Multiple Biomarkers and the Risk of Incident Hypertension


Abstract—An understanding of mechanisms underlying the development of essential hypertension is critical for designing prevention and treatment strategies. Selected biomarkers may be elevated before the onset of hypertension, but previous studies are limited by cross-sectional designs or a focus on single biomarkers. We prospectively studied 1456 nonhypertensive individuals who had baseline measurement of 9 biomarkers: C-reactive protein (inflammation); fibrinogen (inflammation and thrombosis); plasminogen activator inhibitor-1 (fibrinolytic potential); aldosterone, renin, B-type natriuretic peptide, and N-terminal proatrial natriuretic peptide (neurohormonal activity); homocysteine (renal function and oxidant stress); and urinary albumin/creatinine ratio (glomerular endothelial function). Incident hypertension, defined as blood pressure ≥140/90 mm Hg or antihypertensive therapy, developed in 232 participants over a mean follow-up of 3 years. After adjustment for clinical risk factors, the biomarker panel was significantly associated with incident hypertension (P=0.002). Three (of 9) biomarkers were significantly related to incident hypertension on backward elimination (multivariable-adjusted odds ratios, per SD increment in biomarker): C-reactive protein (1.26; 95% CI: 1.05 to 1.51), plasminogen activator inhibitor-1 (1.28; 95% CI: 1.05 to 1.57), and urinary albumin/creatinine ratio (1.21; 95% CI: 1.02 to 1.43). The incidence of hypertension was 4.5, 6.4, and 9.9 per 100 person years for participants with 0, 1, and ≥2 elevated biomarkers, respectively (elevation defined as ≥1 SD above the mean). The threshold of ≥2 elevated biomarkers for predicting hypertension was associated with high specificity (0.92) but low sensitivity (0.15). Biomarkers of inflammation, reduced fibrinolytic potential, and low-grade albuminuria are jointly associated with the incidence of hypertension. These data support the premise that abnormalities in multiple biological pathways antedate the onset of overt hypertension. (Hypertension. 2007;49:432-438.)

Key Words: epidemiology ■ hypertension ■ C-reactive protein ■ plasminogen activator inhibitor-1 ■ aldosterone ■ albuminuria

Hypertension is a key modifiable risk factor for cardiovascular morbidity and mortality. Accordingly, there has been a growing emphasis in national practice guidelines on the importance of preventing hypertension to reduce the public health burden of cardiovascular disease.1 To accomplish this goal, however, it is critical to understand the most common mechanisms underlying the development of hypertension, as well as to formulate screening strategies that can reliably identify individuals most likely to develop hypertension in the short and medium term.

The pathogenesis of essential hypertension is multifactorial.2 Numerous physiological alterations have been described in hypertensive individuals, including abnormalities of renal sodium handling,3 neurohormonal and adrenergic overactivity,4-6 endothelial dysfunction,5 vascular hypertrophy,6,7 systemic inflammation,8,9 reduced fibrinolytic potential,10,11 and enhanced oxidative stress.12-14 Data concerning these abnormalities derive primarily from cross-sectional studies, although several longitudinal studies have demonstrated that biomarkers representative of key biological pathways, such as C-reactive protein ([CRP] marker of inflammation) and aldosterone (neurohormonal activity), are elevated before the onset of overt hypertension.15-17

Previous studies are generally limited by their focus on individual biomarkers representing single pathways. As such, it is not known whether multiple biomarkers are independently associated with hypertension risk. The association of some biomarkers with hypertension could be superseded by the measurement of other biomarkers, because levels of many biomarkers are correlated with each other.18-20 In addition,
most biomarkers are only modestly associated with hypertension risk,15,16 raising the question whether a “multimarker” approach using several biomarkers simultaneously would increase the ability to predict hypertension.

Accordingly, we performed a prospective study to investigate the association of 9 biomarkers with the development of hypertension in a large, well-defined cohort of nonhypertensive individuals. Each of these biomarkers has been individually related to hypertension in cross-sectional studies (see the table in an online supplement at http://hyper.ahajournals.org) and some in longitudinal studies.15-17,21 We sought to identify biomarkers with the strongest association with future hypertension risk and to evaluate the performance characteristics of a “multimarker” approach to predicting the incidence of hypertension.

Methods

Study Sample

The Framingham Offspring Study was initiated in 1971, with the enrollment of 5124 offspring (and their spouses) of the original Framingham Heart Study participants.22 Participants in the offspring study, who are overwhelmingly white, have attended examinations in the Framingham Heart Study clinic approximately every 4 years. The study protocols were approved by the Boston University Medical Center Institutional Review Board, and all of the participants provided written informed consent.

Participants attending the sixth examination cycle (n=3532; 1995–1998) were eligible for the present investigation. We excluded 2076 attendees for the following reasons: prevalent hypertension (systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, use of antihypertensive medications,1,23,24 missing blood pressure information; n=1470 at the baseline examination), history of heart failure or myocardial infarction (n=87), serum creatinine $>2.0$ mg/dL (n=1), missing data for $\geq 1$ biomarker (n=378), missing covariates (n=1), nonattendance or missing blood pressure information at the follow-up examination (n=84), and incident heart failure or myocardial infarction between the sixth and seventh examination (n=55). Participants with interim heart failure or myocardial infarction were excluded, because these events may influence either blood pressure or the use of cardiovascular medications. After these exclusions, 1456 nonhypertensive attendees (58% women) remained eligible. The mean interval between the sixth and seventh examination cycles was $\approx 3$ years (range: 1.0 to 6.5 years).

Clinical Evaluation and Blood Pressure Measurement

Participants underwent a routine medical history, measurement of height and weight, physical examination, and laboratory assessment of cardiovascular disease risk factors. At each examination, physician investigators measured blood pressures using a mercury column sphygmomanometer and a cuff of appropriate size. The standardized protocol involved measurement of systolic and diastolic blood pressures in the left arm after participants had been seated quietly for $\geq 5$ minutes. All of the physician examiners are recertified yearly at the Framingham Heart Study for blood pressure measurement, and adjusted-mean blood pressure readings and digit preference are assessed quarterly across examiners. The average of 2 systolic and diastolic blood pressure measurements obtained at the examination was used for our analyses. Hypertension was defined as systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or use of antihypertensive medications.1,23,24

Biomarker Selection and Measurement

We investigated 9 biomarkers from pathways implicated in the pathogenesis of hypertension (Table 1). The biomarkers were selected on the basis of biological plausibility, evidence from previous clinical studies, and availability at the sixth examination cycle. An association between each of the biomarkers and blood pressure has been reported in cross-sectional studies.8–11,14,25–35 Serum aldosterone and plasma renin were considered as the ratio of aldosterone/renin (primary analysis), as well as separately.32 Biomarkers were measured on baseline blood samples collected in the morning after an overnight fast. Participants were in the supine position for $\approx 5$ to 10 minutes before venipuncture. Blood was immediately centrifuged, and plasma and serum specimens were stored at $-70^\circ C$ until they were assayed. High-sensitivity CRP was measured with a Dade Behring BN100 nephelometer. Plasma B-type natriuretic peptide and N-terminal proatrial natriuretic peptide were measured with high-sensitivity immunoradiometric assays (Shionogi).36 Plasma levels of plasminogen activator-1 (PAI-1) antigen were determined using a commercially available ELISA, as described by Declerck et al37 (TinElize PAI-1, Biopool AB). Fibrinogen was measured according to the method of Clauss.38 Serum aldosterone was measured from extracted and fractionated serum using a radioimmunoassay (Quest Diagnostics).16 Direct plasma renin was measured by immunoenzymometric assay (Nichols assay, Quest Diagnostics).39 Total plasma homocysteine was measured using high-performance liquid chromatography with fluorometric detection.40,41 The average interassay coefficients of variation for each biomarker were as follows: N-terminal proatrial natriuretic peptide (12.7%), B-type natriuretic peptide (12.2%), PAI-1 (7.7%), fibrinogen (2.6%), CRP (2.2%), aldosterone (4.0% for high concentrations and 9.8% for low concentrations), renin (2.0% for high concentrations and 10.0% for low concentrations), and homocysteine (9%).

The urinary albumin/creatinine ratio (UACR, in milligrams per gram) was measured on a single-void morning urine specimen. Urinary albumin was determined by immunoturbidimetry (Tinaquant Albumin assay, Roche Diagnostics), and urinary creatinine was measured using a modified Jaffe method. Coefficients of variation were 7.2% and 2.3%, respectively, for the urine albumin and urine creatinine assays.42

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of the Study Sample</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Mean age, y</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<tr>
<td>Body mass index, $kg/m^2$</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Change in weight, kg*</td>
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<tr>
<td>Current smoker, %</td>
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<tr>
<td>Diabetes mellitus, %</td>
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<tr>
<td>Serum creatinine, mg/dL</td>
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<tr>
<td>Median biomarker levels (25th percentile, 75th percentile)</td>
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<tr>
<td>CRP, mg/L</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
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<tr>
<td>PAI-1, ng/mL</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
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<tr>
<td>Renin, mUL</td>
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<tr>
<td>Aldosterone/renin ratio</td>
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<tr>
<td>BNP, pg/mL</td>
</tr>
<tr>
<td>NA-NP, pmol/L</td>
</tr>
<tr>
<td>Homocysteine, $\mu$mol/L</td>
</tr>
<tr>
<td>UACR, mg/g</td>
</tr>
</tbody>
</table>

Values are mean±SD or percentages. BNP indicates B-type natriuretic peptide; NA-NP, N-terminal proatrial natriuretic peptide.

*Change in weight from examination 6 to examination 7.
Statistical Analyses
We chose a multistage analytical approach to reduce the risk of false-positive results from multiple statistical testing. First, we performed multivariable logistic regression analysis to examine the association of the entire set of biomarkers with the risk of developing hypertension between the baseline and follow-up examination.43 A "global" P value was determined for the biomarker panel as a whole, using a likelihood ratio test, in which −2 log-likelihood for the model with clinical covariates and biomarkers was subtracted from −2 log-likelihood for the model with clinical covariates only. Subsequent analyses were performed only if the global P value was <0.05. Second, a final set of informative biomarkers was selected via backward elimination, using individual P<0.05 for retention in the model. We also examined the use of the selected biomarkers for predicting hypertension by examining the hypertension incidence rate according to the number of elevated biomarkers (candidate biomarkers chosen from the previous step), stratified by baseline blood pressure category. For this purpose, an elevated biomarker level was defined empirically as ≥1 SD above the mean.

Biomarker values were log transformed. Continuous variables were standardized to a mean of 0 and SD of 1 to facilitate comparison of β coefficients. All of the logistic regression models were adjusted for the following covariates, based on their use in previous studies43: age, sex, baseline systolic and diastolic blood pressure, baseline body mass index, diabetes mellitus, serum creatinine (all defined at baseline), and percentage of weight change from baseline to follow-up.

In secondary analyses, we examined multivariable-adjusted models including multiplicative interaction terms for biomarker levels and age, sex, and body mass index to test for effect modification. All of the analyses were performed using SAS software version 8 (SAS Institute).

Results
Baseline characteristics of the study sample are shown in Table 1. Age- and sex-adjusted Spearman correlations among the biomarkers are shown in Table 2. The highest correlations were noted for B-type natriuretic peptide and N-terminal proatrial natriuretic peptide (r=0.51; P<0.001), CRP and fibrinogen (r=0.48; P<0.001), and renin and aldosterone (r=0.36; P<0.001).

Between the baseline and follow-up examinations, 232 participants (16%; 121 women) developed hypertension. In multivariable logistic regression, the panel of biomarkers was associated with incident hypertension (global P=0.002).

Results of backward elimination models for selecting a parsimonious set of biomarkers (of 9 eligible ones) related to hypertension incidence are shown in Table 3. Three biomarkers were retained in the final multivariable model: CRP (P=0.013), PAI-1 (P=0.016), and UACR (P=0.027). The magnitude of the association of each biomarker with incident hypertension was similar. An SD increment in log-

### TABLE 3. Biomarker Levels and Incident Hypertension

<table>
<thead>
<tr>
<th>Description of Model</th>
<th>Adjusted Odds Ratio* (95% CI)</th>
<th>χ² Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global test of all biomarkers†</td>
<td></td>
<td>24.53</td>
<td>0.002</td>
</tr>
<tr>
<td>Final model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, per SD increment</td>
<td>1.26 (1.05 to 1.51)</td>
<td>6.15</td>
<td>0.013</td>
</tr>
<tr>
<td>PAI-1, per SD increment</td>
<td>1.28 (1.05 to 1.57)</td>
<td>5.84</td>
<td>0.016</td>
</tr>
<tr>
<td>UACR, per SD increment</td>
<td>1.21 (1.02 to 1.43)</td>
<td>4.87</td>
<td>0.027</td>
</tr>
</tbody>
</table>

*Odds of incident hypertension associated with a 1-SD increment in the natural logarithm of the biomarker. Results are shown only for variables retained by backward elimination, using P<0.05 as the threshold for retention.
†Based on likelihood ratio test. Odds ratios were adjusted for age, sex, baseline systolic and diastolic blood pressure, baseline blood pressure category, baseline serum creatinine, diabetes mellitus, cigarette smoking, baseline body mass index, and percentage of weight change from baseline to follow-up.
transformed biomarker levels was associated with 21% (UACR), 26% (CRP), and 28% (PAI-1) increases in the odds of developing hypertension during follow-up.

Neither serum aldosterone nor plasma renin entered the final multivariable model for hypertension, although there was a borderline statistically significant association with serum aldosterone ($P=0.066$) in the presence of the 3 significant biomarkers. When entered into the model alone, serum aldosterone was a significant predictor of incident hypertension as reported previously by our group. In additional analyses, age, sex, and body mass index did not modify the association of any of the final 3 biomarkers with incident hypertension.

**Number of Elevated Biomarkers and Risk of Hypertension**

All 3 biomarkers (CRP, PAI-1, and UACR) had similar regression coefficients, and, accordingly, they were weighted equally in a biomarker score based on the number of elevated markers ($\geq1$ SD above the mean). Nine percent of participants had 2 or 3 biomarkers elevated, whereas 27% had only 1 biomarker elevated. The incidence of hypertension was 4.5, 6.4, and 9.9 per 100 person years for participants with 0, 1, and $\geq2$ elevated biomarkers, respectively. The threshold of $\geq2$ elevated biomarkers for predicting future hypertension was associated with high specificity (0.92) but low sensitivity (0.15), whereas the threshold of $\geq1$ elevated biomarker was associated with specificity and sensitivity of 0.66 and 0.47, respectively.

**Discussion**

We investigated a panel of 9 biomarkers representing key biological pathways implicated in the pathogenesis of hypertension. We identified a parsimonious set of 3 biomarkers, higher values of which were most strongly associated with risk of developing hypertension: CRP (inflammation), PAI-1 (fibrinolytic potential), and UACR (glomerular endothelial function). To our knowledge, the present study is the first to examine the use of multiple biomarkers to predict the development of hypertension. The validity of our results is strengthened by the prospective study design; the large, well-defined cohort in which blood pressure was ascertained in a standardized manner (rather than self-reported); the use of a multistage conservative analytical strategy to reduce the risk of multiple testing; and the inclusion of biomarkers that were both biologically plausible and supported by previous clinical data.

Our findings extend the results of previous studies from Framingham and other cohorts examining the association between individual biomarkers and the future risk of hypertension. For instance, we reported previously that urinary albumin excretion and serum aldosterone are separately associated with hypertension risk, whereas Sesso et al have reported similar findings for CRP in women. The demonstration that multiple biomarkers concurrently predict hypertension supports the multifactorial pathogenesis of this disorder and emphasizes that alterations in several biological pathways precede the onset of overt hypertension.

**Inflammation and Hypertension**

Data from previous prospective and cross-sectional studies suggest that hypertension is associated with systemic inflammation. The present study shows that the association with CRP persists after accounting for other biomarkers, such as UACR, PAI-1, and fibrinogen, which are closely related to CRP by virtue of their associations with systemic inflammation and the metabolic syndrome. The link between inflammatory markers and hypertension may involve several pathophysiological mechanisms. Experimental studies suggest that CRP promotes endothelial dysfunction by directly suppressing production of NO by endothelial cells. Vascular inflammation is also closely related to activation of the renin–angiotensin system. In vascular smooth muscle, CRP upregulates type 1 angiotensin receptors, which are responsible for the vasoconstrictor and proatherogenic actions of angiotensin II. In turn, there is positive feedback of angiotensin II on vascular inflammation via promotion of oxidant stress, recruitment of monocytes, and production of proinflammatory cytokines.

**Reduced Fibrinolytic Potential and Hypertension**

A novel finding of the present study is that circulating PAI-1 levels predicted incident hypertension. PAI-1 is a serine protease inhibitor produced by a variety of cells, including endothelial cells, hepatocytes, adipocytes, vascular smooth muscle cells, and mesangial cells. Because PAI-1 is a major endogenous inhibitor of tissue plasminogen activator, elevated PAI-1 levels are regarded as a marker of reduced fibrinolytic potential. Several cross-sectional studies have documented elevated PAI-1 levels in hypertensive individuals, but it is generally assumed that hypertension leads to elevated PAI-1 levels rather than the converse, as a result of hypertension-induced shear stress and/or endothelial activation.

Our prospective findings suggest that elevated PAI-1 levels antedate the onset of hypertension. Several factors may account for this observation. Higher PAI-1 levels may reflect endothelial dysfunction, which may precede hypertension. Interestingly, both CRP and the renin–angiotensin–aldosterone system induce expression of PAI-1, suggesting a link between PAI-1 and several other pathways implicated in the pathogenesis of hypertension. In this regard, an important finding is that the association of PAI-1 with incident hypertension persisted after adjustment for CRP, aldosterone, and renin. Reduced fibrinolytic potential is also a prominent feature of the metabolic syndrome, raising the added possibility that elevated PAI-1 levels reflect metabolic abnormalities, such as insulin resistance, that predispose to the development of hypertension. Finally, overproduction of vascular PAI-1 seems to accelerate perivascular and medial fibrosis, whereas suppression of PAI-1 protects against the vascular changes observed in an experimental model of hypertension.

**Urinary Albumin Excretion and Hypertension**

Urinary albumin excretion also predicted incident hypertension, above and beyond CRP and PAI-1. This finding extends the results of a previous study involving a subsample of our cohort, as well as cross-sectional studies that have reported...
an association between urinary albumin excretion and blood pressure. Our data underscore the potential role of endothelial dysfunction in the kidneys in the pathogenesis of hypertension. According to 1 proposed model, acquired or congenital reductions in the number of functional nephrons may lead to elevated intraglomerular pressures in the remaining nephrons, establishing a cycle of hyperfiltration, glomerular injury, and sodium retention. The association between urinary albumin excretion and incident hypertension may also involve extrarenal mechanisms. Urinary albumin excretion, which reflects glomerular endothelial dysfunction, may also involve extrarenal mechanisms. Urinary albumin excretion, which reflects glomerular endothelial dysfunction, may serve as a marker of diffuse endothelial dysfunction. 

Aldosterone, Renin, and Hypertension

We have observed previously that increased serum aldosterone levels predispose to the development of hypertension, which may be attributable to sodium retention, direct vascular effects, and/or undetected primary aldosteronism. In the present investigation, the association between serum aldosterone and incident hypertension was not significant after adjustment for CRP, PAI-1, and UACR, suggesting that interactions between aldosterone and the other pathways may exist. Experimental data and clinical studies of individuals with primary aldosteronism suggest that aldosterone produces target organ damage in the kidneys, resulting in hyperfiltration and increased urinary albumin excretion. Furthermore, this process may be mediated by plasma PAI-1. Thus, whereas our data indicate that serum aldosterone may not provide incremental information to other biomarkers for the prediction of hypertension, they do not exclude an important biological role for aldosterone in the pathogenesis of hypertension.

Clinical Implications

Recent national practice guidelines emphasize the prevention of hypertension as a critical component of public health efforts to reduce cardiovascular morbidity and mortality. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure considers individuals with systolic blood pressure ≥120 mm Hg or diastolic blood pressure ≥80 mm Hg at risk of progressing to overt hypertension and in need of close follow up. However, there is considerable interindividual variability in rates of blood pressure progression. Because 70 million adults in the United States meet criteria for “prehypertension” according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (blood pressure 120 to 139/80 to 89 mm Hg), physicians face the challenging task of identifying individuals within this broad category who are at greatest risk of progressing to overt hypertension in the short term to guide initiation of nonpharmacological interventions and targeted follow-up.

Our data suggest that, despite the association of biomarker levels with hypertension incidence, the performance characteristics of a “multimarker” score for predicting hypertension are modest. The overall specificity of the multimarker score (≥2 biomarkers elevated) for detecting hypertension was high (0.92), but the sensitivity was low (0.15). A lower threshold (≥1 elevated biomarker) resulted in moderate specificity and sensitivity. Whether the identification of additional, novel biomarkers would improve the performance characteristics a “multimarker” score for assessing future hypertension risk requires further investigation.

Study Limitations

Several limitations of our study deserve comment. We selected biomarkers to represent biologically relevant pathways based on experimental and clinical data and guided by their availability in our cohort at the examination cycle of interest. Thus, we did not include uric acid levels, insulin resistance, or additional inflammatory or hemostatic markers in the analyses, because they were not assessed concurrently with the biomarkers studied. We submit, however, that any investigation using a multimarker approach will be limited by practical constraints (presently it is not feasible for any given study to examine all biomarkers) and that the biomarkers for inclusion will vary over time with advancements in medical knowledge.

We did not test the association of individual biomarkers with incident hypertension to reduce multiple testing. In a posthoc analysis, we confirmed our previous report relating serum aldosterone by itself (without other biomarkers in the model) to hypertension incidence. Multimarker analyses favor more informative biomarkers, eliminating biomarkers with less powerful associations, more variability, or overlapping information. Accordingly, the failure of a biomarker to be retained in the final model does not exclude a significant relation with incident hypertension.

To minimize ascertainment bias, we used only investigator-measured blood pressures, obtained at the Framingham study clinic examinations. We lacked ambulatory blood pressure information. Although use of study blood pressures could have resulted in misclassification of blood pressure status for some individuals, we expect that misclassification would have been random and associated with a conservative bias. Because the duration of follow-up was relatively short (≈3 years), we cannot exclude the possibility that elevated biomarkers in some individuals reflected existing, subclinical hypertension rather than prehypertension. Also, because the Framingham cohort is predominantly white, our findings may not be generalizable to individuals of other ethnicities/races.

Perspectives

In summary, our findings suggest that inflammation, reduced fibrinolytic potential, and low-grade microalbuminuria are associated with hypertension risk in nonhypertensive individuals. These data support the premise that abnormalities in multiple pathways antedate the onset of overt hypertension. Nonetheless, the predictive value of existing biomarkers for assessing future hypertension risk is modest. Identification of additional biomarkers would be necessary before “multimarker” strategies for predicting hypertension could be considered useful.
Sources of Funding
This work was supported by National Institutes of Health/National Heart, Lung, and Blood Institute grants N01-HC-25195, K23-HL-074077 (T.J.W.), and 2K24-HL-04334 (R.S.V.) and an American Diabetes Association career development award (J.B.M.).

Disclosures
T.J.W. has received remuneration for contributing to an electronic textbook sponsored by Novartis Institutes for Biomedical Research. The remaining authors report no conflicts.

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Hypertension. 2007;49:432-438; originally published online January 22, 2007;
doi: 10.1161/01.HYP.0000256956.61872.aa

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/49/3/432

Data Supplement (unedited) at:
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