High-Normal Blood Pressure and the Risk of Cardiovascular Disease

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The guidelines of the Joint National Committee 7 from the USA on hypertension have unified the normal and high-normal blood pressure categories into a single entity termed ‘prehypertension’. In contrast, the European Guidelines for the management of hypertension in 2007 considered ‘prehypertensive’ to be divided into normal and high-normal blood pressure. These patients with high-normal blood pressure or prehypertension might progress to hypertension over time. Previous studies have shown that high-normal blood pressure is a risk factor for cardiovascular disease (CVD) in Western countries and Japan. The combination of high-normal blood pressure and other cardiovascular risk factors increases the risks of CVD. Recently, metabolic syndrome has also been shown to be a risk factor for CVD. In Japan, the association between metabolic syndrome and CVD was also found to be significant. The risks for CVD incidence were similar among participants who had the same number of components, regardless of the presence of abdominal obesity. In the Japanese guidelines for the management of hypertension published in 2009, patients are considered to be in a high-risk group if they have diabetes, chronic kidney disease, 3 or more risk factors, target organ damage or CVD, even if they have only high-normal blood pressure, and appropriate antihypertensive therapy should be initiated. (Circ J 2009; 73: 1381–1385)

Key Words: Blood pressure category; Cardiovascular diseases; General population; Prospective studies; Risk factors

Hypertension is a strong risk factor for cardiovascular disease (CVD) worldwide1–3. Approximately, 50% in men and 30% in women with CVD incidence could be described as excessive incidence because of higher blood pressure (≥120/80 mmHg). A decline in the annual stroke incidence has been observed over a long period in the Framingham Heart Study, the Hisayama Study, and other cohorts4–7 in response to lowering blood pressure and decreasing the smoking rate.8 Recently, slightly elevated blood pressure has been found to be associated with the incidence of CVD.9,10 To prevent CVD, blood pressure should be kept as low as possible. The European Society of Hypertension and the European Society of Cardiology (ESH-ESC) guidelines for the management of arterial hypertension consider prehypertension to be categorized into ‘normal blood pressure’ (systolic blood pressure (SBP) 120 to 129 mmHg or diastolic blood pressure (DBP) 80 to 84 mmHg) and ‘high-normal blood pressure’ (SBP 130 to 139 mmHg or DBP 85 to 89 mmHg).10 In contrast, the guidelines of the Joint National Committee 7 from the USA (JNC 7) on hypertension have unified the normal and high-normal blood pressure categories into a single entity termed ‘prehypertension’.11 In this article, high-normal blood pressure is compared with prehypertension, and this category is reviewed as a risk factor for CVD.

High-Normal Blood Pressure and Prehypertension

In 2003, the JNC 7 on hypertension unified the normal and high-normal blood pressure categories into a single entity termed ‘prehypertension’.11 This change was based on evidence from the Framingham Heart Study that the chance of developing hypertension is higher in these ‘prehypertensive’ patients than in those with optimal blood pressure (<120/80 mmHg) at all ages.12,13 It has been estimated that 31% of the general adult population in USA16 falls into the prehypertensive category, as do 38% of men and 33% of women in a general urban Japanese population.

Previous studies have reported that individuals with high-normal blood pressure have a higher progression rate and risk of hypertension, compared with those with normal blood pressure.14,15 In 2007, the ESH-ESC Committee has decided not to use the term ‘prehypertension’ for the following reasons: (1) even in the Framingham Heart study, the risk of developing hypertension was definitely higher in patients with high-normal blood pressure than in those with normal blood pressure;9,14 (2) because of the serious meaning of the word hypertension for general populations, the term ‘prehypertension’ might create anxiety and lead to unnecessary consultations with a doctor; (3) this category is a highly differentiated one in practice, with the extremes consisting of patients in no need of any intervention as well as of those with a very high-risk profile such as diabetics, chronic kidney disease (CKD), or hyperlipidemia for whom drug treatment is required, although lifestyle changes recommended by the JNC 7 for all prehypertensive individuals can be a valuable population strategy.11
High-Normal Blood Pressure Progression to Hypertension

Optimal, normal, and high-normal blood pressure might progress to hypertension over time. In the Framingham Heart Study, the progression rates to hypertension over a 4-year period were 5%, 18%, and 37% for the younger age (aged 35 to 64 years) groups with optimal, normal, and high-normal blood pressure, respectively, and were 16%, 26%, and 50% for the older (aged 65 to 94 years) age groups with optimal, normal, and high-normal blood pressure, respectively. Clinical trial data from patients with high-normal blood pressure showed that 40% over 2 years and 63% over 4 years developed hypertension; this is consistent with the Framingham Heart study. There are several potential reasons for progression to hypertension in individuals with high-normal blood pressure relative to optimal and normal blood pressure groups. First, individuals with high-normal blood pressure require a smaller increment of blood pressure on follow-up to progress to hypertension than the other groups. Second, risk factors for hypertension are more common in the high-normal blood pressure group.

High-Normal Blood Pressure and Precursors of CVD

Elevated concentrations of C-reactive protein, tumor necrosis factor-α, homocysteine, oxidized low-density lipoprotein, gamma-glutamyltransferase, microalbuminuria, and other inflammatory markers are associated with higher blood pressure. High-normal blood pressure has been associated with increased carotid intima and media thickness, altered cardiac morphological features, and diastolic ventricular dysfunction; which might be precursors of cardiovascular events. The additive effect of more than 1 risk factor on the risk of CVD has been well established. Thus, high-normal blood pressure is considered to be associated with an increased risk of ischemic heart disease and stroke compared with optimal blood pressure.

High-Normal Blood Pressure and CVD in Caucasians

The Framingham Heart study has indicated that men and women with high-normal blood pressure have a more than 2-fold increase in relative risk for CVD compared with those who have optimal blood pressure. This finding was further confirmed by tests for trend (P for trend=0.01 for men and <0.001 for women). In analyses accounting for the blood pressure category during follow-up, the association of high-normal blood pressure with an increased risk of cardiovascular events persisted in men (hazard ratio=1.6, 95% confidence intervals: 1.1–2.3) but was attenuated in women (hazard ratio=1.8, 95% confidence intervals: 1.0–3.1).

Compared with optimal blood pressure, the hazard ratio of CVD is 2.3 (95% confidence intervals: 1.9–2.9) for high-normal blood pressure, and is 1.8 (95% confidence intervals: 1.5–2.2) for normal blood pressure among blacks. A positive association of normal blood pressure and stage I hypertension with coronary heart disease were observed in men, compared with optimal blood pressure. The Framingham Heart study showed that 17.6% and 37.3% of individuals 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 might be precursors of CVD.

High-Normal Blood Pressure and CVD in Japan

Of the prospective studies examining the incidence of CVD in Japanese populations, the Suita study showed that the risks of myocardial infarction and stroke for high-normal blood pressure and hypertension (Stage ≥1 group) were observed in men (hazard ratio=2.3, 95% confidence intervals: 1.0–5.3 and hazard ratio=3.4, 95% confidence intervals: 1.6–6.8 for myocardial infarction; hazard ratios=2.0, 95% confidence intervals: 1.0–4.2 and hazard ratios=3.3, 95% confidence intervals: 1.8–6.2 for stroke, respectively). The multivariable hazard ratio of CVD incidence in women was 2.1 (95% confidence intervals: 1.3–3.6) for the hypertension (Stage ≥1 groups). The Ohsama study showed that high-normal blood pressure is a risk factor for stroke by using home blood pressure rather than 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 is not a risk factor for cerebral infarction. This cohort was approximately half the size of the participants of the Suita study, and the patients were older and observed for longer periods.

Hypertensive risk for CVD decreased with advancing age. Over very long periods, confounding factors, including advancing age, menopause, lifestyle modifications, and medication, might affect the 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 (WHO/ISH) criteria, is not a risk factor for CVD in comparison to optimal and normal blood pressures, because of the small sample size.

Some prospective studies have looked at mortality from CVD in Japanese populations. Murakami et al have summarized a relationship between prehypertension and overall mortality by performing a meta-analysis of data from 13 population-based cohort studies conducted in Japan (176,389 participants). In this study, the interactions between age and SBP for all causes of mortality were statistically significant (P for interaction=0.01 for men and 0.02 for women). The primary prevention of high blood pressure for all-cause of mortality reduction has a greater benefit for younger than for older groups, although the absolute levels of all causes of mortality are lower for those who are younger. Sairenchi et al have showed that high-normal blood pressure is associated with an increased risk of CVD mortality in Japanese men. The NIPPON DATA 80 also indicate that high blood pressure is a risk factor for mortality from all-causes as well as death from CVD among Japanese. All of these studies have used endpoints of mortality. The risk of CVD incidence, as 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.

Recently, 2 larger cohort studies have been investigated in Japan. The Ohsaki study showed that hazard ratios (95% confidence interval) for CVD mortality for prehypertension and hypertension were 1.3 (0.6–2.9) and 3.0 (1.4–6.4) in the middle-aged group, and 1.0 (0.6–1.7) and 1.7 (1.0–2.6) in...
Table 1. Previous Criteria Proposed for the Definition of Metabolic Syndrome

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<tbody>
<tr>
<td>Insulin resistance</td>
<td>IGT, IFG, Type 2 DM, or lowered insulin sensitivity. Plus any 2 of the following 5 components</td>
<td>Any 3 of the following 5 components</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Obesity</td>
<td>WHR &gt;0.9 for men and &gt;0.85 and/or BMI &gt;30 kg/m²</td>
<td>WC ≥102 cm in men or ≥88 cm in women</td>
<td>Increased WC, population-specific. Plus any 2 of the following</td>
<td>WC ≥25 cm in men or ≥20 cm in women. Plus any 2 of the following</td>
</tr>
<tr>
<td>Lipids</td>
<td>TG ≥150 mg/dl and/or HDL &lt;35 mg/dl in men or &lt;35 mg/dl in women</td>
<td>TG ≥150 mg/dl and/or HDL &lt;40 mg/dl in men or &lt;50 mg/dl in women</td>
<td>TG ≥150 mg/dl and/or HDL &lt;40 mg/dl</td>
<td>TG ≥150 mg/dl and/or HDL &lt;40 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥140/90 mmHg</td>
<td>≥130/85 mmHg</td>
<td>≥130/85 mmHg</td>
<td>≥130/85 mmHg</td>
</tr>
<tr>
<td>Glucose</td>
<td>IGT, IFG, or type 2 DM including diabetes</td>
<td>≥110 mg/dl*</td>
<td>≥100 mg/dl including diabetes</td>
<td>≥110 mg/dl including diabetes</td>
</tr>
<tr>
<td>Other</td>
<td>Microalbuminuria</td>
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IGT, impaired glucose intolerance; IFG, impaired fasting glucose; WC, waist circumference; BMI, body mass index; TG, triglycerides.

Subjects taking medication for hypertension, hyperlipidemia, or diabetes were included as having that component.

*The 2001 definition identified fasting plasma glucose of ≥110 mg/dl. This was modified in 2004 to be ≥100 mg/dl, in accordance with the American Diabetes Association’s updated definition of IFG.

Table 2. Stratification of Cardiovascular Risk in 4 Categories on the Basis of Blood Pressure Classification and Risk Strata

<table>
<thead>
<tr>
<th>Risk strata (risk factors other than blood pressure)</th>
<th>High-normal blood pressure</th>
<th>Grade I hypertension</th>
<th>Grade II hypertension</th>
<th>Grade II hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors</td>
<td>No additive risk</td>
<td>Low risk</td>
<td>Moderate risk</td>
<td>High risk</td>
</tr>
<tr>
<td>1 to 2 risk factors (other than diabetes) or metabolic syndrome</td>
<td>Moderate risk</td>
<td>Moderate risk</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>3 or more risk factors, diabetes, chronic kidney disease, target organ damage/cardiovascular disease)</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Combination of Higher Blood Pressure and Cardiovascular Risk factors

The combination of higher blood pressure and cardiovascular risk factors leads to an increased risk of CVD. Recently, metabolic syndrome, which involves a clustering of impaired glucose metabolism, abdominal fat accumulation, dyslipidemia (hypertriglyceridemia and hypo high-density lipoprotein cholesterol), and elevated blood pressure, has also been shown to be a risk factor for CVD. Metabolic syndrome has been defined in several ways by several groups (Table 1), including WHO, the European Group for the Study of Insulin Resistance, the American Association of Clinical Endocrinologists, and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII). However, these definitions are aimed primarily at Western countries. The International Diabetes Foundation (IDF) and the American Heart Association have recently introduced alternative definitions that can be applied worldwide. The Japanese Committee on the Criteria for metabolic syndrome has recently proposed a definition for metabolic syndrome. Under both the IDF and Japanese definitions, the presence of abdominal obesity is the essential component for a diagnosis of metabolic syndrome. Among the several definitions of metabolic syndrome, the definitions of higher blood pressure was 140/90 mmHg based on the World Health Organization criteria and 130/85 mmHg (high-normal blood pressure) based on the NCEP-ATPIII, IDF, and the Japanese criteria.

In a general urban Japanese population, the association between metabolic syndrome and CVD was found to be significant when the NCEP-ATPIII definition is applied. Metabolic syndrome based on the Japanese criteria was associated with CVD incidence in women, whereas in men, the association was found only in those under 60 years of age. In addition, the risks for CVD incidence were similar among participants who had the same number of components regardless of the presence of abdominal obesity. We have shown that the components of metabolic syndrome synergistically increase CVD risk. Abdominal obesity does not affect the association between the number of metabolic syndrome components and the risk for CVD incidence. The combination of risk factors per se is therefore more important than abdominal obesity for conferring risk.

The Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension published their guidelines in 2009. In these guidelines, patients are considered to belong to a high-risk group if they have diabetes mellitus, CKD, 3 or more risk factors, target organ damage or CVD, even those with high-normal blood pressure, and appropriate antihypertensive therapy must be initiated (Table 2).

In the Suita study, compared with the optimal blood pres-
ure participants without CKD, the normal blood pressure, high-normal blood pressure, and hypertensive participants without CKD showed increased risks of CVD and stroke; however, the impact of each blood pressure category on CVD and stroke was more evident in men with CKD.

Using data from 10 community-based cohort studies in Japan, the age- and sex-adjusted hazard ratios of CVD increased in a log-linear fashion with increasing blood pressure levels in the normal, prehypertension, stage 1 hypertension, and stage 2 hypertension groups in participants with a glomerular filtration rate (GFR) ≥60 ml·min⁻¹·1.73 m⁻² (hazard ratios = 1.0 [reference], 1.7 [95% confidence intervals: 1.2–2.4], 2.7 [1.9–3.7], and 3.4 [2.3–4.8]; P for trend <0.001) and in those with a GFR <60 ml·min⁻¹·1.73 m⁻² 1.0 [reference], 2.6 [0.91–7.55], 3.8 [1.3–10.7], and 5.2 [1.8–15.1]; P for trend 0.001).

### Conclusions

Normal and high-normal blood pressure might progress to hypertension over time. Previous studies have shown that high-normal blood pressure is a risk factor for ischemic heart disease and stroke in Western countries and Japan. The combination of high-normal blood pressure and cardiovascular risk factors, such as type 2 diabetes mellitus, CKD, and hyperlipidemia increase further the risk of CVD. Recently, metabolic syndrome has also been found to be a risk factor for CVD. In a general urban Japanese population, the risks for CVD incidence were similar among participants who had the same number of components with and without abdominal obesity. The Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension published their guidelines in 2009. In these guidelines, patients are considered to belong to a high-risk group if they have diabetes mellitus, CKD, 3 or more risk factors, target organ damage or CVD, even in those with high-normal blood pressure, and appropriate antihypertensive therapy should be initiated.

### Disclosures

None.

### References


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