β₂-Adrenergic Receptor Polymorphisms and Risk of Incident Cardiovascular Events in the Elderly

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Background—Genetic polymorphisms at codons 16 and 27 of the β₂-adrenergic receptor have been associated with altered response to sympathetic stimulation. We examined these polymorphisms in relation to cardiovascular event risk in the Cardiovascular Health Study.

Methods and Results—A total of 808 black and 4441 white participants (mean age, 73 years) were genotyped for the Arg16Gly and Gln27Glu polymorphisms of the β₂-adrenergic receptor. There were 702 incident coronary events, 438 ischemic strokes, and 1136 combined cardiovascular events during 7 to 10 years of follow-up. Allele frequencies differed by race but not by age or hypertension status. Glu27 carriers had a lower risk of coronary events than Gln27 homozygotes (hazard ratio, 0.82; 95% CI, 0.70 to 0.95), and there was a suggestion of decreased risk among Gly16 carriers compared with Arg16 homozygotes (hazard ratio, 0.88; 95% CI, 0.72 to 1.07). There was no association of β₂-adrenergic receptor genotype with ischemic stroke or combined cardiovascular events.

Conclusions—The Glu27 allele of the β₂-adrenergic receptor was associated with a lower risk of incident coronary events in this elderly population. (Circulation. 2003;107:2021-2024.)

Key Words: coronary disease ■ epidemiology ■ genetics ■ hypertension ■ stroke
in 4 communities in the United States. This study was approved by institutional review committees at each site, and the subjects gave informed consent. Participants were excluded from this analysis if they did not self-identify as black or white (n=39), did not consent to the use of their genetic information for the study of cardiovascular disease (n=273), had no DNA sample available (n=213), or were missing data on either genotype (n=273), had no DNA sample available (n=213), or were missing data on either genotype (n=273), had no DNA sample available (n=213), or were missing data on either genotype (n=273). The allele frequencies for the 2 β2-adrenergic receptor polymorphisms differed between the 4441 white and 808 black participants (Gly16: 62% versus 50%; Glu27: 43% versus 19%; P for difference by race for each polymorphism <0.001). The 2 polymorphisms were tightly linked, with the Glu27 allele almost always linked to the Gly16 allele. Both polymorphisms were in Hardy-Weinberg equilibrium within each racial group for each end-point analysis. There were no differences in participant characteristics at baseline according to genotype at codon 27 (Table 1) or codon 16 within either racial group.

Clinical cardiovascular disease at baseline was defined as a history of angina, myocardial infarction, ischemic stroke, heart failure, peripheral vascular disease, or coronary revascularization. Hypertension was defined as the self-report of a physician diagnosis of hypertension and the use of an antihypertensive medication. Differences in participant characteristics by genotype were assessed using the χ² test or ANOVA. The association of genotype with cardiovascular event risk was assessed with Cox regression. Subjects were censored at (1) death attributable to other causes, (2) loss to follow-up, or (3) June 30, 2000.

The relative importance of the 2 polymorphisms for cardiovascular event risk was evaluated by comparing a series of nested regression models, as described by Cordell and Clayton. Models for event risk including just the polymorphism at codon 27 were the simplest and best-fitting models. Because cardiovascular event rates did not differ between GlnGlu27 heterozygotes and Glu27 homozygotes in white or black participants, the GlnGlu27 heterozygotes and Glu27 homozygotes were combined. In analyses of combined white and black participants, results were adjusted for race.

For the analysis of each cardiovascular end point, we excluded participants with a history of that end point at baseline; 520 participants had a history of myocardial infarction, 220 had a history of stroke, and 1279 had a history of angina, myocardial infarction, transient ischemic attack, stroke, or peripheral vascular disease. These analyses were based on an updated CHS database incorporating minor corrections through September 4, 2002.

**Results**

The allele frequencies for the 2 β2-adrenergic receptor polymorphisms differed between the 4441 white and 808 black participants (Gly16: 62% versus 50%; Glu27: 43% versus 19%; P for difference by race for each polymorphism <0.001). The 2 polymorphisms were tightly linked, with the Glu27 allele almost always linked to the Gly16 allele. Both polymorphisms were in Hardy-Weinberg equilibrium within each racial group for each end-point analysis. There were no differences in participant characteristics at baseline according to genotype at codon 27 (Table 1) or codon 16 within either race group.

There were 702 incident coronary events, 438 ischemic strokes, and 1136 combined cardiovascular events during a median of 10.2 and 7.2 years of follow-up in the cohorts recruited in 1989 to 1990 and 1992 to 1993, respectively. Among black and white participants considered together, coronary event risk for carriers of 1 or 2 copies of the Glu27 allele was lower than for Gln27 homozygotes (hazard ratio [HR], 0.82; 95% CI, 0.70 to 0.95; Table 2). Results were similar in white (HR, 0.81; 95% CI, 0.69 to 0.96) and black (HR, 0.85; 95% CI, 0.55 to 1.31) participants. For the end points of ischemic stroke and combined cardiovascular events, there was no association with genotype in the overall population or in either race group (overall HR for ischemic

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**TABLE 1. Baseline Characteristics of White and Black Participants According to Genotype at Codon 27 of the β2-Adrenergic Receptor**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White Participants</th>
<th>Black Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>GlnGln27</td>
</tr>
<tr>
<td>No.</td>
<td>4441</td>
<td>1442</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.7</td>
<td>72.8</td>
</tr>
<tr>
<td>Female, %</td>
<td>56.5</td>
<td>56.2</td>
</tr>
<tr>
<td>Treated HTN, %</td>
<td>34.7</td>
<td>36.1</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>135.4</td>
<td>135.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.9</td>
<td>64.7</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>11.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>14.7</td>
<td>15.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4</td>
<td>26.4</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Clinical CVD, %</td>
<td>24.2</td>
<td>24.8</td>
</tr>
</tbody>
</table>

There were no significant differences at P<0.05 in the characteristics listed by genotype in either racial group. HTN indicates hypertension; SBP, systolic blood pressure; bpm, beats per minute; BMI, body mass index (weight in kilograms/height in meters squared); and clinical CVD, a history at baseline of angina, myocardial infarction, ischemic stroke, heart failure, peripheral vascular disease, or coronary revascularization.
stroke, 0.94; 95% CI, 0.77 to 1.15; for combined cardiovascular events, HR, 0.93; 95% CI, 0.82 to 1.05).

The decreased risk of coronary events associated with the Glu27 allele was changed in only trivial ways after adjustment for age, sex, clinic location, baseline clinical cardiovascular disease, cholesterol level, smoking status, diabetes, hypertension, systolic blood pressure, and use of medications and was similar for fatal and nonfatal events. The protective association was similar in subgroups defined by gender, age, diabetes, cholesterol level, and systolic blood pressure. Nonetheless, in participants without baseline clinical cardiovascular disease, the risk of coronary events was lower in Glu27 carriers than in Gln27 homozygotes (HR, 0.72; 95% CI, 0.60 to 0.86), whereas in those with baseline clinical cardiovascular disease, there was no association (HR, 1.20; 95% CI, 0.89 to 1.61; \( P \) for interaction=0.002). Similarly, in those without treated hypertension, we observed a decreased coronary event risk associated with the Glu27 allele (HR, 0.68; 95% CI, 0.54 to 0.86), but this association was not present in participants with treated hypertension (HR, 1.02; 95% CI, 0.82 to 1.27; \( P \) for interaction=0.01).

As expected because of the high degree of linkage disequilibrium between the Gly16 and Glu27 alleles, there was a suggestion of decreased coronary event risk among Gly16 carriers compared with Arg16 homozygotes (overall HR, 0.88; 95% CI, 0.72 to 1.07) that was similar in white and black participants. Like the Gln27Glu polymorphism, the Arg16Gly polymorphism was not associated with the risk of ischemic stroke or combined cardiovascular disease.

Discussion

The findings of this study indicate that carriers of the Glu27 allele of the \( \beta_2 \)-adrenergic receptor had a lower risk of incident coronary events than Gln27 homozygotes. Results were similar in white and black participants and were not changed by adjustment for clinical characteristics. The protective association was particularly evident in participants without baseline clinical cardiovascular disease and in those without treated hypertension. As expected because of the tight linkage between the polymorphisms at codons 16 and 27, there was also a suggestion of decreased coronary event risk for carriers of the Gly16 polymorphism compared with Arg16 homozygotes. There was no association of these \( \beta_2 \)-adrenergic receptor genotypes with incident ischemic stroke or combined cardiovascular events.

The allele frequencies observed in this study for whites and blacks are similar to those previously reported.\textsuperscript{10,11} Our finding of decreased coronary event risk among carriers of the Glu27 allele agrees with an Italian study of young men with dyslipidemia\textsuperscript{12} but contrasts with findings of no association in a European study of nonfatal myocardial infarction\textsuperscript{13} and a clinic-based Japanese study of myocardial infarction.\textsuperscript{14} Differences in case subject inclusion criteria and choice of control subjects\textsuperscript{15} may be related to the differences in results.

\( \beta_2 \)-Adrenergic receptor polymorphisms have been associated with hypertension in some studies\textsuperscript{16–18} but not others,\textsuperscript{11,13} and the direction of the association has been inconsistent. In the present study, there was no association with hypertension or with baseline blood pressure, but the association with coronary events was found to differ according to the presence or absence of clinically recognized cardiovascular disease and treated hypertension. The reasons for these differences are not clear but might be related to alterations in \( \beta_2 \)-receptor function associated with hypertension or atherosclerosis or with their medical treatment.

The strengths of this analysis include the large population-based sample of white and black participants and careful ascertainment of risk factors and cardiovascular events. There was no association of \( \beta_2 \)-adrenergic receptor genotype with age, suggesting that the genotypes studied may not be associated with early mortality. Limitations of the study include the possibility of uncontrolled confounding or population admixture. Adjustment for clinical site did not affect the association of genotype with coronary events. Although the selected polymorphisms of the \( \beta_2 \)-adrenergic receptor are thought to have potentially important biological and pharmacological effects,\textsuperscript{2,3} it is possible that the associations observed reflect other susceptibility loci in linkage disequilib-
rium with the polymorphisms under study, either in the β2-adrenergic receptor gene or a nearby gene. Finally, the associations observed in this elderly population may not apply to younger populations.

In this study of the elderly, the Glu27 allele of the β2-adrenergic receptor was associated with lower risk of incident coronary events, and this protective association was particularly evident in those without clinical cardiovascular disease and those without treated hypertension. If confirmed in other populations, the findings from the present study may be modified by genetic variation in the β2-adrenergic receptor gene or a nearby gene. Finally, the associations observed in this elderly population may not apply to younger populations.

Acknowledgments
This research was supported by grants AG15366 and AG09556 from the National Institute on Aging, Bethesda, Md, and by contracts N01-HC-85079–N01-HC-85086, N01-HC-35129, and N01-HC-15103 from the National Heart, Lung, and Blood Institute. For a full list of participating CHS investigators and institutions, see “About CHS: Principal Investigators and Study Sites” at http://chs-nhlbi.org. L.A. Hindorff is a Howard Hughes Medical Institute Predoctoral Fellow.

References
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Circulation. 2003;107:2021-2024; originally published online April 7, 2003;
doi: 10.1161/01.CIR.0000065231.07729.92
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/15/2021

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