Clinical and Translational Science

ARTICLE OPEN ACCESS

The Beta-Blocker Pharmacogenetic Puzzle: More Pieces of Evidence for Pharmacodynamic Candidate Variants

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Received: 11 September 2024 | **Revised:** 20 February 2025 | **Accepted:** 15 April 2025

Funding: This work was supported by the National Institutes of Health (NIH): K08HL146990 (J.A.L); F31HL167561 (S.D.R.L.); T32TR004371 (A.I.L-M.); R01HL103871, R01HL132154, and P50MD01735 (D.E.L.).

Keywords: *ADRA2C* | *ADRB1* | *ADRB2* | ancestry | beta-blocker | *GRK4* | *GRK5* | heart failure | pharmacogenetics | survival

ABSTRACT

Previous pharmacogenetic findings for beta-blocker pharmacodynamic candidate genes (*ADRB1*, *ADRB2*, *ADRA2C, GRK4,* and *GRK5)* have been inconsistent. Therefore, the purpose of this study was to determine whether interactions of pharmacodynamic variants with beta-blocker exposure significantly associated with survival in patients with heart failure with reduced ejection (HFrEF). The 893 patients were 51% self-reported African American and 49% self-reported White race, 36% female, and 240 died (27%) over a median follow-up of 2.8 years. The primary outcome was all-cause mortality. Using Cox proportional hazards models with time-varying beta-blocker exposure and adjusted for clinical risk factors and ancestry, interactions of *ADRB1* Arg389Gly, *ADRB1* Ser49-Arg389Gly haplotype, *ADRA2C* $Del_{322\text{-}325}$, and *GRK4* Ala486Val with beta-blocker exposure were significant before correction for multiple comparisons ($p < 0.1$), but only *GRK4* Ala486Val remained significant in African Americans after correction for multiple comparisons using the adaptive Hochberg method ($p = 0.022$). Beta-blocker exposure only associated with a significant reduction in the risk of mortality in the African American HFrEF patients with the *GRK4* Ala486/Ala486 genotype (HR = 0.44; 95% CI = 0.20–0.96; $p = 0.04$). In conclusion, the interaction of *GRK4* Ala486Val with beta-blocker exposure significantly associated with survival in African American HFrEF patients. Larger sample sizes or meta-analyses are needed to have more statistical power to better assess beta-blocker pharmacogenetic interactions for *ADRB1* Arg389Gly, *ADRB1* Ser49-Arg389Gly haplotype, and *ADRA2C* $Del_{322\text{-}325}$ in the future.

1 | Introduction

Heart failure (HF) remains a major global health burden, affecting millions of individuals with high morbidity, mortality, and costs [1]. Beta-blockers are a cornerstone treatment for heart failure with reduced ejection fraction (HFrEF) because they significantly improve HFrEF patient survival and other outcomes in large, randomized controlled trials [2]. However, those large clinical trials measured beta-blocker benefit in HFrEF patients *on average*, but the *individual* HFrEF patient responses to beta-blockers vary. Only ~22% of HFrEF patients have a marked and sustained improvement in left ventricular ejection fraction (LVEF) with beta-blockers [3, 4]. The change in heart rate in response to beta-blockers, that is, the difference between an individual HFrEF patient's heart rate at baseline before beta-blocker therapy and after maximal beta-blocker dose titration, varies by

Summary

- What is the current knowledge on the topic?
  - Beta-blockers are a cornerstone treatment to prolong the survival of patients with heart failure with reduced ejection fraction (HFrEF), but some HFrEF patients' responses to beta-blockers are variable and unpredictable. Previous pharmacogenetic findings for the effects of genetic variants in beta-blocker pharmacodynamic candidate genes (*ADRB1*, *ADRB2*, *ADRA2C, GRK4*, and *GRK5*) have been inconsistent.
- What question did this study address?
  - Do pharmacodynamic genetic variants in *ADRB1*, *ADRB2*, *ADRA2C, GRK4*, and *GRK5* significantly interact with beta-blocker exposure to influence survival in a large and well-characterized prospective registry of African American and White HFrEF patients?
- What does this study add to our knowledge?
  - Pharmacogenetic interactions of *ADRB1* Arg389Gly, *ADRB1* Ser49-Arg389Gly haplotype, *ADRA2C* $Del_{322\text{-}325}$, and *GRK4* Ala486Val with beta-blocker exposure were significantly associated with survival time in HFrEF patients before correction for multiple comparisons, but only the interaction of *GRK4* Ala486Val with beta-blocker exposure in the African American patients remained statistically significant after correction for multiple comparisons. Beta-blocker exposure was only associated with a significant reduction in the risk of mortality in the African American HFrEF patients with the *GRK4* Ala486/Ala486 genotype.
- How might this change clinical pharmacology or translational science?
  - Beta-blocker therapy may be personalized in African American HFrEF patients according to *GRK4* Ala486Val genotype in the future if additional studies confirm this interaction. Future studies with larger sample sizes are needed to confirm the beta-blocker pharmacogenetic interactions for *ADRB1* Arg389Gly, *ADRB1* Ser49-Arg389Gly haplotype, and *ADRA2C* $Del_{322\text{-}325}$.

nearly 2-fold among HFrEF patients [5]. Unfortunately, clinical characteristics do not fully explain this variability in beta-blocker response [6]. Therefore, studies have investigated the effects of genetics on beta-blocker response in HFrEF patients [7]. Many of those pharmacogenetic studies focused on candidate genes involved in beta-blocker pharmacodynamics, that is, genes for adrenergic receptors (*ADRB1*, *ADRB2*, and *ADRA2C*) [8–10] and the G-protein coupled receptor kinases that desensitize adrenergic receptors (*GRK4* and *GRK5*) [11, 12]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recently published a clinical practice guideline that evaluated the strength of the evidence for those pharmacodynamic genes and a pharmacokinetic gene (*CYP2D6*) on beta-blocker response [13]. They concluded that the evidence was strong for the pharmacokinetic gene *CYP2D6* and metoprolol, but the evidence for the pharmacodynamic genetic variants on beta-blocker responses was inconsistent and therefore rated as weak. As a result, the guideline authors concluded that there was insufficient evidence at this time to make clinical recommendations for the pharmacodynamic genetic variants and beta-blockers. Therefore, the purpose of this study was to provide additional pharmacogenetic evidence for pharmacodynamic variants in *ADRB1*, *ADRB2*, *ADRA2C, GRK4*, and *GRK5* with beta-blocker benefit in a large and well-characterized registry of HFrEF patients with long-term follow-up, time-varying beta-blocker exposure data available from pharmacy claims, and robust genetic and statistical analysis methods. We hypothesized that alleles reducing adrenergic function in these pharmacodynamic genes would be associated with a diminished survival benefit from beta-blocker therapy in HFrEF patients.

2 | Methods

2.1 | Patient Data

The prospective HF PharmacoGenomic Registry (HFPGR) was designed to discover novel ways to predict HF prognoses and responses to HF therapies [14]. The HFPGR enrolled patients from October 2007 to March 2015 at the Henry Ford Health System in Detroit, MI, USA. Inclusion criteria were as follows: age $\geq$ 18 years; self-reported African American or White race; a diagnosis of HF using the Framingham Heart Study criteria; and at least one documented LVEF $<$ 50%. This LVEF cutoff was chosen because the registry started prior to more recent reclassifications that define HFrEF with LVEF $\leq$ 40% [2]. All patients were covered by the same health insurance plan, the Health Alliance Plan, which allowed access to claims data. Patients were excluded if they required dialysis or supplementary oxygen. Detailed clinical information (e.g., demographics, physical examination, past medical history, laboratory values, functional status, and medications) and blood samples were collected at enrollment. At the time of enrollment into the registry, some of these HFrEF patients may have already had beta-blocker exposure at baseline as part of standard medical care. Deaths were identified using the Social Security Administration Death Master File, the Michigan State Division of Vital Records, and administrative data from the Henry Ford Health System through 30 April 2017. The study received approval from the Institutional Review Board of the Henry Ford Health System. All patients provided written informed consent prior to study participation.

2.2 | Beta-Blocker Exposure

Beta-blocker exposure over time was calculated from pharmacy claims data as previously described [14] and illustrated in Figure S1. Briefly, beta-blocker doses were standardized into daily dose equivalents using the target doses defined in HFrEF clinical practice guidelines [2] or, for the beta-blockers not specifically guideline-recommended for HFrEF (e.g., metoprolol tartrate or atenolol), the maximum recommended daily doses. The following daily doses were used: atenolol, 100 mg; bisoprolol, 10 mg; carvedilol, 50 mg; labetalol, 600 mg; and metoprolol, 200 mg (all formulations). Beta-blocker exposure was calculated over a 6-month rolling period by multiplying the standardized daily dose equivalents by the total quantity of medication dispensed during the period and then dividing by the total number of days during the period. We have previously shown that this method more strongly

TABLE 1 | Summary of beta-blocker pharmacodynamic candidate variant functional effects and hypothesized clinical associations in HFrEF patients.

Gene	Variant[a]	rsID	Functional effect	Hypothesized interaction with beta-blocker exposure and association with survival benefit
ADRB1	A > **G** Ser49 > **Gly49**	rs1801252	Gly49 has greater agonist-promoted downregulation and desensitization [16, 17]	Gly49 ↓ BB benefit
	C > **G** Arg389 > **Gly389**	rs1801253	Arg389 has greater basal and agonist-simulated activity [18]	Gly389 ↓ BB benefit
ADRB2	**G** > A **Gly16** > Arg16	rs1042713	Gly16 has greater agonist-promoted downregulation [19]	Gly16 ↓ BB benefit
	C > G **Gln27** > Glu27	rs1042714	Glu27 is resistant to agonist-promoted downregulation [19]	Gln27 ↓ BB benefit
ADRA2C	**C** > T **Ins** > $Del_{322-325}$	rs7434630[b]	$Del_{322-325}$ impairs intracellular receptor coupling [20] and increases the release of norepinephrine [21]	Ins ↓ BB benefit
GRK4	G > **T** Arg65 > **Leu65**	rs2960306	Leu65 enhances desensitization of G-protein coupled receptors [22]	Leu65 ↓ BB benefit
	C > **T** Ala142 > **Val142**	rs1024323	Val142 enhances desensitization of G-protein coupled receptors [22]	Val142 ↓ BB benefit
	C > **T** Ala486 > **Val486**	rs1801058	Val486 enhances desensitization of G-protein coupled receptors [22]	Val486 ↓ BB benefit
GRK5	A > **T** Gln41 > **Leu41**	rs2230345	Leu41 enhances beta-adrenergic receptor desensitization [11]	Leu41 ↓ BB benefit

Abbreviations: BB, beta-blocker; Del, deletion; Ins, insertion; rsID, reference sequence identifier.
[a]Bolded and underlined alleles decrease adrenergic function and are hypothesized to improve survival but decrease beta-blocker response.
[b]Used as a proxy for the *ADRA2C* $Ins/Del_{322-325}$ variant (rs61767072).

correlates with relevant HFrEF outcomes (e.g., heart rate, hospitalization, mortality) than single time point calculations for beta-blocker exposure (e.g., discharge medication status) [15].

2.3 | Selection of Pharmacodynamic Candidate Genetic Variants

A total of 9 genetic variants in 5 pharmacodynamic genes (*ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5*) were selected because they were recently evaluated in the beta-blocker CPIC guideline [13]. These variants were chosen because they have a priori evidence supporting effects on adrenergic function [7] and they were previously studied for associations with beta-blocker response in patients (Table 1). In general, alleles that decrease adrenergic function were hypothesized to improve HFrEF patient survival but decrease beta-blocker-associated survival benefit. Previous pharmacogenetic studies assessing clinical associations of these variants with beta-blocker responses are summarized in the CPIC guideline and previous literature reviews [7, 13].

2.4 | Genetic Data

Genotyping was performed by the Advanced Genomics Core laboratory at the University of Michigan (Ann Arbor, MI, USA) using the Axiom Biobank Genotyping Array (Affymetrix; Santa Clara, CA, USA) [14]. This array includes the following ~600 K genetic variants: (1) ~300 K genome-wide variants with minor allele frequencies > 1%; (2) ~250 K low frequency (< 1%) coding variants from global exome sequencing projects; and (3) an additional ~50 K variants to improve African ancestry coverage (Yoruba in Ibadan, Nigeria [YRI] booster). Imputation was performed using the Michigan Imputation Server with Minimac3 and the 1000 Genomes Project as the reference panel (all imputation scores $r^2 > 0.8$) [23]. Methods for quality control were previously described [24]. Briefly, the following filters were applied to the genotype data: call rate < 95%, minor allele frequency (MAF) < 0.01, Hardy–Weinberg Equilibrium (HWE) p-value $< 1.0^{-8}$, imputation score $r^2 < 0.8$, duplicate samples identified by identity-by-state distances, and monomorphic variants. The proportion of YRI ancestry in each patient was estimated using ANCESTRYMAP2.0 [25]. The *ADRA2C* $Del_{322-325}$ variant (rs61767072) was not covered by the array or imputation. Thus, rs7434630 was used as a proxy for rs61767072 because they are in strong linkage disequilibrium ($r^2 = 0.86$ and $D' = 1.0$ in Africans and $r^2 = 0.98$ and $D' = 1.0$ in Europeans) [26]. The imputed genotypes were used for four of the variants: rs1801253, rs7434630, rs1042714, and rs2230345. All of the other variants were directly genotyped by the array.

2.5 | Statistical Analysis

The distribution of continuous variables was assessed by the Kolmogorov–Smirnov test and visual inspection of distribution plots. Most of the continuous variables did not have a normal

distribution; thus, they were summarized by median (interquartile range) and compared using the Mann Whitney U Test. Categorical variables were summarized by counts and percentages and compared by using χ^2 tests or Fisher's exact tests when appropriate. Pairwise linkage disequilibrium was tested between variants within the same genes using the genetics package in R v.4.3.2 within each race group. Haplotypes were estimated within each race group using PHASE v2.1.1 [27]. The Meta-Analysis Global Group in Chronic (MAGGIC) HF risk score [28] (minus beta-blocker as an input variable) was calculated for each patient using their baseline characteristics. The beta-blocker propensity score [29] was calculated for every patient based on the baseline characteristics with $p < 0.05$ for the difference between patients that were treated with a beta-blocker at baseline versus those that were not.

Cox proportional hazards models were used to test the interaction of each genetic variant and haplotype with time-varying beta-blocker exposure (genotype/haplotype*beta-blocker exposure) for association with time-to all-cause mortality. Models were adjusted for the following covariates: beta-blocker propensity score, MAGGIC (minus beta-blocker as an input variable), and proportion of YRI ancestry. The Spearman correlation coefficient for beta-blocker propensity score and MAGGIC risk score was −0.20. Therefore, collinearity between these two covariates is unlikely to be a significant issue in our Cox models. Genotype- and haplotype-stratified analyses were also performed. Cox proportional hazards models were also used to test the independent association of each genetic variant and haplotype with survival. Genotypes were tested in the additive genetic model (0, 1, or 2 alleles), and haplotypes were tested by count. The alleles and haplotypes were coded according to their effects on adrenergic function (Table 1). Alleles or haplotypes that decrease adrenergic function were coded as higher numbers. The genotype or number of haplotypes with the greatest adrenergic function was coded as the reference. Race-stratified and race-combined analyses were performed because we have previously shown similar beta-blocker survival benefit regardless of race [14]. *p*-values from the Cox proportional hazards models were corrected for multiple comparisons using the adaptive Hochberg method [30]. $p < 0.1$ after correction for multiple comparisons was a priori defined as statistically significant for the pharmacogenetic interaction tests and $p < 0.05$ for the survival analyses. Unless otherwise noted, statistical analyses were performed using SAS v.9.4.

3 | Results

3.1 | Clinical & Genetic Characteristics

A total of 893 patients (454 African American [51%] and 439 White [49%] self-reported race) had beta-blocker exposure and genotype data available for analysis (454/470 [96.6%] and 439/452 [97.1%] genotype call rates in the African American and White patients, respectively). Table 2 shows the baseline and follow-up characteristics overall and stratified by race and beta-blocker treatment status at baseline. Overall, 36% (321/893) were female, the median age was 69 years, 51% (454/893) African American race, and 74% (665/893) were treated with beta-blocker at baseline. The median (interquartile range) length of follow-up was 2.8 (1.6–4.2) years overall, and the total person-years of follow-up was 2701 overall. The death rate was 9 per 100 person-years overall (240 deaths/2701 person-years). The most used beta-blockers at baseline overall were carvedilol at 32% (288/893) and metoprolol succinate at 24% (215/893). When compared by self-reported race, African American patients had significantly more women, a younger age, lower LVEF, and higher rates of several comorbidities, including hypertension, chronic kidney disease, and diabetes. HFrEF medication use, including beta-blockers, was similar by race, except significantly more African Americans used aldosterone antagonists than White patients (25% [115/454] vs. 18% [79/439], respectively). More African Americans were taking carvedilol and metoprolol succinate, and more White patients were taking metoprolol tartrate. The length of follow-up (median 2.7 vs. 2.8 years in African American and White patients, respectively) and the mortality rate were similar by race (27% [240/893] in both race groups). The person-years of follow-up were also similar between race groups (African Americans = 1371 and White = 1330; $p = 0.938$).

When compared by beta-blocker treatment status at baseline, the patients taking beta-blockers were significantly older, had more ischemic heart disease and diabetes, and higher use of other HFrEF medications than the patients that were not using beta-blockers at baseline. The median length of follow-up was significantly longer in the patients taking beta-blockers at baseline versus those that were not (2.9 vs. 2.5 years; $p < 0.001$), but the mortality rates were similar (177/665 [27%] vs. 63/228 [28%]; $p = 0.765$). The length of follow-up in person-years was also significantly longer in the patients treated with beta-blockers at baseline: 2091 versus 609 ($p = 0.001$). Sex, LVEF, systolic blood pressure, and heart rate were not significantly different between the patients that were and were not taking beta-blockers at baseline. The overall covariate-adjusted association of time-varying beta-blocker exposure with time to all-cause mortality (without any genetic variables) was hazard ratio (HR; 95% confidence interval) = 0.62 (0.39–98) $p = 0.041$. This result is particularly noteworthy as it demonstrates that our model approach in this observational study detects similar reductions in the risk for mortality with beta-blocker exposure, in the absence of any genetic variables, as those observed in the landmark randomized controlled trials of beta-blockers in HFrEF patients [2]. Minor allele frequencies were similar to public databases (Table S1), and all Hardy-Weinberg Equilibrium (HWE) *p*-values were > 0.05. Variants within the same genes were in linkage disequilibrium (Table S2). Genotype and haplotype counts are shown in the figures as the corresponding "n". Associations of the variants and haplotypes with mortality independent of beta-blocker exposure and the other covariates are in Figures S2–S4. Only one variant remained significantly associated with survival after correction for multiple comparisons. *GRK4* Ala142Val significantly associated with increased risk of mortality in the White patients: HR = 1.39 (95% CI = 1.07–1.81) corrected $p = 0.039$ (Figure S4).

TABLE 2 | Baseline characteristics overall and stratified by self-reported race and beta-blocker treatment status at baseline.

	Overall $n = 893$ (100%)	African–American race $n = 454$ (51%)	White race $n = 439$ (49%)	p[a]	BB at baseline $n = 665$ (74%)	No BB at baseline $n = 228$ (26%)	p[b]
Female	321 (36.0%)	186 (41.0%)	135 (30.8%)	**0.002**	247 (37.1%)	74 (32.5%)	0.203
Age (years)	69 (60–77)	64 (57–74)	72 (64–80)	**< 0.001**	69 (61–78)	66 (58–76)	**0.032**
African American race	454 (50.8%)	454 (100%)	0 (0%)	—	346 (52.0%)	108 (47.4%)	0.224
YRI ancestry (%)	48 (0–90)	90 (81–96)	0 (0–0)	**< 0.001**	60 (0–90)	3 (0–90)	0.845
LVEF (%)	35 (26–40)	34 (25–40)	35 (30–42)	**< 0.001**	35 (25–40)	35 (27–40)	0.595
Ischemic etiology	394 (44.1%)	152 (33.5%)	242 (55.1%)	**< 0.001**	311 (46.8%)	83 (36.4%)	**0.007**
Hypertension	800 (89.6%)	423 (93.2%)	377 (85.9%)	**< 0.001**	603 (90.7%)	197 (86.4%)	0.068
COPD	209 (23.4%)	100 (22.0%)	109 (24.8%)	0.323	152 (22.9%)	57 (25.0%)	0.510
Chronic kidney disease	208 (23.3%)	133 (29.3%)	75 (17.1%)	**< 0.001**	161 (24.2%)	47 (20.6%)	0.268
Atrial fibrillation	255 (28.6%)	90 (19.8%)	165 (37.6%)	**< 0.001**	188 (28.3%)	67 (29.4%)	0.748
Stroke/TIA	114 (12.8%)	61 (13.4%)	53 (12.1%)	0.542	92 (13.8%)	22 (10.4%)	0.102
Diabetes	381 (42.8%)	212 (46.7%)	169 (38.5%)	**0.013**	301 (45.3%)	80 (35.1%)	**0.007**
Body mass index (kg/m^2)	30 (26–34)	30 (26–35)	30 (25–34)	0.095	30 (26–34)	30 (26–35)	0.576
SBP (mmHg)	127 (111–142)	131 (114–146)	124 (110–140)	**< 0.001**	127 (113–142)	126 (110–142)	0.478
HR (bpm)	70 (62–79)	71 (63–80)	69 (62–78)	**0.013**	69 (62–78)	72 (64–82)	0.055
NYHA class	1 (1–3)	1 (1–3)	1 (1–3)	0.287	1 (1–3)	1 (1–2)	0.263
NT pro-BNP (pg/mL)	224 (87–534)	199 (69–523)	269 (117–555)	**0.002**	228 (91–544)	204 (75–524)	0.240
Serum creatinine (mg/dL)	1.1 (0.9–1.5)	1.2 (0.9–1.5)	1.1 (0.8–1.4)	**< 0.001**	1.1 (0.9–1.5)	1.1 (0.9–1.5)	0.491
MAGGIC risk score[c]	20 (15–26)	19 (14–25)	21 (15–27)	**0.003**	20 (15–26)	20 (14–26)	0.363
Beta-blocker	665 (74.5%)	346 (76.2%)	319 (72.7%)	0.224	666 (100%)	0 (0.0%)	—
Beta-blocker name							
Atenolol	35 (3.9%)	16 (3.5%)	19 (4.3%)	**< 0.001**	35 (5.3%)	0 (0.0%)	**< 0.001**
Bisoprolol	1 (0.1%)	0 (0.0%)	1 (0.2%)		1 (0.2%)	0 (0.0%)	
Carvedilol	288 (32.3%)	162 (35.7%)	126 (28.7%)		288 (43.3%)	0 (0.0%)	
Metoprolol succinate	215 (24.1%)	115 (25.3%)	100 (22.8%)		215 (32.3%)	0 (0.0%)	
Metoprolol tartrate	91 (10.2%)	29 (6.4%)	62 (14.1%)		91 (13.7%)	0 (0.0%)	

(Continues)

TABLE 2 | (Continued)

	Overall $n = 893$ (100%)	African–American race $n = 454$ (51%)	White race $n = 439$ (49%)	p[a]	BB at baseline $n = 665$ (74%)	No BB at baseline $n = 228$ (26%)	p[b]
Other	4 (0.5%)	4 (0.9%)	0 (0.0%)		4 (0.6%)	0 (0.0%)	
Unknown	31 (3.5%)	20 (4.4%)	11 (2.5%)		31 (4.7%)	0 (0.0%)	
ACEi or ARB	629 (70.4%)	321 (70.7%)	308 (70.2%)	0.858	587 (88.3%)	42 (18.4%)	**< 0.001**
Aldosterone antagonist	194 (21.7%)	115 (25.3%)	79 (18.0%)	**0.008**	181 (27.2%)	13 (5.7%)	**< 0.001**
Loop diuretic	547 (61.3%)	272 (59.9%)	275 (62.6%)	0.402	479 (72.0%)	68 (29.8%)	**< 0.001**
Length of follow-up (years)	2.8 (1.6–4.2)	2.7 (1.6–4.2)	2.8 (1.6–4.2)	0.952	2.9 (1.6–4.4)	2.5 (1.4–3.4)	**< 0.001**
Deaths	240 (26.9%)	123 (27.1%)	117 (26.7%)	0.882	177 (26.6%)	63 (27.6%)	0.765

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HR, heart rate; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure risk score; NT pro-BNP, *N*-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischemic attack; YRI, Yoruba in Ibadan, Nigeria.

[a]p-values are for the comparison between self-identified African–American versus White race. Bolded p-values indicate $p < 0.05$.

[b]p-values are for the comparison between patients treated with beta-blocker at baseline versus those that were not. Bolded p-values indicate $p < 0.05$.

[c]MAGGIC risk score was calculated without beta-blocker as an input variable.

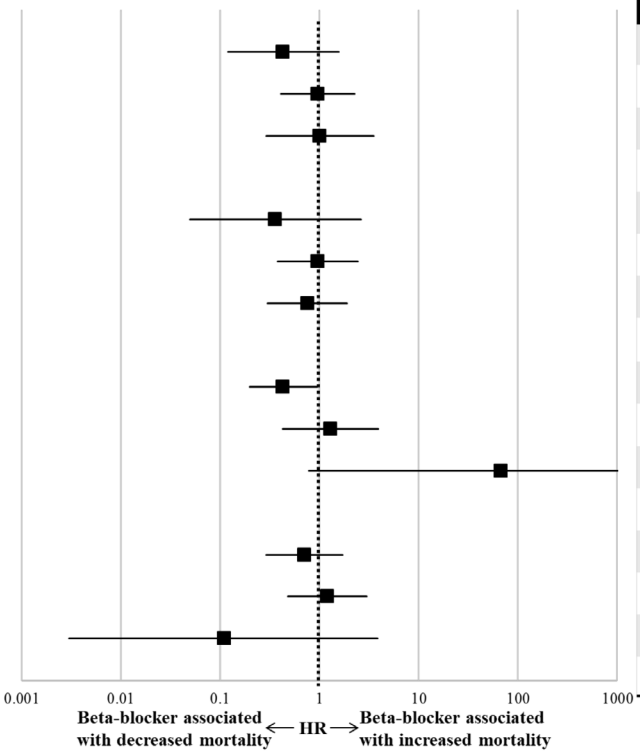
3.2 | Association of Pharmacogenetic Interactions of Pharmacodynamic Candidate Genetic Variants With Beta-Blocker Exposure With Survival in HFrEF Patients

Figures 1–3 and Figures S5–S16 show the pharmacogenetic interactions and genotype- and haplotype-stratified analyses of the 9 candidate genetic variants in *ADRB1*, *ADRB2*, *ADRA2C, GRK4*, and *GRK5* with beta-blocker exposure and their association with survival in HFrEF patients. Only one pharmacogenetic interaction was statistically significant after correction for multiple comparisons. The p-values for the *GRK4* Ala486Val*beta-blocker interaction were $p = 0.002$ and $p = 0.022$ before and after correction for multiple comparisons, respectively, in the African Americans (Figure 1). The *GRK4* Ala486Val genotype-stratified analyses trended in the hypothesized direction (Table 1), in which beta-blocker exposure was associated with less survival benefit in the African American HFrEF patients with additional alleles that decrease receptor function (Val486).

A few more of the pharmacogenetic interactions would have been statistically significant before correction for multiple comparisons but were not after. In the race-combined analyses of *ADRB1* variants and haplotype, the Arg389Gly*beta-blocker exposure and Ser49-Arg389 haplotype*beta-blocker exposure interactions had $p = 0.094$ and $p = 0.033$ before correction for multiple comparisons, respectively, but the p-values were $p = 0.994$ and $p = 0.363$ after correction for multiple comparisons (Figure 2). In the genotype- and haplotype-stratified analyses, the hazard ratios for these *ADRB1* variants and haplotype trend in the hypothesized direction (Table 1), in which the alleles that decrease adrenergic activity (*ADRB1* Gly49 and Gly389) are associated with less beta-blocker benefit. Indeed, patients with two copies of the increased adrenergic function Ser49-Arg389 haplotype appeared to have the most survival benefit from beta-blocker exposure. The interaction of *ADRA2C* $Del_{322\text{-}325}$*beta-blocker exposure had $p = 0.057$ and $p = 0.627$ before and after correction for multiple comparisons, respectively, in African Americans (Figure 3). The *ADRA2C* $Del_{322\text{-}325}$ genotype-stratified analyses trend in the hypothesized direction (Table 1). African American patients that are homozygous for *ADRA2C* $Del_{322\text{-}325}$ ($n = 53$) appear to have the most survival benefit from beta-blocker exposure.

4 | Discussion

Results from previous beta-blocker pharmacogenetic studies of the pharmacodynamic candidate genes *ADRB1*, *ADRB2*, *ADRA2C, GRK4*, and *GRK5* have been inconsistent [13]. Therefore, the purpose of this study was to provide additional evidence for or against their interaction with beta-blocker exposure in terms of survival benefit in a large and well-characterized cohort of HFrEF patients. Only one pharmacogenetic interaction reached statistical significance after correction for multiple comparisons: the interaction of *GRK4* Ala486Val with beta-blocker exposure significantly associated survival in African American HFrEF patients. Beta-blocker exposure only associated with a significant reduction in the risk for mortality in African Americans who were homozygous for the *GRK4* Ala486



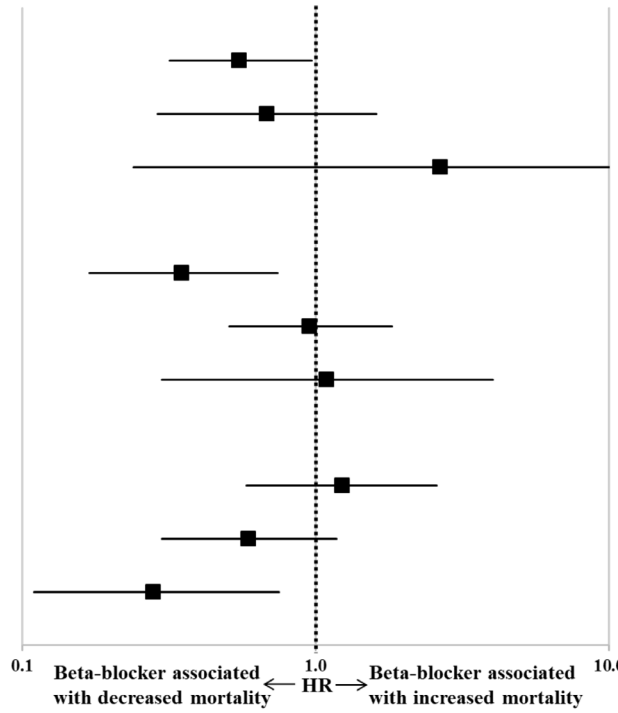
GRK4 Genotype/Haplotype	BB HR (95% CI)	p	p cor.	n
Arg65/Arg65	0.43 (0.12-1.55)	0.198	1.000	120
Arg65/Leu65	0.96 (0.41-2.27)	0.934	1.000	211
Leu65/Leu65	1.00 (0.29-3.49)	1.000	1.000	123
Arg65Leu*Beta-blocker interaction		0.261	0.888	454
Ala142/Ala142	0.36 (0.05-2.61)	0.310	1.000	64
Ala142/Val142	0.97 (0.38-2.48)	0.954	1.000	216
Val142/Val142	0.76 (0.30-1.90)	0.550	1.000	174
Ala142Val*Beta-blocker interaction		0.396	0.888	454
Ala486/Ala486	0.44 (0.20-0.96)	0.040	1.000	314
Ala486/Val486	1.29 (0.43-3.90)	0.656	1.000	129
Val486/Val486	65.2 (0.78-5,474)	0.065	1.000	11
Ala486Val*Beta-blocker interaction		0.002	**0.022**	454
0 Arg65-Ala142-Ala486 haplotypes	0.70 (0.29-1.70)	0.434	1.000	213
1 Arg65-Ala142-Ala486 haplotype	1.21 (0.49-3.02)	0.681	1.000	203
2 Arg65-Ala142-Ala486 haplotypes	0.10 (0.003-3.83)	0.219	1.000	38
Arg65-Ala142-Ala486 haplotype count*Beta-blocker interaction		0.342	0.888	454

FIGURE 1 | Pharmacogenetic interactions and associations of time-varying beta-blocker exposure with all-cause mortality stratified by the *GRK4* genotypes and haplotype in 454 African American HFrEF patients. Arg65Leu = rs2960306; Ala142Val = rs1024323; Ala486Val = rs1801058. BB = beta-blocker. Underlined alleles decrease adrenergic activity (Table 1) and are therefore expected to decrease beta-blocker-associated survival benefit (i.e., have a higher hazard ratio [HR] than the alternate allele). Models were adjusted for beta-blocker propensity score [29], MAGGIC (minus beta-blocker as an input variable) [28], and proportion of YRI (Yoruba in Ibadan, Nigeria) ancestry [25]. "P cor." refers to the *p*-value after correction for multiple comparisons by the adaptive Hochberg method [30]. "n" refers to the number of patients in the corresponding analysis. $p < 0.1$ for interaction tests after correction for multiple comparisons was a priori defined as statistically significant. Bolded *p*-values met this definition for statistical significance. The *x*-axis is on logarithmic scale. Black squares indicate the HR, and horizontal black lines indicate the 95% confidence intervals. The vertical dotted black line indicates HR = 1.

allele. One of the variants in *GRK4* also remained significantly associated with survival after correction for multiple comparisons, Ala142Val, in which it significantly associated with increased risk of mortality in the White patients independent of beta-blocker exposure. A few other pharmacogenetic results are possibly of interest, reaching significance in initial analysis but did not withstand adjustment for multiple comparisons. These included well-described variants in *ADRB1* (Arg389Gly and Ser49-Arg389Gly haplotype) and *ADRA2C* ($Del_{322\text{-}325}$; in African American HFrEF patients only). Thus, unfortunately, our study alone does not provide additional clarity to historically inconsistent results, but as our findings trend in the hypothesized direction, they may contribute to more definitive meta-analyses in the future.

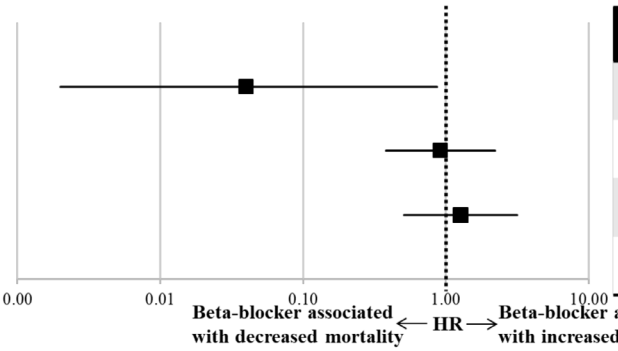
GRK4 desensitizes G-protein coupled receptors that regulate blood pressure, including dopamine receptors and potentially beta-1 adrenergic receptors (the primary target of beta-blockers) [12]. The 3 *GRK4* variants analyzed in this study all increase the ability of GRK4 to desensitize G-protein coupled receptors [12], and thus they have been hypothesized to act as an "endogenous beta-blocker" [12]. This means they are expected to protect against adverse cardiovascular outcomes but decrease patients' responses to exogenous beta-blockers. To our knowledge, only 2 previous studies investigated these *GRK4* variants with cardiovascular clinical outcomes and beta-blocker response [12, 31]. Bhatnagar et al. [31] found that *GRK4* Leu65 and Val142 significantly associated with longer time to achieve blood pressure response from metoprolol in 197 hypertensive African American men (but not hypertensive African American women). Vandell et al. [12] found that *GRK4* Leu65-Val142 haplotype associated with significantly reduced blood pressure response to atenolol in 768 African American and White hypertensive patients. The results from those 2 previous studies and ours for *GRK4* Ala486Val in African American HFrEF patients (but not in White patients) all support the "endogenous beta-blocker" hypothesis for these *GRK4* variants. However, there are still inconsistencies as to which specific *GRK4* variant or haplotype is associated with pharmacogenetic effect and in which race, sex, and beta-blocker indication (i.e., hypertension vs. HFrEF). Therefore, future research is still needed to elucidate the true effects of these 3 *GRK4* variants on beta-blocker response and the differences observed by sex, race, and indication.

Many previous pharmacogenetic studies have assessed *ADRB1* Ser49Gly and Arg389Gly with beta-blocker response because the beta-1 adrenergic receptor is the primary target of beta-blockers;



ADRB1 Genotype/Haplotype	BB HR (95% CI)	p	p cor.	n
Ser49/Ser49	0.56 (0.32-0.97)	0.038	0.912	587
Ser49/Gly49	0.68 (0.29-1.60)	0.374	0.913	270
Gly49/Gly49	2.65 (0.24-28.85)	0.425	0.913	36
Ser49Gly*Beta-blocker interaction		0.448	0.994	893
Arg389/Arg389	0.35 (0.17-0.74)	0.006	0.144	436
Arg389/Gly389	0.97 (0.51-1.82)	0.913	0.913	359
Gly389/Gly389	1.09 (0.30-4.01)	0.900	0.913	98
Arg389Gly*Beta-blocker interaction		0.094	0.994	893
0 Ser49-Arg389 haplotypes	1.23 (0.58-2.59)	0.594	0.913	248
1 Ser49-Arg389 haplotype	0.59 (0.30-1.18)	0.135	0.913	401
2 Ser49-Arg389 haplotypes	0.28 (0.11-0.75)	0.012	0.288	244
Ser49-Arg389 haplotype count*Beta-blocker interaction		0.033	0.363	893

FIGURE 2 | Pharmacogenetic interactions and associations of time-varying beta-blocker exposure with all-cause mortality stratified by *ADRB1* Ser49Gly and Arg389Gly genotypes and haplotype in 893 African American and White HFrEF patients. Ser49Gly = rs1801252 and Arg389Gly = rs1801253. BB = beta-blocker. Underlined alleles decrease adrenergic activity (Table 1) and are therefore expected to decrease beta-blocker-associated survival benefit (i.e., have a higher hazard ratio [HR] than the alternate allele). Models were adjusted for beta-blocker propensity score [29], MAGGIC (minus beta-blocker as an input variable) [28], and proportion of YRI (Yoruba in Ibadan, Nigeria) ancestry [25]. "P cor." refers to the *p*-value after correction for multiple comparisons by the adaptive Hochberg method [30]. "n" refers to the number of patients in the corresponding analysis. $p < 0.1$ for interaction tests after correction for multiple comparisons was a priori defined as statistically significant. The *x*-axis is on logarithmic scale. Black squares indicate the HR, and horizontal black lines indicate the 95% confidence intervals. The vertical dotted black line indicates HR = 1.



ADRA2C Genotype	BB HR (95% CI)	p	p cor.	n
Del/Del	0.05 (0.002-0.88)	0.041	1.000	53
Del/Ins	0.92 (0.38-2.23)	0.854	1.000	206
Ins/Ins	1.26 (0.51-3.14)	0.615	1.000	195
Del/Ins*Beta-blocker interaction		0.057	0.627	454

FIGURE 3 | Pharmacogenetic interactions and associations of time-varying beta-blocker exposure with all-cause mortality stratified by the *ADRA2C* Ins/$Del_{322\text{-}325}$ genotypes in 454 African American HFrEF patients. Rs7434630 (C > T) was used as a proxy for the *ADRA2C* Ins > $Del_{322\text{-}325}$ variant rs61767072. BB = beta-blocker. Underlined alleles decrease adrenergic activity (Table 1) and are therefore expected to decrease beta-blocker-associated survival benefit (i.e., have a higher hazard ratio [HR] than the alternate allele). Models were adjusted for beta-blocker propensity score [29], MAGGIC (minus beta-blocker as an input variable) [28], and proportion of YRI (Yoruba in Ibadan, Nigeria) ancestry [25]. "P cor." refers to the *p*-value after correction for multiple comparisons by the adaptive Hochberg method [30]. "n" refers to the number of patients in the corresponding analysis. $p < 0.1$ for interaction tests after correction for multiple comparisons was a priori defined as statistically significant. The *x*-axis is on logarithmic scale. Black squares indicate the HR, and horizontal black lines indicate the 95% confidence intervals. The vertical dotted black line indicates HR = 1.

the variants are common and nonsynonymous; and there is evidence to support functional effects of these variants in vitro, ex vivo, and in vivo [7, 13]. However, the findings from clinical studies of these *ADRB1* variants have been inconsistent [7, 13]. The CPIC beta-blocker guideline pointed out a trend in the clinical studies for the *ADRB1* Arg389Gly variant. When clinical pharmacogenetic studies took beta-blocker dose into account, and not just a binary beta-blocker treatment status as yes or no,

then the clinical evidence for a pharmacogenetic interaction of Arg389Gly (and possibly the Ser49-Arg389 haplotype as well) with beta-blocker response becomes more consistent. Our study, which also took beta-blocker dose into account, possibly supports that trend as well. Our results suggest that beta-blocker exposure is more effective in HFrEF patients that have more copies of the increased adrenergic function Ser49-Arg389 haplotype. However, future research is still needed in larger sample sizes or meta-analyses to confirm our results for *ADRB1* genotypes and haplotype because they were no longer statistically significant after correction for multiple comparisons.

Like the *ADRB1* variants, several pharmacogenetic studies have also analyzed the *ADRA2C* $Del_{322\text{-}325}$ variant and beta-blocker response because *ADRA2C* $Del_{322\text{-}325}$ is also common, nonsynonymous, and has in vitro and in vivo evidence to support effects on adrenergic function [7, 13]. There are also high-quality pharmacogenetic studies that have detected a significant association of *ADRA2C* $Del_{322\text{-}325}$ with beta-blocker response and those that have not [7, 13]. Our results suggest that beta-blocker exposure is more effective in African American HFrEF patients that are homozygous for the $Del_{322\text{-}325}$ allele, which is consistent with the increased adrenergic function with that allele. Given the much lower frequency of *ADRA2C* $Del_{322\text{-}325}$ in Europeans, our study was underpowered to detect a pharmacogenetic interaction in the White HFrEF patients. Future research is still needed in larger sample sizes or meta-analyses to confirm our results for *ADRA2C* $Del_{322\text{-}325}$ because they were no longer statistically significant after correction for multiple comparisons.

Other than our findings for *GRK4, ADRB1*, and *ADRA2C* variants described above, our study did not support hypotheses for the other pharmacodynamic candidate variants in *GRK5* or *ADRB2* [7, 13]. There are many possible reasons for nonreplication of pharmacogenetic findings, which is a very common problem. Only ~3% of pharmacogenetic findings are successfully replicated [32]. Methodological concerns and the "winner's curse" have been reviewed in detail elsewhere [33, 34]. Even though our sample size is relatively large, and we used one of the less conservative methods for controlling familywise type I error rate, our study was probably still underpowered to detect significant interactions after correction for multiple comparisons. However, given that the purpose of this study was validation and not discovery, and the results could have profound public health impact, we argue that a conservative approach for controlling the type I error rate was necessary. Another possible reason for nonreplication is that pharmacodynamic variants are expected to have more subtle effects than pharmacokinetic variants [35]. Variants with strong effects on adrenergic function, like loss-of-function variants in pharmacokinetic genes, would be harmful to the individual and thus not likely to be common. Aggregation of the individually small effects from multiple pharmacodynamic variants within the same pathway may have a cumulatively larger effect size that is more likely to be detectable (e.g., polygenic scores) [36, 37]. Moreover, it is very difficult to predict the best pharmacogenetic candidate genes from among the ~20,000 protein-coding genes in the human genome. Indeed, our previous study showed that 94% of significant genes identified in pharmacogenomic genome-wide association studies (GWAS) are *not* previously studied candidate genes [38]. In contrast to the candidate gene approach used in this and most previous beta-blocker pharmacogenetic studies [7, 13], we had consistent replication of results when we used a GWAS-based, polygenic score to predict beta-blocker-associated survival benefit in 4 independent datasets with nearly 8600 European ancestry HFrEF patients [36, 37]. Consistent with our previous analysis of other pharmacogenomic GWAS [38], none of the 44 genetic variants in our GWAS-based beta-blocker polygenic score are in the candidate pharmacodynamic genes analyzed in this study and others. Furthermore, none of these candidate pharmacodynamic genetic variants were detected in our GWAS of beta-blocker exposure and survival of HFrEF patients [24]. This suggests that future beta-blocker pharmacogenetic research should prioritize GWAS-based and polygenic approaches.

5 | Strengths & Limitations

Our study has several strengths and limitations. Strengths include the analysis of a clinical outcome instead of a surrogate measure of beta-blocker response, such as change in heart rate. We also analyzed time-varying beta-blocker exposure, and we calculated beta-blocker exposure from pharmacy claims instead of prescription data. We had similar representation of patients identifying as African American and White race, and we accounted for ancestry. We also did formal tests for pharmacogenetic interactions in addition to genotype-stratified analyses and corrected for multiple comparisons. Limitations of our study include that it is observational and single center, and it does not include patients identifying as races other than African American or White. The enrollment and follow-up periods occurred before the HF guidelines started recommending newer therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors. This study only analyzed the interaction of each individual genetic variant with beta-blocker exposure, and not the combined effects of multiple pharmacodynamic genetic variants, such as with a polygenic score or more complex epistatic interactions. This study did not assess other kinds of clinical outcomes, such as hospitalizations or heart transplants, nor did it assess specific causes of death. This study was probably still underpowered to detect significant interactions after correction for multiple comparisons and interactions with specific beta-blockers.

6 | Conclusions

Interactions of *ADRB1* Arg389Gly, *ADRB1* Ser49-Arg389Gly haplotype, *ADRA2C* $Del_{322\text{-}325}$, and *GRK4* Ala486Val with beta-blocker exposure in survival models of African American and White patients with HFrEF were significant before correction for multiple comparisons, but only the interaction for *GRK4* Ala486Val remained significant in African Americans after correction for multiple comparisons. Beta-blocker exposure only associated with a significant reduction in the risk of mortality in the African American HFrEF patients with the *GRK4* Ala486/Ala486 genotype. Larger sample sizes or meta-analyses are needed to have more statistical power to better assess beta-blocker pharmacogenetic interactions for *ADRB1* Arg389Gly, *ADRB1* Ser49-Arg389Gly haplotype, and *ADRA2C* $Del_{322\text{-}325}$ in the future.

Author Contributions

J.A.L., S.D.R.L., A.I.L.M., B.L., R.S., and D.E.L. wrote the manuscript; J.A.L. and D.E.L. designed the research; J.A.L., S.D.R.L., A.I.L.M., B.L., and R.S. performed the research; J.A.L., S.D.R.L., A.I.L.M., and R.S. analyzed the data.

Acknowledgments

The following AI tools were used in drafting assistance and only to improve readability and language: University of Michigan GPT and Perplexity AI. The authors reviewed all AI responses and remain responsible for all submitted work. The authors would also like to thank Amisha Kalmat for assisting with formatting the manuscript for submission.

Conflicts of Interest

J.A.L. is a consultant for Ariel Precision Medicine. D.E.L. is a consultant for Abbott Laboratories, Astra Zeneca, Illumina, Janssen, Martin Pharmaceuticals, DCRI (Novartis), and ARMGO, and has participated in clinical research from Akros, AstraZeneca, Pfizer, Lilly, Novartis, Somalogic, and Janssen, and has a patent (held by Henry Ford Health) for a beta-blocker response polygenic score. All other authors declared no competing interests for this work.

Data Availability Statement

Much of the data underlying this article are publicly available in the National Center for Biotechnology and Information (NCBI) Database of Genotypes and Phenotypes (dbGaP) at https://www.ncbi.nlm.nih.gov/gap/ and can be accessed with dbGaP Study Accession: phs001501.v1.p1, and additional data can be provided by request.

References

1. B. Shahim, C. J. Kapelios, G. Savarese, and L. H. Lund, "Global Public Health Burden of Heart Failure: An Updated Review," *Cardiac Failure Review* 9 (2023): e11.

2. P. A. Heidenreich, B. Bozkurt, D. Aguilar, et al., "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," *Circulation* 145, no. 18 (2022): 101161cir0000000000001063, https://doi.org/10.1161/CIR.0000000000001063.

3. M. Metra, S. Nodari, G. Parrinello, R. Giubbini, C. Manca, and L. Dei Cas, "Marked Improvement in Left Ventricular Ejection Fraction During Long-Term Beta-Blockade in Patients With Chronic Heart Failure: Clinical Correlates and Prognostic Significance," *American Heart Journal* 145, no. 2 (2003): 292–299.

4. J. Lupón, C. Díez-López, M. de Antonio, et al., "Recovered Heart Failure With Reduced Ejection Fraction and Outcomes: A Prospective Study," *European Journal of Heart Failure* 19, no. 12 (2017): 1615–1623.

5. L. Gullestad, J. Wikstrand, P. Deedwania, et al., "What Resting Heart Rate Should One Aim for When Treating Patients With Heart Failure With a Beta-Blocker? Experiences From the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF)," *Journal of the American College of Cardiology* 45, no. 2 (2005): 252–259.

6. MERIT-HF Investigators, "Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)," *Lancet* 353, no. 9169 (1999): 2001–2007.

7. J. A. Talameh and D. E. Lanfear, "Pharmacogenetics in Chronic Heart Failure: New Developments and Current Challenges," *Current Heart Failure Reports* 9, no. 1 (2012): 23–32.

8. K. S. Parikh, M. Fiuzat, G. Davis, et al., "Dose Response of β-Blockers in Adrenergic Receptor Polymorphism Genotypes," *Circulation: Genomic and Precision Medicine* 11, no. 8 (2018): e002210.

9. L. A. Guerra, C. Lteif, M. J. Arwood, et al., "Genetic Polymorphisms in ADRB2 and ADRB1 Are Associated With Differential Survival in Heart Failure Patients Taking β-Blockers," *Pharmacogenomics Journal* 22, no. 1 (2022): 62–68, https://doi.org/10.1038/s41397-021-00257-1.

10. J. A. Luzum, J. D. English, U. S. Ahmad, et al., "Association of Genetic Polymorphisms in the Beta-1 Adrenergic Receptor With Recovery of Left Ventricular Ejection Fraction in Patients With Heart Failure," *Journal of Cardiovascular Translational Research* 12, no. 4 (2019): 280–289.

11. S. B. Liggett, S. Cresci, R. J. Kelly, et al., "A GRK5 Polymorphism That Inhibits Beta-Adrenergic Receptor Signaling Is Protective in Heart Failure," *Nature Medicine* 14, no. 5 (2008): 510–517.

12. A. G. Vandell, M. T. Lobmeyer, B. E. Gawronski, et al., "G Protein Receptor Kinase 4 Polymorphisms: β-Blocker Pharmacogenetics and Treatment-Related Outcomes in Hypertension," *Hypertension* 60, no. 4 (2012): 957–964.

13. J. D. Duarte, C. D. Thomas, C. R. Lee, et al., "Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6, ADRB1, ADRB2, ADRA2C, GRK4, and GRK5 Genotypes and Beta-Blocker Therapy," *Clinical Pharmacology and Therapeutics* 116, no. 4 (2024): 939–947.

14. J. A. Luzum, E. Peterson, J. Li, et al., "Race and Beta-Blocker Survival Benefit in Patients With Heart Failure: An Investigation of Self-Reported Race and Proportion of African Genetic Ancestry," *Journal of the American Heart Association* 7, no. 10 (2018): e007956.

15. D. Lanfear, E. Peterson, K. Wells, and L. K. Williams, "Discharge Medication Status Compares Poorly With Claims-Based Outpatient Medication Exposure Estimates," *Circulation. Cardiovascular Quality and Outcomes* 4, no. Suppl 2 (2015): AP234.

16. M. C. Levin, S. Marullo, O. Muntaner, B. Andersson, and Y. Magnusson, "The Myocardium-Protective Gly-49 Variant of the Beta 1-Adrenergic Receptor Exhibits Constitutive Activity and Increased Desensitization and Down-Regulation," *Journal of Biological Chemistry* 277, no. 34 (2002): 30429–30435.

17. D. A. Rathz, K. M. Brown, L. A. Kramer, and S. B. Liggett, "Amino Acid 49 Polymorphisms of the Human beta1-Adrenergic Receptor Affect Agonist-Promoted Trafficking," *Journal of Cardiovascular Pharmacology* 39, no. 2 (2002): 155–160.

18. D. A. Mason, J. D. Moore, S. A. Green, and S. B. Liggett, "A Gain-Of-Function Polymorphism in a G-Protein Coupling Domain of the Human Beta1-Adrenergic Receptor," *Journal of Biological Chemistry* 274, no. 18 (1999): 12670–12674.

19. S. A. Green, J. Turki, M. Innis, and S. B. Liggett, "Amino-Terminal Polymorphisms of the Human Beta 2-Adrenergic Receptor Impart Distinct Agonist-Promoted Regulatory Properties," *Biochemistry* 33, no. 32 (1994): 9414–9419.

20. K. M. Small, S. L. Forbes, F. F. Rahman, K. M. Bridges, and S. B. Liggett, "A Four Amino Acid Deletion Polymorphism in the Third Intracellular Loop of the Human Alpha 2C-Adrenergic Receptor Confers Impaired Coupling to Multiple Effectors," *Journal of Biological Chemistry* 275, no. 30 (2000): 23059–23064.

21. A. Neumeister, D. S. Charney, I. Belfer, et al., "Sympathoneural and Adrenomedullary Functional Effects of alpha2C-Adrenoreceptor Gene Polymorphism in Healthy Humans," *Pharmacogenetics and Genomics* 15, no. 3 (2005): 143–149.

22. R. A. Felder, H. Sanada, J. Xu, et al., "G Protein-Coupled Receptor Kinase 4 Gene Variants in Human Essential Hypertension," *Proceedings of the National Academy of Sciences of the United States of America* 99, no. 6 (2002): 3872–3877.

23. S. Das, L. Forer, S. Schonherr, et al., "Next-Generation Genotype Imputation Service and Methods," *Nature Genetics* 48, no. 10 (2016): 1284–1287.

24. J. A. Luzum, A. M. Campos-Staffico, J. Li, et al., "Genome-Wide Association Study of Beta-Blocker Survival Benefit in Black and White Patients With Heart Failure With Reduced Ejection Fraction," *Genes (Basel)* 14, no. 11 (2023): 2019.

25. N. Patterson, N. Hattangadi, B. Lane, et al., "Methods for High-Density Admixture Mapping of Disease Genes," *American Journal of Human Genetics* 74, no. 5 (2004): 979–1000.

26. M. J. Machiela and S. J. Chanock, "LDlink: A Web-Based Application for Exploring Population-Specific Haplotype Structure and Linking Correlated Alleles of Possible Functional Variants," *Bioinformatics* 31, no. 21 (2015): 3555–3557.

27. M. Stephens, N. J. Smith, and P. Donnelly, "A New Statistical Method for Haplotype Reconstruction From Population Data," *American Journal of Human Genetics* 68, no. 4 (2001): 978–989.

28. S. J. Pocock, C. A. Ariti, J. J. McMurray, et al., "Predicting Survival in Heart Failure: A Risk Score Based on 39 372 Patients From 30 Studies," *European Heart Journal* 34, no. 19 (2013): 1404–1413.

29. R. B. D'Agostino, Jr., "Propensity Score Methods for Bias Reduction in the Comparison of a Treatment to a Non-Randomized Control Group," *Statistics in Medicine* 17 (1998): 2265–2281, https://doi.org/10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b.

30. Y. Hochberg and Y. Benjamini, "More Powerful Procedures for Multiple Significance Testing," *Statistics in Medicine* 9, no. 7 (1990): 811–818.

31. V. Bhatnagar, D. T. O'Connor, V. H. Brophy, et al., "G-Protein-Coupled Receptor Kinase 4 Polymorphisms and Blood Pressure Response to Metoprolol Among African Americans: Sex-Specificity and Interactions," *American Journal of Hypertension* 22, no. 3 (2009): 332–338.

32. S. Aslibekyan, S. A. Claas, and D. K. Arnett, "To Replicate or Not to Replicate: The Case of Pharmacogenetic Studies: Establishing Validity of Pharmacogenomic Findings: From Replication to Triangulation," *Circulation. Cardiovascular Genetics* 6, no. 4 (2013): 409–412.

33. A. L. Jorgensen and P. R. Williamson, "Methodological Quality of Pharmacogenetic Studies: Issues of Concern," *Statistics in Medicine* 27, no. 30 (2008): 6547–6569.

34. J. A. Talameh and H. L. McLeod, "PON1 Q192R and Clopidogrel: A Case of the Winner's Curse or Inadequate Replication?," *Clinical Pharmacology and Therapeutics* 90, no. 6 (2011): 771–774, https://doi.org/10.1038/clpt.2011.226.

35. J. A. Johnson and J. J. Lima, "Drug Receptor/Effector Polymorphisms and Pharmacogenetics: Current Status and Challenges," *Pharmacogenetics* 13, no. 9 (2003): 525–534.

36. D. E. Lanfear, J. A. Luzum, R. She, et al., "Polygenic Score for β-Blocker Survival Benefit in European Ancestry Patients With Reduced Ejection Fraction Heart Failure," *Circulation. Heart Failure* 13, no. 12 (2020): e007012, https://doi.org/10.1161/CIRCHEARTFAILURE.119.007012.

37. D. E. Lanfear, J. A. Luzum, R. She, et al., "Validation of a Polygenic Score for Beta-Blocker Survival Benefit in Patients With Heart Failure Using the United Kingdom Biobank," *Circulation: Genomic and Precision Medicine* 16, no. 2 (2023): e003835.

38. D. W. Linskey, D. C. Linskey, H. L. McLeod, and J. A. Luzum, "The Need to Shift Pharmacogenetic Research From Candidate Gene to Genome-Wide Association Studies," *Pharmacogenomics* 22, no. 17 (2021): 1143–1150.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.