Natriuretic Peptide Precursor A Gene Polymorphisms and Risk of Blood Pressure Progression and Incident Hypertension

David Conen, Robert J. Glynn, Julie E. Buring, Paul M Ridker, Robert Y.L. Zee

Abstract—We tested the hypothesis that natriuretic peptide precursor A gene polymorphisms are significantly associated with blood pressure progression and incident hypertension among healthy, middle-aged women. We performed a prospective cohort study among 18 437 white women participating in the Women’s Health Study who were free of hypertension at baseline. Two previously characterized single nucleotide polymorphisms within the natriuretic peptide precursor A gene (rs5063 G>A and rs5065 T>C) were genotyped. Blood pressure progression at 48 months and incident hypertension during the entire follow-up according to the different genotypes and inferred haplotypes were assessed by logistic regression and Cox proportional hazards models, respectively. At 48 months, 47.4% of women had blood pressure progression. The odds ratio (95% CIs) for blood pressure progression associated with the rs5063 variant was 0.85 (0.76 to 0.94; P=0.002). For the rs5065 variant, the corresponding odds ratio was 0.94 (0.88 to 1.00; P=0.050). During 9.8 years of follow-up, 29.6% of women developed incident hypertension. Hazard ratios (95% CIs) for incident hypertension were 0.88 (0.80 to 0.96; P=0.005) for the rs5063 variant and 0.95 (0.90 to 1.00; P=0.068) for the rs5065 variant. The odds ratios (95% CIs) of blood pressure progression for the G-T, G-C, and A-T haplotypes were 1.0 (referent), 0.91 (0.85 to 0.98; P=0.007), and 0.80 (0.71 to 0.89; P<0.001), respectively. For incident hypertension, the corresponding hazard ratios were 1.0 (referent), 0.95 (0.90 to 1.01; P=0.095), and 0.90 (0.81 to 0.99; P=0.031), respectively. If corroborated by other large-scale, prospective studies, our findings indicate that the natriuretic peptide precursor A gene plays a significant role in blood pressure regulation and development of hypertension. (Hypertension. 2007;50:1114-1119.)

Key Words: blood pressure ■ hypertension ■ natriuretic peptide precursor A ■ gene polymorphism ■ atrial natriuretic peptide

In a Western population, the cumulative lifetime risk of developing hypertension approaches 90%.1 Although obesity and other environmental factors2 substantially contribute to the high incidence of hypertension, twin studies suggest that, in human beings, up to one third of the interindividual variability of blood pressure is heritable.3 Thus, it is important to understand genetic influences on blood pressure and hypertension. However, genetic studies of multifactorial disorders such as hypertension have proven difficult because of the multiplicity of genes underlying complex phenotypes and the modest effect of an individual polymorphism or gene.

Atrial natriuretic peptide plays a significant role in the regulation of vascular tone and sodium homeostasis. A4 Experimental studies showed that underexpression of the natriuretic peptide precursor A gene (NPPA; gene ID 4878, chromosome location 1p36.21) is associated with elevated blood pressure in transgenic mice, whereas overexpression of NPPA leads to decreased blood pressure levels.6 In humans, few studies revealing controversial findings are available on the association between hypertension and polymorphisms within the NPPA gene.7–10

The large sample size and long follow-up of the Women’s Health Study provide a unique opportunity to prospectively analyze genetic influences on multifactorial disorders. We, therefore, tested the hypothesis that NPPA gene polymorphisms are significantly associated with blood pressure progression and incident hypertension in initially healthy, middle-aged women.

Methods

Participants

All of the study subjects were participants of the Women’s Health Study, a completed randomized trial evaluating the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among female health professionals. Details of the study design have been described previously.11–13 Briefly, information on baseline variables was collected using mailed questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every 6

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months during the first year and every 12 months thereafter. Follow-up information from randomization through the end of the trial, March 31, 2004, was used for the present analysis. For the present study, we included 18,437 white women who were free of hypertension at baseline and had both NPPA genotypes determined. Median follow-up for this sample population was 9.8 years (interquartile range: 6.6 to 10.5 years). Written informed consent was obtained from all of the participants.

Study Variables
Blood pressure at randomization was self-reported by the female health professionals, a group where self-report of blood pressure has proven highly accurate.14–16 Women were classified into 3 predefined blood pressure categories: <120 mm Hg for systolic and 75 mm Hg for diastolic blood pressure; 120 to 129 mm Hg for systolic or 75 to 84 mm Hg for diastolic blood pressure; and 130 to 139 mm Hg for systolic or 85 to 89 mm Hg for diastolic blood pressure.17 Women with discordant systolic and diastolic blood pressure categories were classified into the higher category. Covariates of interest were ascertained at study entry and included age, smoking, history of hypercholesterolemia (self-reported cholesterol of ≥240 mg/dL; 6.22 mmol/L), body mass index (weight in kilograms divided by the square of height in meters), history of diabetes, exercise, alcohol consumption, and highest education level achieved.

Outcome Assessment
Blood pressure information at 48 months was missing in 1874 women, and 182 women with complete blood pressure information had a cardiovascular event or died during the first 48 months of follow-up. After excluding these women, 16,381 women remained in the analysis for blood pressure progression at 48 months. To assess blood pressure progression, we created categories of self-reported blood pressure at 48 months of follow-up identical to those at baseline. Blood pressure progression was defined by progressing ≥1 blood pressure category compared with baseline or by a new diagnosis of hypertension during the first 48 months.

Incident cases of hypertension were defined by meeting ≥1 of the following criteria: self-report of a new physician diagnosis of hypertension assessed at years 1 and 3 and yearly thereafter; self-report of antihypertensive treatment assessed at years 1, 3, and 4; or self-reported systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg assessed at years 1 and 4.

Women reporting a new physician diagnosis of hypertension also provided month and year of diagnosis. For a diagnosis defined by another criterion or a missing date for a physician diagnosis, a date between the current and the previous questionnaire was randomly assigned. Women who developed cardiovascular disease, for which the management may affect blood pressure levels, were censored at the date of diagnosis and not considered at risk for incident hypertension thereafter. All 18,437 of the women were included in the incident hypertension analyses.

NPPA Genotype Determination
We analyzed 2 previously described polymorphisms in the NPPA gene: rs5063 (664 G>A) and rs5065 (2238 T>C). Genotyping was performed in the context of a multimarker assay using an immobilized probe approach, as described previously (Roche Molecular Systems).18 In brief, each DNA sample was amplified by PCR with biotinylated primers. Each PCR product pool was then hybridized to a panel of sequence-specific oligonucleotide probes immobilized in a linear array. The colorimetric detection method was based on the use of streptavidin-horseradish peroxidase conjugate with hydrogen peroxide and 3,3′,5,5′-tetramethylbenzidine as substrates. To confirm genotype assignment, scoring was carried out by 2 independent observers. Discordant results (<1% of all scoring) were resolved by a joint reading and, where necessary, a repeat genotyping.

Statistical Analysis
We calculated allele frequencies and performed a Hardy-Weinberg equilibrium test using the Fisher probability test statistics. Baseline characteristics according to NPPA genotype groups were compared using χ² tests for categorical variables and ANOVA for continuous variables.

Next, we performed logistic regression analysis to examine the association between blood pressure progression at 48 months and NPPA genotype groups assuming an additive model. Separate models were created for each polymorphism. The common wild type was used as the reference group. In a first step, age-adjusted models are presented. Thereafter, we fitted a multivariable model adjusting for age, smoking, baseline blood pressure category, history of diabetes, body mass index, history of hypercholesterolemia, exercise, alcohol consumption, highest education level, and randomized treatment assignments (aspirin, vitamin E, and β-carotene).

Subsequently, we fitted Cox proportional hazards models to compare the risk of incident hypertension during the entire follow-up period across NPPA genotype groups. Again, an additive model was assumed. This analysis was adjusted for the same variables described above.

To further assess the independent effect of the NPPA genotype groups on blood pressure progression and incident hypertension, we stratified the study sample in 3 groups according to baseline blood pressure category. Subsequently, we repeated all of the regression analyses described above within each blood pressure stratum. Differences according to baseline blood pressure category were also assessed by including baseline blood pressure by genotype interaction terms into the nonstratified models. The significance of the interaction was assessed by comparing the likelihood ratio with and without the interaction terms in the model.

Pairwise linkage disequilibrium was examined as described by Devlin and Risch.19 Haplotype estimation and inference was determined using PHASE version 2.1.1.20–22 Subsequently, the same multivariable regression models as described above were constructed using inferred haplotypes as the predictor of interest. Only women with an inferred haplotype probability of 1.0 were considered for these analyses. We prespecified that haplotypes with a inferred frequency <0.01 would not be analyzed individually. Accordingly, the A-C haplotype was not assessed. Statistical significance was based on a likelihood ratio test with and without all of the haplotype indicator variables in the fully adjusted models. Only if this overall test was statistically significant were the indicator variables analyzed for individual statistical significance. The most common haplotype (G-T) was used as a reference category for all of the analyses.

Categorical variables were entered in the regression models using binary indicator variables. The proportional hazards assumption was examined for all of the models by including a genotype by logarithm of time interaction term in each model.20 No violation of this assumption was found. All of the analyses were carried out using SAS version 9 (SAS Institute Inc.). A 2-tailed P<0.05 was considered to indicate statistical significance.

Results
Baseline characteristics of the 18,437 women are shown in Table 1. Minor allele frequencies were 0.05 for rs5063 (A) and 0.15 for rs5065 (C). There were no significant differences in characteristics according to NPPA genotype groups, except for the baseline blood pressure category for the rs5063 polymorphism. Women with the AA genotype had a lower proportion of blood pressure levels between 130 to 139 and 85 to 89 mm Hg compared with the GG or GA genotypes. The distribution of the genotypes was in Hardy-Weinberg equilibrium (P=0.27 for rs5063 and P=0.73 for rs5065).

Furthermore, the 2 polymorphisms tested were in strong pairwise linkage disequilibrium (D’=0.84).

At 48 months of follow-up, 7,756 of 16,381 women (47.4%) had blood pressure progression. The risk of blood pressure...
progression among women with the rs5063 GG, GA, and AA genotypes was 47.8%, 43.4%, and 43.9%, respectively. The risk of blood pressure progression for the rs5065 TT, TC, and CC genotypes was 47.9%, 46.0%, and 46.0%, respectively.

During 9.8 years of follow-up, 5452 (29.6%) of 18,437 women developed incident hypertension. Among women with the rs5063 GG, GA, and AA genotypes, 29.8%, 28.1%, and 15.7% became hypertensive during follow-up. The corresponding numbers for the rs5065 TT, TC, and CC genotypes were 29.8%, 29.1%, and 26.3%, respectively.

Risk of blood pressure progression according to NPPA genotype group is shown in Table 2. The A allele of the rs5063 polymorphism was consistently associated with a lower risk of blood pressure progression compared with the G allele. Multivariable adjustment only minimally influenced the effect estimates and 95% CIs. The C allele of the rs5065 polymorphism was significantly associated with a lower risk of blood pressure progression (P<0.050). However, the lower risk of incident hypertension did not reach statistical significance in the Cox model (P=0.068) for the entire follow-up period.

After stratification according to baseline blood pressure category, consistent results were obtained for both poly-

Table 1. Baseline Characteristics According to NPPA Polymorphisms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NPPA rs5063</th>
<th></th>
<th>NPPA rs5065</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
<td>GA</td>
<td>AA</td>
<td>TT</td>
</tr>
<tr>
<td>No.</td>
<td>16,683</td>
<td>1703</td>
<td>51</td>
<td>13,390</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>54.7±7</td>
<td>54.7±7</td>
<td>53.6±6</td>
<td>54±7</td>
</tr>
<tr>
<td>Body mass index, mean±SD, kg/m²</td>
<td>25.1±4.3</td>
<td>25.1±4.4</td>
<td>26.3±5.7</td>
<td>25.1±4.4</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>1.2</td>
<td>0.9</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>History of hypercholesterolemia, %</td>
<td>25.0</td>
<td>24.3</td>
<td>19.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>11.9</td>
<td>11.3</td>
<td>15.7</td>
<td>11.7</td>
</tr>
<tr>
<td>Exercise, times/wk, %</td>
<td>35.1</td>
<td>34.8</td>
<td>47.1</td>
<td>34.8</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td>41.7</td>
<td>41.2</td>
<td>56.9</td>
<td>41.7</td>
</tr>
<tr>
<td>Highest education level, %</td>
<td>54.0</td>
<td>55.2</td>
<td>60.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Baseline blood pressure category, %</td>
<td>44.5</td>
<td>44.0</td>
<td>31.4</td>
<td>44.3</td>
</tr>
<tr>
<td></td>
<td>39.1</td>
<td>39.4</td>
<td>60.8</td>
<td>39.4</td>
</tr>
<tr>
<td></td>
<td>16.5</td>
<td>16.6</td>
<td>7.8</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Because of rounding, percentages may not equal 100.

*p=0.03 for the comparison across rs5063 variants.

Inferred haplotype frequencies for the present sample were 0.80 for the G-T haplotype, 0.15 for the G-C haplotype, 0.05 for the A-T haplotype, and <0.01 for the A-C haplotype. Multivariable regression analyses using inferred haplotype indicators are shown in Table 4. Overall likelihood ratio tests for blood pressure progression within 48 months and incident hypertension during overall follow-up were all statistically significant (P<0.001 and P=0.037, respectively). The logistic regression analysis showed a strong and consistent reduction in blood pressure progression of the G-C and the A-T haplotypes. In the Cox proportional hazards analysis, only the A-T haplotype but not the G-C haplotype was associated with a significantly lower incidence of hypertension during follow-up.
Gene variations and hypertension. To our knowledge, this is the first large-scale prospective study analyzing the relationship between NPPA gene variations and incident hypertension during follow-up. A cross-sectional study in Europe among 1033 subjects found a lower prevalence of the rs5065 C allele in hypertensive subjects compared with control subjects. Interestingly, Gruchala et al reported that, among 847 subjects with coronary heart disease, those carrying the C allele had less severe disease based on coronary angiography, suggesting that even in individuals with prevalent disease, this polymorphism might have a protective effect. A small study of 104 African Americans did not find a significant difference in the prevalence of rs5065 gene variants between normotensive and hypertensive participants.

Data are somewhat more equivocal concerning the A allele of the rs5063 polymorphism. Zhang et al documented a lower diastolic but not systolic blood pressure among 756 Chinese hypertensive patients carrying ≥1 copy of the A allele. However, in a small European study, among 203

### Table 2. Relative Risk of Blood Pressure Progression and Incident Hypertension According to NPPA Gene Variants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NPPA rs5063</th>
<th>NPPA rs5065</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure progression, odds ratio (95% CI)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.85 (0.77 to 0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable adjusted†</td>
<td>0.85 (0.76 to 0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Incident hypertension, hazard ratio (95% CI)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.90 (0.82 to 0.99)</td>
<td>0.022</td>
</tr>
<tr>
<td>Multivariable adjusted†</td>
<td>0.88 (0.80 to 0.96)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The multivariable (age-adjusted) blood pressure progression models are based on 7495 (7756) events in 15 806 (16 381) women; the multivariable (age-adjusted) incident hypertension models are based on 5246 (5452) incident events in 17 771 (18 437) women. Women with the common wild type constitute the reference group.

*Blood pressure progression was defined as progression of ≥1 blood pressure category or progressing to hypertension during the first 48 months of follow-up. Incident hypertension was defined as developing hypertension during the entire follow-up period.

†Data are adjusted for age, smoking, blood pressure category, history of hypercholesterolemia, diabetes, body mass index, exercise, alcohol consumption, highest education level, and randomized treatment assignments (aspirin, vitamin E, and β-carotene).

### Table 3. Relative Risk of Blood Pressure Progression and Incident Hypertension According to NPPA Gene Variants and Stratified by Baseline Blood Pressure Category

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NPPA rs5063</th>
<th>NPPA rs5065</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure progression, odds ratio (95% CI)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120/75 mm Hg (n=7116)</td>
<td>0.86 (0.74 to 1.01)</td>
<td>0.95 (0.86 to 1.04)</td>
</tr>
<tr>
<td>120 to 129/75 to 84 mm Hg (n=6124)</td>
<td>0.90 (0.76 to 1.07)</td>
<td>0.95 (0.85 to 1.05)</td>
</tr>
<tr>
<td>130 to 139/85 to 89 mm Hg (n=2566)</td>
<td>0.70 (0.54 to 0.91)</td>
<td>0.90 (0.77 to 1.06)</td>
</tr>
<tr>
<td>Incident hypertension, hazard ratio (95% CI)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120/75 mm Hg (n=7914)</td>
<td>0.85 (0.69 to 1.05)</td>
<td>0.96 (0.86 to 1.08)</td>
</tr>
<tr>
<td>120 to 129/75 to 84 mm Hg (n=6959)</td>
<td>0.96 (0.84 to 1.09)</td>
<td>0.95 (0.87 to 1.03)</td>
</tr>
<tr>
<td>130 to 139/85 to 89 mm Hg (n=2898)</td>
<td>0.79 (0.67 to 0.93)</td>
<td>0.95 (0.87 to 1.05)</td>
</tr>
</tbody>
</table>

Women with the common wild type constitute the reference group. All of the relative risks are adjusted for age, smoking, history of hypercholesterolemia, diabetes, body mass index, exercise, alcohol consumption, highest education level, and randomized treatment assignments (aspirin, vitamin E, and β-carotene).

*P value for heterogeneity of the genotype effect on blood pressure progression and incident hypertension across different baseline blood pressure categories.

†Blood pressure progression was defined as progression of ≥1 blood pressure category or progressing to hypertension during the first 48 months of follow-up. Incident hypertension was defined as developing hypertension during the entire follow-up period.
untreated hypertensive subjects, a greater left ventricular mass index was documented among carriers of the A allele.9 These results must be interpreted with caution in light of the absence of nondiseased control subjects and small sample sizes. Only 11 participants of this study were heterozygous, and none of the participants was homozygous for the rs5063 variant.

The functional roles of the genetic polymorphisms described in the present study are not known. However, the direct effects of natriuretic peptides on the systemic vasculature and the kidney make the association between NPPA polymorphisms and blood pressure progression plausible.4 Furthermore, animal studies have shown the involvement of atrial natriuretic peptide in blood pressure regulation and development of hypertension.5,6 Finally, rs5065 and rs5065 both encode changes to the amino acid sequence of the NPPA gene and are, thus, intrinsically candidates for altering its biological function. The valine-to-methionine substitution encoded by the minor allele of rs5063 is not predicted to be deleterious, but it may affect function in other ways.25 The major allele of rs5065 encodes termination of the NPPA gene 3 amino acids (tyrosine, arginine, and arginine) earlier than the minor allele. Remarkably, the minor allele is likely the ancestral allele, because it and the extra 3 amino acids are found in the sequences from chimpanzee and macaque. Although the NPPA locus was not identified as a site of linkage disequilibrium with the NPPA polymorphisms assessed in this study.

**Strengths and Limitations**

Strengths of the present study are the large sample size, the prospective design, and the complete long-term follow-up with a large number of events. Furthermore, our study highlights the challenges of genetic investigations in complex diseases such as hypertension, in which a substantial sample size is needed to detect low-to-moderate effects of 1 individual polymorphism. Some potential limitations of our study require discussion. First, we used self-reported blood pressure and hypertension status. However, the prognostic value of self-reported blood pressure in cohort studies involving US health professionals is similar compared with directly measured blood pressure values in participants of other cohort studies.14 Furthermore, the validity of this approach has been examined in the comparable Nurses’ Health Study, where 99% of the women who reported high blood pressure levels had their diagnosis confirmed based on medical chart review.15 Finally, self-reported blood pressure, total cholesterol, and body mass index have been shown previously in the Women’s Health Study to be strong predictors of cardiovascular risk, with relative risks consistent in magnitude with those observed in other major studies.28–30 Second, this study included only white female health professionals, and our findings may not be generalizable to other populations. Third, plasma levels of natriuretic peptides are not available in the present study. Finally, we cannot exclude that the observed associations are caused by yet-to-be identified susceptibility gene(s)/locus(i) in linkage disequilibrium with the NPPA polymorphisms assessed in this study.

**Perspectives**

This prospective study provides evidence that NPPA gene polymorphisms are associated with a protective effect on blood pressure progression and incident hypertension. If corroborated by other large-scale prospective studies, these data suggest an important role for natriuretic peptides in blood pressure regulation and development of hypertension in humans.

**Acknowledgments**

We are indebted to the participants of the Women’s Health Study for their outstanding commitment and cooperation and to the entire Women’s Health Study staff for their expert and unfailing assistance. We thank Roche Molecular Systems, Inc (Alameda, Calif), and F. Hoffmann La-Roche Ltd (Basel, Switzerland) for supporting the genotype determinations financially and with in-kind contribution of reagents and consumables.

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**Table 4. Haplotype-Based Regression Analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haplotype G-T*</th>
<th>Haplotype G-C</th>
<th>P</th>
<th>Haplotype A-T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>0.91 (0.85 to 0.97)</td>
<td>0.003</td>
<td>0.79 (0.71 to 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable model†</td>
<td>1.00</td>
<td>0.91 (0.85 to 0.98)</td>
<td>0.007</td>
<td>0.80 (0.71 to 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident hypertension, hazard ratio (95% CI)†</td>
<td>1.00</td>
<td>0.95 (0.90 to 1.01)</td>
<td>0.080</td>
<td>0.91 (0.82 to 1.00)</td>
<td>0.048</td>
</tr>
<tr>
<td>Multivariable model†</td>
<td>1.00</td>
<td>0.95 (0.90 to 1.01)</td>
<td>0.095</td>
<td>0.90 (0.81 to 0.99)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

*Reference group.
†Blood pressure progression was defined as progression of ≥ 1 blood pressure category or progressing to hypertension during the first 48 months of follow-up. Incident hypertension was defined as developing hypertension during the entire follow-up period.
‡Data are adjusted for age, smoking, blood pressure category, history of hypercholesterolemia, diabetes, body mass index, exercise, alcohol consumption, highest education level, and randomized treatment assignments (aspirin, vitamin E, and β-carotene).
Disclosures

None.

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