Relation between the Updated Blood Pressure Classification according to the American College of Cardiology/American Heart Association Guidelines and Carotid Intima-Media Thickness

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American College of Cardiology/American Heart Association recently updated their guidelines for hypertension, and lowered the threshold of normal blood pressure (BP). However, the validity of the updated guidelines remains controversial. We investigated the relation between the revised BP classification and carotid intima-media thickness, using a community-based cohort. We examined 1,241 subjects who underwent health check-ups at our institute. They were divided into 3 groups based on their BP levels: normal blood pressure (sBP <130 mm Hg and dBP <80 mm Hg, n = 556); stage 1 hypertension (130 mm Hg ≤sBP <140 mm Hg or 80 mm Hg ≤ dBP <90 mm Hg, n = 236); and stage 2 hypertension (sBP ≥140 mm Hg or dBP ≥90 mm Hg, including subjects prescribed with antihypertensive medications, n = 449). With an increase in BP, increase in the mean age, proportion of males, and prevalence of CVD risk factors was seen. The prevalence of carotid plaque, defined as intima-media thickness ≥1.1 mm, also increased with increase in BP. After adjustment with covariates, higher BP was seen to be associated with carotid plaque presence. Atherosclerotic changes are present in stage 1 hypertension even in the healthy population, suggesting the importance of aggressive antihypertensive treatment based on the updated American College of Cardiology/American Heart Association guidelines. **(Am J Cardiol 2019;124:396−401)**

Hypertension is a major risk factor for cardiovascular disease (CVD)s.[1−4] The updated American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for hypertension lowered the threshold of normal blood pressure (BP) and defined stage 1 hypertension as 130 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic.[5] However, it is unknown whether this updated recommendation is applicable to the general population. Carotid intima-media thickness (IMT) is a well-known marker of atherosclerosis in the general population, and is a good predictor of CVD.[6−10] In this study, we aimed to clarify the relation between the new BP categories according to the updated ACC/AHA guidelines and IMT in the general population. The validity of updated guidelines for hypertension is still controversial; however, it might influence the clinical practice and guidelines for hypertension in other regions. Hence, it is critical to evaluate the validity of the updated ACC/AHA guidelines for hypertension in the general population at this timing.

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Methods

We examined 1,243 patients who underwent medical check-ups at the University of Tokyo Hospital, between August 2014 and May 2018. In Japan, there is a unique and popular health check-up examination system, so called "Ningen Dock", for the promotion of health care through voluntary medical examinations.[11,12] Subjects aged 18 years or previously mentioned and willing to participate in the study were considered eligible. We excluded 2 patients whose IMT data was unavailable, and included 1,241 subjects in this study. (Patient flowchart is shown in Figure 1.)

This study was approved by the Medical Ethics Committee of the University of Tokyo. We performed this study in accordance with the Declaration of Helsinki.

During the health check, the BP of each subject was measured once or twice after 10 to 15 minutes of rest, using a sphygmomanometer (UDEX-i; Canon Lifecare Solutions Inc Tokyo Japan). During the BP examination, the participant remained comfortably seated, with the arm at the level of the heart. We defined normal BP pressure as systolic blood pressure (SBP) <130 mm Hg and diastolic blood pressure (DBP) <80 mm Hg; stage 1 hypertension as 130 mm Hg ≤ SBP <140 mm Hg or 80 mm Hg ≤DBP <90 mm Hg; and stage 2 hypertension as SBP ≥140 mm Hg or DBP ≥90 mm Hg, including subjects prescribed with antihypertensive medications.

IMT was measured using a B-mode ultra-sound imager (Aplio 300 Toshiba, Tokyo, Japan). Bilateral carotid artery

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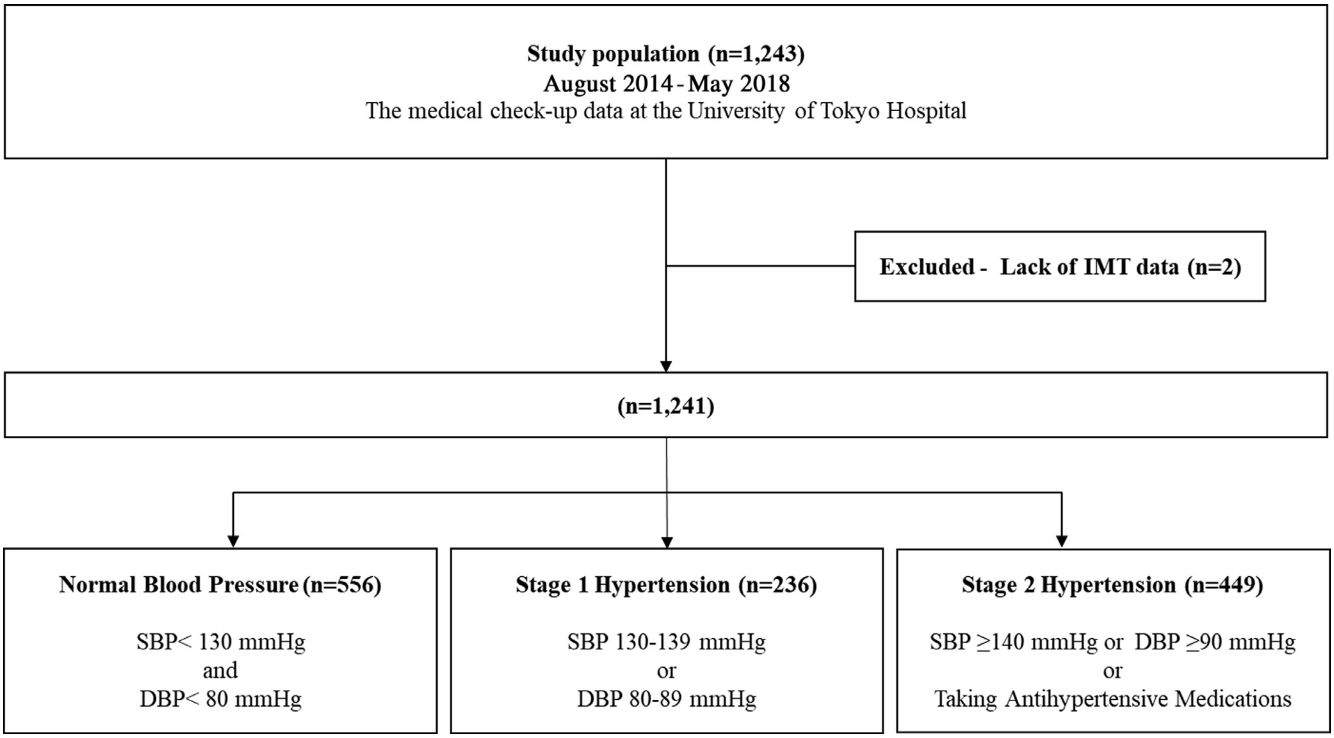

Figure 1. Patient flowchart.
DBP = diastolic blood pressure; IMT = intima-media thickness; SBP = systolic blood pressure. We excluded 2 patients whose IMT data was unavailable, and finally included 1,241 subjects in this study.

was examined with a 7.5 MHz probe. The diameter of the internal lumen was calculated by manual trace along the same length as the IMT, by averaging the distance between the near and far lumen−intima interfaces. The average of the right and left side measurements was used to calculate the IMT. We defined carotid plaque as IMT ≥1.1 mm as previously reported.[13]

We collected the information regarding the presence of cardiovascular risk factors including diabetes mellitus and hypercholesterolemia from medical records of each subject and self-administrated questionnaire. We assumed the presence of diabetes mellitus when they were on antidiabetic medications or with a fasting glucose of ≥126 mg/dL, and the presence of hypercholesterolemia when they were on antihyperlipidemic medications or with a total serum cholesterol >240 mg/dL. We defined obesity as body mass index ≥25 kg/m^2.

Study subjects were divided into 2 groups, based on age or gender. The association between the BP category and carotid plaque presence was assessed in each subgroup, according to age (< 60 years old, and ≥60 years old) and gender.

Categorical and consecutive data of the baseline characteristics are presented as number (%) and mean ± standard deviation, respectively. Chi-square analysis was used to compare the categorical variables. Consecutive data were compared by one-way analysis of variance, and the statistical significance of difference was calculated using the Tukey *t* test. Univariate logistic regression analysis was used to assess the association between the BP category and carotid plaque presence. Multivariable logistic regression analysis including parameters like age ≥60 years, male gender, obesity, diabetes mellitus, hypercholesterolemia (including subjects prescribed with statins), coronary artery disease, smoking, and BP category was performed to determine the independent predictors of carotid plaque presence. A probability value of <0.05 was considered to indicate statistical significance. We performed statistical analysis using SPSS (SPSS Inc., Chicago, IL) version 25 software.

Results

Baseline characteristics of the study subjects are summarized in Table 1. Out of 1,241 subjects, 236 subjects (19.0%) and 449 subjects (36.2%) were categorized in the stage 1 and stage 2 hypertension groups, respectively. Among the stage 2 hypertension group, 348 subjects (77.5%) patients were taking antihypertensive medications, percentage of male gender, and age increased with BP category. Classic CVD risk factors such as diabetes mellitus and hypercholesterolemia were common in subjects in the hypertension groups. The values of IMT and the prevalence of carotid plaque is shown in Figure 2. IMT increased as the BP category progressed from normal BP to stage 2 hypertension (Figure 2A). The prevalence of carotid plaque also increased with an increase in BP (Figure 2B). Univariate regression analysis showed the linear association between the BP category and prevalence of carotid plaque (Table 2). Multivariable logistic regression analysis demonstrated that BP category as well as age ≥60 years, male gender, obesity, body mass index ≥25 kg/m^2, and diabetes mellitus were independently associated with carotid plaque presence (Table 3). BP category was associated with the prevalence of carotid plaque presence in any subgroup

Table 1
Baseline clinical characteristics

Variable	Normal blood pressure (n = 556)	Stage 1 hypertension (n = 236)	Stage 2 hypertension (n = 449)	p Value
Age (year)	60.1 ± 12.0	62.3 ± 10.7	65.9 ± 11.1	<0.001
Age ≥60 years	305 (54.9%)	143 (60.6%)	325 (72.4%)	<0.001
Men	274 (49.3%)	142 (60.2%)	283 (63.0%)	<0.001
Body mass index (kg/m^2)	22.3 ± 3.0	23.7 ± 3.1	24.9 ± 4.0	<0.001
Obesity	99 (17.8%)	86 (36.4%)	199 (44.3%)	<0.001
Diabetes mellitus	36 (6.5%)	20 (8.5%)	76 (16.9%)	<0.001
Hypercholesterolemia	184 (33.1%)	79 (33.5%)	198 (44.1%)	0.001
Coronary artery disease	7 (1.3%)	4 (1.7%)	21 (4.7%)	0.002
Smoker	216 (38.8%)	88 (37.3%)	165 (36.7%)	0.780
Glucose (mg/dL)	96.2 ± 16.3	98.7 ± 13.4	105.5 ± 25.3	<0.001
HbA1c (%)	5.8 ± 0.5	5.8 ± 0.5	6.0 ± 0.7	<0.001
T-cholesterol (mg/dL)	208.3 ± 33.5	208.7 ± 35.8	199.2 ± 33.6	<0.001
LDL-C (mg/dL)	125.6 ± 29.4	128.6 ± 32.7	119.9 ± 30.0	0.001
HDL-C (mg/dL)	69.1 ± 19.3	63.4 ± 17.9	61.7 ± 16.9	<0.001
TG (mg/dL)	98.3 ± 71.9	117.4 ± 88.9	123.1 ± 82.6	<0.001

Data are expressed as mean ± standard deviation or number (percentage).
LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, Triglyceride.

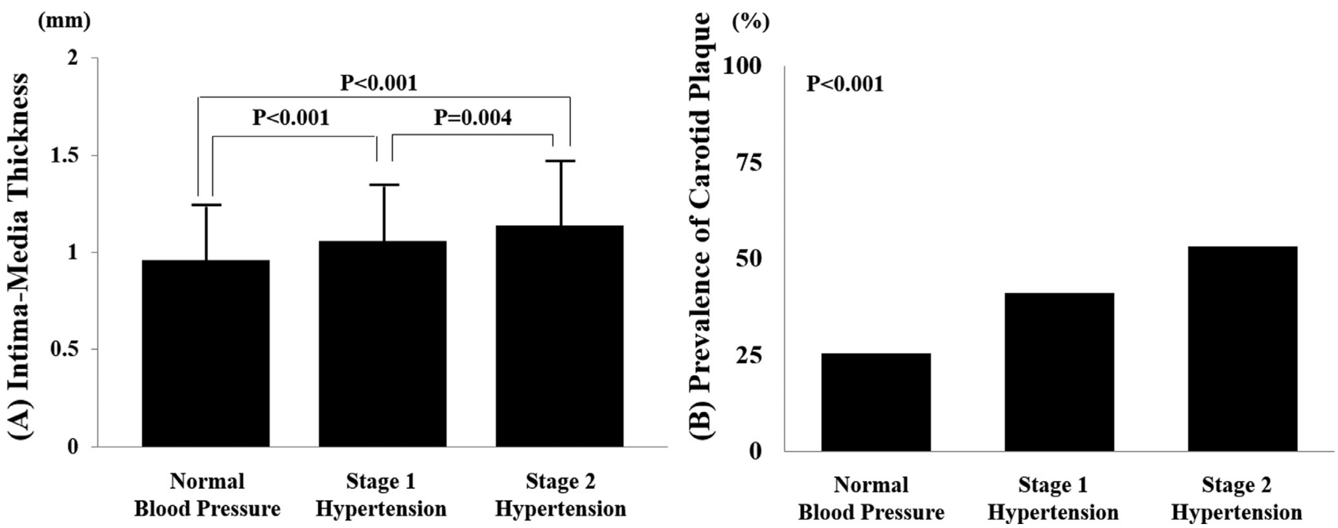

Figure 2. Intima-media thickness (A) and prevalence of carotid plaque (B).
IMT increased as the BP category progressed from normal BP to stage 2 hypertension. The prevalence of carotid plaque also increased with an increase in BP.

Table 2
Univariate analysis for carotid plaque

Variable	p value	Odds ratio	95% confidence interval
Blood pressure category			
Normal blood pressure		(reference)	
Stage 1 hypertension	< 0.001	2.054	1.488-2.834
Stage 2 hypertension	< 0.001	3.350	2.567-4.371

divided by age (<60 years old and ≥60 years old) or gender (Figure 3).

Discussion

Hypertension is a major healthcare concern due to its high prevalence and impact on mortality, disability, and CVD worldwide.[3,14,15] ACC/AHA recently updated the guidelines for hypertension, and lowered the threshold of hypertension. The major driver for lowering the threshold of hypertension was SPRINT (Systolic Blood Pressure Intervention Trial) which suggested the importance of strict BP control in patients at high risk of CVD.[16] However,

Table 3
Determinants of carotid plaque

Variable	p Value	Odds ratio	95% confidence interval
Age ≥60 years	<0.001	4.799	3.557−6.474
Men	<0.001	2.176	1.622−2.918
Obesity	0.007	1.485	1.114−1.978
Diabetes mellitus	0.008	1.753	1.161−2.646
Blood pressure			
Normal blood pressure		(reference)	
Stage 1 hypertension	0.001	1.795	1.266−2.549
Stage 2 hypertension	< 0.001	2.335	1.737−3.139

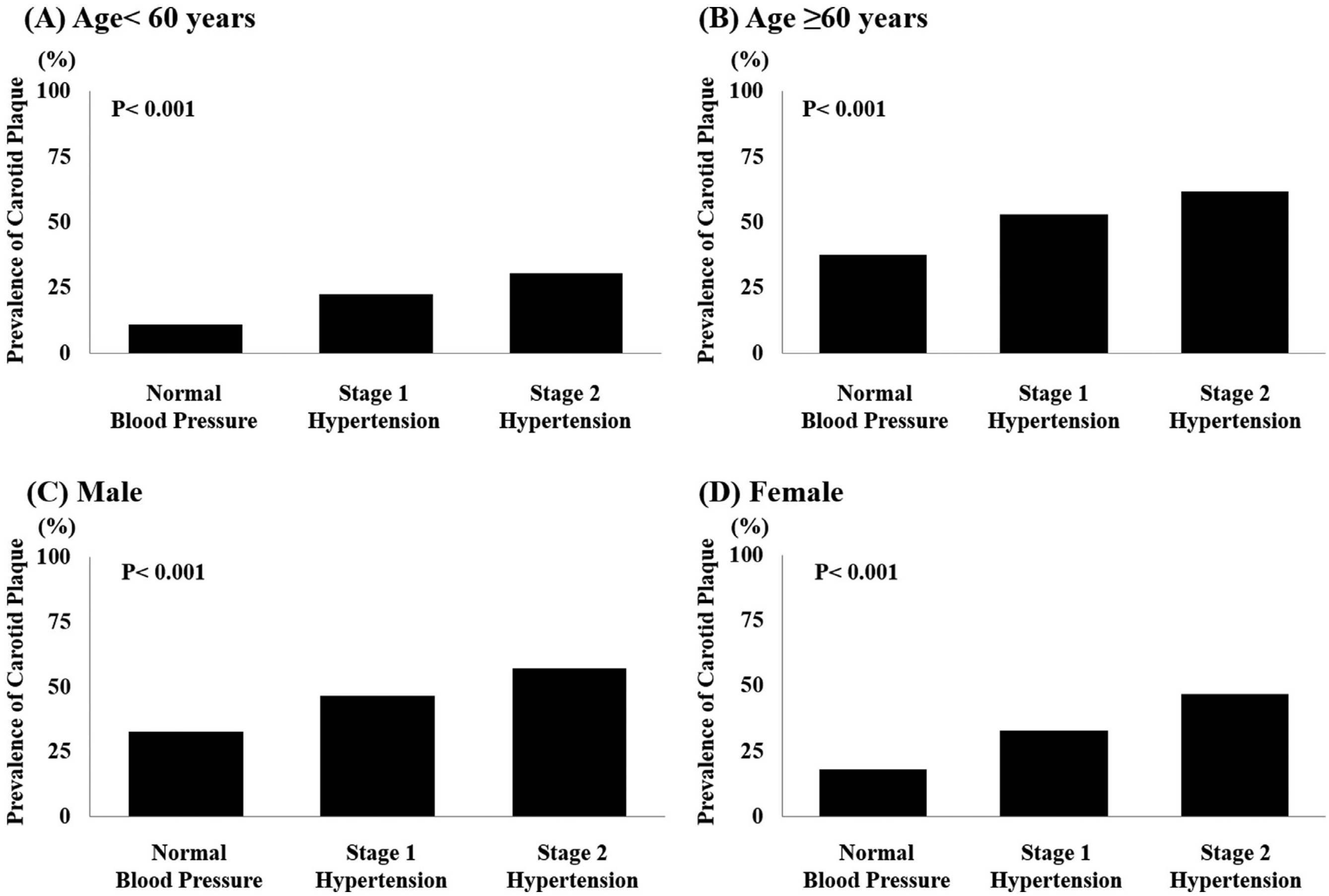

Figure 3. Prevalence of carotid plaque in subjects with age <60 years (A), ≥60 years (B), male gender (C), and female gender (D).
BP category was associated with the prevalence of carotid plaque presence in any subgroup divided by age (<60 years old, and ≥60 years old) or gender.

SPRINT included hypertensive patients at high risk for CVD, while the clinical benefit of aggressive pharmacological treatment for people at low-risk for CVD is not yet established. Furthermore, it remains unclear whether stage 1 hypertension is associated with an increased risk of CVD in low-risk subjects.

As a community-based cohort, we enrolled consecutive subjects who underwent medical check-ups, in this study. In comparison with other population-based cohort studies,[2,17−20] the prevalence of established CVD risk factors is equal or relatively low in this study. Thus, we believe that our study can provide an ideal snapshot of low-risk subjects. Since IMT is accepted as an indicator of early-phase atherosclerosis and future CVD events,[21−23] we believe that IMT is an useful tool for the assessment of atherosclerosis in the general population with low risk of CVD.

Our study demonstrated the linear association between the BP category based on the updated ACC/AHA guidelines and IMT. In line with previous studies, IMT was higher in patients with stage 2 hypertension (old definition of hypertension) compared to those with normal BP. Furthermore, IMT thickening was also observed in stage 1 hypertension. It is well known that IMT is higher in males and increases with age. However, the subgroup analysis showed that the increase in IMT showed a linear increase with increase in BP, irrespective of age and gender. To the best of our knowledge, this is the first study to demonstrate that early phase atherosclerosis, can develop during stage 1 hypertension in the general population. Our result might validate the updated ACC/AHA guidelines for the general population. Recently, 2 nationwide population-based studies concluded that stage 1 and stage 2 hypertension were associated with a higher risk for subsequent CVD events, compared to normal BP.[24,25] Considering the results of 2 nationwide studies and our study together, we speculate that stage 1 hypertension may accelerate atherogenesis, and result in future CVD events.

Among various risk factors for CVD, BP is one of the modifiable risk factors. Aggressive intervention using antihypertensive medications can decrease the CVD risk and prevent future clinical consequences. Additionally, judging from our present findings, the beneficial effect of BP-lowering can be expected even in stage 1 hypertension. However, it should be appreciated that treatment strategy for high blood pressure (hypertension) must be directed by blood pressure values, and it remains unclear BP lowering should be started in subjects with stage 1 hypertension. There are several lines of evidence suggesting that antihypertensive treatment should not be generalized to all individuals with systolic blood pressure in the range of 130 to 139 mm Hg.[26−28] Therefore, further study is required to clarify whether aggressive BP lowering is beneficial for subjects with stage 1 hypertension.

We acknowledge several limitations in the present study. First, the data are from a single center and the sample size is limited. Therefore, the statistical power might not be sufficient for any nonassociated data to be conclusive. Second, the BP was not monitored at home, which is recommended to check the efficacy of treatment. Third, we did not analyze the effect of medication in detail, particularly the type of antihypertensive medications.

In conclusion, IMT increases in stage 1 hypertension, and increases further in stage 2 hypertension in the general population, suggesting that the updated ACC/AHA guidelines for hypertension will enable early preventive interventions, even in the low-risk subjects. Further study is required to clarify the effect of aggressive BP lowering treatment for stage 1 hypertension on long-term clinical outcomes including subsequent CVD.

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