Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 54, No. 5, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.05.009

Clinical and Genetic Modifiers of Long-Term Survival in Heart Failure

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Objectives This study sought to identify genetic modifiers of β-blocker response and long-term survival in heart failure (HF).

Background Differences in β-blocker treatment effect between Caucasians and African Americans with HF have been reported.

Methods This was a prospective cohort study of 2,460 patients (711 African American, 1,749 Caucasian) enrolled between 1999 and 2007; 2,039 patients (81.7%) were treated with a β-blocker. Each was genotyped for β1-adrenergic receptor (*ADRB1*) Arg389>Gly and G-protein receptor kinase 5 (*GRK5*) Gln41>Leu polymorphisms, which are more prevalent among African Americans than Caucasians. The primary end point was survival time from HF onset.

Results There were 765 deaths during follow-up (median 46 months). β-blocker treatment increased survival in Caucasians (log-rank p = 0.00038) but not African Americans (log-rank p = 0.327). Among patients not taking β-blockers, *ADRB1* Gly389 was associated with decreased survival in Caucasians (hazard ratio [HR]: 1.98, 95% confidence interval [CI]: 1.1 to 3.7, p = 0.03) whereas *GRK5* Leu41 was associated with improved survival in African Americans (HR: 0.325, CI: 0.133 to 0.796, p = 0.01). African Americans with *ADRB1* Gly389Gly *GRK5* Gln41Gln derived a similar survival benefit from β-blocker therapy (HR: 0.385, 95% CI: 0.182 to 0.813, p = 0.012) as Caucasians with the same genotype (HR: 0.529, 95% CI: 0.326 to 0.858, p = 0.0098).

Conclusions These data show that differences caused by β-adrenergic receptor signaling pathway gene polymorphisms, rather than race, are the major factors contributing to apparent differences in the β-blocker treatment effect between Caucasians and African Americans; proper evaluation of treatment response should account for genetic variance. (J Am Coll Cardiol 2009;54:432–44) © 2009 by the American College of Cardiology Foundation

Heart failure (HF) affects approximately 5 million Americans, with over one-half million new cases diagnosed every year (1). Abnormalities of cardiac β-adrenergic signaling that contribute to the pathophysiology of HF include increased circulating epinephrine levels and down-regulation or functional uncoupling of cardiotoxic β1-adrenergic receptors (2,3). Accordingly, β-blockers, which antagonize catecholamine-stimulated β-adrenergic receptor signaling in the heart and elsewhere, represent one of the most important nonsurgical therapeutic options for this disease, reducing morbidity and mortality (4,5). There is a class I indication for β-blocker treatment in HF (6). However, individual responses to β-blocker treatment vary widely, and there is a need to identify nonresponders within the broader clinical group that shows aggregate benefit as well as to predict responders within groups in which treatment effects are less clear.

Variability in HF risk and clinical course is objectively revealed by population surveys and prospective clinical trials that have identified ethnic differences in disease incidence, progression, and response to specific therapies (7–9). Ac-

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Manuscript received March 31, 2009; revised manuscript received May 11, 2009, accepted May 14, 2009.

cordingly, the American College of Cardiology/American Heart Association guidelines for evaluation and management of HF in the adult concluded that "heart failure progresses more rapidly in black than white patients" (6). The mechanisms responsible for these types of differences have not been clearly identified, and undoubtedly include social influences, access to care, and the quality of care (10). Individual genetic factors may also play a role (11). Evidence is accumulating in support of specific genetic loci that contribute to the overrepresentation of other complex diseases, such as hypertension and type 2 diabetes mellitus, in individuals of African heritage (12–16). A genetic or pharmacogenomic basis for differences in drug effect between individuals of African and European descent also has been proposed (17), supported by associations between variable drug clearance and functionally significant polymorphisms of genes encoding enzymes important for drug metabolism, cytochrome P450 (*CYPB6*), and N-acetyltransferase (*NAT2*) (18–20). Thus, ethnically diverse populations show differences in drug response that may, in part, be caused by variations within genes essential to the drug effect.

In evaluating the potential for genetic variation to influence HF outcome, it is notable that functional polymorphisms are common in the genes encoding the β-blocker target, β-adrenergic receptors (*ADRB1* and *ADRB2*), and a gene that critically regulates β-adrenergic receptor signaling, G-protein receptor kinase 5 (*GRK5*) (21,22). Previous pharmacogenomic studies have proposed that the *ADRB1* Arg389>Gly (23) and *GRK5* Gln41>Leu (22) polymorphisms, both of which are over-represented in African Americans, may play roles in determining individual clinical responses to β-blockade in HF. The biological mechanisms for the effects of both alleles were established by expressing recombinant polymorphic proteins in cultured cells and in transgenic mice (22,24). However, studies of their impact on HF outcome in different ethnic groups, and comparisons of these 2 putative genetic risk factors with standard clinical risk factors for HF progression, have not been performed. Herein we report the results of a prospective longitudinal study examining the impact of *ADRB1* and *GRK5* genotype on β-blocker modulation of long-term outcome in subjects with systolic HF who presented to the specialized HF/heart transplant programs of 2 major U.S. urban medical centers.

Methods

Study subjects. Subjects presenting to the HF referral programs at the University of Cincinnati or the University of Pennsylvania were prospectively recruited into 1 of 2 noninterventional longitudinal genomics studies of HF funded by the National Heart, Lung, and Blood Institute (NHLBI) (P50 HL77101 and R01 HL88577). African American inclusion at >25% of the total cohort was part of the study design approved by NHLBI, and subgroup analysis of outcomes in Caucasians and African Americans was pre-specified. Human study protocols were approved by institutional review boards of the University of Cincinnati and the University of Pennsylvania. All subjects provided written informed consent. Enrollment criteria were age between 18 and 80 years and documented systolic HF with a left ventricular ejection fraction of <40%. The study recruited 2,460 HF patients, of which 711 (29%) were African American; 1,783 subjects (1,164 Caucasian Americans and 619 African Americans) were enrolled between 2000 and 2007 in Cincinnati, and 677 subjects (585 Caucasian Americans and 92 African Americans) were enrolled in Philadelphia between 2003 and 2005. The cohorts were combined to provide a sufficient number of African Americans to power an analysis of racial subgroups. Racial classification was self-reported. The study end points were death or cardiac transplantation. Median follow-up was 46.3 months. Use of β-blocker was determined by the subjects' physicians (66% carvedilol, 24% metoprolol, 10% other β-blockers) and defined as continuous therapy for at least 6 months. Medication usage was confirmed at hospital clinic visits by personal interview. Follow-up data for each study subject were obtained at least yearly, either by personal interview, by mail, or by telephone conversation.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CI = confidence interval
HF = heart failure
HR = hazard ratio
NHLBI = National Heart, Lung, and Blood Institute
PCR = polymerase chain reaction

Genotyping. Genomic deoxyribonucleic acid (DNA) for genotyping was isolated and extracted using the Gentra Puregene genomic DNA purification kit (Qiagen, Valencia, California). The DNA segments containing the region of interest were amplified with the polymerase chain reaction (PCR). The PCR primers were designed using Primer3 online software (25), and pyrosequencing primers were designed using the Pyrosequencing SNP Primer Design version 1.01 software (Biotage AB, Uppsala, Sweden). Before use, PCR primer sequences were screened across the human genome using the National Center for Biotechnology Information Blast program to ensure their specificity for the gene of interest. The PCR and pyrosequencing were performed as previously described (26). Primers and conditions are listed in the Online Table. The *GRK5* Gln41Leu genotyping was performed by pyrosequencing (University of Cincinnati cohort) or using a Sequenome MassArray platform (Sequenome, San Diego, California) (University of Pennsylvania cohort) with conservative genotype calls in 99.8% of samples. The *ADRB1* Arg389Gly genotyping was performed using Assays-on-Demand (Applied Biosystems, Foster City, California) assay number C_8898494_10 according to the manufacturer's directions.

Statistical analysis. Student *t* tests and chi-square tests were used to assess significant differences in variables between ethnic groups and between genotype classes within ethnic groups. The Hardy-Weinberg equilibrium was assessed in each ethnic group separately. The primary out-

come was time to transplantation or all-cause mortality through 350 months. Differences in time from diagnosis to end point were assessed using Kaplan-Meier curves and log-rank tests (27). Relative risks were obtained by Cox proportional hazards modeling using an additive genetic model after adjustment for age at diagnosis and sex. All analyses were carried out using the R Statistical Language (28). An alpha level of 0.05 was used to designate significance.

Results

Clinical characteristics of the study population. Clinical characteristics of the HF study cohort, grouped by race, are shown in Table 1. The 2 racial groups were well matched in terms of age, height and weight, sex, and severity of left ventricular dysfunction. As has been noted previously (29,30), hypertension, renal dysfunction, and cerebrovascular events are more common among African Americans with HF, but in this cohort, diabetes was only slightly more prevalent. Coronary artery disease and ischemic cardiomyopathy were more common in Caucasians with HF. As might be expected at tertiary referral centers specializing in HF, pharmacological treatment of HF was similar between the 2 ethnic groups, with ~80% to 85% of subjects receiving a β-blocker (approximately two-thirds treated with carvedilol, one-fourth with metoprolol, and 10% another agent), ~75% to 80% receiving an angiotensin-converting enzyme (ACE) inhibitor, ~22% receiving an angiotensin receptor blocker, and slightly more than 30% receiving an aldosterone antagonist. (Fewer than 50 subjects in each group were treated with hydralazine/isosorbide dinitrate.) Similar proportions of both ethnic groups received automatic implanted defibrillators (24% to 29%). However, only one-half as many (~7%) African Americans underwent cardiac transplantation (averaging 74.7 months after diagnosis) as did Caucasians (~15%; averaging 67.3 months after diagnosis). Average survival time from first objective HF diagnosis was 79.9 ± 78.1 months (mean ± SD) for Caucasians, compared with 69.8 ± 68.6 months for African Americans ($p = 0.17$). Together, these data demonstrate that this population of HF study subjects recruited from the comprehensive HF/heart transplantation programs of 2 metropolitan medical schools has similar clinical characteristics and ethnic differences as observed in previous large HF trials (1,6,9,29).

The impact of standard clinical risk factors on HF survival in the study cohort is shown in Table 2. All of the analyses presented in Table 2 are univariate Cox proportional hazards models. Among Caucasians, increasing age, hypertension, coronary artery disease, and diabetes each

Table 1 Clinical Characteristics of the Heart Failure Study Population

	Combined		Caucasian American		African American	
Variable	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age at enrollment (yrs)	2,440	53.4 (14.1)	1,698	54.4 (14.0)	702	51.4 (14.1)
Height (inches)	2,498	67.6 (4.2)	1,746	67.8 (4.2)	710	67.2 (4.3)
Weight (lbs)	2,498	193.3 (50.7)	1,746	191.8 (48.7)	710	197.7 (55.6)
Ejection fraction (%)	1,911	31.2 (15.3)	1,545	31.4 (15.4)	335	30.8 (14.7)
Follow-up time (months)	2,421	67.6 (70.4)	1,682	70.9 (75.3)	699	60.5 (57.0)
		%		%		%
Heart failure etiology						
Ischemic	1,216	48.80	894	51.30	304	43.10
Nonischemic	1,275	51.20	849	48.70	402	56.90
Female	896	35.80	555	31.70	323	45.40
Diabetes	870	35.00	585	33.40	272	38.40
Hypertension	1,591	63.90	998	56.80	591	83.60
Coronary disease	1,312	58.40	924	60.00	372	54.80
Cerebrovascular event	260	12.10	150	10.30	106	15.90
Dyslipidemia	1,269	52.00	907	52.80	354	50.90
Renal insufficiency	592	25.90	355	22.50	233	34.10
β-blocker use	2,039	81.70	1,392	79.80	611	86.20
Carvedilol	1,348	66.00	926	66.50	396	64.60
Metoprolol	488	23.90	327	23.50	154	25.10
Other	206	10.10	140	10.10	63	10.30
ACE inhibitor use	1,896	76.30	1,302	74.40	572	80.90
ARB use	467	21.60	313	21.20	146	22.10
Aldosterone antagonist use	708	32.20	490	32.40	206	31.10
Statin use	1,216	57.80	890	59.30	311	53.80
AICD	628	27.90	461	29.30	157	24.00
Transplanted	330	13.20	273	15.40	49	6.90

ACE = angiotensin-converting enzyme; AICD = automatic implantable cardioverter-defibrillator; ARB = angiotensin receptor blocker.

Table 2 Clinical Factors Affecting Heart Failure Survival

	Combined		Caucasian American		African American	
Variable	HR	p Value	HR	p Value	HR	p Value
Age at study entry	1.03	<0.0001	1.03	<0.0001	1.03	2.8E-9
Female	0.783	0.019	0.812	0.12	0.623	0.007
Diabetes	1.95	6.9E-12	2.19	3.9E-11	1.27	0.17
Hypertension	2.53	<0.0001	2.35	9.1E-12	2.09	0.0034
Coronary disease	1.69	4.2E-6	1.93	9.6E-6	1.42	0.055
Ejection fraction <25%	0.85	0.11	0.98	0.87	0.634	0.03

HR = hazard ratio.

approximately doubled the mortality risk, whereas among the smaller African-American cohort, only age and hypertension achieved significance as risk factors for increased mortality, although the clear trend was for all 3 clinical factors to decrease survival. Male sex was a significant risk factor among African Americans, but not Caucasians. In contrast, the relationship between left ventricular ejection fraction at presentation and long-term clinical outcome was not consistent, as previously observed (29). The Cox proportional hazards models presented in the following sections are adjusted for age at HF onset and sex. Although other clinical factors were significantly associated with survival univariately, including age and sex in the Cox proportional hazards model greatly reduced or eliminated the significance of these variables' relationship with survival.

β-blocker treatment effects on mortality in HF. The group mean benefit of β-blocker treatment in HF is not disputable (6). However, results of individual studies have varied, particularly regarding the effects of β-blocker treatment in African Americans (31,32). Factors that may have contributed to differing results include underrepresentation of African Americans in some trials (33), different effects of β-blockers with unique pharmacological characteristics (32), and real mechanistic differences in the magnitude of treatment effect between ethnic groups, as has been reported with ACE inhibitors versus other vasodilator therapy (34,35). To determine whether there were differences in apparent β-blocker treatment effect between Caucasians and African Americans within our study population, we examined mortality as a function of β-blocker treatment status in the overall HF cohort, and then separately in Caucasians and African Americans. A summary of the clinical characteristics stratified by β-blocker and race ethnicity is given in Table 3. In the combined cohort, β-blocker treatment significantly increased survival time (β-blocker–untreated n = 455, β-blocker–treated n = 2,038, log-rank p = 0.00074) (Fig. 1A) and reduced mortality risk (age- and sex-adjusted hazard ratio [HR]: 0.71, 95% confidence interval [CI]: 0.566 to 0.887, p = 0.003). The effects of metoprolol and carvedilol seemed similar (not shown). When the survival data were analyzed in the Caucasian subgroup, increased survival with β-blocker treatment (β-blocker–untreated n = 351, β-blocker–treated n = 1,391, log-rank p = 0.00038) (Fig. 1A, top inset) and reduced risk of death or transplant (age- and sex-adjusted HR: 0.679, 95% CI: 0.519 to 0.888, p = 0.005) were again statistically significant. However, a β-blocker treatment effect on survival was not as clear in the African American subgroup (β-blocker–untreated n = 98, β-blocker–treated n = 611, log-rank p = 0.327) (Fig. 1A, bottom inset), with a trend toward reduced risk (age- and sex-adjusted HR: 0.698, 95% CI: 0.453 to 1.08, p = 0.1). These data show that the HRs for β-blocker treatment effect on mortality between the 2 races are similar, but the effects did not achieve statistical significance in African Americans because the CIs are much broader, notwithstanding adequate numbers of subjects and experimental end points. Therefore, we further examined survival as a function of β-blocker treatment status in the 2 ethnic groups by comparing mortality within each treatment group. Survival times were not significantly different between Caucasians and African Americans in β-blocker–untreated subjects (Fig. 1B) (Caucasian n = 351, African American n = 98, 82.8 ± 69.3 months for African Americans vs. 71.0 ± 73.4 months for Caucasians, p = 0.46, log-rank p = 0.5213), whereas among subjects taking β-blockers, African Americans had shorter survival times than Caucasians (Fig. 1C) (Caucasian n = 1,391, African American n = 611, 66.8 ± 68.4 months in African Americans vs. 82.2 ± 79.5 months in Caucasians, p = 0.057, log-rank p = 0.0005). Thus, the mortality benefit from β-blockade seems greater in Caucasians than African Americans from these clinical populations.

***ADRB1* Gly389 in HF.** We considered that the broader confidence intervals for β-blocker treatment effect in African Americans might indicate a greater degree of interindividual variability in this subgroup, possibly as a consequence of genetic factors. We further noted that the only 2 functionally significant β-receptor pathway gene polymorphisms reported to affect the response to β-blocker therapy in HF are both over-represented in African Americans (23,36). The first reported such polymorphism substitutes Gly for Arg at position 389, within the signal transduction domain of the major cardiac β-blocker target, β1-adrenergic receptors (37). Therefore, we genotyped our cohort for this polymorphism and examined whether it was associated with a difference in β-blocker treatment effect. Allele frequencies of the minor *ADRB1* Gly389 allele were

Table 3 Characteristics of Heart Failure Subjects by β-Blocker Use

Variables	Caucasians		African American	
	β-Blocker Untreated (n = 351)	β-Blocker Treated (n = 1,391)	β-Blocker Untreated (n = 98)	β-Blocker Treated (n = 611)
Age at enrollment (yrs)	52.3	52.6	47.5	51.6
Height (inches)	67.8	67.9	67.2	67.0
Weight (lbs)	179.8	194.6	197.0	198.0
Ejection fraction (%)	32.0	31.1	32.2	30.6
Follow-up (months)	60.5	73.2	70.2	58.6
Heart failure etiology				
Ischemic	51.6	48.1	64.3*	56.1†
Nonischemic	48.4	51.9	35.7	43.9
Female	31.3	31.9	50.0*	44.7†
Diabetes	37.8	38.7	30.6	34.6
Hypertension	75.5	84.9	53.7*‡	57.1†
Coronary disease	42.1‡	56.8	54.2‡	61.4
Cerebrovascular event	9.6‡	17.0	15.4	9.2†
Dyslipidemia	38.1‡	53.1	43.6‡	55.3
Renal insufficiency	36.5‡	33.7	32.2	20.5†
ACE inhibitor use	65.3‡	83.4	63.3	77.4†
ARB use	18.5	22.7	20.9	21.5
Aldosterone antagonist use	21.3‡	32.7	24.3‡	34.0
Statin use	41.0‡	55.9	50.2‡	61.6†
AICD	8.1‡	26.5	22.4*‡	31.2†
Transplanted	18.4‡	5.1	39.3*‡	9.6†
Achieved end point	45.9‡	23.8	59.8*‡	25.3

Values are % unless otherwise indicated. *$p < 0.05$ versus β–blocker–untreated Caucasians. †$p < 0.05$ versus β–blocker–treated Caucasians. ‡$p < 0.05$ versus β–blocker–treated subjects of the same race.
Abbreviations as in Table 1.

0.298 in Caucasians and 0.392 in African Americans. Genotypes were in Hardy-Weinberg equilibrium (African American p = 0.67; Caucasian American p = 0.98) and similar to the reported allele frequencies in normal subjects (Caucasians, 0.12 to 0.25 and African Americans, 0.23 to 0.38, respectively (21,36). Thus, as previously reported, this allelic variant is more common among African Americans than Caucasians, but its prevalence within racial subgroups is similar between HF subjects and nonaffected control subjects, supporting previous conclusions that this polymorphism does not, by itself, modify the risk of developing HF (38).

Functional allelic variants that are not independent risk factors for disease may nevertheless modify the course of that disease or its response to specific therapies. This may particularly apply to polymorphisms of β-receptor pathway genes in HF because hyperactivation of cardiac catecholaminergic signaling occurs early in the course of the disease. In our study cohort, there were no differences in the clinical characteristics of HF subjects stratified by *ADRB1* genotype (Table 4). Before adjusting for clinical risk modifiers, the *ADRB1* Gly389 polymorphism tended to be associated with decreased HF survival times in subjects not taking β-blockers when examined for the overall cohort (Arg389 homozygous n = 543, Gly389 carriers n = 597, log-rank p = 0.0587) (Fig. 2A), or separately for Caucasians (Arg389 homozygous n = 422, Gly389 carriers n = 369, log-rank p = 0.0436) (Fig. 2A, top inset), but not in African Americans (Arg389 homozygous n = 119, Gly389 carriers n = 223, log-rank p = 0.546) (Fig. 2A, bottom inset). After adjusting for age and sex, however, the Gly389 association with increase mortality risk in β-blocker–untreated subjects was clearly significant in the entire cohort (HR: 1.76, 95% CI: 1.09 to 2.85, p = 0.02) as well as in Caucasian Americans analyzed as a separate subgroup (HR: 1.98, 95% CI: 1.07 to 3.65, p = 0.03). (The number of African Americans not taking β-blockers and carrying the minor allele [n = 34] was insufficient to properly power this subgroup analysis.) These results suggest a modest benefit for being homozygous (wild-type) Arg389 among β-blocker–untreated subjects, as has previously been reported (39).

Among subjects treated with the β-blockers carvedilol or metoprolol (as were approximately 90% of the treated subjects in our study), there was no significant association between survival and *ADRB1* Arg389Gly genotype in the entire cohort (Arg389 homozygous n = 396, Gly389 carriers n = 463, log-rank p = 0.7974 [Fig. 2B], age- and sex-adjusted HR: 0.953, 95% CI: 0.736 to 1.24, p = 0.501), or when ethnic groups were analyzed separately (for Caucasian Americans: Arg389 homozygous n = 299, Gly389 carriers n = 271, log-rank p = 0.421 [Fig. 2B, top inset], adjusted HR: 0.884, 95% CI: 0.638 to 1.23, p = 0.46; for African Americans: Arg389 homozygous n = 96, Gly389 carriers n = 188, log-rank p = 0.3928 [Fig. 2B, bottom inset];

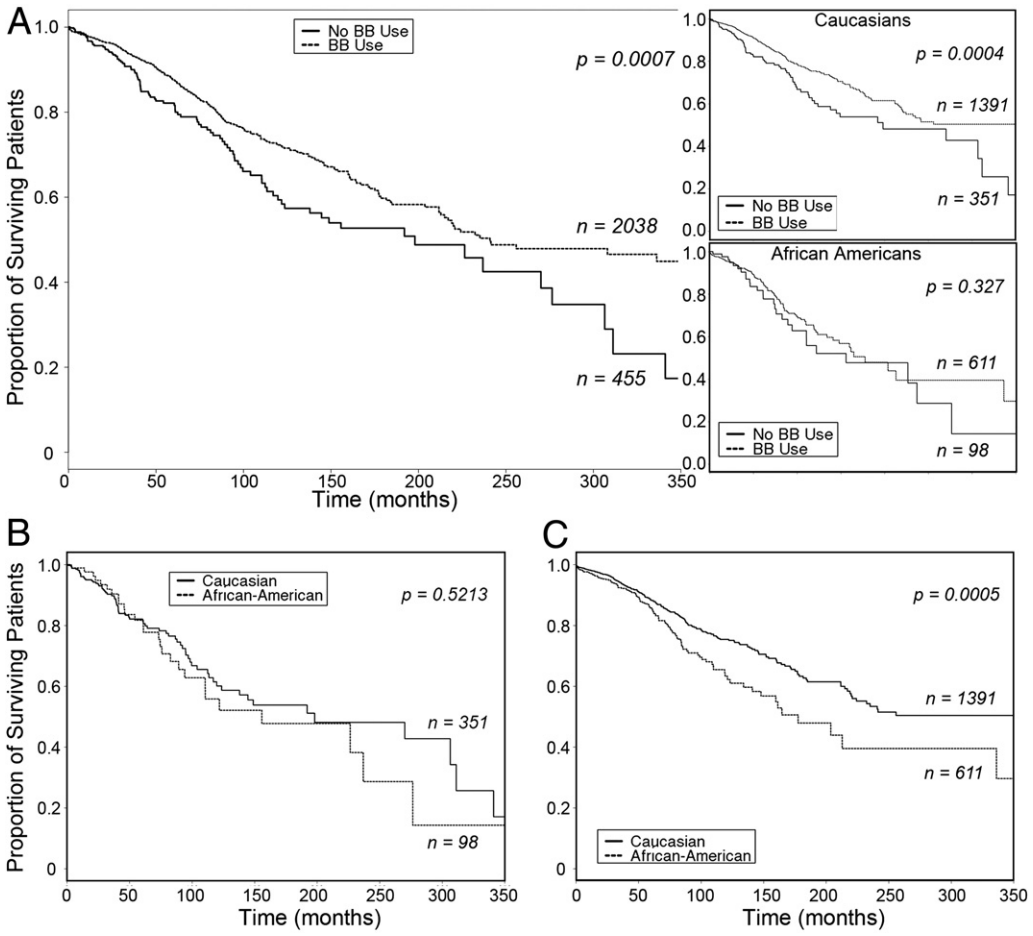

Figure 1 **Kaplan-Meier Curves of β-Blocker Treatment Effect on Heart Failure Survival**

(A) Combined heart failure cohort, stratified by β-blocker usage (**top inset**, Caucasian Americans; **bottom inset**, African Americans). **Solid line** = β-blocker–untreated; **dashed line** = β-blocker–treated. **(B)** Survival of β-blocker–untreated heart failure subjects, stratified by race. **(C)** Survival of β-blocker–treated heart failure subjects, stratified by race. **Solid line** = Caucasian; **dashed line** = African American.

adjusted HR: 0.813, 95% CI: 0.515 to 1.28, p = 0.37). These data suggest that the Arg389 *ADRB1* genotype does not predict a treatment effect for carvedilol or metoprolol.

***GRK5* Leu41 in HF.** The second adrenergic signaling polymorphism reported to affect the response to β-blocker therapy in HF substitutes Leu for Gln at position 41 of GRK5, one of the G-protein receptor kinases that desensitize cardiac β-adrenergic receptors (22,40). The GRK5 Leu41 variant shows greater desensitization than the more common wild-type GRK5 Gln41 (41). For this reason, we genotyped the HF cohort and examined whether possessing this polymorphism was associated with any difference in HF outcome or β-blocker treatment effect. Allele frequencies of the minor *GRK5* Leu41 allele were 0.017 for Caucasians and 0.231 for African Americans. Genotypes were in Hardy-Weinberg equilibrium (African American p = 0.63; Caucasians p = 0.39) and are similar to the reported allele distributions in normal subjects (0.013 and 0.23, respectively) (22). Except for slight differences in age at enrollment, there were no differences in the clinical characteristics between subjects homozygous for wild-type *GRK5* Leu41 polymorphism versus those carrying at least 1 polymorphic *GRK5* Gln41 allele (Table 4).

In an aggregate analysis of β-blocker–untreated subjects, there was no evidence for an effect of *GRK5* Leu41 genotype on HF survival (Gln41 homozygous n = 390, Leu41 carriers n = 47, log-rank p = 0.8211) (Fig. 3A) or for decreased mortality risk (age- and sex-adjusted HR for death: 0.755, 95% CI: 0.399 to 1.43, p = 0.39). When the data were analyzed according to ethnic group, we found only 3 subjects in the Caucasian subgroup that carried a Leu41 allele were not taking β-blockers, and achieved the mortality end point during the study period (Fig. 3A, top inset). Thus, we are underpowered for this analysis. Among β-blocker–untreated African Americans, however, in which nearly equal numbers of subjects carry a *GRK5* Leu41 allele versus are homozygous Gln41 wild-type, the presence of at least 1 *GRK5* Leu41 allele was associated with longer

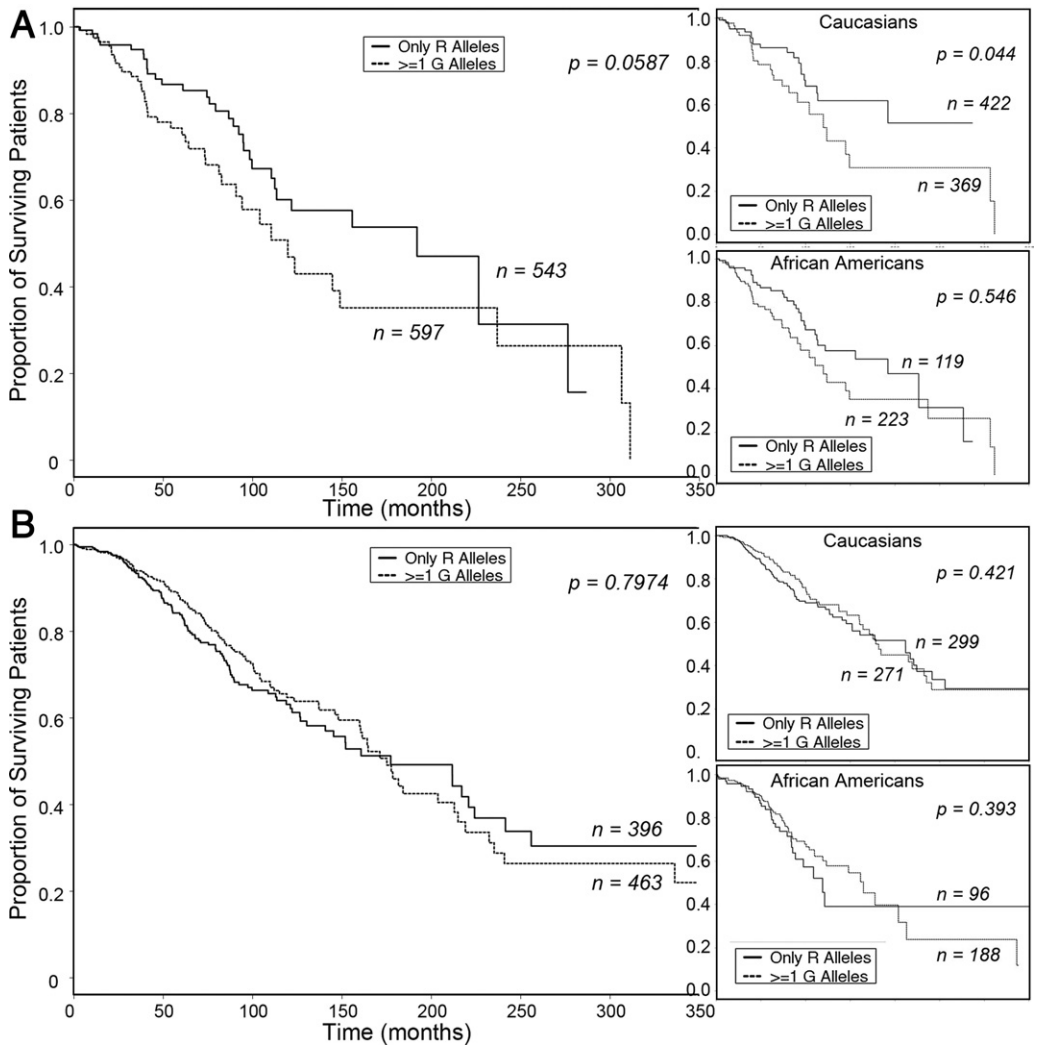

Figure 2 **Kaplan-Meier Curves of *ADRB1* Arg/Gly 389 Effect on Heart Failure Survival**

(A) β-blocker–untreated subjects stratified by *ADRB1* 389Gly carrier status (**top inset**, Caucasian Americans; **bottom inset**, African Americans). **(B)** β-blocker–treated subjects stratified by ADRB1 389Gly carrier status (**top inset**, Caucasian Americans; **bottom inset**, African Americans). **Solid line** = Arg/Arg 389; **dashed line** = Gly 389 carriers.

survival (Gln41 homozygous n = 56, Leu41 carriers n = 35, log-rank p = 0.0181) (Fig. 3A, bottom inset), and with a significant decrease in mortality risk after adjustment for age and sex (HR: 0.325, 95% CI: 0.133 to 0.796, p = 0.01).

Interestingly, when β-blocker–treated subjects within the cohort were analyzed as a whole for consequences of the GRK5 polymorphism, a significant detrimental effect of GRK5 Leu41 was detected (Gln41 homozygous n = 1,602, Leu41 carriers n = 272, log-rank p = 0.0052) (Fig. 3B). However, the apparent difference by genotype is actually attributable to the general difference in outcome observed between β-blocker–treated Caucasians and African Americans (compare Fig. 3B with Fig. 1C) because the Leu41 variant is 10 times more common among African Americans and there were only 10 Caucasian subjects that carried a Leu41 allele, were taking β-blockers, and reached the study end point (Fig. 3B, top inset). In contrast, among β-blocker treated African-American subjects (in whom there was roughly equal distribution of homozygous Gln41 wild-type vs. Leu41 carriers), there was no association between *GRK5* Gln41 polymorphism genotype and HF outcome (Gln41 homozygous n = 317, Leu41 carriers n = 227, log-rank p = 0.7166) (Fig. 3B, bottom inset).

HF risk profiling using clinical and genetic factors. Genotyping of our study cohort for 2 functional β-adrenergic receptor signaling polymorphisms showed 1 genotype, *ADRB1* Arg389, that is associated with significantly decreased mortality risk in β-blocker–untreated Caucasians, and another, *GRK5* Leu41, that is associated with decreased mortality risk in β-blocker–untreated African

Table 4 Characteristics of Heart Failure Subjects by *ADRB1* and *GRK5* Genotype

	ADRB1				*GRK5*			
	Caucasian		African American		Caucasian		African American	
Variable	Gly389 (n = 369)	Arg389 (n = 422)	Gly389 (n = 223)	Arg389 (n = 119)	Gln41 (n = 1,587)	Leu41 (n = 53)	Gln41 (n = 374)	Leu41 (n = 263)
Age at enrollment (yrs)	51.2	50.5	48.4	50.1	52.5	46.5*	51.6	45.5*
Height (inches)	67.9	67.9	67.8	67.0	67.9	68.0	67.5	67.0
Weight (lbs)	191.1	192.1	204.9	194.7	191.2	191.9	199.9	197.5
Ejection fraction	32.1	31.0	30.8	34.8	31.4	29.7	33.2	30.2
Follow-up (months)	79.2	80.0	75.5	79.7	73.7	60.3*	63.8	61.8
Heart failure etiology								
Ischemic	50.0	54.7	45.4	40.4	49.6	56.6	41.7	42.6
Nonischemic	50.0	45.3	54.6	59.6	50.4	43.4	58.3	57.4
Female	47.1	47.5	31.5	32.0	31.6	26.4	43.9	48.3
Diabetes	36.4	39.6	29.0	42.2	32.6	45.3	39.3	33.7
Hypertension	66.1	59.9	86.6	84.7	54.6	60.4	81.7	83.2
Coronary disease	58.0	60.6	48.2	40.1	57.7	64.3	51.0	52.6
Cerebrovascular event	16.4	16.0	17.5	19.1	10.6	05.7	14.5	17.8
Dyslipidemia	56.4	51.1	37.9	43.9	51.1	56.9	50.4	48.2
Renal insufficiency	35.7	42.3	39.1	42.7	23.1	28.9	39.3	31.1
β-blocker use								
Carvedilol	50.7	56.6	57.1	63.7	54.8	67.9	57.4	55.7
Metoprolol	16.1	13.3	19.3	17.0	20.1	11.3	23.3	23.3
Other	4.0	3.8	4.2	4.0	4.2	0	4.3	7.6
ACE inhibitor use	81.0	81.3	84.0	86.6	74.5	77.4	80.9	82.1
ARB use	29.6	24.4	25.7	26.0	21.8	19.5	22.2	22.3
Aldosterone antagonist use	33.7	33.6	34.6	35.0	33.1	44.4	29.3	36.5
Statin use	62.5	64.5	50.0	46.9	58.2	59.5	53.5	51.2
AICD	35.9	35.9	25.5	24.7	30.0	37.8	25.4	25.1
Transplanted	24.9	26.8	10.9	8.5	16.4	18.9	7.2	7.6
Achieved end point	49.1	51.7	44.5	39.9	33.6	45.3	30.2	27.5

Values are % unless otherwise indicated. *$p < 0.05$ versus major allele within same subgroup.
Abbreviations as in Table 1.

Americans, with no evidence for a multiplicative interaction between these *ADRB1* and *GRK5* variants. We considered that these genetic factors might contribute to the apparent differences in HF outcomes and β-blocker response observed between Caucasians and African Americans in our cohort, and re-examined outcome in subjects matched for these 2 polymorphisms, that is, in *ADRB1* Gly389Gly *GRK5* Gln41Gln individuals. When *ADRB1* Gly389Gly *GRK5* Gln41Gln patients were analyzed, β-blocker treatment significantly increased survival time (β-blocker–untreated n = 110, β-blocker–treated n = 371, log-rank p = 0.00058) (Fig. 4A) and reduced mortality risk (age- and sex-adjusted HR: 0.530, 95% CI: 0.357 to 0.788, p = 0.0017) in the combined cohort. The same was true for β-blocker treatment in Caucasians (β-blocker–untreated n = 87, β-blocker–treated n = 256, log-rank p = 0.0053, Fig. 4A top inset; age- and sex-adjusted HR: 0.529, 95% CI: 0.326 to 0.858, p = 0.0098). When this analysis was applied to African Americans without considering genotype, it had failed to show a β-blocker treatment effect in this cohort (Fig. 1A, right inset). However, when the *ADRB1* Gly389 *GRK5* Gln41Gln subgroup of African Americans was analyzed, β-blocker treatment enhancement of survival was evident (β-blocker–untreated n = 22, β-blocker–treated n = 111, log-rank p = 0.0373) (Fig. 4A, bottom inset), as was a significant reduction in mortality risk (age- and sex-adjusted HR: 0.385, 95% CI: 0.182 to 0.813, p = 0.012). Survival times were similar in genotype-matched Caucasian and African-American β-blocker–untreated subjects (Caucasian n = 87, African American n = 22, log-rank p = 0.2368 [Fig. 4B]; age- and sex-adjusted HR: 1.46, 95% CI: 0.611 to 3.51, p = 0.39) and β-blocker–treated subjects (Caucasian n = 256, African American n = 111, log-rank p = 0.2283) (Fig. 4C), although there was still a trend toward shorter survival times in β-blocker–treated African Americans after adjusting for age and sex (adjusted HR: 1.55, 95% CI: 0.992 to 2.43, p = 0.054). Another way to conceptualize the interaction of genotype and β-blocker treatment is to examine the effect of genotype within treatment class. By comparing the *ADRB1* Gly389Gly *GRK5* Gln41Gln genotype with all other genotypes pooled, we found that genotype had no effect among β-blocker–treated subjects (Caucasians HR: 0.854, p = 0.35; African Americans HR: 0.829, p = 0.39) but did have

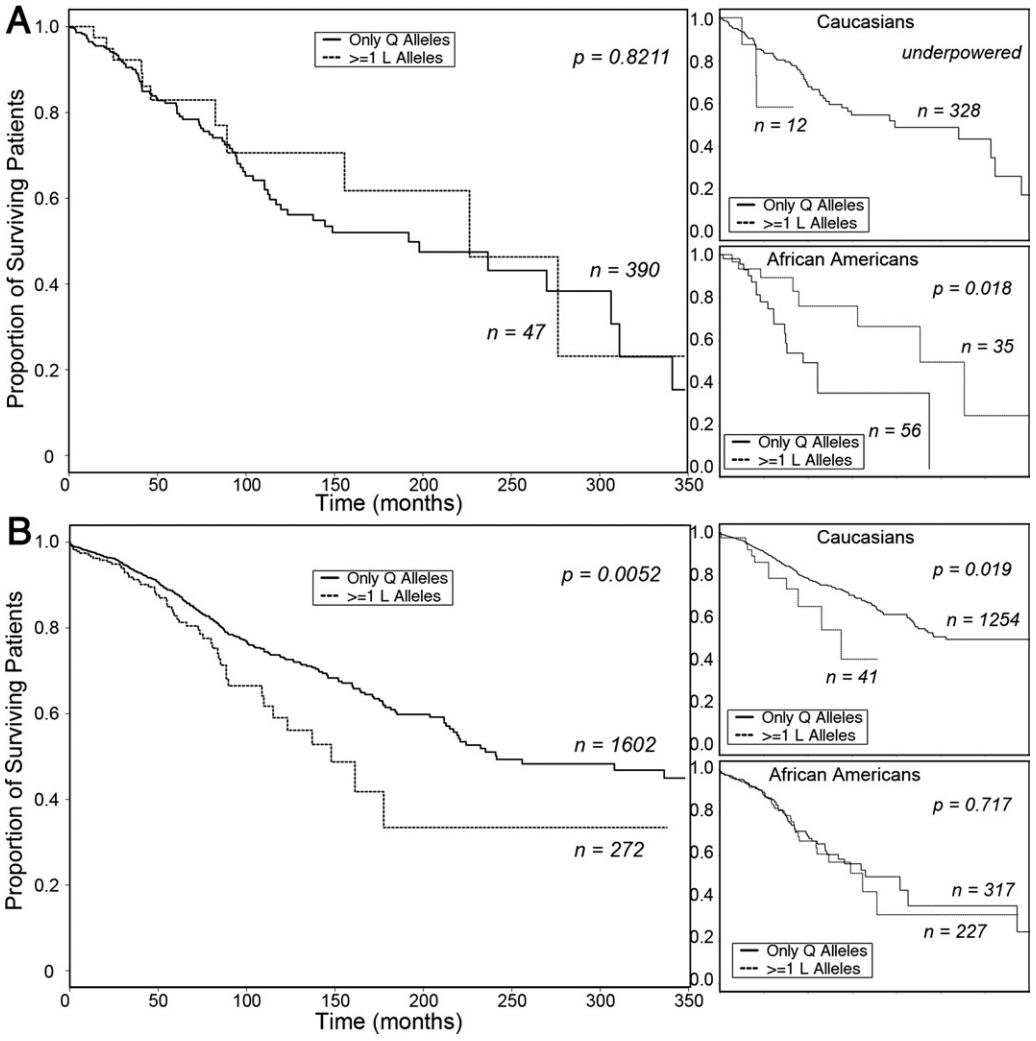

Figure 3 Kaplan-Meier Curves of GRK5 Gln/Leu 41 Effect on Heart Failure Survival

(A) β-blocker–untreated subjects stratified by *GRK5* 41Leu carrier status (**top inset**, Caucasian Americans; **bottom inset**, African Americans). **(B)** β-blocker–treated subjects stratified by *GRK5* 41Leu carrier status (**top inset**, Caucasian Americans; **bottom inset**, African Americans). **Solid line** = Gln/Gln 41; **dashed line** = Leu 41 carriers.

a significant effect among β-blocker–untreated Caucasians (Caucasians HR: 2.09, p = 0.02; African Americans: HR: 1.77, p = 0.19). These data suggest that in this HF population, differences caused by β-adrenergic receptor signaling pathway gene polymorphisms, rather than race, are the major factor contributing to apparent differences in β-blocker treatment effect between Caucasians and African Americans.

Discussion

The major finding of this study is that genetic polymorphisms of the major cardiac β-blocker target, the β1-adrenergic receptor, and a kinase that terminates its signaling, GRK5, can significantly impact HF outcomes, and that adjusting for these gene variants abrogates the apparent ethnic differences in β-blocker treatment effect on HF survival.

In HF patients with similar clinical presentations, some will have a more rapid disease course, whereas disease progression is less aggressive in others (42,43), and the benefits of recent advances in pharmacological and mechanical therapies for HF have not been equally shared among all patient groups. In particular, management of HF remains a challenge for the African-American population. African Americans have a 50% higher prevalence of HF, with earlier and more severe onset of disease and decreased survival (9,44). There are many possible reasons for racial differences in health care outcome, including differences in HF etiology, clinical risk factors, or management practices, as well as the absence of pre-specified analysis of African Americans as a separate subgroup in many large clinical trials and a

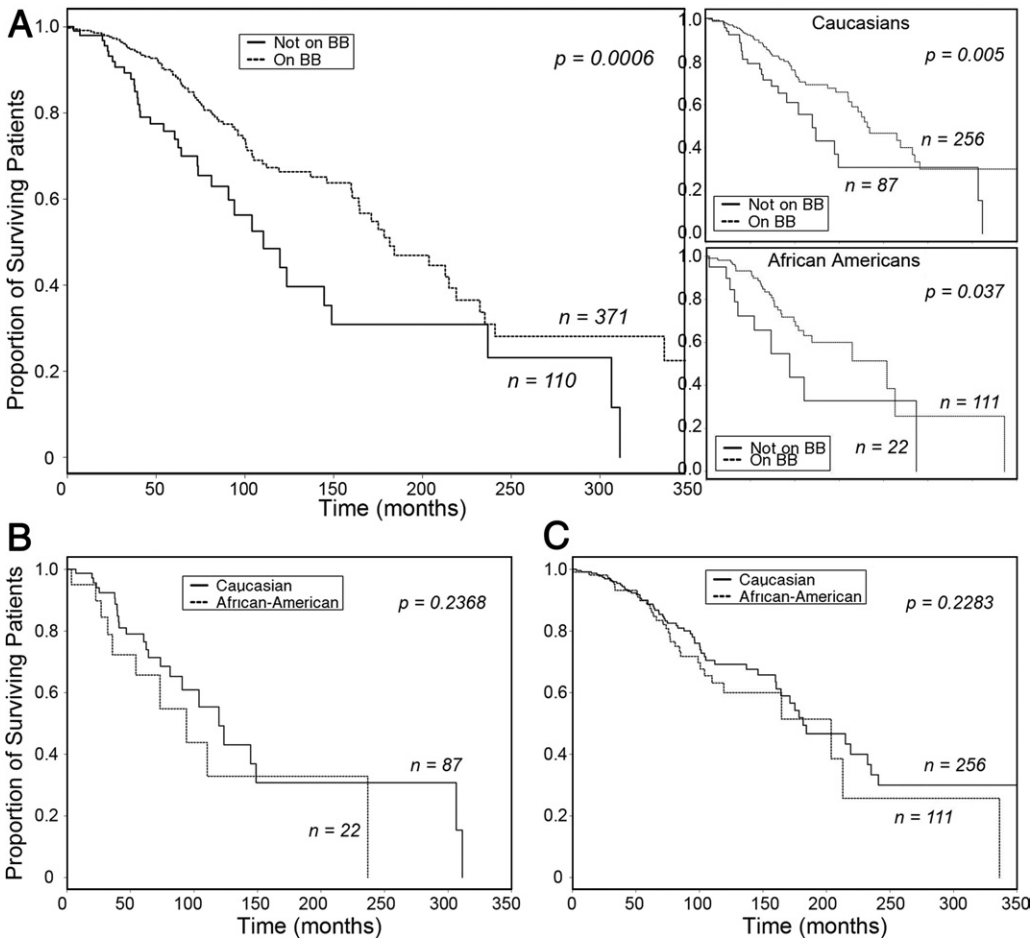

Figure 4 **Kaplan-Meier Curves of β-Blocker Treatment Effect on Heart Failure Survival in Subjects Matched for *ADRB1* Gly 389 and *GRK5* Gln 41 Homozygous Genotype**

(A) Combined heart failure cohort, stratified by β-blocker usage (**top inset**, Caucasian Americans; **bottom inset**, African Americans). **Solid line** = β-blocker untreated; **dashed line** = β-blocker treated. **(B)** Survival of β-blocker–untreated heart failure subjects, stratified by race. **(C)** Survival of β-blocker–treated heart failure subjects, stratified by race. **Solid line** = Caucasian; **dashed line** = African American.

tendency for African Americans to be under-represented in these studies (45). Our study was specifically designed to have proportional representation of African Americans and to minimize differences in clinical risk factors and management practices that may contribute to ethnic differences in heart disease. Thus, HF patients were recruited from 2 large municipal tertiary referral HF/heart transplant programs, affording a consistent standard of care that has been shown to reduce or eliminate ethnic differences in mortality (46). The 2 ethnic cohorts were well matched for ventricular function, ACE inhibitor and β-blocker treatment, and automatic implantable cardioverter-defibrillator use. Nevertheless, African Americans had significantly higher mortality rates, had a less clear response to β-blocker therapy, and underwent transplantation only one-half as often as Caucasians. For this reason, the end point for these studies was all-cause mortality, and our multivariate risk factor analysis adjusted for differences in sex and age.

The mortality from treated HF exceeds that of most cancers (47), and β-blockers are 1 of only 2 drug classes that increase survival (the other being ACE inhibitors). β-blockers are in general highly effective in prolonging survival in HF patients, but interindividual differences in treatment effect continue to complicate disease management. Therefore, our focus in these studies was on 2 critical components of the signaling pathway targeted by β-blockers, the β1-adrenergic receptor itself (48), and GRK5, an abundant kinase in myocardium that terminates β-adrenergic receptor signaling (40,41,49). The β1-adrenergic receptor, encoded by the *ADRB1* gene, is the major cardiac target of β-blockers. Unique to humans is a common polymorphic variation of *ADRB1* encoding either Gly or Arg at amino acid 389, located within the intracellular G-protein coupling domain (23). This region of β1-adrenergic receptor is highly conserved between species, with the human Gly variant being the only known instance

of divergence from Arg at this position. The functional consequence of introducing Gly is diminished coupling between the β1-adrenergic receptor variant and Gαs (50) and decreased responsiveness to β-blockers in genetic mouse models (51). Human studies have been inconsistent as to whether there are meaningful associations between this polymorphism and HF outcome (24,38,39,52–58). The more common Arg389 β1-adrenergic receptor shows enhanced functional coupling, is less prevalent in African Americans, and is associated with a favorable response to the experimental β-blocker bucindolol, whereas carriers of the Gly389 minor allele reportedly show no survival benefit from bucindolol (23). An investigation of adrenergic receptor gene polymorphisms on cardiovascular outcomes in the Woman's Ischemia Syndrome Evaluation (39) found that carriers of the Gly389 allele were at increased risk for HF and all-cause mortality. The current findings of a trend for improved HF survival in Caucasians homozygous for Arg389, and the experimental findings of Akhter et al. (59) that Arg389 transgenic mice recover from ischemic insults faster than Gly389 mice, also suggest a more complex role for this β-receptor variant in primary myocardial disease than has generally been recognized.

The other polymorphism we evaluated is 10 times more common in African Americans than Caucasian Americans, substituting Leu for Gln at position 41 of GRK5. GRK5 helps to terminate β-adrenergic receptor signaling by phosphorylating and uncoupling agonist-occupied receptors from their Gαs signal transducers (40,49). Amino acid 41 is in a putative regulatory domain for the kinase, and (as with the β1-adrenergic receptor 389 polymorphism) the GRK5 amino acid sequence is conserved at this position across human, bovine, mouse, rat, dog, and zebrafish homologs, except for the human variant (22). Compared with the wild-type GRK5, the Leu41 variant promotes more rapid agonist-mediated desensitization, phosphorylation, and internalization of the β1-adrenergic receptor (41), and mimics β-blockers in genetic mouse models (22). In a previous report, which is the only report to date of this polymorphism in a human study, we described a pharmacogenomic interaction with β-blockers for the combined end point of cardiac transplantation or death in a small cohort of African Americans with HF (22). Here, we have greatly expanded the number of HF subjects studied, doubling the number of African-American study subjects to 711, and compared outcomes with those of almost 1,800 Caucasians recruited from the same 2 academic centers. In so doing, we demonstrate a significant increase in HF survival in African Americans carrying at least 1 GRK5 Leu41 allele.

The gene modifier effects for the *ADRB1* 389 polymorphism have greater significance for Caucasians, and the *GRK5* 41 polymorphism is significant only in African Americans, but these findings do not necessarily indicate different disease mechanisms between these ethnic groups. Both the *ADRB1* and *GRK5* polymorphisms show significant differences in prevalence between populations of European and African descent, and natural variations in polymorphism allele frequency between different ethnic groups can result in correspondingly different pathological roles for these genetic events in different study populations. For example, the 8q24 locus associated with prostate cancer is associated with a higher prevalence of this disease among African Americans not because of a greater individual gene effect in African-American individuals, but because the risk allele occurs with greater frequency in this population, and thereby contributes to increased incidence (60). Thus, the most important aspect of the current results is not what impact specific adrenergic signaling pathway polymorphisms have on HF, because these effects have been shown to vary between different populations, with different treatment practices, and in different cardiovascular conditions (24,38,39,52–58). Instead, the take-home message is that polymorphisms such as these 2 that clearly alter functional pathways in experimental systems have the potential to produce variability of disease prognosis and outcome in the same manner as clinical risk modifiers. Therefore, proper evaluation of disease risk and treatment response should account for genetic variance, either by matching subjects by relevant genotype as herein, or by including relevant genotypes in multivariate models.

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JACC Vol. 54, No. 5, 2009
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Key Words: heart failure ■ beta-blocker ■ gene polymorphism ■ beta adrenergic receptor ■ G-protein receptor kinase.

APPENDIX

For the supplemental table, please see the online version of this article.