Subclinical Coronary Atherosclerosis Predicts Cardiovascular Risk in Different Stages of Hypertension

Result of the Heinz Nixdorf Recall Study


Abstract—Prehypertension is a frequent condition and has been demonstrated to increase cardiovascular risk. However, the association with coronary atherosclerosis as part of target organ damage is not well understood. We investigated the cross-sectional relationship and longitudinal outcome between blood pressure categories and coronary artery calcification (CAC), quantified by electron beam computed tomography, in 4181 participants from the population-based Heinz Nixdorf Recall Study cohort. At baseline, we observed a continuous increase in calcium scores with increasing blood pressure categories. During a median follow-up period of 7.18 years, 115 primary end points (2.8%; fatal and nonfatal myocardial infarction) and 152 secondary end points (3.6%; stroke and coronary revascularization) occurred. We observed a continuous increase in age- and risk factor-adjusted secondary endpoints (hazard ratios [95% CI]) with increasing blood pressure categories (referent: normotension) in men: prehypertension, 1.80 (0.53–6.13); stage 1 hypertension, 2.27 (0.66–7.81); and stage 2 hypertension, 4.10 (1.27–13.24) and in women: prehypertension, 1.13 (0.34–3.74); stage 1 hypertension, 2.14 (0.67–6.85); and stage 2 hypertension, 3.33 (1.24–8.90), respectively, but not in primary endpoints. Cumulative event rates were determined by blood pressure categories and the CAC. In prehypertension, the adjusted hazard ratios for all of the events were, for CAC 1 to 99, 2.05 (0.80–5.23; stage 1 hypertension, 2.14 (0.67–6.85); and stage 2 hypertension, 3.33 (1.24–8.90), respectively, but not in primary endpoints. Risk of myocardial infarction and stroke in hypertension but also in prehypertension depends on the degree of CAC. This marker of target-organ damage might be included, when lifestyle modification and pharmacotherapeutic effects in prehypertensive individuals are tested to avoid exposure to risk and increase benefit. (Hypertension. 2012;59:44-53.) ● Online Data Supplement

Key Words: prehypertension ■ hypertension ■ subclinical atherosclerosis ■ coronary artery calcium ■ risk prediction ■ target organ damage

Atherosclerosis is the primary cause of coronary heart disease, and coronary heart disease events are the result of a complex interaction of multiple risk factors. These factors include arterial hypertension, smoking, hypercholesterolemia, and diabetes mellitus.1 Worldwide, the number of adults with hypertension has been estimated to amount to 972 million in 2000; 639 million live in developing countries. The total number has expected to increase to 1.56 billion in 2005.2 Epidemiological data show that coronary event rates are highest in those with hypertension, intermediate in those with prehypertension, also called borderline or high-normal blood pressure (BP), and lowest in those with normal BP.3–5 The most common first major events after hypertension onset are hard ischemic heart disease events with acute myocardial infarction and unstable angina in a continuous graded manner with no indication of a critical value.9,10 The long time delay between onset of the disease and clinical manifestation of atherosclerosis is providing the opportunity for early detection, prevention, and interventional strategies.11 In this aspect, abnormal coronary endothelial function represents one of the earliest stages in vascular damage and is associated with atherosclerosis-related events.11 In prehypertension, even an impaired repair capacity of endothelial progenitor cells could be demonstrated.12 Also, retinal vessel narrowing was found,13 as well as an increased intima-media thickness and left ventricular mass.14 For incidental hypertension, coronary

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artery calcification (CAC) was described as a direct sign of target organ damage of the coronary arteries, which can noninvasively be detected by computed tomography (CT). However, the association between different stages of BP and CAC has not been well analyzed. This seems, however, to be important, because the degree of CAC is an excellent prognostic marker for coronary and other cardiovascular events. Compared with hypertension, for which treatment strategies are standardized, treatment of prehypertension is still under debate. Therefore, we tested whether the inclusion of CAC could improve risk prediction for coronary and other events in a cohort with prehypertensive adults in comparison with normotensive and hypertensive individuals.

Methods

Study Population

The study was performed as part of the Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcium, and Lifestyle) Study, a population-based cohort study designed to assess the predictive value of subclinical coronary atherosclerosis. Participants were randomly selected from mandatory city registries in Bochum, Essen, and Mülheim, Germany, and invited to participate in the study. A total of 4814 subjects aged 45 to 75 years were included between December 2000 and August 2003. All of the subjects with physician-diagnosed coronary artery disease, that is, a history of myocardial infarction or coronary revascularization (n=327), were excluded from the study, as well as those with a history of stroke (n=124). In 182 participants, values of CAC and/or BP were unavailable, leaving 4181 subjects (53% women) for this analysis. Patients with a history of stroke or revascularization (n=327), were excluded from the study, as well as those with a history of stroke (n=124). In 182 participants, values of CAC and/or BP were unavailable, leaving 4181 subjects (53% women) for this analysis. In 182 participants, values of CAC and/or BP were unavailable, leaving 4181 subjects (53% women) for this analysis.

Risk Factors of Atherosclerosis and Questionnaires

Trained technicians took 3 blood pressure measurements with an automated oscillometric blood pressure device (Omron, HEM-705CP, OMRON Corporation, Hooibroek, the Netherlands), with appropriate 14- or 16-cm cuff sizes and the participants in the sitting position. The mean of the second and third value of 3 measurements, recorded with a 3-minute interval, was taken in accordance with the Seventh Joint National Committee for Prevention Detection and Treatment of High Blood Pressure (JNC 7) guidelines. Participants with systolic/diastolic BP <120/80 mm Hg were categorized as normotensive. Prehypertension was defined as systolic BP 120 to 139 mm Hg or diastolic BP 80 to 89 mm Hg. Hypertension was defined as systolic or diastolic BP =140 or =90 mm Hg, respectively, and subdivided in stage 1 hypertension with either systolic BP 140 to 159 mm Hg or diastolic BP 90 to 99 mm Hg and stage 2 hypertension with either systolic or diastolic BP =160 or =100 mm Hg. Participants were asked to bring their medication to verify whether antihypertensive medication was used to validate some answers in the questionnaire concerning the presence of hypertension. Only if antihypertensive medication was verified, did we categorize these participants as in stage 2 hypertension.

Assessment of Confounders

Body mass index was calculated from standardized measurements of height and weight. Current smoking was defined as a history of cigarette smoking during the past year. Standard enzymatic methods were used to measure serum total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides using the ADVIA 1650 System (Siemens Healthcare Diagnostics, Eschborn, Germany). Participants were considered diabetic if they reported a physician diagnosis of diabetes mellitus or were taking antidiabetic medication. From these risk factors, the Framingham risk score (ie, predicted 10-year risk) was computed. Serum creatinine was measured by the Jaffe method (kinetic alkaline picrate). Glomerular filtration rate (GFR in milliliters per minute per 1.73 m² of BSA) was estimated using the abbreviated Modification of Diet in Renal Disease equation: GFR=186 × (serum creatinine)−1.154 × age−0.203 × (0.742 for women). Homocysteine was measured using fluorescence polarization immunoassay on the IMx analyzer (Abbott Laboratories, Abbott Park, IL).

Electron Beam CT

To quantify CAC, nonenhanced electron beam CTs were performed with a C-100 or C-150 scanner (GE Imatron, South San Francisco, CA).
CA). Prospective ECG triggering was done at 80% of the R-R interval. Contiguous 3-mm-thick sections to the apex of the heart were obtained at an image acquisition time of 100 ms.\textsuperscript{21} CAC was defined as a focus of $\geq$4 contiguous pixels with a CT density of $\geq$130 Hounsfield units. The CAC Agatston score was computed by summing the CAC scores of all of the foci in the epicardial coronary system.\textsuperscript{20} Results of CT concerning the CAC were not communicated to either the participants or their treating physician.\textsuperscript{21,27}

**Primary and Secondary End Points**

Annual postal questionnaires assessed the morbidity status during follow-up, that is, medication, hospital admissions, and outpatient diagnoses of primary and secondary end points. Self-reported incident morbidity and fatal events were validated by review of hospital records and records of the attending physicians.\textsuperscript{30} All of the death certificates of the 3 cities under study were regularly screened. In parallel, deceased participants were tracked back to obtain as much information as possible to verify causes of death. Participants were followed for a median of 7.18 years (25th and 75th percentiles: 6.98, 8.24 years). Primary end points for this study were based on unequivocally documented incident hard coronary events (fatal and nonfatal myocardial infarction) that met predefined study criteria.\textsuperscript{21} We considered a myocardial infarction event based on symptoms, electrocardiographic signs, and enzymes (levels of creatinine kinase), as well as troponin T or I, and necropsy as nonfatal acute myocardial infarction and coronary death, which occurred after the baseline examination.\textsuperscript{30} In addition, we studied the following predefined secondary end points: coronary revascularization defined as percutaneous transluminal coronary angioplasty, usually with stent placement or coronary artery bypass graft surgery according to hospital or physician records and stroke, defined as focal neurological deficits over a period of $\geq$24 hours of presumed cerebrovascular origin. For all of the study end points, hospital and nursing home records, including electrocardiograms, laboratory values, and pathology reports, were collected.\textsuperscript{30} For deceased subjects, death certificates were collected, and interviews with general practitioners, relatives, and eyewitnesses were undertaken where possible.\textsuperscript{30} Medical charts were obtained for all of the reported end points. All of the events were verified and classified by an independent end point committee. Committee members had no information about the results of CAC scoring.

**Statistical Methods**

Continuous data are given as mean $\pm$SD, and in the case of substantially skewed distribution also as median with 25th and 75th percentile (Q1, Q3). Count data are given as frequency and percentage. A trend of continuous data with JNC 7 BP categories was found in prehypertensive women but not in prehypertensive men. The association between age and CAC scores was strongly dependent on BP categories both in men and in women but to different degrees. The CAC scores were strongly associated with JNC 7 categories both in crude and adjusted models (Table 2) in men and women. The association between age and CAC scores was strongly dependent on BP categories but more in women than in men (Figure 2). Age-dependent higher degrees of CAC were found in prehypertensive women but not in prehypertensive men compared with normotensive participants (Figure 2). Nonetheless, the factor of increase in CAC $+1$ with 10-mm Hg systolic BP was very similar in men and women, that is, 1.14 (95% CI: 1.09–1.21; $P<0.0001$) and 1.13 (95% CI: 1.09–1.18; $P<0.0001$), respectively (model 2).

**Primary and Secondary End Points**

Kaplan-Meier estimates of event-free survival probabilities for primary end points (fatal or nonfatal myocardial infarction), secondary end points (stroke or coronary revascularization), or the combination of both were calculated in strata defined by JNC 7 BP categories, as well as CAC score categories, and evaluated with a log-rank test of trend. We used multivariable Cox proportional hazard regression to calculate unadjusted and adjusted hazard ratios (HRs) and corresponding 95% CIs with respect to BP or CAC categories for the time to occurrence of end points. Stratification was with respect to sex or JNC 7 categories; adjustment was with respect to age, sex, total cholesterol, history of diabetes mellitus and ever versus never smoking. Analysis of Schoenfeld residuals\textsuperscript{31} and a Kolmogorov-type supremum test (based on Reference\textsuperscript{32}) confirmed validity of the proportional hazards assumption. All of the computations were performed using SAS version 9.2 (SAS Institute, Cary, NC).

**Distribution of Risk Factors in BP Categories**

Table 1 presents the baseline characteristics of our study population in the 4 different BP categories. Prehypertensive participants already showed higher prevalences of risk factors. Hypertensive subjects were older, showed higher body mass indexes, and higher cholesterol and triglyceride levels. Prevalence of diabetes mellitus increased as well. Most obviously the percentages of participants with present smoking decreased significantly from normotensives (33.5% and 28.0% for men and women) to stage 2 hypertension (19.5% and 15.2%, respectively). The Framingham risk score increased. Participants with events had a higher risk profile than those without (Table S1, available in the online Data Supplement at http://hyper.ahajournals.org).

**Association of CAC Scores With JNC 7 Categories**

The amount of CAC increased with the level of BP (Table 1) both in men and in women but to different degrees. The CAC scores were strongly associated with JNC 7 categories both in crude and adjusted models (Table 2) in men and women. The association between age and CAC scores was strongly dependent on BP categories but more in women than in men (Figure 2). Age-dependent higher degrees of CAC were found in prehypertensive women but not in prehypertensive men compared with normotensive participants (Figure 2). Nonetheless, the factor of increase in CAC $+1$ with 10-mm Hg systolic BP was very similar in men and women, that is, 1.14 (95% CI: 1.09–1.21; $P<0.0001$) and 1.13 (95% CI: 1.09–1.18; $P<0.0001$), respectively (model 2).

**Primary and Secondary End Points**

After 7.18 years of follow-up, 115 (2.8%) and 152 (3.6%) of 4181 participants experienced primary and secondary events, respectively, with a generally higher risk factor burden in subjects versus those without events (Table S1). The time to events decreased with increasing JNC 7 categories (Figure 3A and 3B). HRs of JNC 7 categories were higher for secondary than for primary end points (Table 3), with little difference between men and women. In comparison with normotensives, HRs for the combined end point were 1.43 (95% CI: 0.82–2.50; $P=0.21$) for prehypertensives, 1.52 (95% CI: 0.85–2.73; $P=0.16$) for stage 1 hypertensives, and
Table 1. Distribution of Risk Variables and CAC Scores in the Different JNC 7 Blood Pressure Categories

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Normal</th>
<th>W</th>
<th>Pre-HT</th>
<th>M</th>
<th>W</th>
<th>Stage 1</th>
<th>M</th>
<th>W</th>
<th>Stage 2</th>
<th>M</th>
<th>W</th>
<th>P For Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>200</td>
<td>618</td>
<td>596</td>
<td>500</td>
<td>397</td>
<td>290</td>
<td>773</td>
<td>807</td>
<td>NA</td>
<td>NA</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±7</td>
<td>56±7</td>
<td>57±7</td>
<td>59±8</td>
<td>60±7</td>
<td>61±7</td>
<td>61±8</td>
<td>62±8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3±3.7</td>
<td>25.3±4.1</td>
<td>27.2±3.3</td>
<td>27±4</td>
<td>28±3.5</td>
<td>28±5</td>
<td>29.2±4.2</td>
<td>29±6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>111±6</td>
<td>107±8</td>
<td>129±6</td>
<td>127±7</td>
<td>146±7</td>
<td>145±8</td>
<td>148±22</td>
<td>139±24</td>
<td>NA</td>
<td>NA</td>
<td>0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71±5</td>
<td>70±6</td>
<td>81±5</td>
<td>79±6</td>
<td>88±7</td>
<td>87±7</td>
<td>89±12</td>
<td>83±12</td>
<td>NA</td>
<td>NA</td>
<td>0.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total serum cholesterol, mg/dL</td>
<td>221±36</td>
<td>226±38</td>
<td>227±39</td>
<td>236±41</td>
<td>233±39</td>
<td>238±37</td>
<td>228±36</td>
<td>238±40</td>
<td>0.09</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL serum cholesterol, mg/dL</td>
<td>144±34</td>
<td>139±36</td>
<td>148±36</td>
<td>148±38</td>
<td>152±37</td>
<td>148±36</td>
<td>146±34</td>
<td>151±36</td>
<td>0.94</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL serum cholesterol, mg/dL</td>
<td>52±15</td>
<td>69±17</td>
<td>53±14</td>
<td>66±16</td>
<td>53±15</td>
<td>66±17</td>
<td>51±15</td>
<td>62±17</td>
<td>0.09</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum triglyceride, mg/dL</td>
<td>133±75</td>
<td>105±50</td>
<td>150±106</td>
<td>127±69</td>
<td>161±97</td>
<td>143±83</td>
<td>186±138</td>
<td>152±89</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.0</td>
<td>1.0</td>
<td>4.5</td>
<td>3.4</td>
<td>7.3</td>
<td>4.8</td>
<td>12.4</td>
<td>12.4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smoking, %</td>
<td>40.0</td>
<td>24.8</td>
<td>38.3</td>
<td>23.0</td>
<td>47.4</td>
<td>21.4</td>
<td>50.1</td>
<td>21.2</td>
<td>&lt;0.0001</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present smoking, %</td>
<td>33.5</td>
<td>28.0</td>
<td>30.1</td>
<td>22.0</td>
<td>24.9</td>
<td>22.4</td>
<td>19.5</td>
<td>15.2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering drugs, %</td>
<td>4.3</td>
<td>3.6</td>
<td>6.0</td>
<td>7.9</td>
<td>7.8</td>
<td>8.7</td>
<td>12.5</td>
<td>16.5</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum hsCRP, median (Q1/Q3), mg/dL</td>
<td>0.8 (0.5/2.0)</td>
<td>1.1 (0.6/2.1)</td>
<td>1.2 (0.6/2.4)</td>
<td>1.4 (0.7/2.8)</td>
<td>1.3 (0.7/2.8)</td>
<td>1.5 (0.7/3.2)</td>
<td>1.6 (0.9/3.1)</td>
<td>1.8 (0.9/3.6)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.0±0.1</td>
<td>0.9±0.2</td>
<td>1.0±0.2</td>
<td>0.8±0.3</td>
<td>1.0±0.2</td>
<td>0.8±0.1</td>
<td>1.0±0.2</td>
<td>0.9±0.2</td>
<td>0.12</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, ml/min per BSA</td>
<td>84±14</td>
<td>77±21</td>
<td>86±18</td>
<td>77±16</td>
<td>84±16</td>
<td>79±19</td>
<td>83±20</td>
<td>74±18</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>11.5±3.2</td>
<td>10.4±3.2</td>
<td>11.9±3.5</td>
<td>10.6±5.3</td>
<td>12.4±4.7</td>
<td>11.3±6.6</td>
<td>12.5±3.9</td>
<td>11.6±4.1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham risk score</td>
<td>9.4±5.2</td>
<td>3.6±2.0</td>
<td>11.5±6.2</td>
<td>7.2±3.3</td>
<td>17.7±8.5</td>
<td>10.6±4.8</td>
<td>19.2±10.4</td>
<td>9.7±5.3</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1-Q3)</td>
<td>9 (6–11)</td>
<td>3 (2–5)</td>
<td>11 (37–14)</td>
<td>6 (5–8)</td>
<td>18 (11–23)</td>
<td>9 (8–11)</td>
<td>18 (11–27)</td>
<td>9 (6–13)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery calcification score, Median (Q1/Q3)</td>
<td>12 (0/87)</td>
<td>0 (0/4)</td>
<td>20 (1/24)</td>
<td>1 (0/29)</td>
<td>58 (5/247)</td>
<td>2 (0/45)</td>
<td>106 (15/45)</td>
<td>9 (0/97)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>= 0, %</td>
<td>31.5</td>
<td>63.9</td>
<td>24.8</td>
<td>47.2</td>
<td>16.1</td>
<td>40.7</td>
<td>10.4</td>
<td>32.0</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0–99, %</td>
<td>46.0</td>
<td>30.9</td>
<td>47.3</td>
<td>41.4</td>
<td>41.8</td>
<td>44.5</td>
<td>38.2</td>
<td>43.2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100–399, %</td>
<td>13.0</td>
<td>3.9</td>
<td>18.3</td>
<td>9.4</td>
<td>26.2</td>
<td>10.7</td>
<td>28.3</td>
<td>16.6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥400, %</td>
<td>9.5</td>
<td>1.3</td>
<td>9.6</td>
<td>2.0</td>
<td>15.8</td>
<td>4.1</td>
<td>23.2</td>
<td>8.1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>5 (2.5)</td>
<td>5 (0.8)</td>
<td>19 (3.2)</td>
<td>7 (1.4)</td>
<td>12 (3.0)</td>
<td>3 (1.0)</td>
<td>44 (5.7)</td>
<td>20 (2.5)</td>
<td>0.009</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary end points†</td>
<td>3 (1.5)</td>
<td>5 (0.8)</td>
<td>18 (3.0)</td>
<td>6 (1.2)</td>
<td>17 (4.3)</td>
<td>7 (2.4)</td>
<td>62 (8.0)</td>
<td>34 (4.2)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined end points</td>
<td>8 (4.0)</td>
<td>9 (1.5)</td>
<td>36 (6.0)</td>
<td>13 (2.6)</td>
<td>28 (7.0)</td>
<td>10 (3.5)</td>
<td>102 (13.2)</td>
<td>51 (6.3)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M indicates men; W, women; HT, hypertension; CAC, coronary artery calcification; JNC 7, Seventh Joint National Committee for Prevention Detection and Treatment of High Blood Pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Q1/Q3, 25th/75th percentiles; GFR, glomerular filtration rate; NA, not applicable.

*Primary end points included fatal and nonfatal myocardial infarction.
†Secondary end points included stroke and coronary revascularization.
2.63 (95% CI: 1.57–4.43; P = 0.0003) for stage 2 hypertensives (model 2).

**Risk Within CAC and JNC 7 Categories**

Within each BP category, adjusted HRs of the combined primary and secondary end points continuously increased by CAC amounts (Figure 4). The increases in HRs within CAC score categories with increasing BP categories were modest, except for the increase in risk in persons with stage 2 hypertension (Figure 4). The time to events decreased with increasing CAC score categories among prehypertensives (Figure 5), with a gradual and strong relationship of risk with the degree of CAC. In persons with hypertension, that is, stage 1 and stage 2, adjusted HRs (model 2) for the combined end point in comparison with persons without CAC were 1.96 (95% CI: 1.06–3.63) for CAC 0 to 99, 3.46 (95% CI: 1.84–6.49; P = 0.0001) for CAC 100 to 399, and 7.55 (95% CI: 4.03–14.15; P < 0.0001) for CAC ≥400 (model 2). Adjusting this relation between CAC and events in hypertensives (stages 1 and 2) further with respect to age, sex, diabetes mellitus, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, former and present smoking, lipid-lowering medication, and body mass index confirmed these results. HRs were 1.68 (95% CI: 0.90–3.15) for CAC 0 to 99, 3.09 (95% CI: 1.63–5.86) for CAC 100 to 399, 7.20 (95% CI: 3.80–13.63) for CAC ≥400, 1.16 (95% CI: 1.03–2.83) for 5 years of age, and 1.61 (95% CI: 1.08–2.41) for diabetes mellitus. All of the 95% CIs for the remaining adjusting parameters in this model included unity, with P values > 0.1. Especially the presence of lipid-lowering therapy in this multivariable analysis showed no sizeable impact, with an HR of 0.93 (95% CI: 0.59–1.42; P = 0.68).

**Discussion**

In our cohort, prehypertension was present in one third of the population and characterized by a high-risk profile. BP was strongly and in a continuous manner correlated with CAC, resulting in corresponding primary and secondary event rates. In each BP category, even in prehypertension, CAC was independently predictive of future coronary events, strokes, and coronary revascularization. Our data suggest that coronary atherosclerosis as a marker of target organ damage might be considered for further risk stratification. This applies particularly to persons with prehypertension, where the clinical significance of antihypertensive medication is controversial. Atherosclerosis imaging may help to guide...
lifestyle modification and pharmacotherapeutic therapy to reduce coronary and cardiovascular morbidity and mortality.33

In the recently published recommendations of the European Society of Cardiology,20 target organ damage of the coronary arteries, that is, CAC, has only been mentioned. Assessment of subclinical organ damage for cardiovascular risk stratification was emphasized,20 focusing on increased carotid intima-media thickness, abnormal pulse wave velocity, silent atherosclerotic lesions detected by MRI, and signs of endothelial dysfunction.20 Also, left ventricular hypertrophy was associated with subsequent cerebrovascular events,34 interpreted as exposure not only to long-term BP but also to hormonal and metabolic factors, as well as genetic predisposition.35 Similarly, CAC can be regarded as a cardiac marker, indicating a worse prognosis not only for coronary heart disease17–19 but also for cerebro-vascular events.30,36 Because of the controversies in prehypertension, the European Society of Cardiology suggested a reclassification strategy for those with pronounced or multiple signs of vascular damage.20 In addition, evidence-based pharmacotherapy in prehypertensives is not available and could be more harmful and risky than nonpharmacologic interventions.37–39 In this respect, CAC scoring may be used for further decision making, because CAC indicates target organ damage, which is accompanied by an excessively higher event rate in those with CAC scores ≥100 and particularly ≥400 compared with lower levels or 0 CAC. Those with target organ damage may be those who possibly benefit most from tight BP control compared with usual control, meaning reduction of BP to <140 mm Hg, as suggested for treatment of diabetic patients.40 This strategy recently failed to demonstrate improved

Figure 3. Kaplan-Meier curves of primary events (fatal and nonfatal myocardial infarction; A) and secondary end points (stroke and coronary revascularization; B) in Seventh Joint National Committee for Prevention Detection and Treatment of High Blood Pressure (JNC 7) blood pressure categories with numbers at risk in each category and adjusted hazard ratios (HRs).
results in a substudy of the International Verapamil SR- Trandolapril Study.\(^{41}\) Although the cardiovascular event rate was 19.8% in uncontrolled hypertension (n = 431), it could be reduced to 12.6% with usual care (n = 249). However, in those with tight control, the event rate could not further be reduced, and amounted to 12.7% (n = 286). This was confirmed for all-cause mortality with 11.0% in the tight control group versus 10.2% in the usual control group.\(^{42}\) However, this study was not designed to answer the question of prehypertension treatment but points to the fact that prospective randomized trials are needed to test our hypothesis.

Interestingly enough, we found a stronger association between BP and secondary end points rather than primary end points despite strong associations of BP to CAC. This is in line with previous epidemiological observations showing that hypertension was the most important risk factor in 77% of persons with incidental strokes and in 69% of those with incidental myocardial infarction.\(^{43}\) The relationship among BP, CAC, and end points is supported by previous cross-sectional analyses from the Multi-Ethnic Study of Atherosclerosis and Heinz Nixdorf Recall, demonstrating that BP was a main determinant of CAC.\(^ {44}\) Similarly, a recent meta-analysis in 73,913 patients demonstrated for intensive blood pressure reduction a positive effect for stroke but not for myocardial infarction in diabetics.\(^ {45}\) Ischemic coronary artery disease based on luminal narrowing can be regarded as a direct consequence of coronary atherosclerosis, and CAC has a high correlation to total plaque burden.\(^ {46}\) Thus, on one hand, a strong association with revascularization can be expected and on the other hand a weaker association with coronary events, because the underlying process is not directly related to CAC but to erosion and plaque rupture of thin cap fibrous atheroma, as visualized at autopsy.\(^ {47}\)

The age- and sex-adjusted percentile distribution of CAC was related to the 4 BP categories. The association between BP with CAC was stronger in women than in men, but men had an \( \approx \)5 times higher amount of CAC. In men, CAC was already found in hypertension stage 2 at the age of 45 years and in women at the age of 50 years, which seems to be related to the lower frequency of hypertension in women compared with men until 45 years of age.\(^ {48}\) In addition, the prevalence and severity of hypertension increase with age in women, so that after 60 years, the majority of women have stage 2 hypertension or receive antihypertensive agents.\(^ {48,49}\) When CAC is used to estimate “arterial age,”\(^ {25-27,50}\) it is \( \approx \)15 years higher in stage 2 hypertensive women than in normo-
tensive women, that is, normotensive women reach any given CAC score \( \approx 15 \) years later than women with stage 2 hypertension. However, even for prehypertension and hypertension stage 1, differences of 7 to 10 years could be demonstrated. In men, however, the differences between the different BP categories were not as striking, but still the estimated vascular age in normotensives was lower than in hypertensives. This may reflect that CAC in men is more strongly influenced by other risk factors than BP alone, including, particularly, smoking.\(^{51,52}\) Smoking was much more prevalent in men than in women, whereas in women \( >60 \) years of age, smoking also increases systolic BP.\(^{51}\) CAC percentile distributions in men and women were similar for smokers, former smokers, and never smokers.\(^{26}\) However, men and women with diabetes mellitus, prediabetes, and no diabetes mellitus showed a similar CAC distribution of percentiles,\(^{25}\) as in this study for BP supporting the hypothesis, that the higher prevalence of smoking in men compared with women may be the main reason for the observed different distribution of CAC percentiles.

**Limitations**

BP was measured only at baseline, but in previous large cohort trials, a single BP recording could demonstrate a strong predictive value for CV events.\(^{5,8}\) The method used could result in an underestimation of the true association because of a regression dilution bias.\(^{53}\) However, the described prevalence of prehypertension corresponds with previous reports.\(^{8,54}\)

The definition of secondary end points could be a point of criticism. During the 7.18-year follow-up, the event rates of primary and secondary end points were significantly higher for hypertension stages 1 and 2 compared with normotensives. However, in prehypertensives, the hazard ratios were borderline after adjustment for age and sex, as reported previously during a follow-up time of 25 years using the group of high normal blood pressure for comparison.\(^{55}\) The Framingham study found an increased risk in those with high normal blood pressure for a 12-year follow-up. The study used JNC 6–based definition, which is more narrow than our JNC 7 definition, and, thus, may explain some of the differences.\(^{6}\) Another difference is related to the definition of end points, which were in addition to death, myocardial infarction, and stroke, as well as heart failure, whereas in our study, instead of heart failure, revascularization was used.

To account for the potential influence of antihypertensive medication, we followed the proposal of the JNC 7 to reclassify those under antihypertensive medication as hypertension stage 2.\(^{24}\) Without this reclassification, similar results were calculated, but the percentile distributions of CAC were more steep for normotensives and prehypertensives (data not shown). This demonstrates even more strikingly the strong association between BP and CAC. Normotensives throughout their life do show nearly no CAC with usual CAC \( <10 \) up to the age of 75 years.

During follow-up, antihypertensive medication may have been initiated or modified, which may have had some effect on outcome. In addition, it has to be expected that noncardiovascular events may be reduced in hypertensive persons using statins, as demonstrated recently.\(^{56}\)

**Perspectives**

This study of a population-based cohort shows that BP is strongly associated with coronary artery calcium evidencing target organ damage in male as well as female participants. Compared with normotensives, prehypertensives demonstrate significantly higher levels of CAC as a sign of coronary atherosclerosis but lower values than those with hypertension stages 1 and 2. In prehypertensives the degree of CAC was a strong predictor of coronary events but even more of secondary end points, including stroke and revascularization. Risk of events was predominantly predicted by CAC, meaning the degree of plaque burden. Thus, assessment of CAC as a sign of subclinical coronary atherosclerosis allows improved risk stratification in individuals with hypertension and even prehypertension. Currently not yet recommended, these signs
and the degree of target organ damage may, in addition, be used for selection of prehypertensives for pharmacotherapeutic interventions outbalancing potential risks.

**Acknowledgments**

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**Disclosures**

None.

**References**


Subclinical Coronary Atherosclerosis Predicts Cardiovascular Risk in Different Stages of Hypertension: Result of the Heinz Nixdorf Recall Study


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Subclinical Coronary Atherosclerosis Predicts Cardiovascular Risk in Different Stages of Hypertension

- Result of the Heinz Nixdorf Recall Study -


From the Department of Cardiology (R.E., S.M., S.C., H.K., M.B.), Institute for Medical Informatics, Biometry & Epidemiology (N.L., S.M., N.D., K.-H.J.), Institute of Institute of Clinical Chemistry and Laboratory Medicine (M.B.-P., K.M.), University Clinic Essen, Germany, Cardioangiological Center Bethanien (A.S.), Frankfurt; Institute of Clinical Epidemiology, Medical Faculty University Halle-Wittenberg, Halle (A.S.), Department of Neurology (C.W.), Institute of Medical Sociology (J.S.), University Clinic Düsseldorf Germany

Short Title: CAC predicts cardiovascular risk in hypertension

*Raimund Erbel and Nils Lehmann participate in equal part to the manuscript authorship

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Table S 1: Distribution of risk variables and CAC scores in participants with versus without events meaning primary endpoints (fatal and non fatal myocardial infarction) and secondary endpoints (stroke and coronary revascularization).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>With Events</th>
<th>Without Events</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>257</td>
<td>3924</td>
<td>n.a.</td>
</tr>
<tr>
<td>Sex (% females)</td>
<td>32.3</td>
<td>54.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63±8</td>
<td>59±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.7±4.3</td>
<td>27.7±4.6</td>
<td>0.0008</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>144.4±23.6</td>
<td>132.0±20.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>84.7±12.4</td>
<td>81.3±10.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antihypertensive medication (%)</td>
<td>48.6</td>
<td>30.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total serum cholesterol (mg/dl)</td>
<td>237±40</td>
<td>231±39</td>
<td>0.0092</td>
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<tr>
<td>LDL serum cholesterol (mg/dl)</td>
<td>156±36</td>
<td>146±36</td>
<td>&lt;0.0001</td>
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<tr>
<td>HDL serum cholesterol (mg/dl)</td>
<td>54±17</td>
<td>59±17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>176±118</td>
<td>145±98</td>
<td>&lt;0.0001</td>
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<tr>
<td>Former smoking (%)</td>
<td>35.4</td>
<td>33.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Present smoking (%)</td>
<td>25.7</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>14.0</td>
<td>6.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipid-lowering drugs (%)</td>
<td>13.4</td>
<td>9.1</td>
<td>0.028</td>
</tr>
<tr>
<td>Serum hsCRP (mg/dL) (Median (Q1/Q3))</td>
<td>2.1</td>
<td>1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0±0.4</td>
<td>0.9±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glomerular infiltratation rate (ml/min/BSA)</td>
<td>79±19</td>
<td>80±19</td>
<td>0.37</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>12.4±4.2</td>
<td>11.5±4.3</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

**Framingham Risk Score**

10-year risk (mean±1SD)          | 17.2±10.6  | 10.9±8.0       | <0.0001 |
Median (Q1-Q3)                   | 14 (9-22)  | 9 (6-14)       |

**Coronary Artery Calcification Score**

<table>
<thead>
<tr>
<th>CAC Score Range</th>
<th>With Events</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 0 [%]</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>&gt; 0 - 99 [%]</td>
<td>30.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>100 – 399 [%]</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>≥ 400 [%]</td>
<td>36.2</td>
<td></td>
</tr>
</tbody>
</table>