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Cardiovascular and Metabolic Predictors of Progression of Prehypertension Into Hypertension

The Strong Heart Study

Marina De Marco, Giovanni de Simone, Mary J. Roman, Marcello Chinali, Elisa T. Lee, Marie Russell, Barbara V. Howard, Richard B. Devereux

Abstract—Prehypertension (defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) frequently evolves to hypertension (HTN) and increases cardiovascular risk. It is unclear whether metabolic and/or cardiac characteristics favor development of HTN in prehypertensive subjects. We evaluated baseline anthropometric, laboratory, and echocardiographic characteristics of 625 untreated prehypertensive participants in the Strong Heart Study, without prevalent cardiovascular disease (63% women; 22% with diabetes mellitus; mean age: 59 ± 7 years) to identify predictors of the 4-year incidence of HTN. Diabetes mellitus was assessed by American Diabetic Association criteria, and a diabetes-specific definition of HTN was used. Four-year incidence of HTN was 38%. Incident HTN was independently predicted by baseline systolic blood pressure (odds ratio [OR]: 1.60 per 10 mm Hg; 95% CI: 1.30 to 2.00; P<0.0001), waist circumference (OR: 1.10 per 10 cm; 95% CI: 1.01 to 1.30; P=0.04), and diabetes mellitus (OR: 2.73; 95% CI=1.77 to 4.21; P<0.0001), with no significant effect for age, sex, hemoglobin A1c, homeostatic model assessment index, C-reactive protein, fibrinogen, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, plasma creatinine, or urine albumin:creatinine ratio. Higher left ventricular mass index (OR: 1.15 per 5 g/m2.04; 95% CI: 1.01 to 1.25; P=0.03) or stroke volume index (OR: 1.25 per 5 mL/m2.04; 95% CI: 1.10 to 1.50; P=0.03) was also identified, together with baseline systolic blood pressure and the presence of diabetes mellitus, as an independent predictor of incident HTN, without an additional predictive contribution from other anthropometric, metabolic, or echocardiographic parameters (all P>0.10). Thus, progression to HTN in 38% of Strong Heart Study prehypertensive participants could be predicted by higher left ventricular mass and stroke volume in addition to baseline systolic blood pressure and prevalent diabetes mellitus. (Hypertension. 2009; 54:974-980.)

Key Words: hypertension ■ diabetes mellitus ■ left ventricular hypertrophy ■ obesity ■ risk factors

Elevated blood pressure (BP) is a major risk factor for cardiovascular (CV) disease.1–3 The Framingham Heart Study showed that 4-year incidence of hypertension (HTN) was higher in participants with high-normal BP than with normal BP.4 There is substantial evidence that systolic BP is continuously related to adverse outcome and that the risk of CV disease extends below 140 mm Hg, so that “nonhypertensives” (<140/90 mm Hg) also harbor increased risk proportional to their BP level.5,6 Accordingly, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, acknowledges the continuous relationship between BP and CV disease, introduced the new category of “pre-HTN,” defined as systolic BP of 120 to 139 mm Hg and/or diastolic BP of 80 to 89 mm Hg.7 On the basis of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, pre-HTN requires attention and health-promoting lifestyle modifications to prevent progression to HTN.7 Pre-HTN is often associated with other CV risk factors, such as obesity, insulin resistance, diabetes mellitus, dyslipidemia, and the phenotypes of metabolic syndrome,8,9 resulting in early vascular abnormalities and progressive atherosclerosis.10 However, it remains uncertain whether prehypertensive BP by itself or other associated risk factors is more important in determining the best preventive strategy.11

A high-risk metabolic profile associated with abnormal cardiac geometry and function is often found in prehyperten-
sive individuals, even at a young age. Obesity, inflammation, and metabolic risk factors, including dyslipidemia and impaired glucose turnover, have vascular and hemodynamic effects that may contribute to the progression to arterial HTN. In addition, cardiac geometry and function might also have some impact on the progression from pre-HTN to overt HTN. It is still unclear whether phenotypes at higher risk of developing HTN are already recognizable in pre-HTN. Accordingly, the present analysis was performed to identify metabolic and CV predictors of incident arterial HTN in prehypertensive participants of the Strong Heart Study (SHS) cohort, a population with a high prevalence of diabetes mellitus and obesity.

Methods

Population
The SHS is a population-based cohort study designed to estimate CV disease mortality and morbidity and the prevalence of CV disease and risk factors in American Indians. A total of 4549 American Indian men and women, aged 45 to 74 years, from 3 communities in Arizona, 7 in southwestern Oklahoma, and 3 in South and North Dakota, participated the SHS first examination from 1989 to 1991 (phase 1). The cohort was followed and re-examined in 1993 to 1995 (phase 2) and 1998 to 1999 (phase 3), respectively. SHS used a standard methodology at each examination, including standardized anthropometric, clinical, and laboratory measurements. A detailed description of the study design and methods of the SHS has been extensively reported. The phase 2 SHS examination evaluated 89% of all of the surviving members of the original cohort and also included standard Doppler echocardiogram. The second SHS examination was, therefore, used as baseline for the present analysis.

Incident HTN was assessed at the time of the third SHS examination (phase 3), 4 years later. For the purpose of this study, we selected participants with baseline pre-HTN who also participated at the follow-up re-examination. Pre-HTN was defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (systolic BP of 120 to 139 mm Hg and/or diastolic BP of 80 to 89 mm Hg in participants without diabetes mellitus). In participants with diabetes mellitus, pre-HTN was defined as systolic BP between 120 and 129 mm Hg and diastolic BP $\leq$90 mm Hg. Participants with diabetes mellitus and systolic BP $>130$ mm Hg and/or diastolic BP $>80$ mm Hg were considered to have HTN and excluded.

Exclusion criteria were as follows: baseline use of antihypertensive drugs, presence of normal BP (systolic BP $<120$ and diastolic BP $<80$ mm Hg) or HTN (defined as follows: systolic BP $\geq 140$ and/or diastolic BP $\geq 90$ mm Hg [or systolic BP $\geq 130$ mm Hg and/or diastolic BP $\geq 80$ mm Hg] in diabetic subjects) or current antihypertensive treatment, significant aortic and/or mitral valvular disease, or prevalent CV disease. Prevalent CV disease (stroke, transient ischemic attack, congestive heart failure, myocardial infarction, or other manifestations of coronary heart disease) was adjudicated by the SHS mortality and morbidity committees, using specified criteria for causes of fatal and nonfatal CV events, as reported previously.

Four-year incidence of HTN in participants with initial pre-HTN was evaluated at the time of the third SHS examination, 46 to 59 months after the baseline visit. Institutional review boards of the participating institutions and the participating tribes approved the study.

Clinical Examination, Laboratory Tests, and Classification of Participants

During both phase 2 and 3 SHS exams, the following standardized data collections were performed for each participant. Clinical examinations and collection of blood samples after a 12-hour fast were done in the morning at local Indian Health Service hospitals and clinics by the study staff and consisted of a personal interview and a physical examination. Questionnaires administered during the inter-
second block with metabolic parameters, including lipid profile, glucose status, inflammation markers, and indicators of renal function ($P$ to enter: $<0.05$ and $P$ to remove: $<0.01$). Thus, echocardiographic variables were alternatively forced to evaluate whether they added to the prediction of HTN. Interaction terms between diabetes mellitus and both systolic BP and LV mass were also generated and tested. Two-tailed $P<0.05$ was considered statistically significant.

**Results**

Among the 2894 participants without prevalent CV disease at the time of the phase 2 SHS examination, 625 (22%) had pre-HTN ($59 \pm 7$ years; 394 women [63%]). Prevalence of CV risk factors was high: 22% had diabetes mellitus, 55% were obese, 33% were current smokers, 17% had LVH, and 8% had concentric LV geometry. Renal dysfunction was detected in 9% on the basis of decreased GFR (GFR < 60 mL/min per 1.73 m$^2$) and in 20% on the basis of the presence of albuminuria.

**Demographic and Metabolic Characteristics**

At the follow-up (third SHS examination), arterial HTN had developed in 235 (38%) of 625 initially prehypertensive participants. At baseline, participants developing HTN during follow-up had higher body mass index, waist circumference, systolic BP, and PP and were more frequently diabetic than those who did not ($P<0.05$), whereas no significant differences were found for low-density lipoprotein cholesterol or renal function.

**Cardiac Phenotype**

Table 3 shows that participants developing HTN had higher baseline LV mass index, RWT for age, SV index, and stroke work and greater prevalence of LVH than those who did not (all $P<0.05$), whereas no significant differences were found for the other echocardiographic parameters. The incidence of HTN was higher in participants with initial LVH compared with those without LVH (50% versus 35%, respectively; $P=0.006$).

**Independent Predictors of Incident HTN**

After 4 years, development of arterial HTN was predicted by higher baseline systolic BP (odds ratio [OR]: 1.60 per 10 mm Hg; 95% CI: 1.30 to 2.00), presence of diabetes

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### Table 1. Baseline Characteristics of Participants Developing or Not Developing Arterial Hypertension at the Follow-Up

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Not Developing Hypertension (n=390)</th>
<th>Developing Hypertension (n=235)</th>
<th>P&lt;.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.3±7.4</td>
<td>59.0±7.6</td>
<td>0.66</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>240 (62)</td>
<td>154 (66)</td>
<td>0.35</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.3±5.8</td>
<td>32.1±6.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>104±14</td>
<td>108±14</td>
<td>0.001</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>206 (53)</td>
<td>137 (58)</td>
<td>0.19</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125.8±5.8</td>
<td>127.1±5.9</td>
<td>0.007</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>50.9±9.3</td>
<td>52.6±8.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74.9±7.0</td>
<td>74.5±7.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±10</td>
<td>66.0±9.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>136 (35)</td>
<td>72 (31)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>65 (17)</td>
<td>73 (31)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

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### Table 2. Baseline Metabolic Findings of Participants Developing or Not Developing Arterial Hypertension at the Follow-Up

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Not Developing Hypertension (n=390)</th>
<th>Developing Hypertension (n=235)</th>
<th>P&lt;.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>122±55</td>
<td>141±75</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA index</td>
<td>4.0 (2.2 to 7.3)</td>
<td>4.9 (2.9 to 9.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>5.3 (4.9 to 6.0)</td>
<td>5.6 (5.1 to 7.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>341±70</td>
<td>355±71</td>
<td>0.02</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.18±0.93</td>
<td>1.40±0.95</td>
<td>0.005</td>
</tr>
<tr>
<td>Urinary albumin:creatinine</td>
<td>9.0 (5.3 to 20.0)</td>
<td>10.0 (5.7 to 26.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Albuminuria, n (%)</td>
<td>66 (17)</td>
<td>54 (23)</td>
<td>0.09</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m²</td>
<td>87±30</td>
<td>86±28</td>
<td>0.91</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9 (0.7 to 1.0)</td>
<td>0.8 (0.7 to 1.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>115 (81 to 167)</td>
<td>129 (93 to 181)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>192±40</td>
<td>192±41</td>
<td>0.90</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44±15</td>
<td>41±13</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>121±35</td>
<td>121±36</td>
<td>0.80</td>
</tr>
</tbody>
</table>

HOMA indicates homeostatic model assessment; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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### Table 3. Baseline Echocardiographic Findings of Participants Developing or Not Developing Arterial Hypertension at the Follow-Up

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Not Developing Hypertension (n=390)</th>
<th>Developing Hypertension (n=235)</th>
<th>P&lt;.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²−7</td>
<td>39.1±8.6</td>
<td>41.6±8.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.34±0.04</td>
<td>0.35±0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>SV index, mLm²−24</td>
<td>25.5±4.2</td>
<td>26.4±4.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke work, mm Hg×mL</td>
<td>128±21</td>
<td>132±24</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac index, L/m²−1.83</td>
<td>1.90±0.40</td>
<td>1.91±0.41</td>
<td>0.77</td>
</tr>
<tr>
<td>PP/SV, mg Hg/mL per beat</td>
<td>0.74±0.18</td>
<td>0.75±0.17</td>
<td>0.57</td>
</tr>
<tr>
<td>Total peripheral resistance, dynes<em>sec</em>cm⁻²</td>
<td>1621±336</td>
<td>1633±317</td>
<td>0.70</td>
</tr>
<tr>
<td>LHV, n (%)</td>
<td>54 (14)</td>
<td>53 (23)</td>
<td>0.006</td>
</tr>
<tr>
<td>LV concentric geometry, n (%)</td>
<td>26.0 (6.7)</td>
<td>22.0 (9.4)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

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Factors Associated With Regression to Normal BP

Among 625 participants with baseline pre-HTN, 86 (14%) showed normal BP at the follow-up examination. Compared with those who developed HTN, pre-HTN participants with follow-up normal BP had lower baseline waist circumference (104 ± 14 versus 108 ± 14 cm; P = 0.008). At follow-up, the waist circumference of participants with regression to normal BP was also significantly lower compared with those with incident HTN and substantially decreased from baseline value (102 ± 14 versus 109 ± 14 cm; all P < 0.002). Compared with participants developing HTN, those becoming normotensive had lower baseline systolic BP (124 ± 4.7 versus 127 ± 5.9 mm Hg; P = 0.001), PP (50 ± 9.0 versus 53 ± 8.9 mm Hg; P = 0.01), LV mass index (38 ± 7.4 versus 42 ± 8.7 g/m²; P = 0.002), SV index (25 ± 3.6 versus 26 ± 4.3 mL per beat per meter²; P = 0.004), and stroke work (121 ± 18 versus 132 ± 24 mm Hg×mL; P = 0.001).

Higher baseline systolic BP (OR: 0.92 per mm Hg; 95% CI: 0.87 to 0.97; P = 0.002), LV mass index (OR: 0.95 per g/m²; 95% CI: 0.92 to 0.99; P = 0.02), or SV index (OR: 0.91 per mL per beat per meter²; 95% CI: 0.84 to 0.98; P = 0.01) was associated with lower likelihood of regression to normal BP, with no significant effect of age, sex, waist circumference, presence of diabetes mellitus, and other metabolic or echocardiographic variables (all P > 0.1).

Discussion

This is the first prospective analysis to identify cardiometabolic phenotypes associated with a higher risk of progression from pre-HTN to overt HTN in a population-based cohort, characterized by a high prevalence of diabetes mellitus and obesity and a high incident rate of HTN. Our results show that previous evidence in normotensive individuals of the effect of baseline systolic BP on the probability of developing arterial HTN4,5,21 is also applicable in the setting of pre-HTN. In addition, we provide evidence that, also in this setting, LV mass is a strong predictor of 4-year incident arterial HTN, independent of other metabolic and anthropometric factors associated with incident HTN.

Increase LV mass in pre-HTN is possibly associated with greater daily hemodynamic load that could not be detected by office BP measurements. Pressure variability (eg, increased BP fluctuations, failure of BP to “dip” at night, etc) or prolonged sustained exposure to higher BP during daily activities could explain the greater values of LV mass in many prehypertensive participants. Despite the standardized protocol used in the SHS for measurements of BP,27 the true hemodynamic load cannot be captured by single office measurements. Similar to other epidemiological studies,8,9,14,17–19,46,47 classification of pre-HTN has been on the basis of measurements of BP taken in a single session, and, therefore, there was a chance of misclassification of subjects with masked HTN. Echocardiographic modifications in diabetic subjects with office pre-HTN and 24-hour ambulatory BP monitoring–masked HTN have been reported recently.48 Masked HTN has been shown to be associated with significant target organ damage, such as increased LV mass.49,50 Progression of pre-HTN to HTN has been associated with increased arterial stiffness.18 In this study, the ratio of PP/SV was used as a raw estimated of arterial stiffness. The possibility that the evolution from pre-HTN to HTN was sustained by a progressive increase in arterial stiffness cannot be demonstrated in this study, because baseline PP/SV was similar in groups with or without incident HTN and did not show a significant impact on the prediction of HTN and because of the lack of a control echocardiogram. However, PP was substantially increased at the time of the third examination in participants developing HTN compared with those who did not (61 ± 16 versus 51 ± 10 mm Hg; P = 0.0001). A consistent increase in arterial stiffness cannot be demonstrated in this study, because baseline PP/SV was similar in groups with or without incident HTN and did not show a significant impact on the prediction of HTN and because of the lack of a control echocardiogram. However, PP was substantially increased at the time of the third examination in participants developing HTN compared with those who did not (61 ± 16 versus 51 ± 10 mm Hg; P = 0.0001). A consistent increase in LV at the third examination in participants developing HTN compared with those who did not (61 ± 16 versus 51 ± 10 mm Hg; P = 0.0001). A consistent increase in arterial stiffness may be speculated.

Finally, in addition to the above scenario, similar to what is already reported in unselected populations21–23 and in population samples with optimal BP,51 our study cannot exclude...
the possibility of reverse causation (ie, LV mass as a factor determining evolution toward HTN, through greater developed force), not necessarily alternative to the possibility that some or many of our participants had masked HTN. Although prehypertensive participants of this study exhibited relatively high prevalence of baseline LVH (17%), reinforcing the possibility of prevalent masked HTN, several previous studies have reported an association of pre-HTN with LVH. In the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Study, the prevalence of LVH in pre-HTN was 21%, and a similar prevalence of LVH was also reported in prehypertensive children and adolescents. The prevalence of LVH was >11% in adolescents and young prehypertensive SHS adults.

The evidence that, independent of a cause-effect relationship, LV mass is a predictor of HTN when the baseline variability of BP is constrained to the pre-HTN range and, therefore, substantially limited, is relevant. In addition, our results suggest that, among adults with pre-HTN, the combination of initially higher systolic BP and LV mass offsets the effects of metabolic factors that we and others have shown to be associated with the rise of BP over time, probably because of the progressive alteration of the arterial tree attributed to atherosclerosis. In the ATTICA Study, Pitsavos et al reported significant independent contribution of age, waist girth, and inflammation markers in the progression from pre-HTN to HTN. Although we did not find any significant contribution of age in the risk of development of HTN, probably because of more limited age range in our population, similar to the ATTICA Study, we found a significant association of higher waist girth and C-reactive protein with incident HTN in a univariate analysis, but their effects in the multivariate model were obscured by other cofactors, including LV mass index, suggesting that an increased LV mass might integrate at least part of the effect of alteration of body size on incident HTN in this population with a high prevalence of obesity. As a mirror of the phenotype predicting HTN, regression of BP to normal value was associated with lower baseline systolic BP and LV mass. The evidence that prehypertensive participants with regression to normal BP had lower baseline body size and significant reduction of waist girth during time might reflect a better weight control and suggest improvement in dietary habits and possibly an increase in physical activity, extending the established indications of lifestyle modifications for arterial HTN to the management of pre-HTN.

Among the potential metabolic predictors of incident HTN, diabetes mellitus emerged as the only major metabolic predictor. Association of pre-HTN with diabetes mellitus is known to markedly increase CV risk. Combination of diabetes mellitus with 2 other major predictors (systolic BP and LV mass index) strongly supports the current guideline recommendations for antihypertensive treatment of pre-HTN in these high-risk patients.

Given the ethnic peculiarity of the SHS, these findings might not necessarily be generalizable and need to be verified in other populations with different genetic and environmental backgrounds, especially because algorithms for risk prediction might be substantially affected by prevalence and distribution of individual risk factors.

Conclusions
We provide evidence that initial systolic BP, diabetes mellitus, and LV mass are predictors of 4-year incident arterial HTN in a population-based sample with pre-HTN and a high prevalence of CV risk factors. Results of the present study may help stratify risk associated with pre-HTN and suggest that particular attention should be paid to prehypertensive individuals with diabetes mellitus and/or increased LV mass.

Perspectives
There are implications of these findings for primary CV prevention. HTN is the leading risk factor for CV mortality and morbidity. Interventions to prevent the development of arterial HTN might help to reduce CV risk and direct and indirect costs related to HTN-related morbidity. The possibility of refining identification of pre-HTN phenotypes at high risk of future HTN, by pooling metabolic and cardiac information, increases the chance to target prehypertensive individuals who might benefit from aggressive BP management while reducing the possibility of overtreating patients with lower-risk CV phenotypes. Specifically, prehypertensive diabetic patients and/or those with increased LV mass are at high risk of HTN and might be referred to more extensive clinical evaluation (ambulatory BP monitoring) and possibly treated to prevent it. Our results also suggest that particular attention should be paid to force prehypertensive individuals into programs to decrease body weight to successfully prevent arterial HTN. Additional studies are warranted to examine the use of echocardiography as an aid in the risk stratification of pre-HTN determining the need for antihypertensive therapy and to assess the effect of earlier intervention on the course of progression to HTN.

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Disclosures
None.

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