Genetic Variants of Angiotensin II Receptors and Cardiovascular Risk in Hypertension

Alun Jones, Sukhbir S. Dhamrait, John R. Payne, Emma Hawe, Ping Li, Iqbal S. Toor, Le Luong, Peter T.E. Wootton, George J. Miller, Steve E. Humphries, Hugh E. Montgomery

Abstract—Renin-angiotensin systems may mediate cardiovascular disease pathogenesis through a balance of actions of angiotensin II on (potentially proatherogenic) constitutive type 1 (AT1,R) and (potentially antiatherogenic) inducible type 2 (AT2,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,R1166AA>C and the X chromosome located AT,R1675A>G and 3123C>A polymorphisms. Baseline characteristics, including blood pressure, were independent of genotype. The AT,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,R1675A allele carriers (P<0.0001), with G allele carriers protected from the risk associated with blood pressure (P=0.18). Hypertensive carriers with the AT,R1675A/3123A haplotype were at most risk, with 37.5% having an event. This is the first study to demonstrate an association of AT,R genotype with coronary risk, an effect that was confined to hypertensive subjects and supports the concept that the inducible AT2,R is protective. Conversely, the AT,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 AT1 receptor (AT1,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 AT1 and inducible AT2 receptors (AT2,R)2,3 may contribute to coronary heart disease (CHD) pathogenesis: AT1,R activation causes vascular smooth muscle cell hypertrophy, extracellular matrix production, and local inflammation, driving atherogenesis and plaque rupture,4 whereas AT2,R agonism inhibits vascular cell proliferation5 and may be antiatherogenic.6 The balance between AT1,R and AT2,R activation may therefore influence CHD risk. However, this remains difficult to explore, and supportive data are sparse. Studies involving selective AT,R antagonism are perhaps less informative than they might at first appear: although lowering CHD risk more than equihypotensive β-blockade,7 this may be partly mediated through AT,R agonism—loss of negative feedback raising Ang II levels and hence binding to the vacant AT,R.8

Could there be a role for both the AT1,R and AT2,R in the development of CHD? Genetic studies may provide insight. A polymorphism of the AT,R gene exists at position 1166, where the C (rather than A) allele is associated with increased Ang II responsivity.9 Meanwhile, the A (rather than G) allele at position 1675 of the X-chromosomal AT,R gene is associated with a greater left ventricular hypertrophic (LVH) response10 and the A (rather than C) allele at position 3123 with greater LVH in hypertrophic cardiomyopathy.11 The AT,R1166C allele may be similarly associated with LVH.12 The putative association of the AT,R1166C allele with CHD13,14 is disputed,15,16 whereas no studies have yet addressed the association of AT,R-genotype with CHD risk. Furthermore, given the reported associations of the AT,R and AT,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,R and AT,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 criteria28), 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.

Genotyping

Genotypes were determined through the use of polymerase chain reaction amplification of leukocyte DNA, with published primers and conditions used for the AT, R1166A>C21 and AT, R3123C>A22 polymorphisms and forward 5′-CACAATCTTGTAAGAGAAAAC- AGCCAGCTAAAGAATT-3′ and reverse 3′-CATTCTGCAGCCTG- AATTITGAAAGG-5′ primers with subsequent EcoRI digestion for the AT, R1675A>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, StataCorp). Subjects with normal blood pressure (n=171) but who reported taking antihypertensive medication at recruitment into the trial were excluded before analysis, leaving 2841 eligible subjects. Subjects were followed for a median 136 (range 2–37) years. Subjects with normal blood pressure at recruitment into the trial were excluded before analysis, leaving 2841 eligible subjects. Subjects were followed for a median 136 (range 2–37) years. Subjects with normal blood pressure (n=171) but who reported taking antihypertensive medication at recruitment into the trial were excluded before analysis. The type of CHD events did not differ by AT, R or AT, R genotype (Table 2).

AT, R1166A>C 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 reports24, there was a greater proportion of AT, R1166CC 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 different in those with systolic or diastolic hypertension.

AT, R1675A>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, R1675A>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). In contrast, the A allele was associated with risk in subjects with systolic hypertension (n=322; HR, 1.82 [0.98

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### 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.
TABLE 2. Acute and Nonacute CHD Events in Subjects Divided by AT1R and AT2R Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Acute CHD Events (Fatal and Nonfatal MI)</th>
<th>Nonacute CHD Events (Silent MI and Coronary Intervention)</th>
<th>Total CHD Events/Subjects, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT1R 1166</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA + AC</td>
<td>102</td>
<td>43</td>
<td>145 / 2074</td>
</tr>
<tr>
<td>CC</td>
<td>15</td>
<td>7</td>
<td>22 / 204</td>
</tr>
<tr>
<td>HR [95% CI]; P*</td>
<td>1.61 [0.93–2.77]; P = 0.09</td>
<td>1.75 [0.78–3.90]; P = 0.15</td>
<td>1.65 [1.05–2.59]; P = 0.03</td>
</tr>
<tr>
<td>AT2R 1675</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>74</td>
<td>26</td>
<td>100 / 1188</td>
</tr>
<tr>
<td>G</td>
<td>59</td>
<td>26</td>
<td>85 / 1027</td>
</tr>
<tr>
<td>HR [95% CI]; P*</td>
<td>0.94 [0.67–1.33]; P = 0.75</td>
<td>1.16 [0.67–2.00]; P = 0.59</td>
<td>1.0 [0.75–1.34]; P = 0.99</td>
</tr>
<tr>
<td>AT2R 3123</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>66</td>
<td>23</td>
<td>89 / 1320</td>
</tr>
<tr>
<td>A</td>
<td>56</td>
<td>31</td>
<td>87 / 1062</td>
</tr>
<tr>
<td>HR [95% CI]; P*</td>
<td>1.10 [0.77–1.57]; P = 0.61</td>
<td>1.66 [0.97–2.85]; P = 0.07</td>
<td>1.25 [0.93–1.68]; P = 0.15</td>
</tr>
</tbody>
</table>

*Risk adjusted for age and practice; MI indicates myocardial infarction.

TABLE 3. Baseline Characteristics of Study Subjects Genotyped for the AT1R1166A>C Polymorphism

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>AT1R1166AA (n = 1192)</th>
<th>AT1R1166AC (n = 882)</th>
<th>AT1R1166CC (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/m²*</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.
There was no requirement to adjust for baseline variables having no association with genotype. However, when such complete adjustments were performed, results were unaffected.

**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, AT1R 1166CC genotype is associated with elevated CHD risk at all levels of SBP, the gradient of increasing risk with rising SBP being independent of AT1R genotype. Conversely, CHD risk is independent of AT1R genotype among normotensive individuals, whereas the AT2R 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 AT1R/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.22 The 1675A>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 AT1R expression and hence increasing cardiovascular risk, and the 1673A 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 AT1R12 and AT2R10,32 specifically—in the common mediation of both CHD and LVH. Both AT1R and AT2R may have more diverse effects other than on vascular form and function,33,6 since Ang II also influences inflammation22 and coagulation.26 Further investigation into the (patho)biological actions of angiotensins at the AT1R, and particularly AT2R, is therefore warranted.
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, A allele) rather than the absence (Deletion, D allele) is associated with reduced tissue ACE activity. Pharmacological ACE inhibition substantially reduces coronary event rate in high-risk patients. 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 (through loss of negative feedback on angiotensinogen and ACE synthesis and conversion of excess Ang I to Ang II through non-ACE pathways). Rather, an alteration in relative AT1 R/AT2 R activity might be responsible: AT1 R expression increases in response to Ang II and may reduce with ACE inhibition, 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. Altered AT1 R/AT2 R balance may also underlie the greater impact of AT1 R antagonism than equihypotensive β-blockade on coronary event rate in hypertensive patients: Loss of negative feedback causes a rise in Ang II levels and hence binding to the (unprotected) AT1 R. Furthermore, cross-talk exists between AT1 and AT2 receptors, and changes in AT1 R expression may occur during treatment with AT1 R antagonists.

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 (or lack of it) of AT1 R genotype with CHD. Indeed, epistatic interaction with ACE genotype, although not detected here (data not shown), has been suggested, 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 or is causally associated with differences in expression. The impact of otherwise small falls in BP on CHD risk may thus be amplified when such reductions are associated with ACE inhibition. 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

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**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>A (n=1062)</td>
<td>C (n=1320)</td>
<td></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 AT1R1166A/C genotype are from the Second Northwick Park Heart Study.

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**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 AT2 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.
The image contains text from a scientific paper discussing the impact of angiotensin receptor gene variants on coronary risk. The text is too dense and formatted for direct transcription, but it appears to discuss the relationship between angiotensin receptor polymorphisms and hypertensive heart disease, with a focus on the potential implications for treatment and prevention.

**Figure 5.** Survival curves of CHD events in subjects with systolic hypertension (SBP ≥ 160 mm Hg) by AT-R genotypes stratified by those at most risk (subjects with both AT-R1675A and AT-R3123A alleles) compared with other haplotypes. Broken line represents 1675A/3123A; unbroken line, other haplotypes.

The text and figures suggest a detailed analysis of genetic factors influencing cardiovascular outcomes, with a particular emphasis on the angiotensin AT1 and AT2 receptors. The discussion includes references to studies on the pharmacotherapeutic implications of these genetic variations and their potential role in the treatment of cardiovascular disease.

**Perspectives**

Polymorphic 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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**References**


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