Race, Common Genetic Variation, and Therapeutic Response Disparities in Heart Failure

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ABSTRACT

Because of its comparatively recent evolution, Homo sapiens exhibit relatively little within-species genomic diversity. However, because of genome size, a proportionately small amount of variation creates ample opportunities for both rare mutations that may cause disease as well as more common genetic variations that may be important in disease modification or pharmacogenetics. Primarily because of the East African origin of modern humans, individuals of African ancestry (AA) exhibit greater degrees of genetic diversity than more recently established populations, such as those of European ancestry (EA) or Asian ancestry. Those population effects extend to differences in frequency of common gene variants that may be important in heart failure natural history or therapy. For cell-signaling mechanisms important in heart failure, we review and present new data for genetic variation between AA and EA populations. Data indicate that: 1) neurohormonal signaling mechanisms frequently (16 of the 19 investigated polymorphisms) exhibit racial differences in the allele frequencies of variants comprising key constituents; 2) some of these differences in allele frequency may differentially affect the natural history of heart failure in AA compared with EA individuals; and 3) in many cases, these differences likely play a role in observed racial differences in drug or device response. (J Am Coll Cardiol HF 2014;2:561–72) © 2014 by the American College of Cardiology Foundation.

Variability in drug response is typical of cardiovascular therapies (1) and may be related to common genetic variation (1–3), operationally defined as a polymorphism with a minor allele frequency of ≥1% (4). Race-associated differences in cardiovascular disease natural history and drug response are well known and may be associated with genetic variation in drug targets or pharmacokinetics (2) that can potentially explain variability in racially based responses to heart failure therapies.

We review and provide new information on race-associated differences in heart failure natural history and therapeutic responses associated with common genetic variation. The information is confined to heart failure with reduced left ventricular ejection fraction (HFrEF, or HF), and race comparisons are made between subjects of Sub-Saharan African ancestry (AA) and those of European ancestry (EA) populations, regardless of geographic location. The overall aim of this review was to explore...
ABBREVIATIONS AND ACRONYMS
AA = African ancestry
ACEI = angiotensin-converting enzyme inhibitor
ACM = all-cause mortality
ARB = angiotensin-receptor blocker
CCDS = consensus coding sequence
CRT = cardiac resynchronization therapy
Del = deletion
EA = European ancestry
HF = heart failure
HFH = heart failure hospitalization
HFHF = heart failure with reduced left ventricular ejection fraction
ICD = implantable cardioverter-defibrillator
Ins = insertion
MRA = mineralocorticoid receptor antagonists
NF = non-heart failure
RAAS = renin-angiotensin-aldosterone system
RES = relative effect size
SNP = single-nucleotide polymorphism

the hypothesis that reported racial differences in HF natural history or therapeutic response are influenced by differences in genetic variations in relevant cardiac myocyte neurohormonal signaling mechanisms.

RACE AND GENETIC VARIATION

An argument for a genetic basis for race-associated differences in disease natural history or therapeutic response is predicated on the idea that different frequencies of genetic variants among racial groups may lead to differentiated outcomes among those groups.

Genetic alteration of a disease or therape-utic phenotype within a racially defined population is dependent on: 1) the frequency of the polymorphism in that population; 2) the difference in the allele frequency of the polymorphism between the indicated population and a general, non-racially selected population; and 3) the extent of the biological or pharmacologic effect of the polymorphism on the disease or therapeutic phenotype.

Extrapolating racial identity from common attributes such as skin color can be problematic due to the assumption that physical characteristics are a proper proxy for variations in biologic phenotype-modifying, non-anthropomorphic genes. Nevertheless, extensive clinical experience supports the fact that phenotype heterogeneity in disease risk, prognosis, and response to therapy can be attributed to self-identified race, and it is appropriate to explore the extent to which genetic variation contributes to these differences (5,6). Understanding the underlying genetic basis of such heterogeneity will help devise new drugs, devices, and diagnostics that improve outcomes.

Genetic diversity in humans is relatively low compared with other species, including other primates (7). This is generally attributed to Homo sapiens’ relatively recent evolution in East Africa approximately 200,000 years ago, and the subsequent immigration of modern populations from Africa in the past 100,000 years (6). Based on the first detailed single-nucleotide polymorphism (SNP) map of the human genome, encompassing 1.42 million variants occurring every 1.9 kb, humans were estimated to be 99.6% to 99.8% identical at the nucleotide level (6,8). The more recent 1000 Genomes Project, in which the goal is to identify pan-genomic and coding region variations down to respective allele frequencies of 1% and 0.1%, identified in its recently published pilot phase (9) approximately 15 million SNPs, 1 in every 800 bases, from whole-genome sequencing of 179 individuals in 3 racial categories. The average number of SNPs per individual was approximately 3 million, and the variation from the reference genome was 0.125% (9). Thus, although the most recent estimate of single-nucleotide variation is approximately 0.1%, the 3 million SNPs per individual plus other types of genetic variation provide ample potential for genomic diversity within and among populations. Despite the notion that most SNPs represent silent (synonymous) variations or an amino acid change (non-synonymous) with no clear biological function effects, substantial effort has been invested in identifying the small fraction of SNPs and other variants that associate with human phenotypes and disease risks.

AA populations exhibit greater degrees of genetic variation than non-African cohorts (10,11). Given that modern European and Asian populations descended from founder groups that diverged from ancestral African populations, it is expected that genetic diversity in non-African groups would be lower because ancestral founder populations would contain only a subset of the total African variation. However, most of the genetic variations in African populations can also be found in non-African populations. Overall, 10% to 15% of all human genetic variation is explained by differences among Sub-Saharan Africans, Northern Europeans, and East Asians. Stated another way, approximately 85% to 90% of known variation is captured by studying any 1 of the 3 “major” population groups (Africa, Asia, and Europe), and only an additional 10% to 15% can be ascertained by inclusion of the other 2 groups (12). Thus, genetic variation among populations is only slightly more different than variation within a given population (13).

These data have relevance for the evaluation of genetic variations related to health and disease. A priori, for any given variant there is an increased probability of it being represented in an AA versus a non-AA population. Furthermore, for any variant locus shared between AA and non-AA populations, the observed allele frequencies may differ, sometimes widely, between racial populations.

ADRA2C insertion (Ins)322–325 deletion (Del) (rs2234888 [Online Refs. 2,11,12]), GRK5 Gln41Leu (rs2230345 [Online Ref. 7]), and SCN5A Ser1103Tyr (rs7626962 [Online Ref. 29]) are examples of polymorphisms whose minor alleles are markedly (7–10 fold) enriched in AA populations. However, even in these highly minor allele-enriched examples, the major allele has a frequency >0.5. Thus, there is a non-trivial percentage of AA individuals who do not
have the minor allele in the heterozygous or homozygous state. Therefore, one can readily appreciate that skin color would be a poor method of determining whether a person carries the minor allele for these polymorphisms.

Despite widespread variation in the frequency of various genetic markers, the associated odds ratios for disease risk in different racial groups appears to be less variable (14). However, data for HF disease progression and therapeutics show there is good evidence that racially based pharmacogenetic differences exist for both effectiveness and safety.

**COMMON GENETIC VARIATION IN SIGNALLING MECHANISMS IMPORTANT IN HF**

Numerous reports have documented substantial polymorphic variations in neurohormonal and associated signaling mechanisms important in HF therapeutics. For example, the β₁-adrenergic receptor (ADRB1) (Figure 1A)—the initiating signal transduction molecule in a system that can cause dilated cardiomyopathy when overexpressed in transgenic mice and is also the primary drug target for a major class of HF therapeutics (β-blockers) (15), exhibits approximately 5 times the average SNP percentage detected in the Encyclopedia of DNA Elements (ENCODE) project regions in the human genome (16) and 2 times that detected in exons in the 1,000 Genomes Project (9), with 26 SNPs in the 1,431 coding region nucleotides, half of which result in an amino acid change (17). Most genomic common variation has no impact on protein function, so the focus of this study is on variants with well-characterized biologic or pharmacologic effects.

**Online Table 1** is a compilation of allele frequency data from selected non synonymous SNPs, insertion-deletions, and other polymorphisms that have been shown to have functional significance in signaling pathway proteins of documented or potential importance in HF natural history or therapeutics. Methods and references for generating and curating

**FIGURE 1** Consensus Coding Sequence

Consensus coding sequences are shown for ADRB1 (A) and ADRB2 (B) (43). Amino acid changes resulting from nonsynonymous single nucleotide polymorphisms (SNPs) are in yellow, and unchanged amino acids at the site of synonymous SNPs are in red. Polymorphisms discussed in the text or listed in the tables are circled, and the ADRB1 Arg389Gly locus is highlighted by an arrow. Modified with permission from Taylor et al. (17).
the data can be found in Online Table 1 are given in the Online Appendix and in the Table footnotes. The basis for combining AA populations from Sub-Saharan Africa and elsewhere is that this alignment forms a distinct genetic group compared with EA populations from the United States, Europe, and elsewhere (18).

Of the 19 selected polymorphisms in 15 genes in non-HF (NF) populations listed in Online Table 1, 16 variants exhibit evidence of racial differences in minor allele frequency (MAF). Moreover, in every case, differences in allele frequency are maintained in HF populations, that is, there is good agreement in MAFs between HF and NF populations. Data in Online Table 1 illustrate that: 1) racially based genetic variation is common in genes encoding proteins that are important in neurohormonal signaling systems; and 2) the racial differences in distribution of polymorphic variants are generally not altered in HF.

For ADRB2 Gln27Glu, GNB3 C825T, NOS3 Glu298Asp, and AGTR1 A1166C, the differences in MAF allele frequencies are very different (i.e., 2.5-fold difference among races) (Online Table 1) and extremely different (>5-fold) for ADRB2 Thr164Ile, ADRA2C Insl322–325Del, ECE1 Thr341Ile, GRK5 Gln41Leu, and SCN5A Ser1103Tyr. Having established that AA and EA racial differences are common in signaling system polymorphisms important in HF, does this have any practical importance? First we consider potential effects on HF natural history.

**DOES COMMON GENETIC VARIATION INFLUENCE HF NATURAL HISTORY IN EITHER AA OR EA POPULATIONS?**

Online Table 2 lists the Online Table 1 polymorphisms with racial differences in MAF, the pharmacologic effects of their minor versus major alleles, the predicted biological or pharmacologic effects of the frequency differences in AA compared with EA individuals, and whether the projected relative signaling effect would be cytoprotective or cytopathic in failing human cardiac myocytes on the basis of the assumption that increases in signaling are harmful and that decreases are beneficial. In 13 of the 14 polymorphisms listed in Online Table 2 (with the exception of ECE1 Thr341Ile, where functional effects are unknown), the minor alleles have effects that differ from those of the major allele and could influence HF risk or progression. Race-associated differential genetic effects on HF natural history could in turn affect therapeutic responses.

In contrast to the low frequency (MAF, <1%) mutations in contractile protein and cytoskeletal and other genes that cause inherited dilated cardiomyopathies, there is no good evidence that any of the cell-signaling polymorphisms listed in Online Table 1 or 2 predispose to the risk of developing HF. The similar MAF distributions in HF and NF indicate that HF populations are not generally enriched in these signaling molecule minor alleles. Although earlier, smaller studies did report enrichment in HF for some of these MAFs (19,20, Online Ref. 3), most subsequent larger studies (21-23), including meta-analyses (24,25), have not confirmed the findings. However, there is a need for well-controlled, prospective studies with large numbers of patients and clinical endpoints to further address this issue.

In terms of possible effects on disease progression, of those HF studies with enough patients and events to provide adequate statistical power, the adrenergic receptor polymorphism substudy (n = 1,040, 193 deaths, and 426 deaths or first HF hospitalizations [HFHs], baseline characteristics in Online Table 3) (Online Refs. 2,3) of the placebo-controlled BEST (β-Blocker Evaluation of Survival Trial) and a large observational study from the Universities of Cincinnati and Pennsylvania (n = 2,460 and 765 deaths) (Online Ref. 7), each with >20% of AA patients, provide the most robust data. Effects of polymorphic variants on natural history of established HF can be assessed in BEST in the 525 placebo-treated patients and in the Cincinnati and Pennsylvania Universities study by effects in patients not treated with β-blockers, as described in the Online Appendix and Online Table 4.

Among the potential candidate gene variants listed in Online Tables 1 and 2, perhaps the most likely to influence the progression of HF is the ADRB1 Arg389Gly polymorphism (Figure 1A). This is because in human ventricular preparations, compared with its Gly389Gly counterpart, the 389Arg version of the receptor has 3 to 4 times the signal transduction capacity (Online Ref. 3); a higher proportion of receptors that are constitutively active as inferred from inverse agonist activity (Online Ref. 3); and a much greater fraction of receptors in a high affinity norepinephrine/agonist binding state (Online Table 2, Online Ref. 34). As a result of this polymorphism-based difference in agonist affinity and the lower affinity of β₁ receptors for norepinephrine, the protein product of ADRB1 389Arg can be considered the norepinephrine receptor in the human heart (15, Online Ref. 34). This is important because increased release and cardiac concentrations of the β₁-selective neurotransmitter norepinephrine produce and lead to the progression of ventricular chamber remodeling and HF (15). Online Table 4 summarizes the ADRB1 Arg389Gly data from placebo-treated patients in BEST (Online Refs. 2,3).
and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) (Online Ref. 6), as well as data from patients not treated with β-blockers in the Cincinnati/Pennsylvania Universities study (Online Ref. 7).

In BEST as well as in MERIT-HF (which did not report pharmacogenetic data by race) (Online Ref. 6), in placebo-treated patients there was no evidence of an effect of ADRB1 Arg389Gly genotype on the outcomes of time to all-cause mortality (ACM) or the combined endpoint of ACM or HFH (Online Table 4). In contrast, in the Cincinnati and Pennsylvania Universities study, EA (but not AA) patients who were not treated with β-blocking agents had improved transplantation-free survival from the time of HF diagnosis if they were ADRB1 389Arg homozygotes, compared with 389Gly genotypes (Online Ref. 7). One possible difference between the clinical trial/placebo groups data from BEST and MERIT-HF compared with that from the Cincinnati and Pennsylvania Universities study, is the much shorter mean or median follow-up times in BEST (2 years) (Online Ref. 3) and MERIT-HF (1 year) (Online Ref. 6), vs. the 46 months in the observational study (Online Ref. 7). It is conceivable that a longer follow-up is necessary to detect genotype-based differences in outcomes for common genetic variations in neurohormonal cell signaling systems. However, the Cincinnati/Pennsylvania Universities data imply a protective effect of the ADRB1 389Arg allele, which is contrary to findings in transgenic cardiac over-expressor mice as well as from multiple cell biology studies that demonstrate that heightened ADRB1 signaling is cytopathic to cardiac myocytes (15).

Thus, natural history and biological plausibility data do not consistently support an effect of the ADRB1 Arg389Gly polymorphism on clinical HF outcomes. However, larger prospective studies with relatively long follow-up periods are needed before reaching firm conclusions.

The Cincinnati/Pennsylvania Universities study produced a very interesting result in patients who were not treated with β-blockers; for the GRK5 Gln41Leu polymorphism, AA patients (but not EA patients or the entire EA plus AA cohort) had improved transplantation-free survival (Online Table 4, Figure 2 L-panels) in 41Leu genotypes compared with 41Gln homozygotes (Online Ref. 7). The 41Leu variant of GRK5 is a gain-of-function polymorphism whose protein product increases β-adrenergic receptor phosphorylation, which produces receptor desensitization and a genetic antiadrenergic effect (26, Online Ref. 7). The approximately 10-fold higher prevalence of GRK5 41Leu genotypes in AA patients than in EA patients may therefore provide a significant amount of “endogenous β-blockade” (26, Online Ref. 7), with the effect detectable in patients not treated with β-blocking agents.

Online Table 4 also gives BEST placebo-treated patient data for adrenergic receptor polymorphisms listed in Online Tables 1 and 2. For the combined EA plus AA cohort, based on the specified statistical analysis plan, there were no differences between major allele homozygotes and MAF carriers for the ADRB1 Ser49Gly, ADRB2, or ADRA2C Ins322–325Del polymorphisms, for either ACM or ACM/HFH endpoints.

In addition to pump dysfunction, the other major clinical component of HF disease progression is the development of serious arrhythmias. The SCN5A 1103Tyr variant of the Nav1.5 sodium channel is found in 6% to 9% of AA individuals but is extremely rare in EA subjects (Online Table 1, Online Refs. 29,30), and it has been associated with a 4-fold increase in implantable cardioverter defibrillator (ICD) discharges for sustained ventricular arrhythmias in AA HF patients (Online Ref. 30). The SCN5A Ser1103Tyr polymorphism clearly has the potential to influence HF progression disproportionately in AA compared with EA populations.

![Figure 2](image-url)
GENETIC VARIATION AND HF THERAPY: INTERACTION OF RACE, SIGNALLING POLYMORPHISMS, AND THERAPEUTIC RESPONSES

There is considerable evidence that several of the polymorphisms in Online Table 1 exert an influence on drug or device therapeutic response. Online Table 5 summarizes pharmacogenetic effects on HF clinical, left ventricular remodeling, or biomarker endpoints that have been reported for some of these polymorphisms, independent of race. Many of the studies referred to in Online Table 5 were underpowered, but some (Online Refs. 2,3,7,34) had adequate sample sizes. In most cases, the results are reinforced by biological plausibility, and in some instances, there are large differences in functional activity between the polymorphic variants that could influence therapeutic phenotype (26, Online Refs. 2,3,6,12,34).

Online Table 6 gives some of the evidence for racial effects on specific HF therapeutic responses that may be influenced by the products of genes listed in Online Table 1. Because HF clinical response racial data are limited in several circumstances, antihypertensive response is included for some drug classes. Decreased effectiveness in AA HF patient populations has been reported for 3 drug classes: standard β-blockers (27, Online Ref. 7); the β-blocker/sympatholytic agent bucindolol (Online Ref. 4); and angiotensin-converting enzyme inhibitors (ACEI) (Online Refs. 42,43). Blunted antihypertensive responses to β-blockers and ACEI have also been reported in AA patients (Online Table 6). In contrast, the response to fixed-dose hydralazine/isosorbide dinitrate appears to be enhanced in AA HF patients (Online Ref. 42), and ICD therapy appears to be more effective in a genetically defined subset of AA HF patients (Online Ref. 30).

There is clearly the potential for some of the polymorphisms listed in Online Tables 1 and 2 to account for the Online Table 6 racial effects, which is given in the last column of Online Table 2. The estimates follow the general paradigm that increased cardiac myocyte neurohormonal signaling is harmful, decreased signaling is beneficial, and the predicted therapeutic effect of an inhibitor is directly related to the degree of signaling. Most of the pharmacogenetic interactions are assigned to the possible (some clinical evidence in support) or predicted (no clinical data in support) category. Some of the polymorphisms listed in Online Table 2 that have pharmacogenetic-race interactions supported by clinical outcome data will now be discussed by therapeutic class.

β-BLOCKERS, INCLUDING THE β-BLOCKER/SYMPATHOLYTIC BUCINDOLOL. ADRB1 Arg389Gly, Ser49Gly.

The higher-functioning 389Arg allele of ADRB1 present at lower frequency in AA patients (Online Tables 1 and 2) was originally hypothesized to confer a greater therapeutic HF response to β-blockers (Online Table 2, Online Ref. 3). However, thus far for clinical outcomes, this seems to be the case only for the β-blocker/sympatholytic agent bucindolol (Online Refs. 3,34), an experimental compound in the development for HF and prevention of atrial fibrillation. In clinical trials with clinical endpoints, at recommended target doses, there is no evidence of a differential ADRB1 Arg389Gly clinical therapeutic effect for standard HF-approved β-blockers (38, Online Refs. 6,7). However, there is evidence that β389Arg homozygotes require higher, close-to-target doses to obtain maximal effects (8). Standard HF-approved β-blockers such as metoprolol succinate or carvedilol are devoid of β389Arg adrenergic receptor inverse agonist effects in isolated preparations of a failing human heart (Online Ref. 3) and also lack systemic sympatholytic properties in HF patients. Both properties likely contribute to a favorable therapeutic effect of bucindolol on the ADRB1 389Arg "norepinephrine receptor" (Online Ref. 34). Thus, the ADRB1 Arg389Gly polymorphism could explain the reduced response to bucindolol in BEST AA patients (Online Ref. 4) and the perhaps smaller racial interaction with carvedilol (Online Ref. 39) or metoprolol (Online Ref. 40). However, the Cincinnati/Pennsylvania Universities study (Online Ref. 7), which contained the largest cohort of β-blocker-treated AA HF patients studied to date, found reduced efficacy with carvedilol and metoprolol (Online Ref. 7). In addition, in a large (n = 1,094, 56% AA, 1,368 primary events) well-controlled health care system retrospective study evaluating the effects of all β-blockers marketed in the United States, the reduction in ACM or first re-HFH in AA HF patients, although statistically significant (p = 0.024 compared with the 20% of patients not treated with β-blockers), was 40% to 50% less than in EA patients (27).

Thus, the weight of the evidence favors a blunted effectiveness of β-blockers in AA compared with EA HF patients. Figures 3 and 4 address the question of whether a lower frequency of the favorable response ADRB1 389Arg homozygous (Arg389Arg) genotype alone explains the attenuated response of bucindolol in AA patients. Baseline characteristics for EA or AA patients in the BEST 1,040-patient adrenergic receptor polymorphism substudy (Online Refs. 2,3,34) are given in Online Table 3, and the differences are typical of other HF studies (Online Ref. 42). For the
primary ACM endpoint of BEST, as in the entire cohort (Online Ref. 4), there was a statistically significant ($p = 0.023$) test for interaction between non-AA and AA patients in the substudy population, with AA patients showing no evidence of a favorable treatment effect. Because there were relatively few ($n = 36$) ACM events in the 207-member AA subgroup, time to ACM/HFH was evaluated in Figure 3 for AA (84 events) and EA (310 events) patients in the substudy parent (all genotypes) population. The AA group has an attenuated hazard ratio (HR: 0.87, $p = 0.52$) compared with that of the EA group (HR: 0.70, $p = 0.002$), a pattern similar to the entire cohort (data not shown). In Figure 4 the treatment effects in the $ADRB1$ Arg389Arg genotype subgroup are enhanced in both racial groups, but attenuation relative to EA persists in AA patients (HR: 0.76 in AA [Figure 4C] vs. 0.57 in EA [Figure 4B]). However, when New York Heart Association (NYHA) functional class IV HF subjects, most of whom in BEST were volume overloaded at the time of randomization (30) and therefore did not meet heart failure guideline criteria for stability, were excluded, the AA HR improved further to 0.66 (Figure 4D), approaching the EA hazard ratio in the same patient population (HR: 0.58 [95% confidence interval: 0.41 to 0.82], data not shown). Using the relative effect size calculation (Online Appendix), compared with all genotypes (Figure 3C) the 32% of patients who were $ADRB1$ Arg389Arg (Figure 4C) had an approximately 2-fold increase in effect size, and then restriction to NYHA functional class III (Figure 4D) results in an approximately 3-fold increase compared with that in Figure 3C. These data suggest that differences in β-blocker/sympatholytic response exist between AA and EA patients beyond the 37% lower $ADRB1$ Arg389Arg genotype in AA but that additional strategies such as more precise clinical phenotyping (3) could be used to bring the AA therapeutic response in line with that of EA.

The 49Gly minor allele of $ADRB1$ (Figure 1A) has an approximately 70% higher MAF in AA than in EA patients (Online Table 1), and this would lead to a greater degree of cardiac myocyte $ADRB1$ receptor down-regulation in AA HF patients that could attenuate β-blocker treatment effects by reducing $ADRB1$ signaling (Online Table 2). There are conflicting reports of effects of the $ADRB1$ Ser49Gly polymorphism on β-blocker effect. A recent report found that open-label carvedilol-treated Brazilian AA patients who were 49Gly carriers had improved hospitalization-free survival compared with 49Ser homozygotes, whereas non-black patients treated with the same 25 mg of twice daily target dose showed no differences between genotypes (31). However, in a large, 75% EA HF patient population studied prospectively and treated with carvedilol or metoprolol, no effect of $ADRB1$ Ser49Gly was found, including no racial

![FIGURE 3 Time to All-Cause Mortality or First Heart Failure Hospitalization in the BEST Adrenergic Receptor Polymorphism Substudy](image)
interaction (28). In BEST, there was no effect of the ADRB1 Ser49Gly polymorphism on bucindolol compared with placebo treatment effects in either AA or EA patients, with respective interaction p values for treatment x genotype of 0.23 and 0.74 for ACM/HFH events. In addition, the possible enhanced effects of \(\beta\)-blockers in ADRB1 49Gly genotypes (31,32) are not supported by biological plausibility, which would predict an attenuated effect (Online Table 2), at least in placebo-controlled studies.

**GRK5 Gln41Leu.** The other good candidate for racial-genetic interaction to \(\beta\)-blocker therapy is the GRK5 Gln41Leu polymorphism investigated in the large (n = 711 AA HF patients; n = 1,749 EA HF patients) Cincinnati/Pennsylvania Universities observational study (Online Ref. 7). Similar to bucindolol in BEST (Figure 3) (Online Ref. 4), carvedilol or metoprolol exhibited no evidence of a beneficial treatment effect in the all-genotype AA population. In AA patients with the GRK5 41Leu genotype who were not treated with \(\beta\)-blocking agents, transplantation-free survival from the time of HF diagnosis was better (age/sex-adjusted hazard ratio: 0.325, \(p = 0.019\)) (Figure 2) than in 41Gln homozygotes. However, in the \(\beta\)-blocker-treated cohort, AA patients with the 41Leu genotype did equally well compared with 41Gln homozygotes, whereas EA patients with the 41Leu genotype (limited by only 10 events) might have fared worse than their Gln homozygous counterparts (\(p = 0.019\) in an unadjusted model) (Figure 2, upper right panel). These data were interpreted as the GRK5 41Leu polymorphism conferring endogenous \(\beta\)-blockade preferentially in AA patients by virtue of their approximately 10-fold higher prevalence for 41Leu genotypes (Online Ref. 7), which then obviated potentially favorable effects of \(\beta\)-blockade.

**ADRB2 Gln27Glu.** This polymorphism is shown in Figure 1B. Two studies have reported that the minor allele of ADRB2 Gln27Glu predicts a positive reverse remodeling response to the \(\beta_1/\beta_2/\alpha_1\) receptor blocker carvedilol: 27Glu carriers in one (Online Ref. 31) and Glu homozygotes (Online Ref. 32) in the other. The ADRB2 27Glu variant is resistant to agonist-induced receptor down-regulation and actually up-regulates in response to agonist exposure (33), which may make the human \(\beta_2\) adrenergic receptor and its subsequent blockade more important in 27Glu genotypes. Although the ADRB2 genotype data relative to race and \(\beta\)-blocker response have not been reported, the allele frequency data in Online Tables 1 and 2 would predict that AA patients may be at a possible disadvantage when treated with nonselective \(\beta\)-blockers (Online Table 2), due to their lower ADRB2 27Glu allele frequency.

**ADRA2C Ins322-325Del.** In HF patients, the ADRA2C Ins322-325Del polymorphism affects the cardiac sympatholytic response to bucindolol (Online Ref. 2), which is a secondary pharmacodynamic property of this nonselective \(\beta\)-blocker (34). The ADRA2C receptor is located prejunctionally on cardiac adrenergic neurons, where it provides tonic inhibition to norepinephrine release, and a 4-amino acid deletion in the third intracytoplasmic loop at positions 322 to 325, completely abolishes functionality (Online Ref. 12). In patients with advanced HF and elevated adrenergic activity, the ADRA2C Ins322-325Del polymorphism does not appreciably affect circulating norepinephrine levels but influences bucindolol’s sympatholytic effects (Online Ref. 2). The norepinephrine-lowering effects of bucindolol and potentially other sympatholytic agents are markedly enhanced in HF patients with 322-325Del genotypes (Online Ref. 2) (Figure 5).

Similar to the GRK5 41Leu genotype, in AA subjects, the 322-325Del or minor allele genotypes are present at a 10-fold higher frequency than in EA subjects (Online Tables 1 and 2 [Online Refs. 2,11,12]). In advanced HF, marked sympatholysis can be

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**FIGURE 4 Time to All-Cause Mortality or First Heart Failure Hospitalization in the BEST Adrenergic Receptor Polymorphism Substudy ADRB1 Arg389Arg Cohort**

(A) European ancestry (EA) and African ancestry (AA) New York Heart Association functional class III and IV patients; (B) EA patients class III and IV; (C) AA patients class III and IV; (D) AA patients class III only. Cox modeling was unadjusted. Abbreviations as in Figure 3.
associated with increased cardiovascular adverse events due to adrenergic support being reduced to levels below those required to support the failing heart (34 [Online Ref. 2]). Because of their markedly higher ADRAC2 322-325Del frequency, AA patients treated with bucindolol are potentially more prone to this type of adverse event, manifested as increased mortality from sudden death or precipitation of HFH (34).

Figure 5 shows that a large effect on bucindolol-associated systemic norepinephrine lowering is conferred by ADRAC2 322-325 genotypes and that the effect is present in both EA and AA patients. However, the clinical impact would be much greater in the EA population because of the ~10-fold higher frequency of ADRAC2 322-325Del genotypes. The exaggerated sympatholysis in ADRAC2 322-325Del genotypes in advanced HF patients is associated with a loss in favorable effects of bucindolol on mortality (Online Ref. 2) (Figure 5), which is especially pronounced in the presence of the ADRB1 389Gly genotype and is not evident in patients who are ADRB1 Arg389Arg carriers because the higher functioning ADRB1 389Arg receptor can compensate for low norepinephrine levels (Online Ref. 34). Data presented in Figure 5 underscore how gene variant differences in allele frequency may impact drug response (2) and how a second gene variant’s pharmacologic effects can act combinatorially to impact outcomes (Online Ref. 34).

Standard HF β-blockers devoid of sympatholytic activity such as carvedilol or metoprolol do not have potential for adverse interactions with ADRAC2 322-325Del genotypes, which was borne out in a large clinical trial (28).

**EDN1 Lys198Asn, ECE1 Thr341Ile.** In the non-ischemic cardiomyopathy subgroup of the BEST DNA bank population, 9 polymorphisms in 6 genes within the endothelin system were measured and tested against the outcome of ACM or HFH (Online Ref. 28). A haplotype including an exon 5, non-synonymous SNP correlated with elevated endothelin-1 levels, EDN1 Lys198Asn, was highly related to the outcome in the bucindolol group, with the minor allele associated with an adverse treatment effect (Online Ref. 28). The finding appeared to be independent of any ADRB1 effects, but the data were generated in only 30% of the total number of DNA substudy patients. Because the EDN1 Lys198Asn allele frequencies do not differ by race (Online Table 1), differential effects in AA versus EA patients would not be expected. However, another endothelin system polymorphism, ECE1 Thr341Ile, does exhibit substantial racial differences, with an approximately 10-fold higher MAF in AA patients (Online Tables 1 and 2). Both the ACE Del/Ins association with standard β-blocker responses (Online Ref. 33) and the EDN1 Lys198Asn or ECE1 Thr341Ile pharmacogenetic interactions with bucindolol are likely examples of indirect (from the primary target(s)) pharmacogenetic interactions, based on inhibitory effects of β-blockers on the renin-angiotensin system and cross-regulation of the endothelin and β-adrenergic systems.

**HYDRAZINE/ISOSORBIDE DINITRATE AND NOS3 GLU298ASP, CYP11B2 T-344C, OR GNB3 C825T.** In a 354-patient DNA bank substudy of the A-HeFT (African-American Heart Failure Trial [35]), McNamara et al. (Online Ref. 16) published data indicating that polymorphisms in the endothelial nitric oxide synthase (NOS3), aldosterone synthase (CYP11B2 [Online Ref. 18]), and guanine nucleotide β subunit (GNB3 [Online Ref. 14]) genes influenced the response to fixed-dose hydralazine/isosorbide dinitrate (BiDil; Arbor Pharmaceuticals, Atlanta, Georgia) in AA patients. The more favorable response genotypes are the major allele homozygotes in NOS3 and CYP11B2 and the minor allele homozygote in GNB3 that is the major allele in AA populations (Online Tables 1 and 2). In each case, the favorable response genotype is present at a higher frequency in AA compared to EA.
populations, and there is evidence that hydralazine/isosorbide dinitrate is more effective in AA than in EA patients (Online Ref. 42). The biological/pharmacological plausibility for the pharmacogenetic interactions of hydralazine/isosorbide dinitrate are not as obvious as for β-blockers, as the modulating polymorphisms are more remote from (Online Refs. 14,16) or even unrelated to (Online Ref. 18) the drug target. Although the A-HeFT DNA/pharmacogenetic substudy was relatively small, these data are highly intriguing and suggest that for at least one type/class of HF therapy, AA patients are at a pharmacogenetic advantage. However, because there are no comparable EA data, these findings are classified as possible in Online Table 2.

ACEIS, ARBS, OR MRAS AND POLYMORPHISMS IN THE RAAS. The RAAS is of undeniable importance in the natural history of myocardial remodeling and HF, and inhibitors of ACEI formation, angiotensin AT-1 receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) all produce substantial favorable effects on HF natural history. With the exception of AGT Thr174Met, all the RAAS polymorphisms listed in Online Table 1 have been associated with effects on cognate gene expression or hormone levels (36–40 [Online Refs. 22,26]), and AGT Thr174Met has been associated with hypertension (Online Ref. 26). The AGTR1 I1166T and the 2 AGT polymorphisms exhibit racial differences in allele frequencies, whereas ACE Del/introm16/Ins and NR3C2 Ile180Val do not. However, in racially unselected HF populations, relatively few (Online Refs. 33,35,36) of these gene variants have been shown to be associated with differential responses to RAAS inhibitors, and there are no data to support a racial-genetic interaction for drug response despite evidence that efficacy may be blunted in AA HF populations (Online Refs. 42,43).

DEVICE THERAPIES AND SIGNALING POLYMORPHISMS. Improvement in left ventricular chamber function by synchronizing contraction with biventricular pacing may be accompanied by decreases in neurohormonal biomarkers, so polymorphic variation in signaling mechanisms could affect cardiac resynchronization therapy (CRT) responses. There are 2 polymorphisms, ADRB2 Gln27Glu (Online Ref. 37) and NR3C2 Ile180Val (Online Ref. 19), whose minor allele genotypes have been reported to be associated with a CRT reverse remodeling response (Online Table 5), but there are no reports relating these variants to race. CRT responses by racial subgroups have been reported from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study (Online Ref. 47) in the absence of any genetic information, where no differences in effectiveness were observed (Online Table 6).

The other device that has proved to be invaluable in HF therapy is the ICD. AA patients may have a disproportionately higher rate of ventricular arrhythmias and sudden cardiac death than EA HF patients (41), which is likely due in part to genetic factors. The nearly exclusive presence in AAs of the Ser1103Tyr variant of SCN5A (Online Tables 1 and 2), the gene that encodes the α subunit of the human Nav1.5 sodium channel and plays a central role in cardiac conduction and repolarization as well as in regulation of [Ca2+], through downstream effects on Na+–Ca2+ exchange (which is also under β-adrenergic regulation), is especially intriguing. It has been proposed that the metabolic abnormalities and cellular derangements accompanying HF may serve as proarrhythmic substrates for 1103Tyr minor allele carriers, and the variant has been shown to increase the “late” or sustained Na+ current under certain conditions (42). The SCN5A 1103Tyr variant is associated with a 4-fold increase in sustained ventricular arrhythmias in HF patients with ICDs (Online Ref. 30), essentially making ICDs more clinically effective (more lives saved from sudden cardiac death) in AA patients with an SCN5A 1103Tyr genotype (Online Tables 5 and 6) (Online Ref. 30).

CONCLUSIONS

Due to population genetics, AA patients exhibit substantial differences in frequencies of functionally important alleles that code for important constituents of neurohormonal cell-signaling pathways compared with EA HF. For at least 2 polymorphisms, Gln41Leu and SCN5A Ser103Tyr, these may differentially affect the progression of HF in AA compared with that in EA patients. Importantly, the effectiveness or safety of several drugs and a device may be influenced by AA compared with EA self-identified race, and it is likely that genetic variation in signaling pathways that are important in HF contribute to this therapeutic heterogeneity. Compared with EA, AA race can be associated with allele frequency-based genetic profiles that: 1) can lead to therapeutic response attenuation (standard β-blockers and the experimental β-blocker/sympatholytic bucindolol); 2) possibly decrease therapeutic response (ACEIs and ARBs); 3) enhance effectiveness (fixed-dose hydralazine/isosorbide dinitrate); or 4) increase event rate, making the therapy more clinically effective (e.g., ICDs). In order to better
understand the basis for heterogeneous therapeutic responses, race, pharmacogenetics, and their interaction need to be considered in the development of drugs and devices for the treatment of HF. As demonstrated, identifying genetic subgroups with an enhanced response is a key to delivering optimal therapies for racial cohorts, regardless of the net effect of the therapeutic agent in the parent population and frequency of the preferred genotype.

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APPENDIX For a supplemental Methods section as well as tables and references, please see the online version of this article.