Clinical and Genetic Correlates of Aldosterone-to-Renin Ratio and Relations to Blood Pressure in a Community Sample


Abstract—Aldosterone:renin ratio (ARR) is used to screen for hyperaldosteronism. Data regarding correlates of ambulatory ARR in the community and its relation to hypertension incidence are limited. We defined clinical correlates of ARR, determined its heritability, tested for association and linkage, and related ARR to blood pressure (BP) progression in nonhypertensive individuals among 3326 individuals from the Framingham Heart Study (53% women; mean age: 59 years). Ambulatory morning ARR (serum aldosterone and plasma renin concentrations) were related to clinical covariates, genetic variation across the REN locus, a 10-cM linkage map, and among nonhypertensive participants (n=1773) to progression of hypertension. Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure BP category (optimal: <120/80 mm Hg, normal: 120 to 129/80 to 84 mm Hg, high normal: 130 to 139/85 to 89 mm Hg, hypertension: ≥140/90 mm Hg), or incident hypertension (systolic BP: ≥140 mm Hg, diastolic BP: ≥90 mm Hg, or use of antihypertensive treatment). ARR was positively associated with age, female sex, untreated hypertension, total/high-density lipoprotein cholesterol ratio, hormone replacement therapy, and β-blocker use, but negatively associated with angiotensin-converting enzyme inhibitor and diuretic use. ARR was heritable (h²=0.40), had modest linkage to chromosome 11p (logarithm of the odds: 1.89), but was not associated with 17 common variants in REN (n=1729). On follow-up (mean: 3 years), 607 nonhypertensive individuals (34.2%) developed BP progression, and 283 (16.0%) developed hypertension. Higher baseline logARR was associated with increased risk of BP progression (odds ratio per SD increment: 1.23; 95% CI: 1.11 to 1.37) and hypertension incidence (odds ratio per SD increment: 1.16; 95% CI: 1.00 to 1.33). ARR is a heritable trait influenced by clinical and genetic factors. There is a continuous gradient of increasing risk of BP progression across ARR levels in nonhypertensive individuals. (Hypertension. 2007;49:846-856.)

Key Words: aldosterone • renin • hypertension, essential • blood pressure • genetics • population • risk factors

Received June 20, 2006; first decision July 10, 2006; revision accepted January 10, 2007.

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Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000258554.87444.91

846
Furthermore, the prognostic significance of ARR in community-based nonhypertensive individuals is unknown. We demonstrated recently that increasing serum aldosterone predicts a future increase in BP and incident hypertension in nonhypertensive participants in the Framingham Heart Study. Subsequent to that investigation, we measured plasma renin concentrations in our cohort to evaluate the independent and conjoint contributions of both hormones to longitudinal BP outcomes using the ARR. Given the interest in ARR as a screening test and the emergence of novel antihypertensive agents targeting both renin and aldosterone, a study of the clinical and genetic correlates of ARR in the community and the influence of ARR on BP progression and hypertension incidence among nonhypertensive subjects could have diagnostic, therapeutic, and prognostic importance. Accordingly, we evaluated the clinical and genetic correlates of ARR and examined the relationship of ARR in nonhypertensive individuals to BP progression and incident hypertension in a large, community-based sample.

Methods

Study Participants

The design and selection criteria of the Framingham Offspring Study have been reported previously. Approximately every 4 years, offspring study participants undergo detailed medical history, assessment of medication use, physical examination, and assessment of vascular risk factors. The present investigation included 3532 participants who attended the sixth examination cycle (1995–1998). The institutional review board at Boston Medical Center approved the study, and all of the participants gave written informed consent.

Participants were excluded if they had a missing value for plasma renin (n=74), serum aldosterone (n=97), or any of the covariates (n=35). After exclusions, 3326 attendees were eligible for the study of clinical correlates. Heritability analyses were conducted in 2271 participants in 998 families. The genetic linkage analysis included 1225 genotyped participants in 328 families (1597 sibling pairs and 4 parent–offspring pairs). The association analysis included 1729 unrelated cohort participants with covariate and genotype data. Analyses of the relations of baseline ARR to BP progression and incident hypertension were restricted to the 1773 nonhypertensive participants at the sixth examination who attended the seventh examination.

Measurements of Plasma Renin, Serum Aldosterone, and BP

Fasting whole blood samples were drawn by venipuncture after ∼10 minutes of rest in a supine position in the morning, typically between 7:30 and 9:00 AM. Participants were instructed to take all routine medications. Blood samples were centrifuged and the serum/plasma fraction stored at −70 to −80°C until it was thawed for analysis. Plasma renin concentration (milliunits per liter) was measured using an immunochemiluminometric assay (Nichols Advantage Direct Renin assay). The assay was sensitive with intraassay coefficients of variation ranging from 2% for high concentrations to 10% for low concentrations. Serum aldosterone (nanograms per liter) was measured using a radioimmunossay (Quest Diagnostics), as described previously. Spot urinary sodium concentration was measured using an automated ion-electrode method and indexed to urinary creatinine (expressed as millimoles of sodium per gram of urinary creatinine), as described previously.

Participants rested in a chair for ∼5 minutes before BP measurement in the Framingham clinic. A physician measured systolic and diastolic BP twice in the left arm of seated participants with a mercury column sphygmomanometer, a cuff of appropriate size, and a standardized written quality control protocol. The average of 2 readings constituted the examination BP.

Clinical Covariates

We considered the following potential covariates of ARR for analyses: age, sex, total:high-density lipoprotein cholesterol ratio, diabetes, menopausal status (premenopausal, postmenopausal with hormone replacement therapy, or postmenopausal without hormone replacement therapy), hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg at the sixth examination), and use of the following classes of antihypertensive agents: diuretics, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, α-1 adrenergic receptor antagonists, and other antihypertensive agents. Methods of risk factor ascertainment in the Framingham Heart Study have been reported elsewhere. Because the urinary sodium:creatinine ratio was only available in a subset of 2850 participants, we performed secondary analyses adjusting for the urinary sodium:creatinine ratio.

Selection and Genotyping of Tag Single Nucleotide Polymorphisms and Microsatellites

We genotyped 32 polymorphic single nucleotide polymorphisms (SNPs) in a reference sample of 93 individuals of European ancestry, spanning a genomic distance of 30 kb surrounding the REN locus. These data revealed 2 blocks of strong linkage disequilibrium (LD) defined using the “spine of LD” method implemented in haplovie 2.03 (Figure S1, available online at http://hyper.ahajournals.org). We selected 14 tag SNPs for genotyping in the Framingham Heart Study samples that captured haplotypes within blocks at frequency ≥0.05 at an r²≥0.8, as well as an additional 3 SNPs to better define the region between the 2 blocks of strong LD. Genotyping of microsatellite markers at an average 10 cm spacing (Weber set 8A) for the linkage analyses in the related sample was conducted through the Mammalian Genotyping Center at Marshfield Clinic as described previously.

Statistical Analysis

Renin and aldosterone levels were natural-log transformed because of their positively skewed distributions. We evaluated the sex-specific distributions of logARR in several participant subgroups: nonhypertensive; untreated hypertensive; and hypertensive on diuretics, ACE inhibitors, or β-blockers, separately. We used stepwise multivariable linear regression to evaluate the clinical correlates of logARR in the entire sample of 3326 participants. We then used generalized estimating equations to account for correlations among the 2 blocks of strong LD. We used stepwise multivariable linear regression to evaluate the clinical correlates of logARR in the entire sample of 3326 participants. We then used generalized estimating equations to account for correlations among the related individuals; a P<0.05 was used for retention in the final multivariable model. We examined the correlates of log-aldosterone and log-renin separately to clarify whether any observed relation of logARR was driven by the relations of covariates to the numerator (aldosterone), the denominator (renin), or both. All of the analyses were carried out in SAS.

Heritability and Genetic Analyses

For genetic analyses, we normalized the residuals from regression models (age-, sex-, and multivariable-adjusted) in the entire sample. Using variance components methods implemented in sequential oligogenic linkage analysis routines (SOLAR), we determined the heritability of logARR residuals from age-, sex-, and multivariable-adjusted models. We carried out multipoint linkage analysis using Genehunter 2.0 for the logARR residuals from both models. Linkage results are reported in logarithm of the odds (LOD) scores. The LOD score is the log base 10 of the likelihood ratio under the hypotheses of linkage and nonlinkage. We tested the association of logARR residuals with each SNP (n=1729 unrelated subjects) individually using a 2-degree of freedom general test. Within the 2 blocks of strong LD, we tested haplotypes with frequency ≥0.05 for association with logARR residuals from age-, sex-, and multivariable-adjusted models using the score-based haplo.stats program (available at http://mayoresearch.mayo.edu/mayo/research/biostat/schaid.cfm). We considered global haplotype tests as the primary statistical test of significance.
ARR Relation to BP Progression and Incident Hypertension

We used multivariable logistic regression to relate ARR (modeled as a continuous, log-transformed variable and as sex-specific quartiles) in nonhypertensive participants at examination 6 to the risk of progression of ≥1 BP category (optimal: <120/80 mm Hg, normal: 120 to 129/80 to 84 mm Hg, high normal: 130 to 139/85 to 89 mm Hg, hypertension: ≥140/90 mm Hg) and incident hypertension (systolic BP: ≥140 mm Hg, diastolic BP: ≥90 mm Hg, or use of antihypertensive treatment) at examination 7 after a mean follow-up of 3 years. We examined a model adjusting for age and sex and a multivariable model adjusting for age, sex, baseline BP stage, systolic BP, diastolic BP, smoking status, diabetes, serum creatinine, body mass index, and weight change percentage on follow-up, as described previously. We performed secondary analyses incorporating urine sodium/creatinine ratio as a covariate. We tested for effect modification by age, sex, body mass index, and urine sodium/creatinine ratio by incorporating appropriate interaction terms in multivariable models with logARR. To understand the relative contributions of aldosterone versus renin to any potential association of ARR with BP progression and incident hypertension, we assessed rates of BP progression and incident hypertension by tertiles of aldosterone cross-classified by tertiles of renin; tertiles were used instead of quartiles to avoid small numbers in individual cells. Furthermore, we examined models that included continuous hormone levels of aldosterone and renin together as a fixed ratio (ARR). On ACE inhibitors 14 9 18 17
On ß-blockers 12 9
On calcium channel blockers 12 8
On α1 AR blockers 3 1
Total cholesterol/HDL ratio 4.9 (2.0) 4.0 (1.4) 4.8 (1.4) 3.8 (1.4)
Diabetes, %‡ 14 9 6 3
Current smoker, % 14 16 18 17
Atrial fibrillation, % 1 0 3 1
Prevalent CVD, % 15 7 2 0
Premenopausal, % 20 27
Postmenopausal on HRT, % 25 25
Postmenopausal no HRT, % 56 48
Serum creatinine, mg/dL 1.3 (0.2) 1.1 (0.2) 1.2 (0.2) 1.1 (0.1)
Urine Na/Cr ratio mmol/g§ 103 (90) 123 (100) 99 (90) 117 (100)
Serum aldosterone ng/L 90 [70 to 130] 110 [70 to 150] 90 [70 to 130] 100 [70 to 130]
Plasma renin, mU/L 14 [8 to 25] 11 [6 to 19] 14.0 [9.0 to 22.5] 11.0 [7.0 to 17.0]
ARR, ng/L per mU/L 6.7 [3.8 to 11.4] 10 [5.5 to 16.7] 6.0 [4 to 10] 10 [6 to 10]
ARR ≥26 ng/L per mU/L, %|| 7 13 3 9

Values are reported as mean (SD) for continuous traits and % for dichotomous traits. Because serum aldosterone, plasma renin and ARR are skewed, median values [25th percentile to 75th percentile] are shown. CVD indicates cardiovascular disease; Na, sodium; Cr, creatinine; AR, adrenergic receptor; HDL, high-density lipoprotein.

*Nonhypertensive participants at baseline exam 6 were defined by systolic BP <140 mm Hg, diastolic BP <90 mm Hg, and absence of antihypertensive treatment.
†Shown are the percentages of participants with treated or untreated hypertension.
‡Diabetes determined by use of hypoglycemic agents or fasting glucose ≥126 mg/dL.
§Note that urine Na/Cr ratio was available for the subset of 1337 men and 1513 women.
||Shown is the percentage exceeding one among many thresholds proposed in screening hypertensive subjects for primary hyperaldosteronism.

Results

Characteristics of the study Cohort

The characteristics of the entire study sample and of the nonhypertensive individuals are shown in Table 1. The cohort is middle-aged to elderly and of European descent.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Entire Sample</th>
<th>Nonhypertensive* Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=1574)</td>
<td>Women (n=1752)</td>
</tr>
<tr>
<td>Age, y</td>
<td>59 (10)</td>
<td>59 (10)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6 (4.4)</td>
<td>27.4 (5.7)</td>
</tr>
<tr>
<td>% change in weight</td>
<td>0.5 (5.8)</td>
<td>0.7 (6.6)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130 (17)</td>
<td>127 (20)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>77 (9)</td>
<td>74 (9)</td>
</tr>
<tr>
<td>Hypertension at exam 6, %†</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>On any treatment</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>On diuretics</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>On ACE inhibitors</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>On ß-blockers</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>On α1 AR blockers</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>4.9 (2.0)</td>
<td>4.0 (1.4)</td>
</tr>
</tbody>
</table>

TABLE 1. Characteristics of Framingham Heart Study Sample and Nonhypertensive Subgroup at Exam 6

The characteristics of the entire study sample and of the nonhypertensive individuals are shown in Table 1. The cohort is middle-aged to elderly and of European descent.
Distribution of ARR

Figure 1 displays the sex-specific distributions of ARR for the following subgroups: nonhypertensive, untreated hypertensive, hypertensive on diuretics, hypertensive on an ACE inhibitor (ACEI), and hypertensive on a β-blocker (BB). A line is drawn at the 26 ng/L/mU/L value suggested previously to indicate an increased probability of primary hyperaldosteronism.49 Because of the right skew of the untransformed ARR measure, values >75 ng/L/mU/L have been set to 75 ng/L/mU/L for display purposes. Shown below the plots are the percentage in each group with an ARR >26 ng/L/mU/L and the ARR values in nanograms per liter per milliunit per liter corresponding with the 5th, 25th, 50th, 75th, and 95th percentiles for each group.

Clinical Correlates of LogARR

Log-renin was positively associated with the use of diuretics and ACE inhibitors and inversely related to age, female sex, hypertensive status, and β-blocker and hormone replacement therapy use (Table 2). We confirmed our previously reported34 finding that serum aldosterone was positively associated with female sex and diuretic use and demonstrated an additional positive association with calcium channel blocker use and a negative association with ACE inhibitor use (Table 2). In stepwise regression modeling, logARR was positively related to age, female sex, hypertensive status, total cholesterol:high-density lipoprotein cholesterol ratio, and β-blocker and hormone replacement therapy use (Table 2). We observed that logARR was inversely related to diuretic and ACE inhibitor use. Several covariates were not significantly related to log-renin or log-aldosterone individually but were significant correlates of logARR (Table 2).

The multivariable-adjusted logARR model explained 28% of the interindividual variation in ARR. The inclusion of urinary sodium:creatinine ratio as a covariate minimally altered the regression coefficients for other covariates (data not shown).

Heritability and Linkage

The heritability for age and sex-adjusted logARR was 0.36 (SE: 0.06; P<10−4) and for multivariable-adjusted logARR was 0.40 (SE: 0.06; P<10−4). The heritability of multivariable-adjusted log-renin was 0.22 (SE: 0.05; P=0.01), quite consistent with our previous report on aldosterone that used slightly different covariates in the model.34 Exclusion of all of the individuals on antihypertensive therapy reduced the sample size substantially (740 sibpairs), so models including antihypertensive users with adjustment for treatment were considered the primary analysis.

The results of genome-wide linkage analysis of multivariable-adjusted logARR are shown in Figure 2. We observed modest evidence of linkage to chromosome 11p with a maximum multipoint LOD score of 1.89 at 2 cM and to chromosome 5p with a maximum multipoint LOD score of 1.60 at 30.8 cM for residuals from multivariable-adjusted models. In an initial analysis, we did not adjust for ACE inhibitor and β-blocker use when generating logARR residuals. In linkage analyses of those residuals, we observed suggestive evidence of linkage to a locus on chromosome 7p21-22 (24.6 cM) with a maximum multipoint
A on hormone replacement therapy. Shown are the analysis on chromosome 7p in participants without ACE inhib-
itor and calcium channel blocker use in the multivariable-adjusted models (our principal analytical strategy) resulted in a LOD score at this locus with an average inter-SNP distance of 880 bp.

Single SNP and Haplotype Association Results
We genotyped 32 SNPs falling in 2 blocks of strong LD in the Centre d’Etude du Polymorphisme Humain (CEPH) refer-
ence samples to construct a high-resolution LD map of the REN locus with an average inter-SNP distance of 880 bp (Figure S1). In the 1729 unrelated participants, we genotyped 17 SNPs that capture the majority of common variation across the REN locus.

We tested 17 SNPs across the REN locus and observed no single SNP to have a nominal P<0.01 for association with logARR (Table S1). We tested all of the haplotypes with frequency ≥5% in the 2 blocks of strong LD across the REN locus and found no global P<0.01.

Relations of ARR to BP Progression and Incident Hypertension
On follow-up (mean: 3.0 years), 607 nonhypertensive individu-
als (34.2%) experienced BP progression, and 283 (16.0%) developed hypertension. The rates of BP progression and hyper-
tension incidence rose across ARR quartiles in graded fashion (Table 3). In multivariable analyses, an SD increment in logARR was associated with a 23% increased risk of BP progression (P<0.0001) and a 16% increased risk of hypertension (P=0.05). The top ARR quartile was associated with an 89% increased risk of BP progression (P<0.0001) and a 53% increased risk of hypertension (P=0.045) compared with the lowest ARR quartile. Models incorporating urine sodium:crea-
tinine ratio yielded essentially similar results (data not shown).

We did not observe any effect modification by age, sex, body mass index, or urine sodium:creatinine ratio on risk of BP progression or incident hypertension.

Rates of BP progression and incident hypertension rose across increasing tertiles of aldosterone (for any tertile of renin) and decreased across increasing tertiles of renin (for any tertile of aldosterone; Figure 3). To better understand the contributions of aldosterone and renin to the prognostic ability of ARR, we compared age-, sex-, and multivariable-
adjusted models predicting BP progression and incident hypertension that incorporated aldosterone and renin, sepa-
ately and together as linear predictors, as well as in a fixed ratio (ARR; Table 4). β-Coefficients for log-aldosterone and log-renin incorporated in separate multivariable models were opposite in direction (positive for log-aldosterone and negative for log-renin) and statistically significant with the exception of log-renin for the outcome of incident hypertension (P=0.004 and 0.02 for log-aldosterone for BP progression and incident hypertension; correspondingly, P=0.04 and 0.77 for log-renin; Table 4). Models incorporating both log-aldosterone and log-renin together as linear predictors had gen-

### Table 2. Multivariable Clinical Correlates of LogARR, Log-Aldosterone and Log-Renin in the Entire Framingham Heart Study Sample

<table>
<thead>
<tr>
<th>Covariate</th>
<th>β (SE)</th>
<th>Fold Change in ARR</th>
<th>95% CI</th>
<th>P</th>
<th>Log-Aldosterone β (SE)</th>
<th>Log-Renin β (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 y</td>
<td>+0.11</td>
<td>1.11</td>
<td>1.07 to 1.15</td>
<td>&lt;0.0001</td>
<td>−0.03 (0.01)</td>
<td>−0.13 (0.02)*</td>
</tr>
<tr>
<td>Sex, women (vs men)</td>
<td>−0.37</td>
<td>1.45</td>
<td>1.31 to 1.60</td>
<td>&lt;0.0001</td>
<td>+0.13 (0.03)†</td>
<td>−0.23 (0.05)*</td>
</tr>
<tr>
<td>Hypertensive‡</td>
<td>+0.18</td>
<td>1.19</td>
<td>1.09 to 1.30</td>
<td>&lt;0.0001</td>
<td>+0.01 (0.03)</td>
<td>−0.17 (0.04)*</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>−0.22</td>
<td>0.80</td>
<td>0.68 to 0.94</td>
<td>0.005</td>
<td>+0.48 (0.04)*</td>
<td>+0.70 (0.08)*</td>
</tr>
<tr>
<td>ACE inhibitor use</td>
<td>−1.58</td>
<td>0.21</td>
<td>0.17 to 0.24</td>
<td>&lt;0.0001</td>
<td>−0.23 (0.03)*</td>
<td>+1.35 (0.08)*</td>
</tr>
<tr>
<td>β-Blocker use</td>
<td>+0.47</td>
<td>1.60</td>
<td>1.40 to 1.83</td>
<td>&lt;0.0001</td>
<td>−0.06 (0.04)</td>
<td>−0.53 (0.07)*</td>
</tr>
<tr>
<td>Calcium channel blocker use</td>
<td>+0.06</td>
<td>1.06</td>
<td>0.92 to 1.21</td>
<td>0.42</td>
<td>+0.14 (0.04)*</td>
<td>+0.09 (0.07)</td>
</tr>
<tr>
<td>α-1 AR blocker use</td>
<td>−0.13</td>
<td>0.87</td>
<td>0.65 to 1.17</td>
<td>0.37</td>
<td>+0.04 (0.08)</td>
<td>+0.16 (0.14)</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>+0.03</td>
<td>1.03</td>
<td>1.02 to 1.05</td>
<td>0.0001</td>
<td>+0.02 (0.01)</td>
<td>−0.01 (0.01)</td>
</tr>
<tr>
<td>Postmenopausal on HRT§</td>
<td>+0.29</td>
<td>1.33</td>
<td>1.19 to 1.49</td>
<td>&lt;0.0001</td>
<td>+0.06 (0.04)</td>
<td>−0.23 (0.06)*</td>
</tr>
<tr>
<td>Postmenopausal no HRT§</td>
<td>−0.06</td>
<td>0.94</td>
<td>0.84 to 1.06</td>
<td>0.32</td>
<td>−0.07 (0.04)</td>
<td>−0.02 (0.06)</td>
</tr>
</tbody>
</table>

β indicates linear regression coefficient; AR, adrenergic receptor; HRT, hormone replacement therapy; HDL, high-density lipoprotein. Covariates tested in stepwise multivariable regression included (data not shown): age, sex, diastolic BP, systolic BP, hypertension, ACE inhibitor use, β-blocker use, calcium channel blocker use, and α-1 adrenergic receptor antagonist use, total high-density lipoprotein cholesterol, postmenopausal on hormone replacement therapy, and postmenopausal not on hormone replacement therapy. Shown are the β-coefficients, fold change in ARR, 95% CI, and P for all covariates significant at P<0.05 in GenMod linear regression modeling, accounting for sibling correlations. For comparison, the β-coefficients (SE) for the covariates in models predicting log-aldosterone and log-renin are shown. Note that coefficients for covariates predicting log-aldosterone differ from those previously published because of differences in regression modeling and samples. A β-coefficient for age of 0.11 indicates that for a 10-year increase in age, the ARR increases 1.11-fold (e^{β}) or by 11%.

*P<0.0001.
†P<0.01.
‡The hypertensive group is compared with the nonhypertensive group.
§The postmenopausal state, on or not on hormone replacement therapy, is compared with the premenopausal state.
erally higher c-statistics compared with models incorporating either hormone alone. In these models, log-aldosterone and log-renin had β-coefficients more extreme in magnitude and, again, opposite in direction (for BP progression, \( P = 0.0002 \) and 0.002 for log-aldosterone and log-renin, respectively; for hypertension incidence, \( P = 0.01 \) and 0.19 for log-aldosterone and log-renin, respectively; Table 4). Models with ARR did not differ substantially from models containing both log-aldosterone and log-renin as separate linear predictors (c-statistics of 0.68 to 0.69 and 0.82 for BP progression and hypertension incidence, respectively, for both sets of models).

**Discussion**

We observed significant association of ARR with several clinical factors in our ambulatory community-based sample. ARR demonstrated significant heritability, and we identified 2 chromosomal regions with modest evidence of linkage to ARR. We did not find significant association of ARR with 17 common variants across the renin gene (\( REN \)) locus. In nonhypertensive participants, we observed that a graded increase in baseline ARR was associated with significantly increased risk of BP progression and incident hypertension in a continuous fashion and that renin and aldosterone are jointly more predictive of BP outcomes than either hormone alone.

To our knowledge, the current report is the largest study of the correlates of ARR in a community-based setting. Olivieri et al\(^4\) have reported the distribution of ARR values in a community-based sample of hypertensive subjects withdrawn from antihypertensive agents, but that study did not examine the entire BP distribution in the community or explore several potential covariate relations to ARR. The significant associations of ARR with age, sex, use of ACE inhibitors, \( β \)-adrenergic receptor blockers, diuretics, and hormone replacement therapy observed in our sample are consistent with previous reports.\(^9,16–22,50–52\) Our finding of the association of higher total:high-density lipoprotein cholesterol ratio with increased ARR differs from the results of a previous report that investigated people on a high-salt diet.\(^25\)

We examined the distribution of ARR in nonhypertensive participants and in untreated and treated hypertensive participants. We observed that ARR level in individuals on ACE inhibitors was significantly lower and on \( β \)-blockers was significantly higher compared with untreated hypertensive individuals. This is in agreement with previous findings in

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**Figure 2.** Genome-wide linkage to logARR. Multipoint linkage analysis of normalized residuals of multivariable-adjusted logARR for 22 autosomes in 1225 Framingham Heart Study participants in 328 families. The x-axis represents genetic distance from the p-terminus in centimorgan (cM) and the y-axis represents LOD score.
which hypertensive subjects were randomly assigned to ACE inhibitor and \( \beta \)-blocker therapy.\(^{19} \) We noted significant heterogeneity in the proportion of hypertensive participants exceeding 1 among many thresholds proposed for PH screening (ARR >26 ng/L per mU/L), according to their sex and treatment status.\(^{49} \) Given the differences in ARR by hypertension and treatment status, as well as by multiple covariates, the use of a single threshold in diagnostic testing of population-based samples may not be appropriate.

We demonstrated the heritability of multivariable-adjusted ARR to be 0.40, higher than for aldosterone\(^{34} \) or renin alone. We are unaware of other studies that have sought to quantify the heritability of ARR in unselected individuals in the community, although familial aggregation of hyperaldosteronism has been demonstrated (eg, familial hyperaldosteronism type II).\(^{53} \) Evidence of substantial heritability of plasma renin activity has been reported in some studies,\(^{54,55} \) but other investigators have reported more modest evidence that heritable factors influence renin.\(^{56,57} \)

We observed modest evidence that a locus on chromosome 11p is linked to ARR (multivariable-adjusted ARR LOD score 1.89) and 5p (LOD 1.60). The \textit{REN} and \textit{CYP11B2} (aldosterone synthase gene) loci, residing on different chromosomes, had no significant linkage signals. A review of known genes under the 2 linkage peaks with LOD >1.5 revealed few obvious candidate genes on the basis of involvement in steroid metabolism or renal physiology: natriuretic peptide receptor C/guanylate cyclase (\textit{NPR3}, chromosome 5) and 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1 (\textit{HMGCS1}, chromosome 5).\(^{58} \) However, the possibility of a false-positive result cannot be excluded. Replication in other samples would be essential before further examination of candidate genes under any linkage peak would be warranted. We note that, in linkage analysis without adjustment for ACE inhibitor or \( \beta \)-blocker use, we observed suggestive evidence of linkage to a region on chromosome 7p that has been linked previously to ARR in families with familial hyperaldosteronism II or nonglucocorticoid remediable hyperaldosteronism.\(^{59,60} \) However, the statistical support for linkage to this locus was markedly attenuated when we adjusted for use of specific antihypertensive therapy. The marked attenuation in the linkage signal observed with exclusion of ACE inhibitor users supports familial aggregation of medication use as a potential cause of the linkage signal that we observed in analyses that did not account for medication use in the regression models. We are unaware of any previous linkage study of ARR in an unselected community-based sample that included a wide spectrum of hypertensive and nonhypertensive subjects.

We observed no clear association of 17 common genetic variants across the \textit{REN} locus with ARR, although small effects could have been missed. Our study of common variants cannot assess the possibility that rare variants at this locus contribute to ARR. Moreover, the lack of linkage to the \textit{REN} locus does not exclude a possible influence of rare or common variants on ARR given the limited statistical power of linkage for complex traits.\(^{61} \)

Among nonhypertensive participants, we observed a strong and graded influence of baseline ARR on the risk of BP progression and incident hypertension on 3-year follow-up.

### TABLE 3. Rates and Odds Ratios for 3-Year Progression by \( \geq 1 \) BP Category and Incident Hypertension for Increasing LogARR Among Individuals Without Hypertension

<table>
<thead>
<tr>
<th>ARR Category</th>
<th>Events/At Risk</th>
<th>Incidence Rate, %*</th>
<th>Age- and Sex-Adjusted Model</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>( P )</td>
</tr>
<tr>
<td>Progression by ( \geq 1 ) BP category at 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD increase logARR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>115/441</td>
<td>27 (19 to 35)</td>
<td>1.29 (1.17 to 1.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q2</td>
<td>151/444</td>
<td>32 (24 to 42)</td>
<td>1.00 (referent)</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>151/456</td>
<td>36 (29 to 44)</td>
<td>1.42 (1.06 to 1.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Q4</td>
<td>190/432</td>
<td>42 (33 to 53)</td>
<td>1.33 (1.00 to 1.78)</td>
<td>0.05</td>
</tr>
<tr>
<td>Per quartile increase</td>
<td></td>
<td></td>
<td>2.09 (1.57 to 2.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incidence of hypertension at 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD increase logARR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>50/441</td>
<td>11 (5 to 21)</td>
<td>1.34 (1.18 to 1.53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q2</td>
<td>63/444</td>
<td>14 (7 to 28)</td>
<td>1.00 (referent)</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>66/456</td>
<td>17 (9 to 29)</td>
<td>1.20 (0.80 to 1.80)</td>
<td>0.37</td>
</tr>
<tr>
<td>Q4</td>
<td>104/432</td>
<td>22 (11 to 37)</td>
<td>1.18 (0.79 to 1.76)</td>
<td>0.41</td>
</tr>
<tr>
<td>Per quartile increase</td>
<td></td>
<td></td>
<td>2.19 (1.50 to 3.18)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\( * \)Age- and sex-adjusted.
These findings extend our earlier report linking serum aldosterone assessed alone to the risk of BP progression and hypertension. We observed that aldosterone and renin independently and jointly predict future BP progression and hypertension and that this effect is not driven by 1 hormone alone. The temporal relationship suggests that the renin–angiotensin system contributes to the development of hypertension in nonhypertensive individuals, but our study cannot exclude the possibility that ARR is simply a marker (as opposed to a risk factor) of incipient hypertension. Examination of the role of the renin–angiotensin system in BP change over time could yield insights into BP physiology and suggest novel targets for preventive strategies. We are not aware of any published reports linking ARR to hypertension incidence in the community.

The large, community-based sample, the adjustment for multiple clinical covariates, the comprehensive evaluation of heritability, linkage and association with variation at the REN locus, and the longitudinal follow-up to assess prognostic significance of ARR strengthen our investigation. Nonetheless, several limitations must be acknowledged. We examined ambulatory ARR measurements in people on a random sodium diet who were not withdrawn from antihypertensive medications. The constraints of a large, longitudinal observational cohort precluded a longer duration in the supine position, standardization of sodium intake, or medication withdrawal. However, not controlling these factors would be expected to bias our findings toward the null rather than toward the false inference of association. Our study reflects a community-based sample and is not directly comparable to the examination of hypertensive subjects in a research setting to diagnose hyperaldosteronism. The middle-age-to-elderly composition and predominant European ancestry of our cohort may limit the generalizability of our results to younger individuals or those of different ancestry; racial differences in serum aldosterone and renin values have been reported. We tested for association with SNPs at the REN locus but not at the CYP11B2 (aldosterone synthase) locus; a comprehensive set of SNP genotypes at CYP11B2 was not available. The finding that ARR predicts BP progression and incident hypertension does not address the use of population-based screening of nonhypertensive subjects, which would require studies designed to address this specific question. Lastly, our community-based study cannot address the role of ARR for identifying individuals with PH, because we did not carry out further diagnostic testing beyond the assessment of ARR.
In our large, community-based sample, ARR varied with some clinical characteristics, suggesting that these features be taken into consideration when interpreting ARR values in ambulatory settings. Genetic factors influence ARR as evidenced by significant heritability; ongoing and planned genome-wide genotyping in the Framingham Heart Study may identify variants that influence ARR. We found that ARR has a higher heritability than either aldosterone or renin alone and that aldosterone and renin are independent predictors of BP progression and incident hypertension. The accruing evidence that interindividual variation in ARR predicts BP progression, hypertension, and myocardial infarction raises the possibility that identifying genetic and nongenetic contributors to ARR could refine our understanding of the biology of the renin–angiotensin system, identify novel therapeutic targets, and improve risk prediction.

Sources of Funding
This work was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (N01-HC-25195), 1RO1HL67288 (R.S.V.), and 2K24 HL04334 (R.S.V.) and the CardioGenomics Program for Genomic Applications. C.N.-C. has been supported by an award from the GlaxoSmithKline Competitive Grants Award Program for Young Investigators, an American Heart Association Scientist Development Grant, a Doris Duke Charitable Foundation Career Scientist Development Award, and K23HL080025. T.J.W. is supported by K23HL074077.

Disclosures
None.

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Clinical and Genetic Correlates of Aldosterone-to-Renin Ratio and Relations to Blood Pressure in a Community Sample


Hypertension. 2007;49:846-856; originally published online February 12, 2007; doi: 10.1161/01.HYP.0000258554.87444.91

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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