Is Prehypertension a Risk Factor for Cardiovascular Diseases?

Adnan I. Qureshi, MD; M. Fareed K. Suri, MD; Jawad F. Kirmani, MD; Afshin A. Divani, PhD; Yousef Mohammad, MD

Background and Purpose—The Joint National Committee on High Blood Pressure identified a new category of blood pressure in adults termed prehypertension. Our objective was to determine the long-term risk of cardiovascular diseases associated with this new category in a well-defined cohort of adults.

Methods—We evaluated the association of prehypertension (120 to 139/80 to 89 mm Hg) and hypertension (≥140/90 mm Hg) with the incidence of atherothrombotic brain infarction (ABI), all strokes, myocardial infarction (MI), and coronary artery disease (CAD) using pooled repeated measures and Cox proportional hazards analyses during follow-up after adjusting for age, gender, obesity, diabetes mellitus, hypercholesterolemia, cigarette smoking, and study period in a cohort of 5181 persons who participated in the Framingham Study.

Results—Among the 11 116 person observations with a mean follow-up period of 9.9±1.0 years, prehypertension was not associated with an increased risk for ABI (relative risk [RR], 2.2; 95% CI, 0.5 to 9.3). Among the 11 802 person observations with a mean follow-up period of 9.7±1.5 years, prehypertension was associated with an increased risk for MI (RR, 3.5; 95% CI, 1.6 to 7.5). Prehypertension was also associated with an increased risk of CADs among the 11 570 person observations (RR, 1.7; 95% CI, 1.2 to 2.4).

Conclusions—Prehypertension appears to be associated with an increased risk of MI and CAD but not stroke. Further studies are required to confirm the anticipated benefits of identifying and intervening in persons with prehypertension.

Key Words: cardiovascular diseases □ cerebrovascular disorders □ myocardial infarction □ stroke

Approximately 50 million individuals in the United States are affected by hypertension. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) designated a new category termed prehypertension and combined stages 2 and 3 of hypertension under 1 category. Because screening and treatment efforts are to be directed for this new category of hypertension in the US population, we sought to determine the risk of cardiovascular diseases associated with prehypertension.

Methods
We used the data from the well-defined cohort of the Framingham Study to determine the effect of prehypertension on the long-term risk of cardiovascular diseases. The study began in 1948, with recruitment of 2336 men and 2873 women residents of Framingham, Mass. The participants received a complete physical examination at baseline, followed by repeat examinations every 2 years during the course of follow-up, as described previously. Subjects who were free of stroke or myocardial infarction (MI) at the baseline evaluation were included.

Measurement of Blood Pressure and Covariates
At each examination, a physician or nurse using a standard protocol measured the systolic and diastolic blood pressure (BP) of the seated subjects. The average of 3 readings was taken as the examination BP of the participants. Only 1 BP reading was available for 2 examinations (contributed as 3% of total observations), and 2 BP readings were available for 1 examination (contributed as 0.8% of total observations). Patients were categorized (based on the JNC 7) as normal if systolic BP was <120 and diastolic BP was <80 mm Hg; prehypertension, 120 to 139/80 to 89 mm Hg; or hypertension, ≥140/90 mm Hg. Patients were also classified as hypertensive based on use of antihypertensive medication at the time of baseline assessment and recategorization.

The status of BP and other covariates was recategorized every 10 years using the information derived from follow-up evaluation. The follow-up evaluation was not conducted in the tenth year in a small proportion of the participants. In those subjects, the next preceding (year 8), or if not available the next succeeding (year 12), examination was used to acquire pertinent information for recategorization of the status of BP and other covariates (eg, serum cholesterol).

Follow-Up and Outcome Events
All study subjects were under continuous surveillance for the development of cardiovascular events and death. The primary

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outcomes were atherothrombotic brain infarction (ABI), all strokes, MI, and coronary artery disease (CAD). CAD was defined by occurrence of angina pectoralis, MI, coronary insufficiency, or death from coronary heart disease. Criteria for these end points have been described previously.3,5,6

Statistical Methods
We used the technique of pooled repeated measures, an approach that allows individuals to contribute multiple person observations to the analysis as long as they meet the inclusion criteria at the beginning of each observation interval.3,5,6 Specifically, persons free of the specific cardiovascular disease at an examination were eligible for the next period of observation for that incident event. For example, patients who had not experienced MI during the first period of observation were included in the screening during the second observation interval for incident MI. Because the BP status varies over time, the pooled repeated measures method was used to account for time-dependent covariates. The technique is a generalized person-years approach in that it treats each observation interval (of equal length) as a mini–follow-up study in which the current risk factor measurements are used to predict an event in the specified interval. Observations over multiple intervals are pooled into a single sample to predict the intermediate-term risk of an event.

Cox proportional hazards regression analyses were performed to examine the association of BP measures with the incidence of a first ABI, all strokes, MI, and CAD over a follow-up period of 10 years after adjusting for established risk factors defined at the baseline examination (age, gender, cigarette smoking, obesity, hypercholesterolemia, diabetes mellitus, and study period) and interaction between BP measures and baseline covariates. Hypercholesterolemia was defined by serum cholesterol concentration >200 mg/dL. Kaplan–Meier analysis was performed to estimate the risk of developing hypertension among persons with normal BP or prehypertension at baseline evaluation during the 50-year follow-up period. We determined the population-attributable risk (PAR) for prehypertension. PAR% expresses the proportion of disease (such as MI or ischemic stroke) in the study population that is attributable to the exposure (prehypertension) and could be eliminated if the exposure was eliminated. The PAR% was calculated as PAR% = (Pe)(RR−1)/(Pe)(RR−1)+1×100, where Pe is the proportion of the population exposed to the risk factor (prehypertension), and RR indicates relative risk (multivariate adjusted). We also determined the effect of age (<45 years, between 45 and 64 years, and ≥65 years), gender, cigarette smoking, obesity, hypercholesterolemia, and diabetes mellitus among prehypertensive person observations on the risk of developing events of interest.

Results
Baseline Characteristics of Participants
Ten persons with previous history of ABI and 18 persons with history of MI at baseline evaluation were excluded from analysis. A total of 5181 persons were included in the analysis. The mean age (±SD) was 44.0±8.6 years; 2314 (45%) were men. The participants were followed for a period of 31±13 years. The baseline demographic and clinical characteristics of participants according to BP status are provided in Table 1.

Risk of Developing Hypertension
The Figure demonstrates the cumulative risk of developing hypertension over the duration of the follow-up period for prehypertensive and normotensive participants. The risk of developing hypertension over time was significantly higher for persons with prehypertension (RR, 2.0; 95% CI, 1.9 to 2.2) compared with normotensive participants. To adjust for change in BP status over time, the data were converted into person observations.

Prehypertension and Risk of ABI and All Strokes
A total of 11 116 person observations with a mean follow-up period of 9.9±1.0 years were categorized as hypertensive (n=5712), prehypertensive (n=4163), and normotensive (n=1241). The observed events rate for ABI was 24 (0.6%) and 207 (3.6%) for prehypertensive and hypertensive person observations, respectively. After adjusting for potential confounders, prehypertension was not associated with an increased risk for ABI (RR, 2.2; 95% CI, 0.5 to 9.3; Table 2). The risk of all strokes was not higher among person with

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**TABLE 1. Baseline Demographic and Clinical Characteristics of the Participants in the Framingham Study**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hypertension (n=2042)</th>
<th>Prehypertension (n=2127)</th>
<th>Normotension (n=1012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years± SD</td>
<td>47.4±8.2*</td>
<td>42.9±8.2*</td>
<td>39.6±7.4</td>
</tr>
<tr>
<td>Men</td>
<td>997 (49%)</td>
<td>997 (47%)</td>
<td>320 (32%)</td>
</tr>
<tr>
<td>Women</td>
<td>1045 (51%)*</td>
<td>1130 (53%)*</td>
<td>692 (68%)</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg± SD</td>
<td>155±20*</td>
<td>128±6*</td>
<td>112±6</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg± SD</td>
<td>95±10*</td>
<td>80±5*</td>
<td>72±5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.2±4.7*</td>
<td>25.7±3.6*</td>
<td>24.0±3.0</td>
</tr>
<tr>
<td>Obesity, body mass index ≥30</td>
<td>597 (29%)*</td>
<td>321 (15%)*</td>
<td>35 (4%)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>1057 (52%)*</td>
<td>1291 (61%)*</td>
<td>621 (61%)</td>
</tr>
<tr>
<td>Previous cigarette smoker</td>
<td>136 (7%)*</td>
<td>115 (5%)*</td>
<td>52 (5%)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>849 (42%)</td>
<td>721 (34%)</td>
<td>339 (33%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>64 (3%)*</td>
<td>24 (1%)*</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL±SD</td>
<td>232±47*</td>
<td>217±43*</td>
<td>205±41</td>
</tr>
</tbody>
</table>

Means and frequencies are compared using ANOVA and χ2 methods, respectively.

*P value of <0.05 for comparison with normotensive participants.
prehypertension (RR, 2.3; 95% CI, 0.8 to 6.3) compared with normotensive persons. Hypertension was associated with an increased risk of ABI and all strokes. Prehypertension was not associated with ABI or all strokes in men or women when the analysis was performed separately by gender.

Prehypertension and Risk of MI and CAD

A total of 11,802 person observations with a mean follow-up period of 9.7 ± 1.5 years were categorized as hypertensive (n = 6292), prehypertensive (n = 4253), and normotensive (n = 1257). The observed events rate for MI was 138 (3.2%) and 647 (10.3%) for prehypertensive and hypertensive person observations, respectively. After adjusting for potential confounders, prehypertension was significantly associated with an increased risk for MI (RR, 3.5; 95% CI, 1.6 to 7.5). The risk of CAD was higher among persons with prehypertension (RR, 1.7; 95% CI, 1.2 to 2.4) compared with normotensive persons (Table 2). Hypertension was associated with an increased risk of MI and CAD. When the analysis was performed separately by gender, prehypertension was associated with MI (RR, 4.2; 95% CI, 1.6 to 12) and CAD (RR, 3.4; 95% CI, 2.0 to 5.6) in men but not in women.

PAR and High-Risk Strata for Prehypertension

The PAR associated with prehypertension was estimated to be 47% (95% CI, 18% to 70%) for MI and 20% (95% CI, 7% to 34%) for CADs. Among the 4219 prehypertensive person observations, the predictors of CADs were as follows: age 45 to 64 years (RR, 2.9; 95% CI, 2.0 to 4.3) and age ≥ 65 years (RR, 4.4; 95% CI, 2.6 to 7.5), men (RR, 2.5; 95% CI, 1.9 to 4.3), diabetes mellitus (RR, 2.1; 95% CI, 1.2 to 3.6), and hypercholesterolemia (RR, 1.5; 95% CI, 1.1 to 2.1). Other variables, including body mass index and cigarette smoking, were not associated with an increased risk for MI. We analyzed the effect of systolic and diastolic BP in participants with prehypertension. We found a relationship between higher systolic BP and increased risk of MI (RR, 1.02; 95% CI, 1.01 to 1.04) and ABI (RR, 1.05; 95% CI, 1.02 to 1.08). There was no relationship observed between higher diastolic BP and risk of MI or ABI.

Discussion

Salient Findings of the Study

We observed that persons classified as prehypertensive were more likely to develop hypertension over the 50-year follow-up period compared with those with normal BP. Therefore, we used the technique of pooled repeated measures to account for the variations in BP status over time. Our study demonstrates that prehypertension is associated with a higher risk of MI and CAD but not ischemic or all strokes. As expected, the risk of MI and CAD associated with prehypertension was lower than the risk observed with hypertension. We did not observe a relationship between prehypertension and risk of ABI. We observed a relationship between systolic BP and ABI in prehypertensive participants, consistent with previous studies,10,11 but not with diastolic BP. It is possible that the relationship between prehypertension and ABI is not observed because of the use of diastolic BP in defining this category. Because we included participant data up to elderly ages, it is possible that the contribution of hypertension to the risk of stroke diminished in the elderly cohort, as suggested in
Previous studies. Another potential explanation is the presence of insulin resistance among persons with borderline to mild hypertension. A study conducted in Japan evaluated the incidence of stroke and MI during a 7-year follow-up in 584 men with borderline to mild hypertension. A greater risk for MI but not stroke was observed and attributed to insulin resistance.

**Mild Elevation of BP and Cardiovascular Diseases**

Previous reports have suggested that mild BP elevations are associated with an increased thickness of the carotid intima and media, altered cardiac morphological features, and diastolic ventricular dysfunction. Vasan et al classified 6859 participants in the Framingham Heart Study who were initially free of hypertension and cardiovascular disease into optimal (systolic BP <120 mm Hg and diastolic BP <80 mm Hg), normal (systolic BP of 120 to 129 mm Hg or diastolic BP of 80 to 84 mm Hg), or high-normal (systolic BP of 130 to 139 mm Hg or diastolic BP of 85 to 89 mm Hg). An increased risk for death resulting from cardiovascular diseases, recognized MI, stroke, or congestive heart failure was observed among persons with high-normal BP compared with optimal BP. Lewington et al reported on 1 million adults with no previous vascular disease evaluated in 61 prospective observational studies of BP and mortality. During 12.7 million person years at risk, there was a direct association observed with vascular (and overall) mortality with elevated BP, even with BP >115/75 mm Hg.

**Population-Attributable Risk**

The public health impact of a risk factor depends not only on the magnitude of the RR but also on the prevalence of the risk factor in the population. Because PAR takes into account the strength of the association and the prevalence of the exposure, the effect of eliminating various risk factors can be compared. The PAR associated with prehypertension was 47% and 20% for MI and CAD, respectively. That implies that 47% of the MI in the population could be reduced by treatment of prehypertension. However, if the risk factors are clustered within individuals, PAR is an overestimate of the effect of a risk factor. Because cardiovascular risk factors do cluster within individuals, PAR may overestimate the effect of a single risk factor such as prehypertension.

**Risk Factors for Cardiovascular Disease in Prehypertensive Patients**

We observed that the risk of CAD with prehypertension was higher among persons aged 45 to 64 years and ≥65 years. Men had twice the risk compared with women. Investigators have suggested a higher threshold before initiating antihypertensive therapy for women because of the lower prevalence of cardiovascular events in middle-aged women compared with men. The adverse cardiovascular consequences of prehypertension were increased in the presence of diabetes mellitus and hypercholesterolemia. Recent studies have suggested a higher risk of cardiovascular events with mildly elevated diastolic BP among diabetics compared with nondiabetics with similar BP levels. The reason for increased susceptibility to cardiovascular events at relatively lower BPs among diabetics is not completely understood.

**Issues Related to Data Interpretation**

The prospective community-based large sample and the comprehensive longitudinal surveillance for cardiovascular events are strengths of the present study. The use of BP measurements as outpatient as opposed to ambulatory monitoring may inaccurately classify some patients as prehypertensive. We used an average of 3 measurements to provide a more accurate categorization of BP status. Because the study included data from ~5 decades of observation, we adjusted for the change in BP status over time by reclassifying the hypertension status in all patients every 10 years. The fact that our sample was predominantly white persons limits the generalizability of our findings. Additionally, some of the factors such as subfractions of cholesterol, sleep status, and physical activity were not adjusted in the model because pertinent data were not collected.

**Conclusions**

Our study suggests that prehypertension is a risk factor for MI and CAD. The PAR is high enough to evaluate the efficacy of antihypertensive treatment for prehypertensive patients in clinical trials, particularly in selected patients.


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