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Genetic Polymorphisms in *ADRB2* and *ADRB1* Are Associated with Differential Survival in Heart Failure Patients Taking β-Blockers

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Abstract

Single nucleotide polymorphisms (SNPs) have been associated with differential beta-blocker (BB) effects on heart rate, blood pressure, and left ventricular ejection fraction in various patient populations. This study aimed to determine if SNPs previously associated with BB response are also associated with differential survival in heart failure (HF) patients receiving BBs. HF patient data were derived from electronic health records and the Social Security Death Index. Associations and interactions between BB dose, SNP genotype, and the outcome of death were assessed using a Cox proportional hazard model adjusting for covariates known to be associated with differential survival in HF patients. Two SNPs, *ADRB1* Arg389Gly and *ADRB2* Glu27Gln, displayed significant interactions (P_{int} = 0.043 and P_{int} = 0.017, respectively) with BB dose and their association with mortality. Our study suggests that *ADRB2* 27Glu and *ADRB1* 389Arg may confer a larger survival benefit with higher BB doses in patients with HF.

INTRODUCTION

Heart failure (HF) is a highly prevalent disease, with an estimated 6 million American adults diagnosed with the disease every year (1). HF is associated with high levels of morbidity and

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Author Contributions

JDD conceived the work; JDD and CL designed the project; MJA, AAD, LHC, and JDD collected the data; LAG, LD, CM and CL completed the analysis; LAG and CL wrote the manuscript; MJA, AAD, LHC, CM, LD and JDD edited the manuscript.

Conflict of interest

The authors declare no competing interests.

mortality. In the U.S., the 5-year mortality rate after hospitalization for HF is approximately 53%, and the yearly financial burden is estimated to be approximately $70 billion by 2030 (1). The disease is delineated by a cascade of interconnecting neurohormonal activations of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system. These activations are compensatory at first, but chronic activation of these systems results in adverse hemodynamic and cardiotoxic effects such as renal sodium retention, ventricular remodeling, and vasoconstriction, all of which can lead to the gradual progression of HF and worsening cardiac function (2, 3).

The first-line pharmacological treatment for HF with reduced ejection fraction (HFrEF) includes either angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), or angiotensin receptor/neprilysin inhibitors (ARNIs), in combination with beta-blockers (BBs) (4, 5). However, for HF with preserved ejection fraction (HFpEF), the use of BBs has not been well-established, with their clinical utility predominantly involving treatment of hypertension in the setting of HFpEF (5). BBs are competitive antagonists of the β-adrenergic receptors, which reduce the level of sympathetic nervous system activation within the cardiovascular system. BB treatment is associated with a reduction in morbidity and mortality risk in HFrEF patients (4-6). Further, we previously found that BB dose escalation was more strongly associated than ACE inhibitor or ARB dose with a reduced mortality risk in a racially diverse mixed HFrEF and HFpEF population (7).

Variability in response to BBs among HF patients may, in part, be explained by interindividual genetic variability (8, 9). Examples of such variations are the single nucleotide polymorphisms (SNPs) in beta-adrenergic signaling genes, such as *ADRB1* and *ADRB2*, which encode for the β_1 - adrenergic receptor (AR) and β_2 – AR, respectively. Genetic variants that modulate the activity of these receptors in response to a BB have been previously described in the literature, with certain genotypes exhibiting a greater reduction in blood pressure, left ventricular ejection fraction (LVEF) improvement, and/or survival benefit with BB use (10). *GNB3* encodes for the regulatory subunit of the trimeric G protein, a key transducer for the AR signals. Previous studies have demonstrated that genetic polymorphisms in the AR signaling pathway such as *ADRB2* Arg16Gly (rs1042713) and Gln27Glu (rs1042714), *ADRB1* Ser49Gly (rs1801252) and Arg389Gly (rs1801253), as well as *GNB3* Ser275Ser (more commonly referred as C825T; rs5443), can influence drug response and cardiovascular risk (Supplementary Table 1) (9, 11-14). However, other studies failed to show associations between all-cause mortality of HF patients on a BB and the variants in these genes (12, 15, 16). Therefore, we aimed to assess the role of these five candidate polymorphisms on BB response variability as measured by survival in a diverse mixed HFrEF and HFpEF population.

METHODS

Study Population

Patients diagnosed with HF, either HFrEF or HFpEF, were recruited from cardiology clinics at the University of Illinois at Chicago (UIC) from November 2001 to September 2015. Follow-up terminated in November 2015. All patients provided written, informed consent prior to participation. The UIC Institutional Review Board approved this study, and the

procedures followed were in accordance with institutional guidelines. Patient data were manually extracted from the electronic health records and the Social Security Death Index. Patients who did not experience an event (i.e., death) during the study period, or were lost to follow-up, were censored. Age was obtained at the time of event or censoring. Age at censoring was defined as the patient's age at their last contact within the observation period or when the Social Security Death Index was last checked, whichever occurred last. Patient data, including medication use, and blood samples for genotyping, were collected as near as possible to the time of recruitment. Medication prescribing and dosing were at the cardiologist's discretion. BBs, ACEIs, ARBs, and loop diuretic doses were separated into low, medium, and high dose levels based on drug manufacturer prescribing information and doses used in published HF trials (Table 1) (6, 17-35). The medication dose levels were categorized based on the doses at enrollment. The mean doses that the patients were on in the major published HF trials were used to define the medium dose ranges. The low dose levels included the starting doses and lower doses of the titration steps, and the high dose levels were defined based on the higher doses of the titration steps and/or the target doses achieved. Our primary analysis aimed to identify the association of the candidate SNPs and their interactions with BB dose levels, with survival in HF patients on BBs using a regression model, as previously described (7).

Genotyping

DNA was isolated from blood samples provided at the time of enrollment. DNA samples were stored at −80 °C, and all samples were genotyped using the Affymetrix Axiom PanAfrican Array (Thermo Fisher Scientific, Waltham, MA) toward the end of recruitment. Genotyping was performed per the manufacturer's recommendations. The Axiom PanAfrican Array is a three-array set that, in addition to comprehensive coverage in those of European descent, offers ≥90% genetic coverage of common and rare variants (MAF >2%) of the Yoruba (West African) genome and >85% coverage of common and rare variants (MAF >2%) of the Luhya and Maasi (East African) genomes (36). It also offers >85% of genomic coverage in admixed populations with West African ancestry (36). Quality control procedures were completed, including the removal of samples with low call rate, sex mismatch, or outliers identified by the identity by state clustering analysis. SNPs with genotyping call rate less than 95% across all plates were removed, and patients with two or more passed plates were included in the final data set. Additional genotypes were imputed using the National Heart, Lung, and Blood Institute TOPMed Imputation Server (37, 38). The genotypes for Arg16Gly and Gln27Glu (in *ADRB2*) were typed. Estimated genotype data for the imputed SNPs – Ser49Gly, Arg389Gly (in *ADRB1*), and Ser275Ser (in *GNB3*) – were assigned and extracted using PLINK v.2.0. Hardy-Weinberg equilibrium was assessed using the chi-square goodness-of-fit test, and SNPs with *P*-values of ≤ 0.05 were flagged.

Statistical Analysis

Patient baseline characteristics were computed as means and standard deviations for normally distributed continuous variables, medians and interquartile ranges for non-normally distributed continuous variables, and percentages and counts for categorical variables. For each drug included in the analyses, high, medium, and low doses were

separated into dose levels as described previously (Table 1) (7). The SNPs, *ADBR2* Arg16Gly and Gln27Glu, *ADBR1* Arg389Gly and Ser49Gly, and *GNB3* Ser275Ser, were selected based on previous evidence in the literature showing some sort of association with beta-blocker response in patients with cardiovascular disease (9, 11-14, 39, 40). Heterogeneity comparisons between genotype and BB dose level were assessed using chi-squared tests.

Associations and interactions between BB dose, SNP genotype, and the outcome of death were assessed using a Cox proportional-hazard model to estimate hazard ratios (HRs) with two-sided 95% confidence intervals (CIs) and are presented with corresponding *P*-values. The model was first tested for a disease-genetic effect by analyzing the association between each SNP genotype and death; then, the interaction between BB dose and SNP genotype was added to test for a pharmacogenetic effect. First, a base model was created and included only well-established variables associated with differential survival in HF patients. Data were collected as close as possible to the recruitment time. These variables included age at event or censoring, self-reported race, sex, BB dose level, smoking history, implantable cardioverter defibrillator and New York Heart Association (NYHA) functional class. These clinical demographics have been shown to be associated with survival in the literature and have been repeatedly included in validated models predicting survival in HF patients (5, 41-44). Second, a comprehensive model, previously developed in our population (7), was used and included the variables from the base model in addition to ACEI/ARB dose level, aldosterone receptor antagonist (ARA) use, loop diuretic dose level, statin use, nitrate use, hydralazine use, and potassium supplement use. It also included additional medical history, such as a history of ischemic cardiomyopathy, atrial fibrillation/flutter, type 2 diabetes mellitus, obesity (body mass index ≥ 30), creatinine clearance (estimated by the Cockcroft-Gault equation), systolic blood pressure, and serum sodium levels (7).

A polygenic score analysis was also performed by combining the BB "dose-response alleles" in *ADBR2* (Glu27 allele) and *ADBR1* (Arg389 allele). The BB dose-response alleles were defined as those associated with a more pronounced survival stratification by BB dose level. The combined score and its interaction with BB dose were analyzed for their association with survival using the comprehensive model described above.

A sensitivity analysis was conducted to determine whether overall results were consistent by race. Because African Americans (AAs) made up a majority of the patient population, we conducted mortality analyses using the comprehensive model as described above in the subpopulation of self-reported AA patients as well as in the non-AA subpopulation. A second sensitivity analysis was conducted using the comprehensive model to determine if the observed effects were consistent between HFrEF and HFpEF patients separately.

Time-to-event data were analyzed using Kaplan-Meier estimates of survival curves, using the patient's age at study enrollment to the occurrence of an event (i.e., death) or censoring. The interaction term was used to establish a difference in BB dose-effect by genotype. The proportional-hazards assumption was tested for each covariate by correlating the corresponding set of scaled Schoenfeld residuals with a suitable time transformation (45). The influential observations or outliers were tested by visualizing the DFBETAS, as

previously described (46). A *P*-value of ≤ 0.05 was considered statistically significant, and all statistical analyses were performed using R version 3.6.2.

RESULTS

Study Cohort

The total HF patient population consisted of 353 patients, with genotype data available for 327 patients after quality control. After removing patients who were not prescribed BBs, the final patient population totaled 308 with 48.7% on metoprolol ER, 41.9% on carvedilol IR and 2.60% on carvedilol ER (Supplementary Table 2 and 3). The population was racially diverse, with 74.1% of African ancestry, 14.6% Latino, 10.4% of European ancestry, and 0.9 % Asian ancestry. The mean age at event or censoring was 62.8 years (Table 2). During the observation period, 70 out of 308 (22.7%) patients died during a mean follow-up of 3.8 years.

All alleles were in Hardy-Weinberg equilibrium. The distribution of BB dose level was similar by genotype, except for Ser275Ser (Chi-squared = 14.16, $P = 0.007$). Due to the differences in the BB dose prescribed by genotype, the *GNB3* Ser275Ser SNP was excluded as these differences could potentially confound our pharmacogenetic analysis (Supplementary Figure 1).

Clinical Outcomes

In the primary survival analysis using the base model, Gln27Glu (in *ADRB2*) was not associated with all-cause mortality in an additive genetic model (adjusted HR = 0.91, 95% CI: 0.62 – 1.34, $P = 0.647$); and the association of the genotype-BB dose interaction with all-cause mortality was not significant ($P_{int} = 0.088$). Using the comprehensive model, Gln27Glu was not associated with all-cause mortality (adjusted HR = 0.96, 95% CI: 0.64 – 1.44; $P = 0.858$); however, we observed a significant interaction between BB dose and genotype with all-cause mortality ($P_{int} = 0.017$). Each addition of a Glu27 allele led to a more pronounced stratification of the curves, with patients with the Glu27Glu genotype appearing to receive the greatest survival benefit from target BB doses (Figure 1). While patients with the Gln27Glu genotypes appeared to benefit from increased BB doses, survival stratification was less prominent; patients with the Gln27Gln genotype did not appear to benefit from target BB doses.

For Arg389Gly (in *ADRB1*), no significant association was identified in the base model between the genotype and survival (adjusted HR = 0.97, 95% CI: 0.68 – 1.39, $P = 0.863$), but a significant association was identified between the genotype-BB dose interaction and survival ($P_{int} = 0.026$). Similar associations were observed with the comprehensive model for the Arg389Gly genotype alone (adjusted HR = 0.99, 95% CI: 0.67 – 1.48, $P = 0.979$) and for the significant association between the genotype-BB dose interaction and survival ($P_{int} = 0.043$). Patients with the Arg389Arg genotype seemed to receive the most benefit from increased BB doses (Figure 2). However, with each addition of the Gly389 allele, the survival curves converge, and patients with the homozygous variant Gly389Gly genotype

appeared to experience an inverse effect, with lower survival observed at higher BB dose (Figure 2).

No significant associations with all-cause mortality or drug-genotype interaction were observed with Arg16Gly (*ADRB2*) or Ser49Gly (*ADRB1*).

For the polygenic score analysis, no significant association was identified in the comprehensive model for the combined genotype alone (adjusted HR = 0.99, 95% CI: 0.75 – 1.30, $P = 0.915$), but there was a significant association between the combined genotype-BB dose interaction and survival ($P_{int} = 0.001$) (Supplementary Table 4). Patients with 0 or 1 response allele at Gln27Glu in *ADRB2* (27Glu) and/or Arg389Gly in *ADRB1* (389Arg) did not seem to receive benefit from increased BB doses (Figure 3). However, patients with 2 response alleles seemed to benefit, and patients with 3 to 4 response alleles seemed to benefit the most from higher BB doses (Figure 3).

To assess whether a subpopulation drove the observed genotype-BB dose effects in our cohort, sensitivity analyses were performed using the comprehensive model. The first sensitivity analysis was conducted by race. In the AA subset, the *ADRB2* Gly27 allele was not associated with all-cause mortality (adjusted HR = 0.90, 95% CI: 0.50 – 1.60, $P = 0.719$), and the genotype-BB dose interaction did not reach significance ($P_{int} = 0.10330$). In the smaller non-AA subset, Gln27Glu and the genotype-BB dose interaction had no significant associations with all-cause mortality (adjusted HR = 1.41, 95% CI: 0.53 – 3.75, $P = 0.489$, and $P_{int} = 0.364$, respectively).

The associations of Arg389Gly and the genotype-BB dose interaction were similar to the overall population in the AA subset, with the genotype not being associated with survival (adjusted HR = 0.64, 95% CI: 0.38 – 1.08, $P = 0.094$), but the genotype-BB dose interaction having a significant association with survival ($P_{int} = 0.045$). However, both Arg389Gly and the genotype-BB dose interaction were not significantly associated with survival in the non-AA subset (adjusted HR = 0.90, 95% CI: 0.31 – 2.59, $P = 0.846$, and $P_{int} = 0.443$, respectively).

Lastly, the second sensitivity analysis involved testing mortality associations by HF type. In the HFrEF subgroup, the direction of effect of Gln27Glu and of the genotype-BB dose interaction with survival appeared consistent with our overall cohort, but with lack of an association for the genotype-BB dose interaction (HR = 0.65, 95% CI: 0.35 – 1.21, $P = 0.174$, and $P_{int} = 0.273$, respectively). These associations were weaker in the smaller HFpEF subset compared with the overall population for the Gln27Glu genotype (HR = 0.97, 95% CI: 0.49 – 1.92, $P = 0.938$), as well as for the genotype-BB dose interaction, which was significant ($P_{int} = 0.049$). As for Arg389Gly, the association of the genotype and of the genotype-BB dose interaction with all-cause mortality were similar to the overall cohort for the HFrEF subset with a significant interaction (HR = 0.75, 95% CI: 0.42 – 1.32, $P = 0.315$ and $P_{int} = 0.023$, respectively), and were not significant in the smaller HFpEF subset (adjusted HR = 1.25, 95% CI: 0.58 – 2.70, $P = 0.563$, and $P_{int} = 0.449$, respectively).

DISCUSSION

The major finding from this study was the interactions of Gln27Glu (*ADRB2*) and Arg389Gly (*ADRB1*) genotypes were significantly associated with BB dose and exhibited a difference in survival by BB dosage in our racially diverse HF population, which is in line with our previous association between BB dose and increased survival without accounting for genotype (7). In this study, we selected five candidate polymorphisms within the adrenergic receptor signaling pathway, based on previous evidence in the literature associating them with differential response to BBs. We then conducted a survival analysis, using real-world data, to test the association of these SNPs and their interaction with BB dose with survival (7). For the *ADRB2* SNP (Gln27Glu), patients with the Gln27Gln genotype achieved nominal benefit from a higher BB dose. However, the Glu27Glu genotype appeared to confer the most survival benefit from a high BB dose, suggesting the importance of a dose increase in patients with this genotype. For the *ADRB1* SNP (Arg389Gly), patients with the Arg389Arg genotype seemed to receive the most benefit from a high BB dose. Compared to the Arg389Arg and Arg389Gly genotypes, HF patients with the Gly389Gly genotype had an inverse relationship to BB dose level, suggesting that increasing BB dosage may not improve clinical outcomes in patients with this specific genotype.

Previous work has suggested that the β_2 -adrenergic receptor may play a significant role in the stimulation of failing hearts due to higher cardiac expression of the receptor in this disease state (47). In fact, homozygous or heterozygous patients for the Glu27 polymorphism (*ADRB2*) were more likely to have an increase in their LVEF or left ventricular fractional shortening with carvedilol treatment in comparison to those who were homozygous for the Gln27 allele (48). Similarly, in another study, the Glu27-homozygous genotype has been associated with a greater increase in left ventricular ejection fraction with carvedilol in patients with chronic HF (49). For Gln27Glu and Arg16Gly in *ADRB2*, a meta-analysis including data from three clinical trials (PEAR, PEAR-2, and INVEST) validated the association of these polymorphisms with negative chronotropic response to β-blockade with atenolol and metoprolol in patients with hypertension (14). The Gln27 allele for Gln27Glu polymorphism was shown to be significantly associated with a reduced heart rate in response to the BBs (14). In the setting of HF, an increase in heart rate maintains cardiac output as stroke volume falls; however, this compensation can be counterproductive in the short term since it gives less time for diastolic filling, and in the long term, a faster heart rate can contribute to myocardial weakening and dysfunction (50). Moreover, the Glu27Glu genotype exhibited the most pronounced survival benefit from high BB doses in our population. Since this genotype was previously associated with less heart rate reduction with BBs with the possible long-term consequences reflected in our survival analysis (14), it emphasizes the importance of titrating particularly BB doses in patients with this genotype.

For our second major finding, Arg389Gly (*ADRB1*) was previously shown not to be associated with left ventricular ejection fraction recovery in patients with HFrEF, but the majority of patients included in that study were of European descent and the authors did not account or adjust for any treatment variables or interactions between genotype and treatment (51). On the other hand, the Arg389Arg homozygous genotype has been associated with

improved left ventricular ejection fraction, heart rate, and blood pressure in response to metoprolol treatment in different racial populations of healthy volunteers, hypertensive patients, or patients with HFrEF (11, 52, 53). A sub-study of HF-ACTION found that Arg389Arg patients with chronic HF had a two-fold increased risk of all-cause mortality on low-dose BB compared with high-dose BB. This significant difference was not seen in Gly389 carriers (54). The sub-study of the BEST trial included HFrEF patients with NYHA class III-IV and showed that all-cause mortality and HF hospitalization were significantly lower in patients with the Arg389Arg genotype treated with bucindolol compared with placebo (55). This significant difference was not detected in carriers of the Gly389 allele (55). While titration of BBs is a key treatment recommendation for HFrEF, our findings combined with previous literature show that patients with the Arg389Arg (*ADRB1*) genotype seem to gain the greatest survival benefit from BBs. Our findings expand these previous findings by showing their consistency in more racially diverse populations.

Studied individually, Gln27Glu (*ADRB2*) and Arg389Gly (*ADRB1*) have not been shown to be consistently associated with mortality (15, 16, 56, 57). As our polygenic analysis showed, the association of the genotype-BB dose interaction with survival was even stronger when taking into consideration the number of BB dose-response alleles at both SNPs combined. Interestingly, one study investigated the combination of both genotypes and found that patients with chronic HF treated with carvedilol and were homozygous for *ADRB1* Arg389 and carriers of *ADRB2* Gln27 had a significantly lower survival rate than patients with other genotype combinations (58). However, this study did not account for the pharmacogenetic effect of the SNPs with BBs; whereas our study analyzed the association of the combined genotype-BB dose interaction with survival, taking into account the pharmacogenetic effect of the two SNPs. This highlights the potential necessity of considering both genotypes when prescribing BBs to patients with HF.

The *ADRB1* SNP Ser49Gly showed no significant associations in our study. This is consistent with previous data in the literature showing that the Ser49Gly SNP is less commonly associated with clinical outcomes compared with the Arg389Gly SNP (54). Lastly, Arg16Gly (in *ADRB2*) was not associated with all-cause mortality. Our findings for Arg16Gly appear inconsistent with a recent study showing that the Gly16 allele was associated with increased response to BBs in an allele-dose-dependent therapy (9). However, this study included a total of 2403 patients, so it may have had more power to detect smaller effects.

Our study had some limitations. Our sample size was relatively small, decreasing our power to detect smaller effects on mortality or mortality effects of less common SNPs. In addition, data were collected close to the recruitment time, so medication information is pertinent to the time of consent, as follow-up on therapy changes was not done. Since patients could have been placed on other therapies during the study period after enrollment, the results could reflect associations related to the changes in medications. Also, not all recruited patients continued to seek medical care exclusively within the University of Illinois Health System. However, the mortality data were collected from both the EHR and the Social Security Death Index for completeness. The validity of our model is corroborated by the association with non-genetic risk factors, such as NYHA functional class, sex, and smoking

history, regardless of genetic polymorphism. Finally, a key strength of our study was the inclusion of a diverse, real-world HF patient population.

CONCLUSION

The clinical implications of pharmacogenetic studies such as ours may help identify high-risk populations that may benefit from genetically tailored therapies. Our study suggests that the 27Glu allele in *ADRB2* and the 389Arg allele in *ADRB1* may confer a larger benefit with higher doses resulting in higher survival rates provided by increased BB doses in patients with HF carrying those alleles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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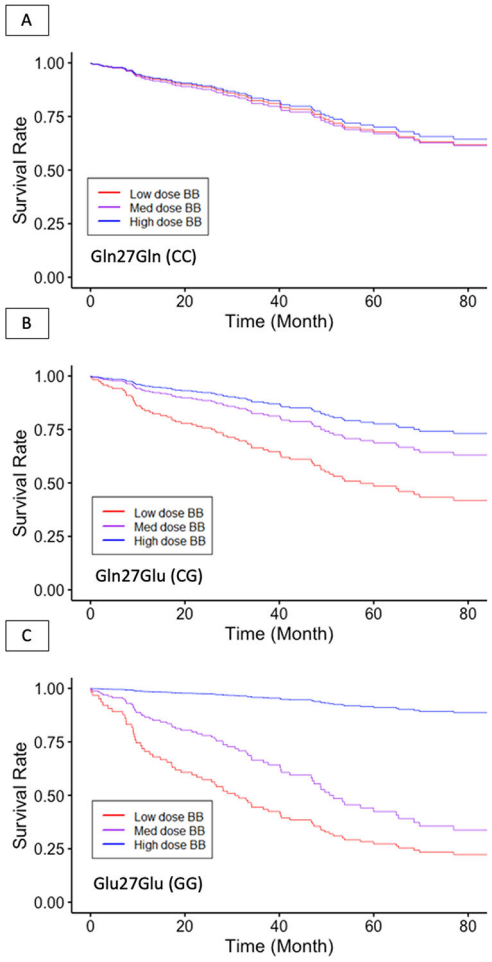

Figure 1.

Adjusted Kaplan-Meier curves for Gln27Glu (in *ADRB2*) genotype associations with all-cause mortality in the PGx comprehensive model by BB dose levels. Survival curve for the homozygous common genotype Gln27Gln (A), the heterozygous genotype Gln27Glu (B), and the homozygous variant genotype Glu27Glu (C) at rs1042714. BB: beta-blocker.

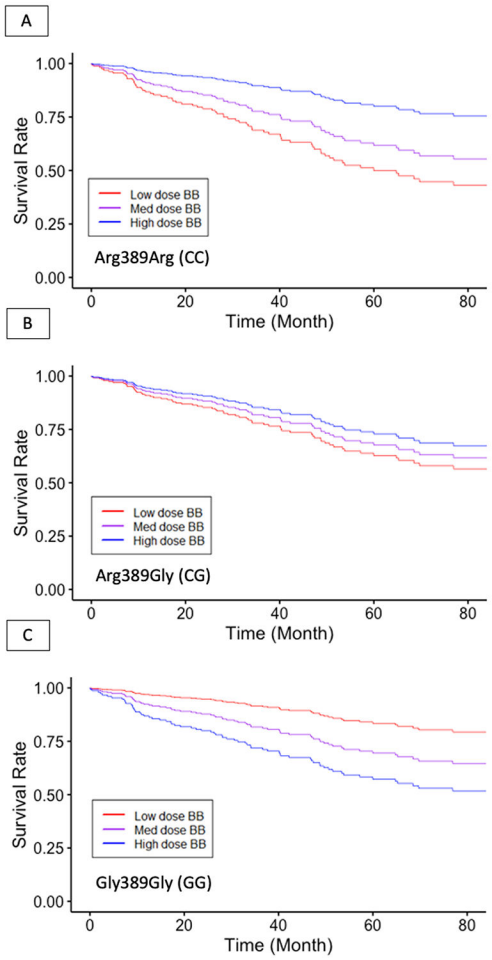

Figure 2.

Adjusted Kaplan-Meier curves for Arg389Gly (in *ADRB1*) genotype associations with all-cause mortality in the PGx comprehensive model, by BB dose levels. Survival curves for the homozygous common genotype Arg389Arg (A), the heterozygous genotype Arg389Gly (B), and the homozygous variant genotype Gly389Gly (C) at rs1801253. BB: beta-blocker.

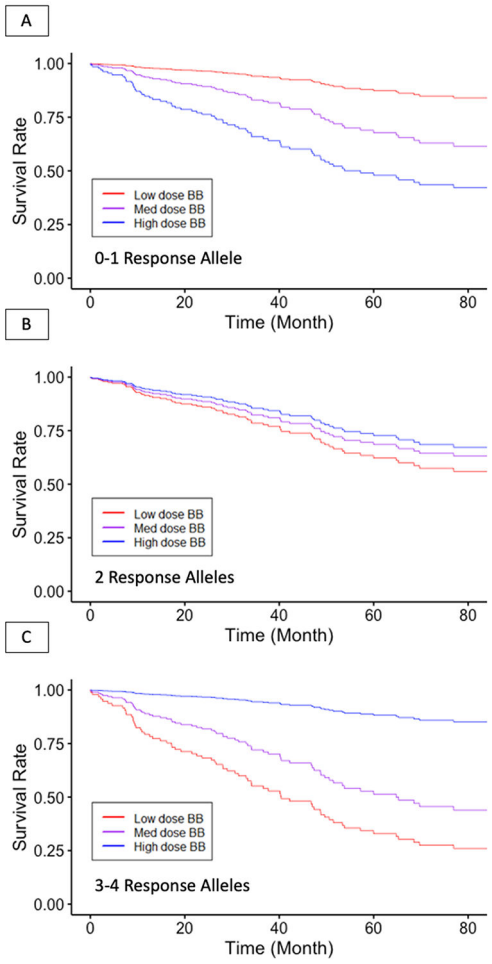

Figure 3.

Adjusted Kaplan-Meier curves for polygenic response allele associations with all-cause mortality in the PGx comprehensive model, by BB dose levels. Survival curve for 0 - 1 response allele (A), 2 response alleles (B), 3 - 4 response alleles. Response allele: 27Glu at Gln27Glu (rs1042714) and/or 389Arg at Arg389Gly (rs1801253). BB: beta-blocker.

Table 1.

Dose level stratification of BBs, ACEIs, ARBs, and Loop Diuretics.

Medication	**High Dose (mg/day)**	**Medium Dose (mg/day)**	**Low Dose (mg/day)**
Beta-Blockers			
Metoprolol	>=200	100 - 199	<100
Carvedilol	>=50	25 - 49	<25
Nebivolol	>=10	5 - 9	<5
Atenolol	>=100	50 - 99	<50
ACEIs			
Captopril	>=150	75 - 149	<75
Enalapril	>=20	10 - 19	<10
Lisinopril	>=20	10 - 19	<10
Ramipril	>=5	2.5 - 4.9	<2.5
Benazepril	>=10	5 - 9	<5
ARBs			
Candesartan	>=32	16-31	<16
Losartan	>=100	50 - 99	<50
Valsartan	>=160	80 - 159	<80
Irbesartan	>=300	150 - 299	<150
Loop Diuretics			
Furosemide	>=120	40 - 119	<40
Torsemide	>=60	20 - 59	<20
Bumetanide	>=4	1 - 3	<1

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, beta blocker

Table 2.

Baseline Characteristics.

Variable	N=308
Age at Event/Censor (years) *	62.8 ± 13.3
Female (%)	151 (49.0)
NYHA (%) *	
I	81 (26.3)
II	93 (30.2)
III	129 (41.9)
IV	5 (1.6)
HFpEF Diagnosis, (%)	114 (37.0)
Ischemic Cardiomyopathy (%)	93 (30.5)
Atrial Fibrillation/Flutter (%)	83 (26.9)
Type 2 Diabetes (%)	155 (50.3)
Obese (%)	194 (63.0)
Creatinine Clearance (mL/min)	83.6 (IQR: 64.8)
Systolic Blood Pressure (mmHg)	124 (IQR: 26.5)
Serum Sodium (mmol/L)	139 (IQR: 3.3)
Smoking Status	
Current Smoker (%) *	131 (42.5)
Past Smoker (%) *	52 (16.9)
Never Smoker (%) *	125 (40.6)
Self-reported Race/Ethnicity	
Black (%) *	229 (74.4)
Non-Latino White (%) *	32 (10.4)
Asian (%) *	3 (0.9)
Hispanic/Latino (%) *	44 (14.3)
BB Dose Level, (%) *	
Low	48 (15.5)
Medium	80 (25.9)
High	180 (58.6)
Loop Diuretic (%)	244 (79.2)
Statin (%)	205 (66.6)
ARA (%)	62 (20.1)
Nitrate (%)	52 (16.9)
Potassium Supplement (%)	68 (22.1)
Hydralazine (%)	53 (17.3)
ACEI (%)	224 (72.7)
ARB (%)	67 (21.8)

All variables reported as Mean (± SD) or median (IQR) or n (%)

* = Base Model Variables

ARA: aldosterone receptor antagonist; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blockers; HFpEF: heart failure with preserved ejection fraction; NYHA: New York Heart Association