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Genetic Variants of Angiotensin II Receptors and Cardiovascular Risk in Hypertension

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Abstract—Renin-angiotensin systems may mediate cardiovascular disease pathogenesis through a balance of actions of angiotensin II on (potentially proatherogenic) constitutive type 1 (AT\(_1\)R) and (potentially antiatherogenic) inducible type 2 (AT\(_2\)R) receptors. We explored such potential roles in a prospective candidate gene association study. Cardiovascular end points (fatal, nonfatal, and silent myocardial infarction and coronary artery bypass surgery/angioplasty) were documented among 2579 healthy UK men (mean age, 56.1±3.5 years; median follow-up, 10.1 years) genotyped for the AT\(_1\)R1166A>C and the X chromosome located AT\(_2\)R1675A>G and 3123C>A polymorphisms. Baseline characteristics, including blood pressure, were independent of genotype. The AT\(_1\)R1166CC genotype was associated with relative cardiovascular risk (hazard ratio, 1.65 [1.05 to 2.59]; \(P=0.03\)) independent of blood pressure. Systolic blood pressure was associated with risk (\(P=0.0005\)), but this association was restricted to AT\(_1\)R1675A allele carriers (\(P<0.00001\)), with G allele carriers protected from the risk associated with blood pressure (\(P=0.18\)). Hypertensive carriers with the AT\(_1\)R1675A/3123A haplotype were at most risk, with 37.5% having an event. This is the first study to demonstrate an association of AT\(_2\)R genotype with coronary risk, an effect that was confined to hypertensive subjects and supports the concept that the inducible AT\(_2\)R is protective. Conversely, the AT\(_1\)R1166CC genotype was associated with cardiovascular risk irrespective of blood pressure. These data are important to our understanding of the divergent role of angiotensin II acting at its receptor subtypes and coronary disease pathogenesis and for the development of future cardiovascular therapies. (Hypertension. 2003;42:500-506.)

Key Words: receptors, angiotensin II • genetics • polymorphism • cardiovascular diseases • hypertension, genetic

As a component of the endocrine renin-angiotensin system (RAS), ACE cleaves angiotensin (Ang) I to yield Ang II. Agonism at the AT\(_1\)R receptor (AT\(_1\)R) raises blood pressure (BP) through vasoconstriction and aldosterone action. Meanwhile, local tissue RAS serve different roles.\(^1\) Coronary vascular ACE drives Ang II synthesis, whose action on local AT\(_1\) and inducible AT\(_2\) receptors (AT\(_2\)R)\(^2\,3\) may contribute to coronary heart disease (CHD) pathogenesis: AT\(_1\)R activation causes vascular smooth muscle cell hypertrophy, extracellular matrix production, and local inflammation, driving atherogenesis and plaque rupture,\(^4\) whereas AT\(_2\)R agonism inhibits vascular cell proliferation\(^5\) and may be antiatherogenic.\(^6\) The balance between AT\(_1\)R and AT\(_2\)R activation may therefore influence CHD risk. However, this remains difficult to explore, and supportive data are sparse. Studies involving selective AT\(_1\)R antagonism are perhaps less informative than they might at first appear: although lowering CHD risk more than equihypotensive \(\beta\)-blockade,\(^7\) this may be partly mediated through AT\(_2\)R agonism—loss of negative feedback raising Ang II levels and hence binding to the vacant AT\(_2\)R.\(^8\)

Could there be a role for both the AT\(_1\)R and AT\(_2\)R in the development of CHD? Genetic studies may provide insight. A polymorphism of the AT\(_1\)R gene exists at position 1166, where the C (rather than A) allele is associated with increased Ang II responsiveness.\(^9\) Meanwhile, the A (rather than G) allele at position 1675 of the X-chromosomal AT\(_2\)R gene is associated with a greater left ventricular hypertrophic (LVH) response\(^10\) and the A (rather than C) allele at position 3123 with greater LVH in hypertrophic cardiomyopathy.\(^11\) The AT\(_1\)R 1166C allele may be similarly associated with LVH.\(^12\)

The putative association of the AT\(_1\)R 1166C allele with CHD\(^13,14\) is disputed,\(^15,16\) whereas no studies have yet addressed the association of AT\(_2\)R-genotype with CHD risk. Furthermore, given the reported associations of the AT\(_1\)R and AT\(_2\)R with a greater hypertensive LVH response, which itself represents an independent risk factor for CHD,\(^17\) it seems likely that polymorphic variation in the AT\(_1\)R and AT\(_2\)R genes may influence the CHD risk associated with hypertension. We therefore sought to clarify these issues through a prospective gene association study.
Methods

Institutional ethics committee approval was granted, and all subjects gave written informed consent.

Study Sample

Subjects were drawn from the Second Northwick Park Heart Study (NPHSII), detailed elsewhere. In brief, NPHSII is a prospective study of 3012 unrelated middle-aged white men (mean±SD age, 56.1±3.5 years) from 9 UK general practices. Those with a history of unstable angina, stroke, or electrocardiographic evidence of previous myocardial infarction (MI) were excluded; 1.1% (34/3012) of individuals were lost to follow-up. At entry, systolic and diastolic (Korotkoff V) blood pressures (SBP and DBP, respectively) were measured with a random zero mercury sphygmomanometer after the subject had been seated for 5 minutes. The mean of 2 readings was recorded. At trial inception, systolic and diastolic hypertension were defined as SBP ≥160 mm Hg and DBP ≥95 mm Hg, respectively. Baseline demographics and conventional risk factors for CHD were documented. CHD events were defined as sudden cardiac death or symptomatic MI (based on history, electrocardiography, cardiac enzymes, and pathology: events classified by World Health Organization criteria25), silent MI, or coronary revascularization (surgical or percutaneous). Rare subclinical events were documented though routine electrocardiography at baseline and sixth annual examination. Time to first event was recorded, yielding one event per subject.

Genotyping

Genotypes were determined through the use of polymerase chain reaction amplification of leukocyte DNA, with published primers and conditions used for the AT,RI166A>G21 and AT,RI123C>A22 polymorphisms and forward 5′-CACAATGTGAAGAAGAACAGCATAAAGAATT-3′ and reverse 3′-CATTCTGACGCCTG-AATTITGAAGG-5′ primers with subsequent EcoRI digestion for the AT,RI675A>G polymorphism. Products were resolved on a 7.5% polyacrylamide gel,23 and genotypes were confirmed by two independent technicians blinded to subject outcome, with discrepancies resolved by repeat genotyping. The failure to genotype all individuals for all genotypes relates to quality and quantity of stored DNA and (being random) is not a source of confounding error.

Statistical Analysis

Analysis was performed with the use of Intercooled STATA software (version 7.0, STATA Corp). Subjects with normal blood pressure (n=171) but who reported taking antihypertensive medications at recruitment into the trial were excluded before analysis, leaving 2841 eligible subjects. Subjects were followed for a median (25th, 75th) of 4 (3, 6) years. Events classified by World Health Organization criteria25,26, silent MI, or coronary revascularization (surgical or percutaneous) were defined. CHD events were defined as sudden cardiac death or symptomatic MI (based on history, electrocardiography, cardiac enzymes, and pathology: events classified by World Health Organization criteria25), silent MI, or coronary revascularization (surgical or percutaneous). Rare subclinical events were documented through routine electrocardiography at baseline and sixth annual examination. Time to first event was recorded, yielding one event per subject.

Results

Baseline characteristics of those with at least one genotype available (n=2579; 90.8% of eligible subjects) are presented by event status in Table 1. There were no statistically significant differences in any baseline characteristic between those genotyped and those who were not. No differences in allele, genotype, or haplotype frequencies or in association strength were identified between practices. The type of CHD events did not differ by AT,R or AT,R genotype (Table 2).

AT,RRI166A>G Polymorphism and CHD Risk

Genotype distribution (AA 1192, AC 882, CC 204) and rare allele frequency (0.28) were similar to those previously reported24 and consistent with Hardy-Weinberg equilibrium. Baseline characteristics, including blood pressure, in the study group overall were independent of AT,R genotype (Table 3). However, in keeping with previous reports,24 there was a greater proportion of AT,RI166CC carriers with systolic hypertension at baseline (19.6% CC versus 14.6% A allele carriers; P=0.05). CHD event rate was higher among those of CC than AC or AA genotypes (proportion with events, 10.8%, 5.7%, and 8.0%, respectively; P=0.02; HR for CC versus A allele carriers 1.65 [1.05 to 2.59]; P=0.03; Table 2). This was confirmed by Kaplan-Meier survival curves (Figure 1), with decreased survival among CC compared with A allele carriers. CHD risk rose exponentially as baseline SBP increased irrespective of genotype (Figures 2a and 2b). The increased CHD risk of CC compared with A allele carriers was independent of blood pressure (HR after adjustment for SBP, 1.62 [1.04 to 2.55]; P=0.05). There was no evidence that the risk associated with AT,R genotype was any particular in those with systolic or diastolic hypertension.

AT,RRI1675A>G Genotype

There were 1188 A allele and 1027 G allele carriers. The rare G allele frequency was 0.46 and similar to previous reports.10 Baseline characteristics, including SBP and DBP, were genotype-independent (Table 4). There was also no association with presence of diastolic (P=0.64) or systolic hypertension (P=0.84) at baseline. There was no association between CHD risk and AT,RRI1675A>G genotype overall (Table 2) or among the 1893 individuals normotensive at baseline (HR for A versus G allele 0.86 [0.61 to 1.20]; P=0.37). There was no difference in survival by genotype in those normotensive at baseline, as demonstrated in the Kaplan-Meier plot (Figure 3).

**Table 1. Baseline Characteristics of Study Subjects Genotyped for at Least One Polymorphism and Stratified by CHD Status**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>CHD Event-Free (n=2389)</th>
<th>CHD Event (n=190)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.0 (3.4)</td>
<td>56.5 (3.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>26.1 (3.4)</td>
<td>26.8 (3.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>136.4 (18.9)</td>
<td>142.2 (20.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>84.0 (11.3)</td>
<td>87.6 (12.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>28.3</td>
<td>39.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.70 (1.01)</td>
<td>6.09 (1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.75 (0.92)</td>
<td>2.11 (1.14)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*For body mass index, systolic blood pressure, diastolic blood pressure, and triglycerides, means are geometric. CHD indicates coronary heart disease.
to 3.38]; \(P=0.05\), as confirmed by decreased survival during follow-up (Figure 3). Among A allele carriers, there was an exponential rise in risk as SBP increased \((P<0.00001; \text{Figure 2c})\). However, G allele carriers were protected from the effects of hypertension, with no association between increasing risk and increasing SBP \((P=0.180; \text{Figure 2d})\). After a threshold of approximately 150 mm Hg, the risk appeared to increase exponentially \((\text{Figure 3})\). Among A allele carriers, there was strong evidence of linkage disequilibrium between the AT\(_2\)R1675 and AT\(_2\)R3123 polymorphisms \((\Delta=0.74, P<0.001)\). Demographic characteristics did not vary by AT\(_2\)R haplotype; 3123A allele carriers were younger than C allele carriers \(55.8\pm3.4\) years versus \(56.2\pm3.4\) years, respectively; \(P=0.008; \text{Table 3}\)\). All other baseline characteristics were independent of genotype, and genotype was unrelated to presence of systolic or diastolic hypertension \((P=0.30\) and \(P=0.63, \text{respectively})\). As for the 1675A>G polymorphism, the 3123C>A genotype was not associated with risk in the whole cohort, after adjustment for age and practice \((A\text{ versus } C\text{ allele }HR 1.26[0.93\text{ to }1.68] ;P=0.15)\). Moreover, there was no evidence of a threshold difference in risk in those with systolic hypertension \((A\text{ versus } C\text{ allele }HR 0.88[0.49\text{ to }1.60] ;P=0.68)\), with risk rising as baseline SBP increased for both genotypes \((\text{Figures 2e and 2f})\). However, in the presence of a 1675A allele, the 16 hypertensive individuals who also carried a 3123A allele appeared to be at higher risk \((HR, 4.08[0.92\text{ to }18.02] ;P=0.09)\) with 6 \(37.5\%\) of such men with an event \((\text{Figure 4})\). Variation at the AT\(_2\)R1675 locus modified the risk in the subset of hypertensive 3123A allele carriers, with those individuals carrying both 3123A and 1675A alleles having a 10-fold greater risk \((HR, 9.95[1.66\text{ to }59.52] ;P=0.007)\) compared with those with 3123A and 1675G haplotype \((\text{Figure 5})\).

### TABLE 3. Baseline Characteristics of Study Subjects Genotyped for the AT\(_2\)R1166A>C Polymorphism

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>AA (n=1192)</th>
<th>AC (n=882)</th>
<th>CC (n=204)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.0 (3.4)</td>
<td>56.2 (3.4)</td>
<td>55.6 (3.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)*</td>
<td>26.3 (3.4)</td>
<td>26.1 (3.3)</td>
<td>26.5 (3.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>138.0 (18.9)</td>
<td>137.0 (18.6)</td>
<td>137.4 (19.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>84.0 (11.3)</td>
<td>83.5 (11.2)</td>
<td>84.5 (11.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>29.0</td>
<td>29.0</td>
<td>26.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.76 (1.02)</td>
<td>5.69 (1.00)</td>
<td>5.80 (1.02)</td>
<td>0.19</td>
</tr>
<tr>
<td>Triglycerides, mmol/L*</td>
<td>1.82 (0.94)</td>
<td>1.77 (0.94)</td>
<td>1.77 (0.90)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* For body mass index, systolic blood pressure, diastolic blood pressure, and triglycerides, means are geometric.
Discussion
The association of SBP with CHD risk is shown to be modulated by AT-receptor genotype in this large prospective study: The risk associated with any given BP is genotype-dependent, whereas the risk associated with any one allele is influenced by SBP. Thus, AT,R1166CC genotype is associated with elevated CHD risk at all levels of SBP, the gradient of increasing risk with rising SBP being independent of AT,R genotype. Conversely, CHD risk is independent of AT,R genotype among normotensive individuals, whereas the AT,R 1675A allele is associated with excess risk among those with systolic hypertension (as dichotomously defined at trial inception as SBP ≥160 mm Hg). Here, the gradient relating risk to SBP rises exponentially among these individuals, whereas 1675G allele carriers are relatively protected from hypertensive risk. The association of AT2R genotype with CHD risk provides the first direct evidence of a role for the AT2R in the pathogenesis of CHD. Subgroup analysis suggests that the majority of the risk associated with hypertension in the 1675A allele carriers was confined to those of 1675A/3123A haplotype (found in 5% of UK men). Indeed, 6 of 16 hypertensive men with the 3123A/1675A AT2R haplotype had an event over a decade. However, given the relatively small number of hypertensive individuals of this haplotype, the great excess risk associated with this haplotype demands confirmation. This will necessitate the construction of larger, long-term prospective epidemiological genetic studies. Although one of the largest prospective gene association studies published, limited event numbers prevent mathematical study of AT,R/AT2R genotype interaction. Larger cohorts must thus be sought and observations extended to those of different race and sex.

The observed effects may depend on altered receptor expression. The X-chromosomal AT2R gene comprises 3 exons, with exon 3 coding the entire protein sequence.27 The 1675A→G polymorphism lies within intron 1 near the region important for gene transcriptional activity,10 whereas the 3123C→A polymorphism is located within the 3′-untranslated region of exon 3.22 Intron 1 contains transcriptional enhancers, and in vitro transcription is highest in constructs containing both intron 1 and exon 3.28 The 1675A allele may thus interfere with enhancer activity, impairing AT,R expression and hence increasing cardiovascular risk, and the 3123A allele may also directly reduce transcription. However, both variants may be in allelic association with other unidentified, functional variants within the gene.

The risk of CHD is strongly associated with the development of LVH in response to hypertension.29 These data would support others30,31 in suggesting a causative role for the renin-angiotensin system—and for the AT,R12 and AT,R10,32 specifically—in the common mediation of both CHD and LVH. Both AT,R and AT,R may have more diverse effects other than on vascular form and function,3,6 since Ang II also influences inflammation25 and coagulation.26 Further investigation into the (patho)biological actions of angiotensins at the AT,R, and particularly AT,R, is therefore warranted.

Figure 1. Survival curves of CHD events in all subjects by AT,R1166A→C genotype. CHD risk is independent of blood pressure. Broken line represents CC; unbroken line, AA/AC.

Figure 2. Systolic blood pressure plotted on a logarithmic scale against CHD risk (dotted lines represent 95% CI) for men from the NPHS II study who are (a) AT,R1166 A allele carriers, (b) AT,R1166CC homozygotes, (c) AT,R1675A allele carriers, (d) AT,R1675G allele carriers, (e) AT,R3123C allele carriers, and (f) AT,R3123A allele carriers. As is to be expected, CHD risk rises steeply as baseline systolic blood pressure rises for AT,R genotypes (a, b) and AT,R3123 genotypes (e, f). However, this model shows no relation between blood pressure and risk among the 1027 AT,R1675G allele carriers (P=0.180) but a highly significant association among the 1168 AT,R1675A allele carriers (P<10−5) with a threshold value of ~150 mm Hg for SBP, after which the risk appeared to increase exponentially only for A allele carriers. This is consistent with the notion that AT,R offers cardioprotection once a threshold of blood pressure is reached after which it is expressed.
TABLE 4. Baseline Characteristics for Study Subjects Genotyped for the AT2R3123C>A and AT1R1675A>G Polymorphisms

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>AT2R3123C&gt;A</th>
<th>AT1R1675A&gt;G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (n=1062)</td>
<td>C (n=1320)</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.8 (3.4)</td>
<td>56.2 (3.4)</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>26.3 (3.3)</td>
<td>26.1 (3.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>136.3 (19.0)</td>
<td>137.1 (19.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>83.6 (11.4)</td>
<td>83.4 (11.3)</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>28.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.74 (1.00)</td>
<td>5.73 (1.01)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L*</td>
<td>1.80 (0.96)</td>
<td>1.80 (0.96)</td>
</tr>
</tbody>
</table>

*For body mass index, systolic blood pressure, diastolic blood pressure, and triglycerides, means are geometric. Baseline characteristics and classical risk factors of individuals with AT1 1166A/C genotype are from the Second Northwick Park Heart Study.

These data have substantial implications for our understanding of the pathogenesis of CHD and of the mechanisms of drug action. They also help explain previously paradoxical data. A common polymorphism of the human ACE gene exists in which the presence (Insertion, I allele) rather than the absence (Deletion, D allele) is associated with reduced tissue ACE activity.\(^{33}\) Pharmacological ACE inhibition substantially reduces coronary event rate in high-risk patients.\(^{31,34}\) However, these benefits cannot be ascribed to simple reductions in Ang II activity at the AT1 R, given that Ang II suppression fails with chronic ACE inhibition.\(^{35}\) Loss of negative feedback on angiotensinogen\(^{36}\) and ACE\(^{37}\) synthesis and conversion of excess Ang I to Ang II through non-ACE pathways\(^{38}\). Rather, an alteration in relative AT1 R/AT2 R activity might be responsible: AT1 R expression increases in response to Ang II\(^{19}\) and may reduce with ACE inhibition,\(^{40}\) leading to an altered ratio of AT1 R/AT2 R activity. Our data would support a role for such a change in mediating CHD risk reduction. Such an effect might also help explain why the effects of pharmacological ACE inhibition on risk are more marked than that of ACE genotype.\(^{41}\) Altered AT1 R:AT2 R balance may also underlie the greater impact of AT1 R antagonism than equihypotensive \(\beta\)-blockade on coronary event rate in hypertensive patients\(^{5}\): Loss of negative feedback causes a rise in Ang II levels and hence binding to the (unprotected) AT2 R.\(^{8}\) Furthermore, cross-talk exists between AT1 and AT2 receptors, and changes in AT2 R expression may occur during treatment with AT1 R antagonists.\(^{42}\)

These results have important implications for gene-association studies. Allele-associated risk depends on its genetic context and will be modulated by other risk factors such as BP. Failure to take such factors into account may lead to the inappropriate dismissal of important data, accounting perhaps for the mixed reports of association\(^{13,14}\) (or lack of it)\(^{15,16}\) of AT1 R genotype with CHD. Indeed, epistatic interaction with ACE genotype, although not detected here (data not shown), has been suggested,\(^{43}\) whereas we have identified an important AT1 R haplotype effect. Second, there are lessons for pharmacotherapy. The risk reduction associated with RAS antagonism (whether ACE inhibition or AT1 R antagonism) may depend on the BP of the individual treated and on the magnitude of the hypotensive response. This will be especially true if the hypertensive phenotype either modulates Ang II receptor expression\(^{44,45}\) or is causally associated with differences in expression.\(^{46}\) The impact of otherwise small falls in BP on CHD risk may thus be amplified when such reductions are associated with ACE inhibition.\(^{31}\) These issues require investigation in further prospective studies. The impact of ACE inhibition and AT1 R antagonism on the balance of AT1 R/AT2 R activity must also be further explored, such that the advantages of monotherapy/combined therapy in patient subpopulations can be explored.

Finally, a drawback of this study is that specific cardiovascular medication received after enrollment was not documented. However, we feel that this is unlikely to have accounted for the data as presented. First, prescription would

Figure 3. Survival curves of CHD events by AT2 R1675 genotype in normotensive (SBP <160 mm Hg) and hypertensive (SBP ≥160 mm Hg) subjects. Broken line represents A allele carriers; unbroken line, G allele carriers.

Figure 4. CHD risk (HRs with 95% CI) associated with AT1 R haplotypes in hypertensive men (SBP ≥160 mm Hg) after adjustment for age, practice, and blood pressure. Haplotypes are shown with number of individuals in each group.
have had to have been strongly predicated by genotype to act as a significant confounder, and statistical analysis denies a significant causative role for the alleles in leading to elevated blood pressure. Thus, need for treatment per se (and its impact on outcome) would not have been confounded by any allele association. Second, treatment for hypertension—where given—would thus have potentially reduced risk (by blood pressure reduction) in a random way across hypertensive patients, weakening any potential association of allele with risk rather than strengthening it. Third, the use of specific RAS antagonists was uncommon in the time frame of study, especially as their role in primary prevention had yet to be elucidated. It does remain possible that risk reduction associated with such treatment might have been genotype-dependent. However, to account for our findings, we would have to suggest almost universal treatment of hypertensive patients and a very strong protective interaction of treatment with the G allele among such patients. Although possible, this seems unlikely. Therefore, it seems implausible that hypertensive therapy would account for our findings. In support, the survival plots diverge by AT,R genotype early in the trial. Nonetheless, pharmacogenomic studies are warranted.

Perspectives
Polyorphic variation in the genes for AT1 and AT2 receptors influences CHD risk. These data have pharmacotherapeutic and mechanistic implications relating to the treatment of hypertension and of CHD.

Acknowledgments
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