanistic explanation for such differences in response. For example, studies have shown that the *ADRB1* Arg389Gly polymorphism is significantly associated with the improvement in left ventricular ejection fraction (LVEF) associated with carvedilol,⁶² metoprolol CR/XL,⁶³ and bisoprolol.⁶⁴ Specifically, in all these studies, the Arg389Arg genotype group had the greatest improvement in LVEF, and given that improvement in LVEF is considered a good surrogate for improvement in survival, such differences may have clinical relevance. The first 2 studies were conducted in the United States, whereas the latter was conducted in China, which also suggests these associations are consistent across ethnic groups.

Consistent with the associations between genotype and improvement in LVEF are data from BEST, which showed that Arg389Arg homozygotes had a significant mortality reduction with bucindolol compared with placebo, but such a benefit was not evident in the Gly389 carriers.⁶⁵ Of importance is that the frequency of the Arg389Arg genotype is lower in blacks than whites, which is consistent with the potential ethnic differences in response. Specifically, among whites, $\approx 55\%$ of the population has the Arg389Arg genotype, compared with $\approx 30\%$ to 35% of blacks. This would not appear to explain the literature that suggests a lack of difference by ethnicity for carvedilol and a more dramatic difference with bucindolol. However, studies by Liggett and colleagues⁶⁵ on the effects of genotype on ex vivo ventricular contractile responses may be insightful. They found that in precontracted ventricular trabeculae, bucindolol behaved as an inverse agonist in the Arg389Arg hearts only, whereas carvedilol was a neutral antagonist in Arg389Arg and Gly389 carriers.⁶⁵ These data suggest that ancillary properties of the drugs might also vary by genotype and thus may influence the variable efficacy between drugs and across ethnic groups.

Another ancillary property of bucindolol that may have influenced its failure to reduce mortality in the overall population is its sympatholytic properties. Specifically, it was shown that a portion of the bucindolol-treated population had dramatic reductions in norepinephrine, due to its sympatholytic effects, and those with the greatest decline in norepinephrine were at increased mortality risk.⁶⁶ Of interest is that the sympatholytic effects of bucindolol may be associated with the amino acid 322 to 325 I/D polymorphism in the α_{2C} -adrenergic receptor (*ADRA2C*), with deletion (Del) carriers having greater norepinephrine reductions with bucindolol.⁶⁷ Additionally, in BEST, *ADRA2C* Del carriers had no benefit from bucindolol relative to placebo, whereas insertion/insertion (Ins/Ins) homozygotes had a significant benefit from bucindolol therapy. The group with the greatest benefit was those with both *ADRA2C* Ins/Ins and *ADRB1* Arg389Arg genotypes. As with the Arg389Gly polymorphism, there are significant ethnic differences in the *ADRA2C* 322 to 325 I/D polymorphism. Specifically, in BEST, 66% of blacks were Del carriers versus 8% of whites. Thus, 2 genes have been associated with different outcomes for bucindolol, and in both cases, blacks are less likely than whites to have the favorable response genotype.

Of interest is that among the β -blockers used to treat heart failure, the sympatholytic effects appear to be confined to bucindolol, so these findings would not translate to the other β -blockers. This may help explain why bucindolol appears to be the most extreme with regard to ethnic differences in response. For example, we found that *ADRA2C* Del carriers had significantly greater improvements in LVEF with metoprolol than Ins/Ins homozygotes.⁶⁸ Additionally, when considered with the *ADRB1* Arg389Gly polymorphism, it appeared that the LVEF improvement in Arg389Arg homozygotes/Del carriers was synergistic relative to those carrying just 1 of the favorable genotypes. This finding is also consistent with the known functional effects of the *ADRA2C* polymorphism, in which the Del carriers have impairment in the normal autoinhibitory function of the receptor, which leads to enhanced norepinephrine release.⁶⁹ In the absence of sympatholytic effects of the drug, Del carriers would be expected to have a greater response to β -blocker therapy. When data from the 2 drugs are considered together, they suggest that the most favorable genotype combination for bucindolol (Arg389Arg plus Ins/Ins) is different from the most favorable combination for metoprolol (Arg389Arg plus Del carrier). Blacks are more likely to have the latter rather than the former genotype combination, consistent with the data suggesting a more minimal difference in response to metoprolol CR/XL between blacks and whites than with bucindolol. Data considering both genes are not available for carvedilol, so it is not possible to know what the most favorable genotype combination might be for this drug.

The pharmacogenetics data for β -blockers in heart failure suggest several things. First, it appears the observed ethnic differences in response in clinical trials might be explained to some degree by pharmacogenetics. The data also suggest that it might be possible to more precisely select β -blocker therapy on the basis of genotype and that such an approach would appear to be superior to selecting therapy on the basis

of a patient's ethnicity. Specifically, although one might conclude from the literature that bucindolol would be a suboptimal therapy in blacks, certain blacks will carry the genotype combination for which it might be an effective therapy. A small pharmaceutical company has purchased the rights to bucindolol and will be filing a new drug application with the FDA, with the drug being most strongly recommended for Arg389Arg plus Ins/Ins genotype patients. Thus, use of genetic information to guide β -blocker selection in heart failure may soon be a clinical reality and would be expected to be a more reliable predictor of response than reliance on data regarding differences or similarities in response by ethnic group.

Challenges to Defining the Role of Pharmacogenetics in Ethnic Differences in Drug Response

Ethnic differences in responses to cardiovascular drugs have been recognized for several decades, and in some cases, ethnicity is used to make decisions about drug therapy. It is intuitively attractive to speculate that pharmacogenetics may contribute to our understanding of ethnic differences in drug response, and some of the examples cited herein support that pharmacogenetics may contribute to such differences. However, there are certain challenges to defining the role of pharmacogenetics in ethnic differences in drug response that must be recognized. First, the heritable contribution to drug response variability is rarely defined experimentally, but if one assumes that it is approximately the same as the heritable contribution to the diseases the drug treats, then on average, this would represent 30% to 60% of variability that has a genetic basis, with the remaining being environmental or demographic. Additionally, it is expected that for most drug responses, the genetic underpinnings will be explained by a variety of genes, thus making any calculation of the role of pharmacogenetics in ethnic differences in response more challenging. It is possible that the examples provided herein are ones for which the genetic contribution from a single gene is larger than normal, thus making the potential contribution of that gene to ethnic differences in response more evident. Additionally, as genetic studies move toward a tag SNP approach, in which the functional polymorphism is unknown, differences in linkage disequilibrium between ancestral populations will add to the challenge of defining an association across different ethnic groups and defining the role of that polymorphism in ethnic differences in response. This has been clearly evident with warfarin and the *VKORC1* SNPs. The contribution of environmental factors to drug response, particularly diet for many of the cardiovascular drugs, and how this may confound the search for the genetic underpinnings of ethnic differences in response remains to be clarified. Finally, there are the challenges associated with translation of any finding or technology to practice. This includes accumulating sufficient data that the genetic (and probably other) information is predictive enough to be useful clinically, followed by the education required of clinicians for adoption to practice.

Despite the many challenges, it appears that in at least some cases, pharmacogenetic findings may help to explain

ethnic differences in response. As the goals of personalized medicine begin to be realized, it is possible that use of genetic and other patient-specific information, including environmental factors, will be superior to use of ethnic information and will help guide drug therapy decisions for certain drugs.

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