Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease in a Japanese Urban Cohort

The Suita Study

Yoshihiro Kokubo, Kei Kamide, Tomonori Okamura, Makoto Watanabe, Aya Higashiyama, Katsuyuki Kawanishi, Akira Okayama, Yuhei Kawano

Abstract—Few prospective studies have examined the association between high-normal blood pressure and cardiovascular disease (CVD) in Asia. We examined the impact of high-normal blood pressure on the incidence of CVD in a general urban population cohort in Japan. We studied 5494 Japanese individuals (ages 30 to 79 years without CVD at baseline) after completing a baseline survey who received follow-up through December 2005. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, we documented the incidence of 346 CVD events. The frequencies of high-normal blood pressure and hypertension Stage 1 and Stage 2 were 18.0%, 20.1%, and 10.1% for men and 15.9%, 15.6%, and 8.8% for women, respectively. Antihypertensive drug users were also classified into the baseline blood pressure categories. Compared with the optimal blood pressure group, the multivariable hazard ratios (95% confidence intervals) of CVD for normal and high-normal blood pressure and hypertension Stage 1 and Stage 2 were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) in men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) in women, respectively. The risks of myocardial infarction and stroke for each blood pressure category were similar to those of CVD. Population-attributable fractions of high-normal blood pressure and hypertension for CVD were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively. In conclusion, high-normal blood pressure is a risk factor for the incidence of stroke and myocardial infarction in a general urban population of Japanese men. (Hypertension. 2008; 52:652-659.)

Key Words: cardiovascular diseases ■ epidemiology ■ general population ■ high-normal blood pressure ■ myocardial infarction ■ prospective studies ■ stroke

Many cohort studies have demonstrated that hypertension is a strong risk factor for total mortality and cardiovascular disease (CVD)1–5 in both developing and developed countries.2,6,7 The guidelines of the Joint National Committee 7 from the United States has recently introduced a category, designated “prehypertension,” for people with blood pressures ranging from 120 to 139 mm Hg for systolic pressure or 80 to 89 mm Hg for diastolic pressure.8 The European Guidelines9 and Japanese Society of Hypertension Guidelines,10 however, divide this population into 2 groups: those with systolic blood pressures between 120 and 129 mm Hg or diastolic blood pressures between 80 and 84 mm Hg are classified as normal, whereas those with systolic blood pressures between 130 and 139 mm Hg or diastolic blood pressures between 85 and 89 mm Hg are classified as high-normal. Although the association of cardiovascular risk with elevated blood pressure is well accepted,1–4,6 only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. The Framingham Heart Study revealed an association of high-normal blood pressure with increased risk of CVD.11 The Framingham coronary heart disease prediction functions perform well for whites and blacks in different settings; these findings can be applied to other ethnic groups, like in the ARIC study, after recalibration for differing prevalence of risk factors for coronary heart disease events.12 Few studies have investigated the association between blood pressure category and the incidence of CVD in Japan,5,13 where there is a higher incidence of stroke and lower incidence of myocardial infarction (MI) than those in Western countries.7 We performed a prospective examination of the risk of stroke and MI in men and women according to blood pressure category comparing normal and high-normal blood pressures in a general urban Japanese population.

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Methods

Study Subjects
The Suita Study,3,14,15 an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 12,200 Japanese residents of Suita. As a baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6,485 men and women underwent regular health checkups between September 1989 and March 1994. Subjects have continued to visit the National Cardiovascular Center every 2 years since that time for regular health checkups.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n = 208), were missing data (n = 170), attended health checkups after analyses if they had a past or present history of CVD at baseline checkups.

Of these, 6,485 men and women underwent regular health checkups between September 1989 and March 1994. Subjects have continued to visit the National Cardiovascular Center every 2 years since that time for regular health checkups.

Confirmation of Strokes and Myocardial Infarctions
Five hospitals in the Suita area were capable of performing CT scans and/or MRI, all of which were the major hospitals to which patients with acute stroke and those with MI were admitted. Medical records were reviewed by registered hospital or research physicians who were blinded to the baseline data. Stroke and MI events were registered if they occurred between the date on which the baseline health examination was performed and December 31, 2005. Strokes were defined according to the US National Survey of Stroke criteria,16 which require rapid onset neurological deficits lasting at least 24 hours or until death. For each stroke subtype (cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definitive diagnosis was established based on CT, MRI or autopsy. Definitive and probable MIs were defined according to the criteria set by the MONICA project,17 which requires electrocardiographic evidence, cardiac enzyme elevations, and/or autopsy. Sudden death was defined as death of unknown origin occurred within 24 hours from onset.

To complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates without registration of CVD incidence, which were defined as probable stroke or MI. CVD was defined as stroke and MI in this study.

End Point Determination
The end points of the current follow-up study were (1) date of the first MI or stroke event; (2) date of death; (3) date of leaving Suita; and (4) December 31, 2005 (censored). To detect MI and stroke occurrences, each participant’s health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. We also obtained informed consent to review in-hospital medical records for 86.2% participants who were suspected to have signs or symptoms related to stroke or MI events.

Statistical Analysis
Analysis of variance and χ² tests were used to compare the mean values and frequencies by sex according to blood pressure category. For each subject, person-years of follow-up were calculated from the date of baseline survey, to the first end point, CVD event, death, emigration, or December 31, 2005. The Cox proportional hazard ratios (HRs) were fit for each blood pressure category after adjusting for age and other potential confounding factors, including age, present illness of hypercholesterolemia or diabetes, smoking status (nonsmoker, past smoker, and current smoker), and drinking status (nondrinker, past drinker, and current drinker) at baseline survey.

To express the impact of blood pressure categories on CVD occurrence in the participants, we estimated the population-attributable fraction (%). Population-attributable fraction was estimated as Pe × (HR – 1)/HR, in which Pe is the proportion of incident cases in the blood pressure category and HR is the multiple-adjusted hazard ratio.18 All statistical analyses were conducted using SAS statistical package software (release version 8.2; SAS Institute Inc, Cary, NC).

Results
At baseline, we observed several differences in the distribution of CVD risk factors according to blood pressure categories (Table 1). The percentages of subjects with optimal, normal, and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively. On average, both men and women with higher blood pressure were older and had higher serum total cholesterol levels, higher body mass index, and higher incidences of hyperlipidemia and diabetes than those with optimal blood pressure. The percentages of antihypertensive drug users classified as having hypertension Stages 1 and ≥2 at baseline were 21.3% and 37.7% for men and 24.2% and 40.6% for women, respectively.
During an average 11.7-year follow-up period, we documented 213 strokes (155 definitive strokes and 58 probable strokes) consisting of 141 cerebral infarctions, 32 intracerebral hemorrhages, and 18 unclassified strokes. We also documented 133 MIs (64 definitive MIs and 69 probable MIs or sudden cardiac deaths). Subjects who moved from Suita (16.8% of the total participants) were censored at that time.

We determined the age- and multivariable-adjusted hazard ratios for CVD, MI, and stroke according to blood pressure categories in the presence or absence of antihypertensive medication (Table 2). In men, the multivariable HRs (95% CIs) of CVD incidence were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) for men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) for women with the normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 groups, respectively. The risks of MI and stroke for each blood pressure category were similar to the risk of CVD.

In a combined analysis of men and women, the multivariable HR of CVD incidence was 1.62 (1.08 to 2.43), 2.08 (1.42 to 3.05), 2.06 (1.42 to 2.98), and 3.53 (2.43 to 5.13) for the normal and high-normal blood pressure and hypertension Stages 1 and ≥2 groups, respectively (data not shown). In addition, the multivariable HR of CVD incidence in men and women younger than 60 years old were similar to those seen in men and women older than 60 years of age (data not shown).

In a second analysis in which all antihypertensive drug users were categorized to the Stage ≥1 group, we determined the age- and multivariable-adjusted HRs for CVD, MI, and stroke according to blood pressure category (Table 3). In men, the multivariable HRs (95% CIs) of CVD incidence were 1.83 (1.05 to 3.20), 2.11 (1.22 to 3.64), and 3.20 (2.01 to 5.01) for men with the normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 groups, respectively.
to 5.09) for normal and high-normal blood pressure subjects without antihypertensive medication and subjects with hypertension Stage ≥1 with or without antihypertensive medication, respectively. In women, the multivariable HR of CVD incidence was 2.13 (1.25 to 3.62) for the hypertension Stage 1 group with or without antihypertensive medications. The risks of MI and stroke for high-normal blood pressure and hypertension Stage 1 group were observed in men (HR = 2.32, 95% CI: 1.02 to 5.27 and HR = 3.35, 95% CI: 1.64 to 6.80 for MI; HR = 2.04, 95% CI: 1.00 to 4.22 and HR = 3.33, 95% CI: 1.80 to 6.15 for stroke, respectively). HRs for CVD according to prehypertensive category excluding subjects taking antihypertensive drugs (Table 3) were similar but slightly lower than that category including subjects taking antihypertensive drugs (Table 2).

Using the HRs, we estimated the positive fraction of CVD attributable to exposure for each blood pressure category at baseline by sex (Figure). For men, 8.3%, 12.2%, 16.8%, and 18.5% of CVD incidence were excessive incidence due to normal and high-normal blood pressures and hypertension Stages 1 and 2 with values of 1.3%, 7.1%, 5.4%, and 18.0%.

Discussion

In this cohort study of a general Japanese urban population, we determined that high-normal blood pressure was a risk factor for the incidence of stroke and MI in men in comparison to subjects with optimal blood pressure. In this study, 20.5% and 8.4% of CVD incidence may derive from prehypertension cases in men and women, respectively. This is the
first cohort study to examine the impact of high-normal blood pressure on the risks of stroke and MI incidence in a general Japanese urban population, who have a relatively higher incidence of stroke and lower incidence of MI than those seen in Western countries.\textsuperscript{7}

Compared with the previous studies, this study has several methodological strengths. First, we evaluated a large prospective cohort of people selected randomly from a general population in Japan, which allowed us to perform subanalyses by age and CVD subtype. Second, our cohort population was selected from an urban population in contrast to the majority of other cohorts in Japan, which have been selected from rural populations. Because approximately 66\% of the Japanese population lives in urban areas, this is an important strength of our analysis. The health status of each participant was examined every 2 years during a clinical visit at the National Cardiovascular Center. In addition, a health questionnaire was administered to each participant yearly by mail or telephone. In combination with frequent evaluation of the CVD registry, we could effectively examine the incidence of CVD events in this population. Finally, we examined the risk of CVD incidence, which is a more direct measure of CVD risk than risk of CVD mortality, because mortality from CVD is significantly influenced by treatment.

This study revealed that normal and high-normal blood pressures were risk factors for CVD in Japanese urban men. The results of a multiple ethnic groups investigation has demonstrated that high-normal blood pressure is a risk factor for incidence of coronary heart disease in both men and women.\textsuperscript{11} Compared with optimal blood pressure, the relative risk of CVD was 2.33 (1.85 to 2.92) for high-normal blood pressure and was 1.81 (1.47 to 2.22) for normal blood pressure among blacks.\textsuperscript{19} An inverse association of optimal blood pressure and a positive association of Stage 1 hyper-

### Table 3. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category

|                  | Optimal | Normal | High-Normal | Stage $\geq 1$
<table>
<thead>
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</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Person-years</td>
<td>9670</td>
<td>5662</td>
<td>4805</td>
<td>9243</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>23</td>
<td>28</td>
<td>35</td>
<td>123</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1</td>
<td>1.80 (1.03--3.13)</td>
<td>2.09 (1.23--3.55)</td>
<td>3.00 (1.91--4.72)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1</td>
<td>1.83 (1.05--3.20)</td>
<td>2.11 (1.22--3.64)</td>
<td>3.20 (2.01--5.09)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>10</td>
<td>11</td>
<td>16</td>
<td>51</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1</td>
<td>1.71 (0.72--4.03)</td>
<td>2.27 (1.02--5.03)</td>
<td>2.98 (1.49--5.93)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1</td>
<td>1.78 (0.75--4.22)</td>
<td>2.32 (1.02--5.27)</td>
<td>3.35 (1.64--6.80)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Case</td>
<td>13</td>
<td>17</td>
<td>19</td>
<td>72</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1</td>
<td>1.93 (0.93--3.98)</td>
<td>2.01 (1.00--4.08)</td>
<td>3.18 (1.75--5.79)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1</td>
<td>1.92 (0.92--3.97)</td>
<td>2.04 (1.00--4.22)</td>
<td>3.33 (1.80--6.15)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>15 293</td>
<td>5890</td>
<td>4834</td>
<td>9002</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>24</td>
<td>12</td>
<td>20</td>
<td>81</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1</td>
<td>0.80 (0.39--1.61)</td>
<td>1.28 (0.69--2.36)</td>
<td>2.12 (1.30--3.44)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1</td>
<td>0.86 (0.42--1.72)</td>
<td>1.32 (0.69--2.53)</td>
<td>2.13 (1.25--3.62)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>7</td>
<td>4</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1</td>
<td>0.91 (0.26--3.14)</td>
<td>1.38 (0.47--4.01)</td>
<td>2.23 (0.94--5.28)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1</td>
<td>1.17 (0.31--4.34)</td>
<td>1.83 (0.58--5.75)</td>
<td>2.97 (1.11--7.91)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>17</td>
<td>8</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1</td>
<td>0.76 (0.32--1.79)</td>
<td>1.22 (0.58--2.58)</td>
<td>2.12 (1.17--3.83)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1</td>
<td>0.77 (0.32--1.83)</td>
<td>1.11 (0.50--2.49)</td>
<td>1.89 (1.00--3.58)</td>
</tr>
</tbody>
</table>

*Optimal blood pressure was defined as systolic pressure $<120$ mm Hg and diastolic pressure $<80$ mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure $\geq160$ mm Hg or a diastolic pressure $\geq100$ mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified into the hypertension Stage $\geq1$ group.
tension with coronary heart disease were observed in men compared with normal blood pressure. The Framingham Heart Study revealed that 17.6% and 37.3% of subjects with baseline normal and high-normal blood pressure, respectively, were diagnosed with hypertension within 4 years. High-normal blood pressure has also been associated with increased risk of carotid atherosclerosis, altered cardiac morphological features, and diastolic ventricular dysfunction, all of which may be precursors of incidence of CVD.

Some prospective studies have looked at mortality from CVD in Japanese populations. Murakami et al demonstrated a relationship between prehypertension and overall mortality by performing a meta-analysis of data from 13 population-based cohort studies conducted in Japan. Sairenchi et al revealed that high-normal blood pressure was associated with an increased risk of CVD mortality in Japanese men. The NIPPON DATA 80 also indicated that high blood pressure was a risk factor for mortality from all causes as well as death from CVD among Japanese. All of these studies used end points of mortality. The risk of CVD incidence, like used in this study, is a more direct measure of CVD risk than is the risk of CVD mortality, which is heavily influenced by treatment.

In prospective studies examining the incidence of CVD in Japanese populations, the Ohasama study demonstrated that high-normal blood pressure was a risk factor for stroke by using homed blood pressure, but not by using causal blood pressure. The Hisayama study, which observed the natural course of untreated hypertension in a general Japanese elderly population over a 32-year period, indicated that high-normal blood pressure was not a risk factor for cerebral infarction. This cohort was approximately half the size of our cohort, and the subjects were older and observed for longer periods of time. Hypertensive risk for CVD decreased with advancing age. Over very long periods, confounding factors, including advancing aging, menopause, lifestyle modifications, and medication, will affect blood pressure classification. The Tanno-Sobetu study determined that high-normal blood pressure, determined according to the 1999 World Health Organization/International Society of Hypertension criteria, was not a risk factor for CVD in comparison to optimal and normal blood pressures.

In this study, we did not find an association between high-normal blood pressure and CVD incidence in women. The association between blood pressure category and coronary heart disease is well documented to be weaker in women than in men. For each racial/ethnic group, the mean SBP and DBP values in men were 6 to 7 and 3 to 5 mm Hg higher, respectively, than the values in women. Postmenopausal effects have been associated with elevated blood pressure. Therefore, the period of hypertension exposure tends to be shorter in women than in men. The incidence of CVD was lower in women (3.9 per 1000 person-year) than in men (7.1 per 1000 person-years) in this study. The percentages of those with hypertension who were aware, treated, and controlled were higher for women than men. Because the frequency of white coat hypertension is higher in women than in men, blood pressure at baseline examination may be underestimated in women, which may result in the absence of an association between high-normal blood pressure and CVD incidence in women.

The multivariable HR of CVD incidence for normal blood pressure was 2-fold higher than that for optimal blood pressure. In the Honolulu heart program and the Puerto Rico heart health program, the multivariable HRs of CVD incidence for normal blood pressure were approximately 2-fold higher than those for optimal blood pressure. Thus, lower blood pressure appears to prevent the incidence of CVD.

The crude 10-year cumulative incidences of CVD in this subjects who had optimal, normal, and high-normal blood pressure were approximately 2%, 6%, and 8% for men and 2%, 3%, and 5% for women, respectively (data not shown). In the Framingham Heart Study, those were 5%, 8%, and 10% for men and 1%, 3%, and 6% for women, respectively. Compared with the Framingham Heart Study, the incidences of CVD for optimal blood pressure in the Suita study trend to be lower in men and similar in women.

Our study has several limitations. The primary limitation is a dilution bias; this study was based on a single-day measurement of blood pressure, which may lead to a misclassification of blood pressure levels. Previous epidemiological evidence has suggested, however, that blood pressure measurements taken on a single day are accurate. Second, approximately 10% of subjects who underwent baseline survey did not respond to our questionnaires thereafter. However, we found no clinical background difference be-
between participants and nonparticipants, because the main den- reason for participation in this study was not a health problem. Age- and sex-adjusted systolic blood pressures were 127 mm Hg for participants and 128 mm Hg for nonparticipants (P=0.08). To achieve a minimum of failure study subjects, we performed close follow-up with health question- naires annually and health checkups every 2 years.

In conclusion, high-normal blood pressure is a risk factor for MI and stroke in general Japanese urban men. Approximately 20% and 8% of CVD incidences can be attributed to normal and high-normal blood pressure in both men and women, respectively. To prevent the incidence of CVD, it is necessary for subjects with high-normal blood pressure to attempt to control these values through lifestyle modifications.

Perspectives
Although it is well accepted that hypertension is a strong risk factor for total mortality and CVD all over the world, only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. In this study, the impact of high-normal blood pressure on the incidence of CVD was examined in a general urban population cohort in Japan. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64,391 person-years of follow-up, 346 CVD events were identified. Compared with the optimal blood pressure group, the multivariable HR of CVD for high-normal blood pressure was 2.5 times in men but was not statistically significant in women. This might be due to a postmenopausal effect, higher frequency of controlled or medication for hypertension, and white coat hypertension in women compared with those in men, but it should be researched further whether these reasons can be applied in women. The risks of MI and stroke for each blood pressure category were similar to those of CVD. Approximately 20% and 8% of CVD incidences can be attributed to prehypertension in men and women, respectively. It is a remarkable finding that one fifth of CVD incidence is derived from prehypertension in men. Our results suggest that it is necessary for subjects with high-normal blood pressure to attempt to control blood pressure through lifestyle modifications to prevent the incidence of CVD.

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Disclosures
None.

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