β₂-Adrenergic Receptor Genotype and Survival Among Patients Receiving β-Blocker Therapy After an Acute Coronary Syndrome

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CARDIOVASCULAR DISEASE, including acute coronary syndromes (ACS), is the major cause of morbidity and mortality in the Western world.¹ Acute and long-term therapy with β-adrenergic antagonists (β-blockers) has become a standard of post-ACS care.²,³ Therapy with β-blockers has been shown to reduce infarct size⁴ and mortality⁵,⁶ among myocardial infarction (MI) patients, most likely by decreasing cardiac energy requirements⁷ and modifying arrhythmic risk.⁸ Based on multiple clinical trials and guidelines, it has also been used as an important marker of health care quality.⁹,¹⁰ Yet clinical trials and guidelines, it has also been shown that specific sequence variants with mortality was observed in either the β-blocker or no β-blocker groups.

Conclusions Patients prescribed β-blocker therapy after an ACS have differential survival associated with their ADRB2 genotypes. Further assessment of the benefits of β-blocker therapy in high-risk genotype groups may be warranted.

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macology. Specifically, there are 4 common, nonsynonymous coding variants in the \( \beta_1 \)-adrenergic receptor (\( \text{ADRB1} \)) and \( \beta_2 \)-adrenergic receptor (\( \text{ADRB2} \)) genes. The \( \text{ADRB1} \) variants Ser49Gly (145 AG) and Arg389Gly (1165 GC) have both been associated with altered receptor activation or G protein coupling, while the \( \text{ADRB2} \) variants, Gln27Glu (79 CG) and Gly16Arg (46 GA), have been linked primarily to altered receptor trafficking and down-regulation.

Underscoring the importance of these polymorphisms is recent data showing that several variants mediate differential therapeutic end points of \( \beta \)-blocker treatment such as blood pressure response in hypertensive patients and improvement of ejection fraction among heart failure patients. For example, \( \text{ADRB2} \) gene Gln27Glu (79 CG) G allele carriers with heart failure were significantly more likely to demonstrate an improved ejection fraction with carvedilol therapy than were patients homozygous for the C allele.

Despite the potential importance of these observed associations of \( \beta \)-adrenergic receptor sequence variants with surrogate end points, no relationship between these variants and the survival of patients receiving \( \beta \)-blocker therapy has been reported. Identifying such an association could provide an important opportunity to further individualize therapy and target it to those patients with the greatest opportunity to benefit. As an initial step, we conducted pharmacogenetic analyses of a prospective registry of ACS patients by examining the association of all-cause mortality, stratified by discharge \( \beta \)-blocker status, with genotypes of 4 common functional polymorphisms in \( \text{ADRB1} \) and \( \text{ADRB2} \) (\( \text{ADRB1} \) 1165 CG, 145 AG and \( \text{ADRB2} \) 46 GA, 79 GC).

**METHODS**

**Patients**

Patients were prospectively enrolled into an ACS registry at 2 Kansas City hospitals, the Mid America Heart Institute and Truman Medical Center. All 10 911 consecutive patients admitted between March 1, 2001, and October 31, 2002, who had a troponin blood test ordered were prospectively screened for a possible ACS. Standard definitions were used to diagnose ACS patients with either MI or unstable angina. Myocardial infarction patients were defined by an elevated troponin value in the setting of symptoms or electrocardiographic changes (both ST-segment elevation and non–ST-segment elevation changes) consistent with an MI. Unstable angina was diagnosed if the patient had a negative troponin blood test and any one of the following: new-onset angina (<2 months) of at least class III of the Canadian Cardiovascular Society Classification, prolonged (>20 minutes) rest angina, recent (<2 months) worsening of angina, or angina that occurred within 2 weeks of an MI. All potential unstable angina patients who were found to have a diagnostic study that excluded obstructive coronary disease (ie, coronary angiography, nuclear or echocardiographic stress testing) or who had an additional diagnostic study confirming an alternative explanation for the patient’s presentation (eg, esophagogastro-duodenoscopy) were subsequently excluded. Three physicians reviewed the charts of all patients for whom diagnostic uncertainty remained and attained consensus on the final diagnosis.

Each participating patient was prospectively interviewed as early as possible during their admission to ascertain sociodemographic, economic, and health status (symptoms, function, and quality of life) characteristics. Patient race was abstracted from hospital admission records. To examine the potential for misclassification of race, we conducted a prospective study of 410 acute MI patients in which a data collector abstracted the patient’s race from the chart and compared this with the patient’s self-reported racial designation. Using patient designation as the gold standard, only 3 (0.7%) patients were misclassified (1 patient who classified himself as black was considered white by chart abstraction and 2 patients who considered themselves to be white were classified as black). Since the same data collectors and hospitals were used for both studies, race classification in this study was considered accurate. Detailed chart abstractions were performed to ascertain patients’ medical history, laboratory results, disease severity, and the processes of inpatient care (including \( \beta \)-blocker administration).

Approval from the institutional review boards of both institutions was obtained prior to the conduct of the study, and written informed consent to participate in the interviews and chart abstractions was signed by each participant. A separate written consent form for the acquisition of blood for genetic analysis was signed by each patient. Although there were no differences in sex (93.2% of men vs 92.2% of women), whites were less likely to consent to DNA testing (91.5% vs 98.3%, \( P < .001 \)) as were older patients (mean [SD] ages for those consenting, 61 [13] years vs 65 [13] years, \( P = .004 \)). A total of 742 patients were enrolled in the genetic studies of this registry; of these, 735 had discharge medication status known, constituting the cohort for the current analyses.

**Mortality Assessment**

The Social Security Administration Death Master File was queried to determine patients’ vital status as of March 1, 2005 (http://www.ntis.gov/products/ssa-dmf.asp).

**Genotyping**

Genomic DNA was isolated using an extraction kit (Genta, Minneapolis, Minn). Genotyping was carried out using genotyping assays (Applied Biosystems, Foster City, Calif). For \( \text{ADRB1} \) 145AG and 1165GC, Assays-on-Demand was used (assay No. C_8898508_10 and No. C_8898494_10, respectively). For \( \text{ADRB2} \) 46 GA and 79 CG, Assays-by-Design was used with the primer and probe sequences listed in TABLE 1. Pairwise linkage (D) and haplotype analysis was carried out using the Polymorphism and Haplotype Analysis Suite (http://ilya.wustl.edu/~pgnr
The 4 variants analyzed were chosen due to their frequency and the strength of evidence linking them to cardiovascular phenotypes, particularly β-blocker response phenotypes. There are 2 other, uncommon, non-synonymous coding variants in ADRB2 (Val34Met and Ile164Thr) that were not included due to very small sizes of specific genotype groups that would greatly limit our analyses (both have frequency of heterozygosity <5%). This study was approved by the Washington University Human Studies Committee. These data have been deposited in the Pharmacogenetics and Pharmacogenomics Knowledge Base (accession No. PS205292).

### Statistical Analysis

Baseline and follow-up characteristics were compared by genotype. Categorical data are reported as frequencies, and differences between groups were compared with χ² or Fisher exact tests if expected cell frequencies were less than 5. Continuous data are reported as the mean (SD), and differences between groups were tested using 1-way analysis of variance. Hardy-Weinberg equilibrium was assessed using χ² tests.

Kaplan-Meier estimates and Cox proportional hazards models were used to describe the association of genotype with patients’ survival. Proportional hazards assumptions were confirmed using Schoenfeld residuals. Follow-up began at the time of discharge from the index hospitalization. To estimate the effect of each polymorphism within β-blocker exposure groups, the population was stratified into those who did or did not receive β-blocker therapy at discharge. To estimate the independent contribution of genotype after adjusting for potential confounders and other clinical predictors, covariates were identified that were either thought to be clinically important or differed significantly by genotype. These included age, race, sex, type of ACS, hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, coronary angiography, and coronary revascularization. Patients’ compound genotypes and inferred diplotypes were analyzed using the same survival models.

As an exploratory analysis, we examined the therapeutic efficacy of β-blocker treatment by genotype. These analyses were considered exploratory because it was anticipated that the study was underpowered to detect mortality differences by genotype within patients not receiving β-blockers or to detect β-blocker-by-genotype interactions. First, a comparison of demographic, clinical, and treatment characteristics by β-blocker therapy was performed (Table 2). Then a nonparsimonious logistic regression model of the propensity to be discharged with β-blockers was created using the variables listed in Table 2 and Table 3. All variables were included as main effects in the model, and second-order terms were included using stepwise selection with P value criteria of <.20. The c statistic of the final model was 0.74. There was sufficient overlap across quintiles of propensity score to permit stratification, and all variables in Table 3 were comparable between β-blocker and no β-blocker patients within quintile of propensity score.

The quintile of propensity for β-blocker use was then included in the Cox proportional hazards models along with genotype, β-blocker use, and a genotype-by-β-blocker interaction term. The latter was used to establish differences in β-blocker efficacy by genotype.

For all analyses, P values <.05 were considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC) and R version 2.1.0.

### RESULTS

A total of 735 patients made up our study cohort; during 3 years of follow-up, 84 patients died. Baseline characteristics of patients by genotype are listed in Table 3. Mean (SD) age was 60 (12.5) years, 64% (n=467) of all patients were male, and 77% (n=567) were identified as white. No significant differences in mortality were observed between races (white vs African American vs other), either by univariable analysis (P=.59) or after adjustment for clinical variables (P=.66). Genotypes were obtained in 86% to 93% of patients (not all variants were successfully genotyped in all patients). None of the variants deviated significantly from Hardy-Weinberg equilibrium within racial groups. The allele frequencies obtained were roughly similar to that reported for the general population and did not vary by sex (P>.08 for all). Other classes of discharge medications (aspirin, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, statins, nitrates, and diuretics) did not differ significantly between genotype groups (all P>.08), except for aspirin across the ADRB1 145 GA genotypes only (P=.02). At discharge, 597 (81.2%) of patients were treated with β-blockers and 138 (18.8%) were not.

### Table 1. Primers and Probes for ADRB2 Genotype Analysis

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Primer/Probe sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRB2 46 GA</td>
<td>Forward 5’-CGGCCAGCCCTTTCCCTG-3’</td>
</tr>
<tr>
<td></td>
<td>Reverse 5’-TCGCTGACGTCTGACGTGC-3’</td>
</tr>
<tr>
<td></td>
<td>Probe 1 VIC 5’-CACCCCAATGGAAAGCC-3’</td>
</tr>
<tr>
<td></td>
<td>Probe 2 FAM 5’-CACCCAATTAGAAGGCT-3’</td>
</tr>
<tr>
<td>ADRB2 79 CG</td>
<td>Forward 5’-CCTCTCTCTGTTGCGAACCAT-3’</td>
</tr>
<tr>
<td></td>
<td>Reverse 5’-TGCCGACCCACCCACAC-3’</td>
</tr>
<tr>
<td></td>
<td>Probe 1 VIC 5’-CTGCTTCTTCCCTGCTGCT-3’</td>
</tr>
<tr>
<td></td>
<td>Probe 2 FAM 5’-GCTCCCTTTGCTGCGT-3’</td>
</tr>
</tbody>
</table>
homzygous for the G allele (3-year Kaplan-Meier mortality rates: 16%, 11%, and 6%, respectively; P = .03). This association remained statistically significant even after adjustment for age, race, sex, ACS type, hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, prior coronary artery bypass graft surgery, renal failure, smoking history, coronary angiography, and coronary revascularization (adjusted hazard ratios [AHRs], 0.51 [95% confidence interval {CI}, 0.30-0.87] for CG vs CC and 0.24 [95% CI, 0.09-0.68] for GG vs CC, P = .004).

No association was identified between genotype and mortality among the patients not discharged with β-blocker therapy (3-year Kaplan-Meier mortality rates: CC, 9%; CG, 10%; GG, 7%; P = .98 [unadjusted], P = .61 [adjusted]; AHRs, 0.41 [95% CI, 0.07-2.44] for CG vs CC and 0.49 [95% CI, 0.04-6.92] for GG vs CC).

**ADRB2 46 GA Genotype and Mortality**

Among patients treated with β-blockers, the ADRB2 46 GA genotype was significantly associated with survival (Figure 2). The 3-year Kaplan-Meier mortality rates were 20% for AA vs 10% in the GA and GG patients (P = .005). This remained significant after multivariable adjustment (AHRs, 0.48 [95% CI, 0.27-0.86] for GA vs AA and 0.44 [95% CI, 0.22-0.85] for GG vs AA, P = .02). No significant association was observed between genotype and mortality among the patients not discharged with β-blocker therapy (3-year Kaplan-Meier mortality rates: AA, 16%; GA, 8%; GG, 8%, P = .49 [unadjusted], P = .63 [adjusted]; AHRs, 0.40 [95% CI, 0.06-2.57] for GA vs AA and 0.47 [95% CI, 0.06-4.05] for GG vs AA).

**ADRB1 Genotypes and Mortality**

No significant association of the ADRB1 1165 CG variant with mortality was observed in either patients discharged with β-blocker therapy (3-year Kaplan-Meier mortality rates: CC, 13%; CG, 10%; GG, 17%, P = .39; AHRs, 0.80 [95% CI, 0.45-1.42] for CG vs CC and 0.91 [95% CI, 0.43-1.91] for GG vs CC, P = .75) or without β-blocker therapy (3-year Kaplan-Meier mortality rates: CC, 10%; CG, 9%; GG, 0%, P = .68; AHRs, 0.95 [95% CI, 0.18-4.97] for CG vs CC, 0 [95% CI, 0-∞] for GG vs CC, P = .99). Similarly, the ADRB1 145 AG variant did not show a significant association with mortality in either the patients discharged with β-blocker therapy (3-year Kaplan-Meier mortality rates: AA, 12%; AG, 12%, GG, 14%, P = .99; AHRs, 0.99 [95% CI, 0.55-1.79] for AG vs AA and 0.47 [95% CI, 0.07-3.13] for GG vs AA, P = .73) or those without β-blocker therapy (3-year Kaplan-Meier mortality rates: AA, 7%; AG, 14%; GG, 0%, P = .38; AHRs, 2.65 [95% CI, 0.54-13.15] for AG vs AA, 0 [95% CI, 0-∞] for GG vs AA, P = .49).

**ADRB2 Haplotypes and Compound Genotypes**

To better assess the impact of both of the ADRB2 polymorphisms together we performed haplotype and compound genotype analyses. The 2 ADRB2 vari-

### Table 2. Baseline Characteristics by Discharge β-Blocker Status*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No β-Blockers (n = 138)</th>
<th>β-Blockers (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.7 (13.0)</td>
<td>60.7 (12.3)</td>
</tr>
<tr>
<td>Male</td>
<td>86 (62.3)</td>
<td>381 (63.3)</td>
</tr>
<tr>
<td>White</td>
<td>100 (72.5)</td>
<td>467 (78.4)</td>
</tr>
<tr>
<td>ACS classification type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>25 (18.1)†</td>
<td>184 (30.8)†</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>36 (26.1)†</td>
<td>188 (31.2)†</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>77 (55.8)†</td>
<td>224 (37.5)†</td>
</tr>
<tr>
<td>Old LBBB/unknown</td>
<td>0 (0.0)†</td>
<td>3 (0.5)†</td>
</tr>
<tr>
<td>History/risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>89 (64.5)</td>
<td>398 (66.7)</td>
</tr>
<tr>
<td>MI</td>
<td>47 (34.1)</td>
<td>199 (33.3)</td>
</tr>
<tr>
<td>PCI</td>
<td>39 (28.3)</td>
<td>191 (32.0)</td>
</tr>
<tr>
<td>CABG</td>
<td>19 (13.8)</td>
<td>112 (18.8)</td>
</tr>
<tr>
<td>CHF</td>
<td>12 (8.7)</td>
<td>44 (7.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (31.2)</td>
<td>162 (27.1)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>71 (51.4)</td>
<td>370 (62.0)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4 (2.9)</td>
<td>15 (2.5)</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>26 (18.8)†</td>
<td>62 (10.4)†</td>
</tr>
<tr>
<td>Admission BMI, mean (SD)</td>
<td>30.0 (6.8)</td>
<td>29.5 (6.2)</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current &lt;30 d</td>
<td>49 (35.5)</td>
<td>214 (35.9)</td>
</tr>
<tr>
<td>Former &gt;30 d</td>
<td>48 (34.8)</td>
<td>218 (36.6)</td>
</tr>
<tr>
<td>Never or &lt;100 cigarettes total</td>
<td>41 (29.7)</td>
<td>164 (27.5)</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>134.3 (27.1)</td>
<td>137.7 (27.0)</td>
</tr>
<tr>
<td>TIMI UA/NSTEMI risk score, mean (SD)</td>
<td>2.6 (1.3)†</td>
<td>3.0 (1.4)†</td>
</tr>
<tr>
<td>TIMI STEMI risk score, mean (SD)</td>
<td>3.6 (2.00)†</td>
<td>3.1 (2.2)†</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>102 (73.9)†</td>
<td>499 (83.6)†</td>
</tr>
<tr>
<td>Primary reperfusion for STEMI</td>
<td>13 (8.2)†</td>
<td>136 (73.9)†</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical management</td>
<td>74 (53.6)†</td>
<td>201 (33.7)†</td>
</tr>
<tr>
<td>PCI</td>
<td>63 (45.7)†</td>
<td>364 (61.0)†</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (0.7)†</td>
<td>32 (5.4)†</td>
</tr>
</tbody>
</table>

*Abreviations: ACS, acute coronary syndrome; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LBBB, left bundle-branch block; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI-UA/NSTEMI, Thrombolysis in Myocardial Infarction unstable angina/non-ST-segment elevation myocardial infarction.

Data are presented as number and percentage unless otherwise indicated.

†P < .05 for comparison of patients discharged with β-blockers vs not discharged with β-blockers.

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ants studied were in linkage disequilibrium (D' = 1, for both African American and whites, both P < .001). Three ADRB2 haplotypes (AC, GC, and GG) were observed, accounting for 42% (562 haplotypes), 21% (283 haplotypes), and 37% (503 haplotypes) of the total, respectively. The ADRB2 diplotype was significantly associated with 3-year mortality among those prescribed β-blocker therapy (P = .04). This divided the β-blocker group into 6 subgroups with 3-year Kaplan-Meier mortality rates ranging from 6% to 20%. To simplify this classification, a composable

Table 3. Baseline Characteristics by Genotype*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADRB1 145 AG (n = 492)</th>
<th>ADRB1 1165 CG (n = 177)</th>
<th>ADRB2 46 GA (n = 227)</th>
<th>ADRB2 79 CG (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.7 (12.4)</td>
<td>60.2 (12.5)</td>
<td>63.8 (14.1)</td>
<td>61.6 (12.0)†</td>
</tr>
<tr>
<td>White</td>
<td>401 (81.7)†</td>
<td>125 (70.6)†</td>
<td>230 (83.5)†</td>
<td>78 (69.0)†</td>
</tr>
<tr>
<td>ADRB type</td>
<td>143 (29.1)</td>
<td>144 (24.9)</td>
<td>133 (21.2)</td>
<td>77 (28.5)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>156 (32.1)</td>
<td>59 (23.5)†</td>
<td>142 (46.8)†</td>
<td>31 (41.9)</td>
</tr>
<tr>
<td>CHF</td>
<td>41 (8.3)</td>
<td>17 (9.7)</td>
<td>11 (9.7)</td>
<td>10 (15.9)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>44 (9.0)</td>
<td>14 (7.9)</td>
<td>10 (7.2)</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Former &lt;100 cigarettes total</td>
<td>145 (29.4)</td>
<td>44 (24.9)</td>
<td>101 (28.8)</td>
<td>66 (27.2)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>137 (27)</td>
<td>138 (29)</td>
<td>139 (29)</td>
<td>137 (27)</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td>170 (34.6)</td>
<td>70 (39.5)</td>
<td>121 (34.3)</td>
<td>94 (37.5)</td>
</tr>
<tr>
<td>PCI (acute or other)</td>
<td>297 (60.4)</td>
<td>100 (56.5)</td>
<td>142 (50.9)</td>
<td>66 (27.2)</td>
</tr>
</tbody>
</table>
| Abbreviations: ACS, acute coronary syndrome; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LBBB, left bundle-branch block; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI UA/NSTEMI, Thrombolysis in Myocardial Infarction unstable angina/non-ST-segment elevation myocardial infarction.

*Data are presented as number and percentage unless otherwise indicated. P<.05 for comparison across genotypes of the given variant.
ite genotype approach was taken (Table 4). Grouping patients by whether they were homozygous for the 79 G allele (group A), homozygous for the 46 A allele (group C), or neither (composite “heterozygotes,” group B), resulted in low-, high-, and intermediate-risk groups (Figure 3, P = .003). Specifically, group C patients were a high-risk subset with a 3-year Kaplan-Meier mortality rate of 20%. Those in group A were at low risk having a 3-year Kaplan-Meier mortality rate of only 6%, while the remaining patients showed an intermediate Kaplan-Meier mortality rate of 11%. This association remained significant after multivariable adjustment (P = .002; AHRs, 5.36 [95% CI, 1.83-15.69] for group C vs group A and 2.41 [95% CI, 0.86-6.74] for group B vs group A). In the no β-blocker group, no significant association of these composite genotypes with survival was observed (3-year Kaplan-Meier mortality rates = 7%, 8%, 16% for groups A, B, and C, respectively, P = .51 [unadjusted], P = .59 [adjusted]; AHRs, 2.29 [95% CI, 0.13-40.48] for group C vs group A and 0.83 [95% CI, 0.07-10.03] for group B vs group A).

Exploratory Analysis of β-Blocker Efficacy by ADRB2 Genotype

As an exploratory analysis, we examined the efficacy of β-blocker therapy within ADRB2 genotypes. Baseline characteristics among those with and without discharge β-blocker therapy are shown in Table 2. Due to small numbers of patients within each genotype who were not treated with β-blockers, no significant interaction was observed for either the 79 CG or 46 GA polymorphisms with β-blocker therapy in terms of mortality (P = .66 and .99, respectively).

COMMENT

In a prospective pharmacogenetic cohort study of patients with ACS, we observed a significant association of ADRB2 genotypes with 3-year survival among those discharged with β-blocker therapy. The 79 C allele was associated with higher mortality in a gene-dose manner. The ADRB2 46 A allele homozygotes were also observed to have higher mortality. Risk stratification was maximized when both genotypes were taken into account, with mortality ranging from 6% in the 46 GG/79 GG group to 20% in the 46 AA/79 CC group. This association remained highly significant after controlling for clinical variables and was only seen in the patients prescribed β-blocker therapy.

This initial description of an association of ADRB2 genotype with survival among patients receiving β-blocker therapy has potentially important implications. The ADRB2 79 CG polymorphism has been previously associated with β-blocker efficacy in heart failure patients, with which our results are consistent. It has not, to our knowledge, been examined in the setting of ACS or shown to predict mortality. A decreased risk of incident coronary events was previously noted among elderly G allele carriers, consistent in direction with our results, but no effect on overall mortality was identified. The 46 GA variant has been associated with response to β-agonists, but has not been previously demonstrated to predict surrogate response to β-blocker therapy or mortality.

The ADRB2 79 G allele has been associated with impaired agonist-mediated down-regulation relative to the C allele. Mechanistic data regarding the 46 GA polymorphism is somewhat conflicting, with some investigators demonstrating impaired agonist-mediated down-regulation associated with the A allele, while others have reported relatively enhanced agonist-mediated desensitization. It is intriguing to consider that impaired desensitization of the β2-adrenergic receptor may allow for a better response to β-blocker therapy since there would theoretically be both greater adrenergic responsiveness and more receptor sites for antagonist binding. Thus, β-blocker treatment may be es-

Table 4. Composite Genotype Groups

<table>
<thead>
<tr>
<th>Composite Genotype Group</th>
<th>46 GA Genotype</th>
<th>79 CG Genotype</th>
<th>Patients in Group, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>GG</td>
<td>GG</td>
<td>89 (13)</td>
</tr>
<tr>
<td>B</td>
<td>AG</td>
<td>CC</td>
<td>124 (18)</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>CG</td>
<td>219 (32)</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>CC</td>
<td>26 (4)</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>CG</td>
<td>109 (16)</td>
</tr>
<tr>
<td>C</td>
<td>AA</td>
<td>CC</td>
<td>112 (16)</td>
</tr>
</tbody>
</table>

*For survival data shown in Figure 3.


CONCLUSION

Among ACS patients discharged with β-blocker therapy, we have identified a genetic association with survival that can assist in the risk stratification of patients. Specifically, the 79 CC and 46 AA groups (39% and 16%, respectively, of our population) are at high risk for long-term mortality and may need additional treatments to optimize their prognosis. Further studies of the efficacy of β-blocker treatment in these patients is warranted to be sure that we are not institutionalizing therapy through the adoption of health care quality performance measures that may offer little benefit, or even potential harm, to these patient subgroups. We strongly encourage further replication of our findings in distinct patient cohorts so that the potential benefit or harm of β-blocker therapy within specific ADRB2 genotype groups can be definitively demonstrated. With further validation, pharmacogenetic targeting of β-blocker therapy may be an opportunity to further improve ACS care and outcomes.

Author Contributions: Drs Lanfear, McLeod, and Spertus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lanfear, Marsh, Cresci, McLeod, Spertus.

Acquisition of data: Lanfear, McLeod, Spertus.

Analysis and interpretation of data: Lanfear, Jones, Marsh, Cresci, McLeod, Spertus.

Drafting of the manuscript: Lanfear, Marsh, McLeod, Spertus.

Critical revision of the manuscript for important intellectual content: Lanfear, Jones, Marsh, Cresci, McLeod, Spertus.

Statistical analysis: Lanfear, Jones, Spertus.

Obtained funding: McLeod, Spertus.

Administrative, technical, or material support: Lanfear, Marsh, McLeod, Spertus.

Study supervision: Marsh, McLeod, Spertus.

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