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

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Context Previous data support an association between polymorphisms of the β₁- and β₂-adrenergic receptors (ADRB1 and ADRB2) and surrogate end points of response to β-adrenergic blocker therapy. However, no associations between these polymorphisms and mortality have been demonstrated.

Objective To evaluate the effect of ADRB1 Arg389Gly (1165 CG), Ser49Gly (145 AG), and ADRB2 Gly16Arg (46 GA), Gln27Glu (79 CG) genotypes on survival among patients discharged with prescribed β-blockers after an acute coronary syndrome (ACS).

Design, Setting, and Patients Prospective cohort study of 735 ACS patients admitted to 2 Kansas City, Mo, medical centers between March 2001 and October 2002; 597 patients were discharged with β-blocker therapy.

Main Outcome Measure Multivariable-adjusted time to all-cause 3-year mortality.

Results There were 84 deaths during follow-up. There was a significant association between ADRB2 genotype and 3-year mortality among patients prescribed β-blocker therapy. For the 79 CG polymorphism, Kaplan-Meier 3-year mortality rates were 16% (35 deaths), 11% (27 deaths), and 6% (4 deaths) for the CC, CG, and GG genotypes, respectively (P = .03; 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). For the ADRB2 46 GA polymorphism, 3-year Kaplan-Meier mortality estimates were 10% (17 deaths), 10% (28 deaths), and 20% (20 deaths) for the GG, GA, and AA genotypes, respectively (P = .005; 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 mortality difference between genotypes was found among patients not discharged with β-blocker therapy for either the 79 CG or 46 GA polymorphisms (P = .98 and P = .49, respectively). The ADRB2 diplotype and compound genotypes were predictive of survival in patients treated with β-blockers (P = .04 and P = .002; AHRs, 5.36 [95% CI, 1.83-15.69] and 2.41 [95% CI, 0.86-6.74] for 46 A homozygous and composite heterozygous vs 79 G homozygous, respectively). No association of the ADRB1 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 β1-adrenergic receptor (ADRB1) and β2-adrenergic receptor (ADRB2) genes. The ADRB1 variants Ser49Gly (145 AG) and Arg389Gly (1165 GC) have both been associated with altered receptor activation or G protein coupling, while the 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 β-blocker treatment such as blood pressure response in hypertensive patients and improvement of ejection fraction among heart failure patients. For example, 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 β-adrenergic receptor sequence variants with surrogate end points, no relationship between these variants and the survival of patients receiving β-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 β-blocker status, with genotypes of 4 common functional polymorphisms in ADRB1 and ADRB2 (ADRB1 1165 CG, 145 AG and 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 β-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] age 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 ADRB1 145AG and 1165GC, Assays-on-Demand was used (assay No. C_8898508_10 and No. C_8898494_10, respectively). For ADRB2 46 GA and 79 CG, Assays-by-Design was used with the primer and probe sequences listed in TABLE I. Pairwise linkage (D’) and haplotype analysis was carried out using the Polymorphism and Haplotype Analysis Suite (http://ilya.wustl.edu/~pgrn/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 diplotype 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 ADDB1 145 GA genotypes only (P=.02). At discharge, 597 (81.2%) of patients were treated with β-blockers and 138 (18.8%) were not.

### ADBR2 79 CG Genotype and Mortality

Among patients treated with β-blockers, the ADDB2 79 CG genotype was significantly associated with survival (Figure 1). Patients homozygous for the C allele had the worst survival, followed by patients heterozygous for the C allele, with the best survival in patients...
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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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-\(\infty\)] 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 \(\beta\)-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 \(\beta\)-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-\(\infty\)] 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-
The table below shows baseline characteristics by genotype:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADRB1 145 AG</th>
<th>ADRB1 1165 CG</th>
<th>ADRB2 46 GA</th>
<th>ADRB2 79 CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.7 (12.4) 60.2 (12.5) 63.8 (14.1)</td>
<td>61.8 (12.3) 58.9 (12.9) 61.8 (12.1)</td>
<td>61.2 (12.8) 60.5 (11.9) 61.8 (12.1)</td>
<td>61.2 (12.8) 60.5 (11.9) 61.8 (12.1)</td>
</tr>
<tr>
<td>Male</td>
<td>318 (64.6) 114 (64.4) 9 (56.3) 213 (60.7) 172 (66.5) 44 (71.0)</td>
<td>73 (64.6) 214 (61.7) 155 (88.3)</td>
<td>166 (61.5) 223 (67.4) 54 (56.7)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>401 (81.7) 125 (70.6) 12 (75.0)</td>
<td>78 (89.0) 266 (76.9) 196 (87.2)</td>
<td>174 (84.6) 283 (85.8) 88 (95.7)</td>
<td></td>
</tr>
<tr>
<td>ACS type</td>
<td>White</td>
<td>401 (81.7) 125 (70.6) 12 (75.0)</td>
<td>78 (89.0) 266 (76.9) 196 (87.2)</td>
<td>174 (84.6) 283 (85.8) 88 (95.7)</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History/risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper tension</td>
<td>312 (63.2) 128 (72.3) 11 (68.8)</td>
<td>229 (65.2) 172 (68.5) 35 (66.5)</td>
<td>86 (76.1) 229 (65.7) 140 (61.7)</td>
<td>190 (70.4) 212 (64.0) 56 (60.9)</td>
</tr>
<tr>
<td>MI</td>
<td>162 (32.9) 60 (33.9) 8 (50.0)</td>
<td>124 (35.3) 89 (35.5) 17 (27.4)</td>
<td>50 (44.2) 31 (16.4)</td>
<td>102 (37.8) 101 (30.5) 29 (31.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>167 (33.9) 49 (27.7) 6 (37.5)</td>
<td>113 (32.2) 84 (33.5) 19 (30.6)</td>
<td>34 (30.1) 116 (33.4)</td>
<td>77 (25.5) 113 (31.4) 32 (34.8)</td>
</tr>
<tr>
<td>CABG</td>
<td>91 (18.5) 31 (17.5) 2 (12.5)</td>
<td>66 (18.8) 43 (17.1) 15 (24.2)</td>
<td>15 (23.7) 69 (19.9)</td>
<td>36 (13.1) 75 (22.7) 13 (14.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>134 (27.2) 52 (28.4) 4 (25.0)</td>
<td>219 (62.4) 150 (59.8) 42 (67.7)</td>
<td>69 (61.1) 200 (59.4)</td>
<td>161 (59.6) 200 (60.4) 59 (64.1)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>15 (3.0) 6 (3.0) 0 (0.0)</td>
<td>5 (1.4) 2 (0.9)</td>
<td>11 (1.8)</td>
<td>11 (1.8) 5 (1.5) 0 (0.0)</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>58 (11.0) 20 (11.1) 1 (0.6)</td>
<td>44 (12.5) 26 (10.4) 6 (6.9)</td>
<td>16 (14.2) 43 (12.4) 23 (10.1)</td>
<td>36 (13.3) 36 (10.9) 9 (9.8)</td>
</tr>
<tr>
<td>Admission BMI, mean (SD)</td>
<td>29.6 (5.5) 29.7 (5.9) 27.7 (5.3)</td>
<td>29.5 (6.0) 29.7 (6.6) 29.3 (6.6)</td>
<td>28.8 (6.0) 29.4 (6.4) 30.2 (6.4)</td>
<td>29.6 (6.2) 29.3 (6.4) 30.3 (5.9)</td>
</tr>
<tr>
<td>Disease severity</td>
<td>TIMI UA/NSTEMI</td>
<td>3.0 (1.4) 3.0 (1.3) 3.0 (1.3) 2.9 (1.3) 2.9 (1.3) 3.0 (1.4) 2.8 (1.3) 3.1 (1.4) 3.1 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI UA/NSTEMI risk score, mean (SD)</td>
<td>3.0 (1.4) 3.0 (1.3) 3.0 (1.3) 2.9 (1.3) 2.9 (1.3) 3.0 (1.4) 2.8 (1.3) 3.1 (1.4) 3.1 (1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Primary</td>
<td>415 (84.3) 410 (85.8) 101 (82.7)</td>
<td>28 (66.7) 14 (66.7) 36 (68.7)</td>
<td>52 (83.9) 28 (66.7) 14 (66.7)</td>
<td>0.05 0.05 0.05</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>137 (21.7) 138 (28) 139 (29)</td>
<td>137 (21.7) 138 (28) 139 (29)</td>
<td>137 (21.7) 138 (28) 139 (29)</td>
<td>137 (21.7) 138 (28) 139 (29)</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td>Medical management</td>
<td>170 (34.6) 102 (59.9) 5 (37.5)</td>
<td>121 (34.5) 94 (37.5) 26 (41.9)</td>
<td>47 (41.6) 128 (36.9) 75 (33.0) 112 (41.5) 105 (31.7) 31 (33.7)</td>
</tr>
<tr>
<td>PCI (acute or other)</td>
<td>297 (60.4) 100 (56.5) 5 (37.5)</td>
<td>218 (62.3) 122 (45.6) 42 (34.8)</td>
<td>20 (74.7) 286 (84.4) 79 (85.9)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>25 (6.1) 7 (4.0) 0 (0.0)</td>
<td>12 (3.4) 15 (6.0) 4 (6.0)</td>
<td>11 (4.1) 15 (4.5) 6 (6.5)</td>
<td></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 especially effective in patients with ADRB2 genotypes associated with higher mortality.
especially beneficial among patients carrying the 79 G or 46 G alleles. Conversely, the relatively enhanced agonist mediated desensitization of the 79 C and 46 A alleles may represent “physiologic β-blockade” and enhanced adaptation to the state of adrenergic activation, thus mitigating the beneficial effects of receptor antagonism.

The lack of association between the ADRB1 1165 CG genotype and the mortality of patients treated with β-blockers is also noteworthy. Several studies have suggested that this variant is indicative of β-blocker response among heart failure patients. It could be that we simply had insufficient power to detect a subtle, but real relationship. It is also possible that this variant is indeed associated with survival among heart failure patients treated with β-blocker therapy, but does not have the same prognostic value among ACS patients. Alternatively, this variant may affect ejection fraction recovery in heart failure, yet not influence mortality. This latter hypothesis is consistent with a substudy of 600 patients from the Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) trial where no mortality difference by ADRB1 1165 CG genotype was found.

Our study has several important limitations. First, it is an observational cohort study from 2 centers, and therefore cannot account for all sources of variability and confounding. Despite this, our study population is typical in their demographic makeup, overall postevent survival, and rates of drug treatment. An additional potential limitation is that we did not have access to adjudicated causes of death. Although cardiovascular causes are likely to predominate, we cannot make direct inferences about the clinical mechanism of the observed effect. Another concern is that not all patients consented to the genetic portion of this registry. While this could introduce bias, it seems unlikely that patients’ genotypes would be associated with their refusal to participate. In addition, we did not have information on continuous medication use throughout the study period. Although we and others have observed that 70% to 90% of patients continue taking their discharge medications long term, we cannot rule out crossover events in terms of β-blocker therapy, although these should bias our results to the null hypothesis.

Most importantly, the number of patients in the no β-blocker group, particularly with minor genotypes, was small. This limited our ability to examine the significance of the association of genotype with mortality in the no β-blocker patients, or to assess the efficacy of β-blocker therapy within genotypes. To definitively address this, a larger cohort of patients not receiving β-blocker therapy is required, or a clinical trial of β-blocker therapy among ADRB2 79 C homozygotes might be considered. Thus, these results provide evidence of a new genetic marker for post-MI risk stratification among patients treated with β-blockers but do not clarify the benefits of β-blocker therapy within specific genotypes.

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.

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