Effect of Blood Pressure on Cardiovascular Diseases at 10-Year Follow-Up

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The American College of Cardiology/American Heart Association (ACC/AHA) recently published a Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. However, the data in other ethnic groups are not well known. We evaluated the prevalence and associated cardiovascular prognosis of Korean subjects with newly reclassified hypertension based on the 2017 ACC/AHA guideline. We analyzed data from the Korean Health and Genome Study (n = 10,038). Supine blood pressure (BP) was measured thrice following a standardized protocol and averaged. There was a significant linear relation between BP profiles and cardiovascular disease (CVD)/mortality. Hazard ratio for CVD increased above a systolic BP of 120 mm Hg. Systolic BP ≥130 mm Hg was significantly associated with increased risk of CVD, coronary heart disease, stroke, CVD death, and total deaths. There was a similar significant linear relation with diastolic BP categories between CVD risk and death. BP is associated with an increased risk of CVD or all-cause mortalities. Moreover, the new BP categories of the 2017 ACC/AHA guideline could be applicable for predicting CVD and death in Korean population. **(Am J Cardiol 2019;123:1654−1659)**

Hypertension is a common co-morbidity and is a major risk factor for death, cardiovascular disease (CVD) and disability worldwide, affecting more than one billion individuals and causing an estimated 9.4 million deaths every year.[1] The relation between blood pressure (BP) level and risk of CVD has been characterized as strong, independent, and significant.[2] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[3] has resulted in the revision of the target systolic BP to below 140 mm Hg according to the European Society of Hypertension-European Society of Cardiology, Joint National Committee VIII guidelines.[4,5] Most guidelines, even the latest one from European Society of Hypertension-European Society of Cardiology, uniformly recommend treating high BP to a systolic BP goal below 140 mm Hg.[5−7] Recently, the Systolic Blood Pressure Intervention Trial study[8] and a meta-analysis of BP lowering at different systolic BP levels were published.[1] Both studies found beneficial effects of antihypertensive treatment in patients already below current goals. Based on these results, the American College of Cardiology/American Heart Association (ACC/AHA) recently published more intensive high BP treatment guideline.[9] Little is known about the effect of these guideline changes in Asian population.[10,11] Therefore, we conducted this longitudinal cohort study to assess the baseline BP and risk of CVD or death from all-causes in a Korean cohort population according to the newly revised guideline.

Methods

The design and baseline characteristics of the Ansung-Ansan community-based cohort study were published elsewhere.[12] Briefly, the study is an ongoing prospective, biennial follow-up study that is part of the Korean Health and Genome Study (KHGS). It is a community-based epidemiological survey to investigate trends in diabetes mellitus and associated risk factors. The baseline examinations were carried out from 2001 to 2002, and biennial follow-up examinations were continued through 2012. As part of the biennial follow-up, researchers contacted all participants who did not attend the scheduled site visit by telephone or a door-to-door visit to encourage them to undergo follow-up examination. A total of 10,038 subjects aged 40−69 years (with the Ansung-Ansan cohort comprising 5,018 subjects from a farming community and 5,020 from an urban community, respectively) were enrolled in the KHGS. Throughout the study, the same trained researchers and instruments were used to collect data. Participants were asked to visit the clinics for comprehensive examination after an 8- to 12-hour overnight fast. Supine position BP measurement

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was performed before venipuncture in the examination. BP was measured in the right arm of supine position participants after at least a 5-minute rest using an appropriately sized cuff and a conventional mercury sphygmomanometer. BP results are mean values of triple measures of BPs. Time interval between BP measurements was at least 30 minutes. Fasting plasma glucose, lipid profiles, and insulin were measured in a central laboratory. The homeostatic model assessment of insulin resistance, which is a method used to quantify insulin resistance, was defined as [fasting insulin (μU/ml) × fasting glucose (mmol/L)] / 22.5. The co-morbidities and smoking status of participants were assessed by questionnaire. Current smokers were defined as those who had smoked at least 1 cigarette per day for at least the previous year. Serum bilirubin concentrations, aspartate aminotransferase, and alanine aminotransferase were measured by a Hitachi 747 automated analyzer. Informed written consent was obtained from all participants. The study protocol was approved by the ethics committee of the Korea Centers for Disease Control and the Institutional Review Board of the Ajou University School of Medicine.

Coronary heart disease (CHD) was defined as myocardial infarction confirmed by electrocardiogram and/or enzyme changes or any angina diagnosis that required intervention after confirmation of coronary artery stenosis by coronary angiography. Stroke included cerebral infarction, hemorrhagic stroke, transient ischemic attack, and vertebrobasilar insufficiency as demonstrated by diagnostic workups, such as, computed tomography, magnetic resonance imaging studies, and accompanying neurologic symptoms and/or signs. CVD was defined as the occurrence of CHD and/or stroke. Persons with medical events reported by the patient directly or found during routine follow-up examinations were asked to provide their medical records. Data on CVD events were also obtained from the reports of study participants. The CVD events reported by participants were corroborated by initial in-depth interviews, as well as interviews repeated at each biennial follow-up visit. We contacted all participants who did not appear for follow-up examinations by telephone or a home visit, and all deaths were reported by the families of participants by way of these methods of contact. At each contact, participants were asked about CVD events and all hospitalizations. Discharge summaries and diagnosis were obtained from all hospitalizations. Death due to CHD or stroke was defined as a CVD death. Information about the death of participants, including the date, place, and cause, was obtained through interviews with the families of participants and reference to death certificates. Initial data were obtained from 10,038 subjects who participated in the KHGS. Among these subjects, 2,057 were excluded for the following reasons: (1) previous history of CVD (n = 230), (2) lack of follow-up examinations after baseline examination (n = 908), (3) subjects already on BP-lowering drugs including thiazide diuretics, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers (n = 917), and (4) missing data (n = 2). After we applied the above exclusion criteria, a total of 7,981 subjects (male 3,906, female 4,075) were eligible for the study.

Statistical analyses were carried out using SPSS version 25.0 (IBM Co., New York). The results are expressed as subject number with percent (%) and mean with standard deviation for each of the characteristics of the study participants. Subjects were categorized into categories according to baseline diastolic and diastolic BP levels. One-way analysis of variance and Pearson's chi-square tests were used to analyze statistical differences in the characteristics of the study participants between groups. Trends between categorical variables were tested for statistical significance using chi-square tests for linear-by-linear association. The hazard ratios (HRs) for the association of BP with CVD events or death were estimated using a multivariable Cox proportional hazard model after adjusting for confounding variables. For all statistical analyses, a 2-sided $p < 0.05$ was considered statistically significant.

Results

We categorized subjects into systolic and diastolic BP categories (normal, elevated, and hypertension group) according to AHA guideline definition.[9] The prevalence of hypertension was 32.8% according to the 2017 ACC/AHA guideline in this study. The clinical and biochemical characteristics of subjects according to systolic BP categories are shown in Table 1**.** Positive relations were observed between the systolic BP categories and age, being male, body mass index, waist circumference, fasting serum glucose, HbA1c, systolic BP, diastolic BP, total cholesterol, triglycerides, and homeostatic model assessment of insulin resistance. Relation between systolic BP categories with high density lipoprotein cholesterol, low density lipoprotein cholesterol, and prevalence of being current smoker was statistically not significant.

During the follow-up period (mean follow-up of 9.8 years), 541 subjects developed CVD events (CHD 337 and stroke 217) and 359 deaths (among them 65 died from CVD). The prevalence of CVD, CVD deaths, and total deaths increased across the systolic BP categories. HR for CVD increased above the systolic BP level of 120 mm Hg. Systolic BP ≥130 mm Hg was associated with increased risk of CVD, CHD, stroke, CVD death, and total death even after adjusting for potential confounders, including age, gender, low density lipoprotein cholesterol, waist circumference, smoking, and fasting plasma glucose. Risk of CVD (HR 1.767, 95% confidence interval [CI] 1.307 to 2.388, $p < 0.05$), CHD (HR 1.807, 95% CI 1.244 to 2.625, $p < 0.05$), and total death (HR 1.817, 95% CI 1.265 to 2.609, $p < 0.05$) was still significant when additionally adjusted for diastolic BP (Table 2). There was a similar significant linear relation with diastolic BP categories and CVD risk and death. Unlike systolic BP, HR for CVD and stroke were more significant in the highest diastolic BP group than in the lowest group. However, all these statistical significances were lost when adjusted for systolic BP in the analysis (Table 3).

Discussion

The present study documents the potential clinical implications of the 2017 ACC/AHA hypertension guideline for Korean adult subjects. Systolic BP ≥130 mm Hg was significantly associated with increased risk of CVD, CHD, and total deaths. Patients classified as having hypertension by

Table 1
Baseline characteristics of the study population based on baseline systolic blood pressure

	Systolic blood pressure categories (mm Hg)			
Characteristics (n = 7,981)	<120 (n = 5,153)	120-129 (n = 1,369)	≥130 (n = 1,459)	p Value
Age (years)	49.64 ± 8.09	53.74 ± 8.81	56.64 ± 8.50*	<0.001
Men	2,461 (47.8%)	744 (54.3%)	701 (48.0%)	<0.001
BMI (kg/m^2)	24.12 ± 2.94	24.77 ± 3.15	24.92 ± 9.03*	<0.001
Waist circumference (cm)	80.80 ± 8.39	84.16 ± 8.25	84.92 ± 9.03*	<0.001
Fasting glucose (mg/dl)	87.14 ± 19.38	90.16 ± 23.77	91.41 ± 24.99*	<0.001
HbA1c (%)	5.68 ± 0.82	5.85 ± 0.96	5.92 ± 1.07*	<0.001
Systolic blood pressure (mm Hg)	105.68 ± 9.16	124.36 ± 2.94	142.66 ± 11.92*	<0.001
Diastolic blood pressure (mm Hg)	69.00 ± 8.36	79.62 ± 6.91	87.72 ± 9.38*	<0.001
Total cholesterol (mg/dl)	190.70 ± 34.61	195.17 ± 36.91	195.87 ± 38.08*	<0.001
Triglycerides (mg/dl)	146.60 ± 99.49	168.13 ± 104.92	176.22 ± 112.72*	<0.001
High density lipoprotein cholesterol (mg/dl)	46.47 ± 10.64	46.26 ± 10.94	46.90 ± 11.62	0.842
Low density lipoprotein cholesterol (mg/dl)	117.61 ± 33.77	119.04 ± 36.62	118.65 ± 38.91	0.261
Homeostasis model of assessment-insulin resistance	1.58 ± 1.07	1.79 ± 1.94	1.87 ± 1.38*	<0.001
Current smoker	1,375 (26.7%)	368 (26.95)	372 (25.6%)	0.661

Values are expressed as mean ± SD or number (%).
* Significantly different from the lowest systolic BP category group (p <0.05).

new guideline-faced risks of composite CVD and death over an average 9.8 years of follow-up.

The risk of CVD increases progressively as BP levels increase, with no apparent threshold beyond which one could safely classify individuals as normotensive or hypertensive.[13] A related issue is that BP is not a binary risk factor. Patients who have higher BP levels are more likely to suffer an event; however, a very large proportion of events will still occur in those with so-called prehypertension simply because it has been overlooked by physicians and the patients themselves.[14] In this regard, the lower systolic BP and diastolic BP levels (130 and 80 mm Hg,

Table 2
Risk of cardiovascular disease and death based on systolic blood pressure during follow-up

	Systolic blood pressure categories (mm Hg)		
n = 7,981	<120	120-129	≥130
Number of subjects	5,153	1,369	1,450
Cardiovascular disease (n = 541)	240 (4.7%)	119 (8.7%)	182 (12.5%)
Coronary heart disease (n = 337)	155 (3.0%)	71 (5.2%)	111 (7.6%)
Stroke (n = 217)	92 (1.8%)	48 (3.5%)	77 (5.3%)
Cardiovascular disease death (n = 65)	21 (0.4%)	14 (1.0%)	30 (2.1%)
Total death (n = 359)	158 (3.1%)	70 (5.1%)	131 (9.0%)
Adjusted hazard ratio (95% CI)			
Multivariate model 1			
Cardiovascular disease	1	1.468 (1.160-1.856)*	1.858 (1.500-2.302)*
Coronary heart disease	1	1.363 (1.016-1.830)*	1.756 (1.347-2.290)*
Stroke	1	1.455 (1.013-2.090)*	1.875 (1.354-2.595)*
Cardiovascular disease death	1	1.599 (0.803-3.185)	2.590 (1.445-4.644)*
Total death	1	1.086 (0.805-1.464)	1.663 (1.287-2.147)*
Multivariate model 2			
Cardiovascular disease	1	1.457 (1.145-1.855)*	1.659 (1.324-2.079)*
Coronary heart disease	1	1.354 (1.001-1.830)*	1.541 (1.164-2.042)*
Stroke	1	1.440 (0.993-2.089)	1.749 (1.246-2.455)*
Cardiovascular disease death	1	1.592 (0.779-3.257)	2.111 (1.126-3.957)*
Total death	1	1.102 (0.805-1.509)	1.573 (1.196-2.069)*
Multivariate model 3			
Cardiovascular disease	1	1.506 (1.157-1.959)*	1.767 (1.307-2.388)*
Coronary heart disease	1	1.472 (1.059-2.046)*	1.807 (1.244-2.625)*
Stroke	1	1.344 (0.900-2.009)	1.529 (0.971-2.408)
Cardiovascular disease death	1	1.449 (0.676-3.106)	1.743 (0.759-4.004)
Total death	1	1.187 (0.847-1.664)	1.817 (1.265-2.609)*

Data are expressed as number of patients (%) or hazard ratio (95% confidence interval) of patients (%).
Model 1: adjusted for age and gender. Model 2: adjusted for age, gender, low density lipoprotein cholesterol, waist circumference, smoking and fasting plasma glucose. Model 3: adjusted for age, gender, low density lipoprotein cholesterol, waist circumference, smoking, fasting plasma glucose and diastolic BP.
* p <0.05.

Table 3
Risk of cardiovascular disease and death based on diastolic blood pressure during follow-up

	Diastolic blood pressure categories (mm Hg)		
n = 7,981	<80	80-89	≥90
Number of subjects	5,643	1,596	742
Cardiovascular disease (n = 541)	324 (5.7%)	138 (8.6%)	79 (10.6%)
Coronary heart disease (n = 337)	210 (3.7%)	84 (5.3%)	43 (5.8%)
Stroke (n = 217)	122 (2.2%)	56 (3.5%)	39 (5.3%)
Cardiovascular disease death (n = 65)	37 (0.7%)	17 (1.1%)	11 (1.5%)
Total death (n = 359)	223 (4.0%)	90 (5.6%)	46 (6.2%)
Adjusted hazard ratio (95% CI)			
Multivariate model 1			
Cardiovascular disease	1	1.299 (1.149-1.469)*	1.080 (1.069-1.091)*
Coronary heart disease	1	1.185 (1.014-1.385)*	1.071 (1.058-1.085)*
Stroke	1	1.441 (1.202-1.726)*	1.086 (1.069-1.103)*
Cardiovascular disease death	1	1.332 (0.957-1.854)	1.135 (1.098-1.173)*
Total death	1	1.125 (0.962-1.315)	1.123 (1.108-1.139)*
Multivariate model 2			
Cardiovascular disease	1	1.218 (0.977-1.519)	1.399 (1.055-1.856)*
Coronary heart disease	1	1.124 (0.854-1.479)	1.073 (0.741-1.553)
Stroke	1	1.305 (0.932-1.829)	1.991 (1.343-2.951)*
Cardiovascular disease death	1	1.297 (0.705-2.386)	1.476 (0.669-3.258)
Total death	1	1.070 (0.812-1.411)	1.186 (0.818-1.718)
Multivariate model 3			
Cardiovascular disease	1	1.030 (0.708-1.498)	1.044 (0.746-1.462)
Coronary heart disease	1	1.398 (0.865-2.262)	1.283 (0.829-1.984)
Stroke	1	0.692 (0.404-1.185)	0.768 (0.477-1.238)
Cardiovascular disease death	1	1.096 (0.392-3.070)	1.110 (0.441-2.794)
Total death	1	1.220 (0.757-1.966)	1.082 (0.698-1.677)

Data are expressed as number of patients (%) or hazard ratio (95% confidence interval) of patients (%).

Model 1: adjusted for age and gender. Model 2: adjusted for age, gender, low density lipoprotein cholesterol, waist circumference and fasting plasma glucose. Model 3: adjusted for age, gender, low density lipoprotein cholesterol, waist circumference, smoking, fasting plasma glucose and systolic BP.

* $p < 0.05$.

respectively) used to define hypertension in the 2017 ACC/AHA guideline was based on data from observational studies and clinical trials.[9] The recommendations also call for earlier treatment with lifestyle changes and, in some patients, with medications. Large observational studies demonstrated a graded association between higher BP and increased risk for CVD, end-stage renal disease, subclinical atherosclerosis, and all-cause death.[13,15] In this study, subjects categorized as the elevated BP group (120 to 129 mm Hg) were also shown to be at increased risk of CVD. Although many studies have reported an increased risk associated with a systolic/diastolic BP of 120 to 129/80 to 84 mm Hg versus <120/80 mm Hg, the association is substantially stronger for an systolic/diastolic BP of 130 to 139/85 to 89 mm Hg versus <120/80 mm Hg.[16−18] Therefore, the 2017 ACC/AHA guideline writing committee concluded that there is not enough evidence to support a recommendation for antihypertensive drug treatment in addition to non-pharmacological therapy for adults with prehypertension and low CVD risk.[9] However, the diagnosis of elevated BP (120 to 129 mm Hg) provides an opportunity for health care providers and patients to discuss the value of nonpharmacological therapy in lowering BP, to implement recommended lifestyle changes, and to emphasize that BP is a risk factor that can be controlled.[19] The robustness of systolic and diastolic BP as risk factors was reinforced by the clear relation of both BP profiles as continuous variables with CVD, independent of all other confounding variables. Prospective cohort studies also reported a continuous log-linear association between BP and vascular events to a BP of 115/75 mm Hg, with no apparent threshold.[13]

The development of effective pharmacological strategies for lowering BP was a major success story of the 20th century in medical science.[20] BP was proven beyond doubt to be causally and continuously related to future risk of CVD,[21] and lowering BP was proven to reduce that risk.[22] Clinical trials have shown that treatment of hypertension reduces the risk of CVD outcomes.[5] Randomized trials have shown that BP lowering can produce rapid reductions in vascular disease risk.[1] These studies also demonstrated that more intensive BP lowering resulted in additional risk reduction, with the benefits proportional to the size of the fall in pressure.[22,23] In the face of such impressive evidence, it is perhaps both surprising and disappointing that elevated BP today remains the leading cause of the global disease burden.[21] In addition, the clinical management of high BP remains less than adequate in most countries, rich or poor.[20] Recent global estimates suggest that less than half of those who have hypertension (defined as BP >140/90 mm Hg) are aware of it, and, of those who are receiving pharmacological treatment, only one-third have BP levels below 140/90 mm Hg.[24] In view of such profound shortcomings in the control of high BP and its associated CVD risks, it is important to reconsider the prevailing strategies for optimal management. However, the optimal target for systolic BP lowering is still uncertain; we could not verify it in this study.

Epidemiological studies have evaluated associations of systolic and diastolic BP with CVD outcomes including Asia Pacific region.[9,25] If just a single measurement of BP is to be used to predict risk then, irrespective of age, the measured systolic BP is slightly more informative than the measured diastolic BP, and the pulse pressure is much less informative.[26] In fact, as many clinical trials and population-based studies have shown, systolic BP is the prime causal factor of hypertension and its adverse cardiovascular sequelae.[27] In this study, systolic BP categories were more significant than those of diastolic BP in predicting CVD and total deaths. Moreover, diastolic BP categories were not significant risk factor for developing CVD or stroke when additionally adjusted for systolic BP.

The results should also be interpreted in the context of known and potential limitations. First, BP was measured at a single visit in KHGS. However, we measured BP of the subjects 3 times at intervals of at least 30 minutes to calculate the average of all readings. Second, misclassification of causes of death may have some effect on the observed associations. Last, we cannot say whether reducing BP is associated with reduced CVD risk or define a treatment target for hypertension management. Nevertheless, this study prospectively showed the effects of BP levels on CVD risk and deaths in a large community-based cohort.

Our study adds substantial evidence that BP is associated with an increased risk of CVD or all-cause deaths. Moreover, the new BP categories of the 2017 ACC/AHA guideline[9] could also be applicable for predicting CVD and deaths in the Korean subjects. In conclusion, screening BP using the new ACC/AHA guideline may help identify a greater number of patients who are at increased risk for death and therefore may foster better and earlier therapeutic decision-making to increase their life expectancy.

Disclosures

All authors have no conflict of interest to disclose.

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