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Prehypertension

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ABSTRACT

The Seventh Report of the Joint National Committee (JNC-7) introduced a new term "prehypertension" and it broadened the range of prehypertension to 120-139/80-89 mmHg. It is estimated that 31% of the US population and 29% of the Korean population have prehypertension. This condition is very prevalent and it's associated with other cardiovascular risk factors, especially obesity and diabetes. These people are at high risk for developing hypertension and subsequent cardiovascular events. Therefore, prehypertension has become a major public health concern, but the treatment standards have not yet been established. The JNC-7 report has recommended healthy lifestyles for all the people with prehypertension and it especially advocated drug treatment for the group of people with diabetes or chronic renal disease. This article reviews the prevalence of prehypertension, the risk and rate of progression to hypertension, the associated cardiovascular disease, the adverse cardiovascular events and the current status of treatment. **(Korean Circ J 2008;38:1-6)**

KEY WORDS: Blood pressure; Prehypertension; Prevalence.

Introduction

Prehypertension was introduced by the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) in 2003.[1)2)] Prehypertension is defined as blood pressure (BP) in the range of 120-139 mmHg (in systole) or 80-89 mmHg (in diastole), which was termed as 'normal blood pressure' or 'high-normal blood pressure' in the JNC-6 report (Table 1).[3)] The new term prehypertension was based on a number of epidemiological studies. Several studies have shown that BP increases with age, and in Framingham Heart Study, about 90% of those whose BP was normal at age 55 years ultimately developed hypertension in their lifetime.[4)] A meta-analysis of the individual data for one million adults in 61 prospective studies showed that the risk of cardiovascular disease (CVD) increased progressively from levels as low as 115/75 mmHg, and each increment of 20/10 mmHg is associated with more than a twofold difference in the stroke death rate and a twofold difference in the death rates from ischemic heart disease (IHD) and from other vascular causes.[5)] After this data was published, there is a need to alert those individuals with BPs above this level about their high cardiovascular risk. Therefore, the introduction of the new term prehypertension was appropriate and well-timed. Prehypertension focuses on a population who were previously called high-normal BP. The recent data has shown the prevalence of prehypertention and its progression rate to hypertension, its association with CVD risk factors and its relationship with the development of CVD. As shown by the well-established, linear relationship between both systolic and diastolic BP and the risk of cardiovascular events,[1)2)] prehypertension is associated with a cardiovascular risk that lies between normotension and hypertension. A 10 mmHg lower usual SBP or 5 mmHg lower usual would be associated with about 40% lower risk of stroke death and about 30% lower risk of death from IHD or other vascular causes throughout middle to old age. So, for the general normotensive population, producing persistent reductions in the average blood pressure of just a few mmHg should avoid large numbers of premature deaths and disabling strokes.[5)] We need to determine how best to prevent the progression to hypertension and how to decrease CVD risk. The treatment recommendations are still lifestyle modification. To introduce pharmacologic treatment into the present treatment paradigm is yet a new challenge. There is a continued need for early clinical detection and intervention for prehypertension and also comprehensive preventive measures and public health efforts.

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Table 1. Blood pressure classification

JNC-7	JNC-6	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	Optimal	<120	and	<80
Prehypertension		120-139	or	80-89
-	Normal	120-129	and	80-84
-	High-normal	130-139	or	85-89
Hypertension:	Hypertension:			
Stage 1	Stage 1	140-159	or	90-99
Stage 2		≥160	or	≥100
-	Stage 2	160-179	or	100-109
-	Stage 3	≥180	or	≥110

JNC: the joint national committee on the prevention, detection, evaluation and treatment of high blood pressure, BP: blood pressure

Prevalence

Many population-based surveys of the US and other countries have shown that prehypertension is common and even more prevalent than hypertension. The prevalence of prehypertension in the US is 31%, while hypertension and normotension are 29 and 39% respectively. Thus, 60% of US adults have prehypertension or hypertension.[6)7)] The age-adjusted prevalence of prehypertension was greater in men (39.0%) than in women (23.1%) and it was lower at older ages because of a higher prevalence of hypertension.[7)] Of note, the prevalence of prehypertension was increased in all demographic groups in the National Health and Nutrition Examination Survey (NHANES) 1999-2000 as compared with 1988-1994.[8)] In the 2005 Korean NHANES data,[9)] the prevalence of prehypertension in adults aged 30 years or over was 29.1% (37.4% in men and 21.2% in women), and this was almost the same as the US data. The age-adjusted overall prevalence of prehypertension among Chunchon city residents aged over 45 or over is 32% (34% in men and 32% in women).[10)] In the Keelung Community-based Integrated Screening study of Taiwan, the prevalence rates were 31.2% for prehypertension and 29.4% for hypertension and these values were similar to the figures from the 1999-2000 NHANES in the US, and they were also consistent with the recent estimates from around the globe.[11)]

Association with Cardiovascular Diseases and Subsequent Adverse Events

Progression to hypertension

Several studies have shown that individuals with prehypertension are at a greater risk for progression to hypertension than those individuals who are normotensive. The rate of progression of prehypertension to hypertension can be relatively rapid, and particularly for those individuals whose BPs lie in the upper prehypertensive range and for the elderly individuals. In the Framingham Heart Study, a stepwise increase in the incidence of hypertension occurred across the three non-hypertensive BP categories; 5.3% of the participants with optimum BP, 17.6% with normal, and 37.3% with high normal BP aged below age 65 years progressed to hypertension over 4 years. Corresponding rates for patients 65 years and older were 16.0%, 25.5% and 49.5%, respectively. Obesity and weight gain also contributed to progression; a 5% weight gain on follow-up was associated with 20-30% increased odds for hypertension.[12)] The data obtained from two British Health and Lifestyle Surveys conducted 7 years apart were used a subsample of 2,048 normotensive men and women. The estimated RR for the normal BP group was 2.0 and that for the high-normals was 2.9. In this result, prehypertension appears to especially effect the younger high-normals, but these estimates are more conservative than the Framingham-based estimates.[13)] In the TRial Of Preventing HYpertension (TROPHY) study, 40% of the prehypertensive individuals receiving a placebo developed hypertension over 2 years of follow-up. Because of these rates of progression, annual or biannual monitoring of BP in prehypertensive persons would seem appropriate.[14)] A community-based integrated screening program in Keelung, Taiwan is the largest study of this type.[11)] That study showed that prehypertension progresses or regresses and the adjusted progression rate for hypertension is age-dependent and progression to stage 1 hypertension was positively related to the male gender, a higher waist circumference and having parents with hypertension. In our data, the 3-year progression rate to hypertension among the prehypertensive local residents aged 45 or over is 56.4% (56.9% for the men and 55.9% for the women).[15)]

Cardiovascular risk factors

The CVD risk factors are more commonly associated with prehypertensive individuals than with normotensive individuals. The 1999 to 2000 NHANES data suggested that 64% of prehypertensive subjects have more than one CVD risk factor (94% for the persons 60 years or over). The people with prehypertension were 1.65 times more likely to have at least 1 other adverse risk factor than were those with normotension ($p<.001$).[7)] The risk ratios for obesity, dyslipidemia, insulin resistance, metabolic syndrome and diabetes are all greater in the prehypertensive subjects than those in the normotensive subjects and they are intermediate between those risk ratios for the subjects with normotension and hypertension.[16-19)] Obesity is often associated with prehypertension.[6)7)17)19)20)] Both general and abdominal obesity could be responsible for the risk of prehypertension.[16)] In several studies, a higher body mass index (BMI) was the strongest predictor of prehypertension.[17)20)21)] Prehypertensive individuals are more likely to have diabetes,[19)] impaired fasting glucose,[20)] me-

tabolic syndrome,[21] hypercholesterolemia,[7][21] raised levels of low density lipoprotein cholesterol (LDL cholesterol) and triglycerides[17][20] and reduced levels of high density lipoprotein cholesterol (HDL cholesterol)[17][20] than normotensive individuals. Risk factors such as C-reactive protein (from Greece,[22] and NHANES III 1988-1994[23]), serum tumor necrosis factor, interleukin 6, and tumor necrosis factor-[alpha],[22][23] amyloid A and homocysteine,[22] resistin and adiponectin[24] and oxidative stress[25] are also more common in people with prehypertension than in those people with normal BP.

Target organ damage

People with prehypertension also have greater degrees of target-organ damage than do the normotensive individuals. In the population-based Rotterdam study,[26] individuals with prehypertension had significantly smaller arteriolar and venular diameters and arteriolar-venular ratios and a greater intima-media thickness of the carotid artery than did those who had normal BP. Notably, these differences predicted the development of hypertension over a 6.6-year follow-up period. Furthermore, in a Korean study, microalbuminuria was significantly more common among subjects with prehypertension than among normotensive subjects (7.9% vs 4.0%, respectively), and the serum uric acid concentrations were higher in the prehypertensives than in the normotensive individuals with albuminuria.[27]

The incidence of cardiovascular disease, its risks and the subsequent events

Prehypertension is associated with an increased incidence of CVD, and particularly in those individuals with upper range prehypertensive BP levels and those individuals with diabetes or glucose intolerance.[19][28][29] The Framingham Heart Study[30] investigated the association between the blood-pressure category at baseline and the incidence of CVD on follow-up among 6859 participants who were initially free of hypertension and CVD. The 10-year cumulative incidence of CVD in the subjects with high-normal BP was 4% for women and 8% for men who were 35 to 64 years old, respectively; for the older subjects (65 to 90 years old), the incidence was 18% for women and 25% for men. As compared with optimal BP, high-normal BP was associated with a risk-factor-adjusted hazard ratio for CVD of 2.5 for women and 1.6 for men. The same conclusion was reached in a meta-analysis of 61 prospective observational studies.[5] In the Atherosclerosis Risk in Communities (ARIC) study[29] that analyzed 8960 middle-aged adults, the outcome was the incidence of CVD, which was defined as fatal/nonfatal coronary heart disease, cardiac procedure, silent myocardial infarction or ischemic stroke. Compared with optimal BP, the relative risk (RR) of CVD for high-normal blood pressure was 2.33 and the RR for normal BP was 1.81. The prehypertensives have an increased risk of developing CVD relative to those with optimal BP levels. The association is pronounced among blacks, diabetics and among those with high BMI and chronic kidney disease. The more recent data from a Swiss study of 22,927 men also showed higher all-cause and cardiovascular-related mortality in prehypertensives than in normotensives.[31] Several analyses of the Framingham Heart Study data have been carried out to identify the types of cardiovascular events that are associated with prehypertension. The original Framingham cohort[32] was also associated with an elevated risk of myocardial infarction (hazard ratio or HR: 3.5), coronary artery disease events (HR: 1.7), atherothrombotic brain infarction (HR: 2.2), and all stroke types (HR: 2.3) in the prehypertensives. The NHANES I Epidemiologic Follow-Up Study (NHEFS) and the NHANES II Mortality Study (1992) have also concluded that prehypertension significantly increases the risk for cardiovascular events. In the Strong Heart Study[19] there was a synergistic effect of prehypertension and diabetes on the occurrence of CVD events; the hazard ratios for CVD were 3.70 for those individuals with both prehypertension and diabetes, 1.80 for those individuals with prehypertension alone and 2.90 for those individuals with diabetes alone. Impaired glucose tolerance or impaired fasting glucose also greatly increased the CVD risk in prehypertensive people. Currently, the Women's Health Initiative[33] is the largest cohort that's reported an elevated risk of cardiovascular events among prehypertensives. Prehypertension is commonly associated with an increased risk of myocardial infarction, stroke, heart failure and cardiovascular death in white and nonwhite postmenopausal women. The Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study[34] enrolled a population-based 2,347 Danish nationals between 1982 and 1984, and the study determined the progression rate to hypertension until 1993-1994, and it followed the prognostic significance of progression until 2003. During 9.4 years, 218 first cardiovascular end points (cardiovascular death, nonfatal stroke and nonfatal coronary heart disease) occurred. The hazard ratios were 1.57 for progression to high-normal BP, 1.64 for progression to hypertension and 1.78 for sustained high-normal BP or hypertension. The absolute 10-year cardiovascular risks were 5.1% for optimal or normal BP without progression, 11.1% and 13.9% for progression to high-normal BP or hypertension, respectively, and 18.7% for sustained high-normal BP or hypertension.

Treatment of Prehypertension

The primary reasons to consider treating prehypertension are the substantial progression to hypertension and the association with increased CVD. Many studies have

shown the progression to hypertension. The current stage of prehypertension includes a broad range of blood pressure. This presents a challenge in defining a treatment paradigm for these individuals because the progression rates vary widely. Based on the Framingham and the TROPHY studies,[12)14)] the 4-year progression rate for those individuals with high-normal BP is approximately 40% (37.3-49.5%). This 4-year rate varies by age and the baseline BP level. Therefore, upper range prehypertensive patients (130-139/85-89 mmHg) have a high rate of progression over 4 years (40-63%), which may warrant a more aggressive approach than for those individuals in the lower range (120-129/80-84 mmHg). The Strong Heart Study,[19)] the ARIC Study[29)] and the Framingham Heart Study[30)] have shown that prehypertension is itself associated with higher cardiovascular risk. How best to manage prehypertension has been the subject of recent debate. At present, the JNC-7 report recommends that adoption of healthy lifestyles by all individuals is critical for the prevention of high BP and to decrease the BP and cardiovascular risk. Drug therapy is recommended for prehypertensives with diabetes or chronic kidney disease.

Lifestyle modifications

Lifestyle modifications are currently recommended to lower BP in those individuals with hypertension or those individuals who are at risk for hypertension.[1)2)36-38)] Major lifestyle modifications include weight reduction in those individuals who are overweight or obese,[21)] adoption of the Dietary Approaches to Stop Hypertension eating plan,[39)] dietary sodium reduction,[39-41)] physical activity[18)42)] and moderation of alcohol consumption.[43)] Nonpharmacological therapies have not prevented cardiovascular events in long-term clinical trials, but lifestyle modifications are necessary for the treatment and prevention of diabetes, dyslipidemia, obesity and other CVDs associated with prehypertension. Weight loss is likely to be the most effective lifestyle modification because of the high prevalence of being overweight and obese (34% and 31%, respectively, in the untreated prehypertensive subjects in the NHANES 1999-2000). In the Framingham study, the participants who successfully reduced their weight by 6.8 kg or more over a 4-year period decreased their risk of developing hypertension by 21-29%. In the Keelung study, the strongest age-independent predictor of regression from prehypertension to normotension was reduction of the BMI. The Dietary Approaches to Stop Hypertension (DASH) eating plan induced a significant lowering of BP, which was reduced even further when dietary sodium was restricted. The PREMIER trial studied the combined effects of lifestyle modification (diet, physical activity and weight reduction) and counseling intervention over an 18-month period.[21)] All the groups demonstrated significant reductions in BP in both the prehypertensive and hypertensive subjects, and even in the group that was given relatively minimal counseling. Although long-term maintenance of lifestyle modifications is admittedly difficult, many individuals modify their lifestyles successfully for long periods of time and the beneficial effects on BP seem to persist. In the Trial of Nonpharmacologic Intervention in the Elderly (TONE), BP reduction was maintained over 30 months without medication and without the occurrence of cardiovascular events in 44% of the 147 people randomized to both weight loss and sodium-intake restriction.[44)] Therefore, now is the time to plan improving patients' lifestyle and we should develop better ways to modify lifestyle and maintain the beneficial effects.

Drug therapies

All the hypertension guidelines now recommend drug therapy for the patients with diabetes and chronic kidney disease and who are in the prehypertensive range.[1)2)36-38)] Others advocate a lower-than-usual BP goal for people with established cardiovascular disease or those at high risk (e.g. African Americans). How about antihypertensive drug treatment for prehypertensive subjects in the absence of diabetes or chronic kidney disease? The TROPHY study is the first randomized, placebo controlled, double-blinded clinical trial of pharmacologic intervention for treating prehypertension.[14)] It was designed to study whether 2 years of treatment with the angiotensin receptor blocker (ARB) candesartan cilexetil at 16 mg daily prevents or delays the development of hypertension during treatment and for up to 2 years after discontinuing treatment in those subjects who are in the upper half of the JNC-7 stage of prehypertension (systolic blood pressure 130-139 mmHg or diastolic blood pressure 85-89 mmHg). 809 study participants were middle-aged (mean age: 49 years old), primarily Caucasian (80% white, 10% African American, 4% Asian and 3% other) and overweight (mean BMI of 29 kg/m^2), and approximately 60% of the subjects were male. Their mean BP was 134±4/85±4 mmHg. They had excess additional cardiovascular risk factors. 95% of them had at least one additional risk factor, 80% had two or more and 31% had four or more risk factors. The primary outcome of the trial was the development of hypertension or the development of target organ damage or diabetes. The results demonstrated that pharmacologic treatment can prevent or postpone the development of hypertension with a 66.3% reduction in the incidence of hypertension relative to placebo over the first 2 years (26.8% absolute reduction). Over all four years, including drug withdrawal of 2 years, there was a 15.6% reduction in the incidence of hypertension relative to placebo (9.8% absolute reduction). There was a net difference of 1.1 years of hypertension free time between the placebo (2.2 years, 95% CI 2.0-2.5) and candesartan groups (3.3 years, 95% CI 3.0-3.8). In addition, treatment

with 16 mg of candesartan cilexetil was not only safe but also well tolerated with a low report of side-effects which was not significantly different from the placebo group. Yet to translate the results of the TROPHY study into daily practice is another challenge because of the current high cost of the required medication, and candesartan did not significantly reduce cardiovascular disease events. Other drug therapy trials like the Program to Improve Life and Longevity (PILL) and the Aliskiren in Visceral Obesity at Risk Patients Out-comes Research (AVIATOR) are now ongoing. On-going research will probably identify which individuals with blood pressure in the prehypertensive range would benefit from drug treatment.

Conclusion

The number of people with prehypertension is substantial and this is increasing worldwide. The continuous relationship of blood pressure to cardiovascular outcomes and the high rate of progression from prehypertension to hypertension is the strongest support for a more aggressive approach to treat prehypertension. Of note, these people are at a high cardiovascular risk and they have other cardiovascular risk factors, they develop sustained hypertension and they eventually require pharmacological therapy to reduce their BP. How best to manage them is controversy. Intensive lifestyle modifications are certainly indicated under the current guideline, but the problem is large-scale implementation and the patients' long-term adherence. The TROPHY study confirmed that drugs (or specifically an angiotensin-receptor blocker) will safely lower BP, but there is still no definitive evidence as to whether drug therapy will significantly reduce cardiovascular disease events. Early treatment with an ARB is reasonable for prehypertensives who have excess cardiovascular risk, renal disease or diabetes.

Summary

Prehypertension is the term coined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, and this report defines prehypertension as persistent office blood pressures between 120-139/80-89 mmHg.

Prehypertensives are more likely to have other cardiovascular risk factors, they develop sustained hypertension and require pharmacological therapy to reduce their blood pressure, and they are at risk for cardiovascular event. Because of the high rates of progression, annual or biannual monitoring of BP would seem appropriate.

Lifestyle modifications, including weight loss, sodium restriction and dietary approaches, should be recommended to, and adopted by, all individuals with prehypertension or hypertension.

Although the feasibility of drug therapy for prehypertension has been shown, there is still no definitive evidence as to whether drug therapy will significantly reduce cardiovascular disease events. Yet drug treatment is reasonable for the prehypertensives who have excess cardiovascular risk, renal disease or diabetes.

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