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Carotid intima-media thickness is a novel predictor of new onset of hypertension in normotensive subjects

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Abstract

Increased carotid intima-media thickness (IMT) in individuals without hypertension might indicate other factors promoting the atherosclerotic process that are often simultaneously clustered in individuals. The present study tested the hypothesis that carotid IMT predicts new onset of hypertension in the normotensive subjects.

A total of 867 participants were enrolled from our yearly physical checkup program and their carotid IMT was measured. After a baseline examination, the subjects were followed up for a median of 1091 days with the endpoint being the development of hypertension.

At baseline, the carotid IMT value was 0.75 ± 0.16 mm. Hypertension developed in 184 subjects during the follow-up (76.9/1000 person-years). The incidence of hypertension was increased across the tertiles of the carotid IMT value (39.6, 70.0, and 134.5/1000 person-years in the first, second, and third tertiles, respectively, $P < .001$ by log-rank test). Multivariate Cox-hazard analysis after adjustment identified carotid IMT, taken as a continuous variable, as a significant predictor of new-onset hypertension (hazard ratio = 7.08, 95% confidence interval = 3.06–15.39). Furthermore, multivariate linear regression analyses indicated a significant correlation between the carotid IMT at baseline and yearly increases in systolic blood pressure during the follow-up period ($\beta = 0.189$, $P < .001$).

Carotid IMT is an independent predictor of hypertension onset in normotensive subjects. The findings also suggested a close association between increased carotid IMT and blood pressure.

Abbreviations: AUC = area under the curve, CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HR = Hazard ratio, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, ROC = receiver operating characteristics curve, SBP = systolic blood pressure.

Keywords: blood pressure, hypertension, intima-media thickness, normotensive, predictor

1. Introduction

Primary prevention of cardiovascular diseases contributes to an extension of healthy life expectancy. Accordingly, preventing or retarding atherosclerotic processes is one of the most important strategies in public health, with hypertension onset one of the major risk factors to target. Unfortunately, the risk of cardiovascular events in hypertensive patients remains high even with strict management of blood pressure, compared to normotensive individuals not taking antihypertensive medication.[1,2] Thus, primary prevention of hypertension is crucial in further reducing cardiovascular morbidity and mortality.

Assessing the target organ damage in hypertensive patients is important for accurately ascertaining the impact of increased blood pressure and the sensitivity of individuals to such increases. Indeed, carotid intima-media thickness (IMT) is an index of atherosclerotic vascular damage that is closely associated with blood pressure levels.[3] Conversely, an increase in carotid IMT suggests the presence of atherosclerotic risk factors, and in individuals without hypertension it suggests that risk factors other than hypertension play a major role in accelerating the process of atherosclerosis. The diagnosis of metabolic syndrome is based on the fundamental concept that each component of the condition is not coincidently clustered and that there are close associations among the components. Thus, an increase of blood pressure might also cluster around risk factors that promote the increase in carotid IMT in individuals without hypertension.

While carotid IMT in hypertensive patients is an important marker of hypertensive organ damage,[4] this index is not widely considered with respect to blood pressure in normotensive subjects. Thus, we investigated whether carotid IMT predicts new onset of hypertension in the normotensive subjects.

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2. Methods

2.1. Study design

We conducted a cohort study from July 2008 to June 2013 to investigate the impact of carotid IMT assessed by ultrasound examination on the incidence of hypertension, using participants who visited our hospital for a yearly physical checkup from July 2008 to December 2011. The study protocol was in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Enshu Hospital. All participants gave written informed consent to participate before the start of the study and at each study visit.

2.2. Study participants and procedures

Participants who underwent carotid ultrasound examination as a part of a routine checkup program (n = 1419) were screened for eligibility for the present study. Participants aged 25 years or older, those without hypertension, and those without a history of coronary heart disease or stroke were enrolled (n = 867) and followed up with the endpoint being the onset of hypertension. Blood pressure was measured 3 times at 2-minute intervals during the annual health checkup using a mercury sphygmomanometer in a sitting position after 5 minutes rest. The mean of the second and third measurements was taken as the blood pressure. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or if they used antihypertensive medications.[4] Participants were defined as having dyslipidemia if their high-density lipoprotein (HDL) cholesterol level was <40 mg/dL, if their low-density lipoprotein (LDL) cholesterol level was ≥140 mg/dL, if their triglyceride level was ≥150 mg/dL, or if they used antidyslipidemic medications.[5] Participants were defined as having diabetes mellitus if their fasting plasma glucose (FPG) level was ≥126 mg/dL or if they used antidiabetic medications. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[6]

2.3. Measurement of IMT

The carotid artery was imaged with an ultrasound system (ProSound SSD-3500SV; Aloka Co., Ltd, Tokyo, Japan). The bilateral common carotid arteries were examined at 1- to 2-cm proximal sites to the carotid bifurcation on a longitudinal, 2-dimensional ultrasound image. The IMT in the posterior wall of the common carotid artery was measured as the distance from the leading edge of the first echogenic line (lumen–intima interface) to the leading edge of the second line (media–adventitia interface).[7] IMT was measured at 3 points, the maximal site and 10 mm distal and proximal of the maximal site, at each side of the common carotid artery, and the average of the 6 measurements was taken as the IMT value.[8] The examiners of the ultrasound images had no access to the subjects' medical information.

2.4. Statistical analysis

All analyses were performed using IBM SPSS statistics 24 software (Chicago, IL). Data in the text and tables are expressed as mean ± standard deviation or the number and percentage of participants. Differences between two means that had a normal distribution were compared using the unpaired Student's *t* test. Chi-square test was used for comparisons between categorical data. The Kaplan–Meier method was applied to calculate cumulative incidence rates of new-onset hypertension. The significance of differences in the cumulative incidence rates was evaluated by the log-rank test and adjusted by multivariate Cox proportional hazard regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The relationship of IMT as a continuous variable to the onset of hypertension was investigated using multivariate Cox proportional hazard regression models. The impact of baseline IMT on changes in blood pressure was assessed by multivariate linear regression analysis. Linear regression analysis was performed for each participant using change in blood pressure as a dependent variable and the follow-up period (in years) as an independent variable, and the slope of the regression line was considered to indicate the yearly change in blood pressure. In participants who started antihypertensive medication during the follow-up period, changes in blood pressure were calculated using data obtained before the prescription of antihypertensive drugs. $P < .05$ was considered significant.

3. Results

Table 1 summarizes the baseline characteristics of subjects in the present study. Cross-sectional analysis using a multiple linear regression model revealed that carotid IMT was correlated with age ($r = 0.406$, $P < .001$), male gender ($r = 0.119$, $P = .011$), body mass index ($r = 0.081$, $P = .018$), SBP ($r = 0.100$, $P = .002$), FPG ($r = 0.077$, $P = .017$), LDL-cholesterol ($r = 0.062$, $P = .049$), and HDL-cholesterol ($r = -0.071$, $P = .029$). The actual follow-up period of the present study was 2393 person-years and the median follow-up period per participant was 1091 days (range 177–1815 days). During the follow-up, 184 subjects developed

Table 1

Baseline characteristics of study subjects.

	Total (n = 867)	Low IMT (n = 410)	High IMT (n = 457)
Age, y	59.1 ± 8.8	55.8 ± 8.7	62.0 ± 7.8†
Gender, male, n (%)	385 (44.4%)	168 (41.0%)	217 (47.5%)
Body mass index, kg/m^2	22.2 ± 2.8	22.0 ± 2.8	22.4 ± 2.9
SBP, mm Hg	119.8 ± 11.8	118.0 ± 11.8	121.4 ± 11.5†
DBP, mm Hg	73.9 ± 7.8	73.2 ± 8.0	74.5 ± 7.7*
Heart rate, bpm	62.7 ± 8.6	63.4 ± 8.9	62.0 ± 8.2*
Serum creatinine, mg/dL	0.72 ± 0.16	0.71 ± 0.15	0.72 ± 0.17
eGFR, mL/min per 1.73 m^2	97.1 ± 10.2	99.4 ± 9.4	95.1 ± 10.4†
Uric acid, mg/dL	5.09 ± 1.23	5.03 ± 1.22	5.14 ± 1.23
FPG, mg/dL	95.9 ± 13.0	94.6 ± 11.0	97.0 ± 14.6*
LDL cholesterol, mg/dL	124.9 ± 27.2	124.3 ± 27.4	125.5 ± 27.1
HDL cholesterol, mg/dL	60.6 ± 13.6	62.0 ± 14.6	59.3 ± 12.6*
Triglyceride, mg/dL	102.5 ± 57.4	103.3 ± 62.3	101.8 ± 52.8
Hemoglobin, g/dL	13.6 ± 1.3	13.6 ± 1.3	13.6 ± 1.2
IMT, mm	0.75 ± 0.16	0.63 ± 0.07	0.86 ± 0.14†
Diabetes mellitus, n (%)	62 (7.2%)	17 (4.1%)	45 (9.8%)*
Dyslipidemia, n (%)	378 (43.6%)	158 (38.5%)	220 (48.1%)*
Current smoking status, n (%)	112 (12.9%)	58 (14.1%)	54 (11.8%)
Family history of HT, n (%)	209 (24.1%)	107 (26.1%)	102 (22.3%)

Values are mean ± standard deviation, the number (%) of participants.

Subjects were divided into low IMT group or high IMT group using the cut-off value (0.75 mm) obtained from the receiver operating characteristics curve analysis for the new onset of hypertension.

DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.

* $P < .05$.

† $P < .001$ vs "Low IMT" (unpaired Student *t* test, Chi-square test [gender, diabetes mellitus, dyslipidemia, current smoking status, family history of HT]).

Table 2

Retrospective analysis of study subjects' characteristics at baseline.

	Without future HT (n = 683)	With future HT (n = 184)
Age, y	58.4 ± 9.0	61.7 ± 7.6†
Gender, male, n (%)	290 (42.5%)	95 (51.6%)*
Body mass index, kg/m^2	22.1 ± 2.8	22.7 ± 2.7*
SBP, mm Hg	118.2 ± 11.8	125.7 ± 11.0†
DBP, mm Hg	73.1 ± 7.6	76.9 ± 8.1†
Heart rate, bpm	62.4 ± 8.6	63.6 ± 8.5
Serum creatinine, mg/dL	0.71 ± 0.14	0.75 ± 0.21*
eGFR, mL/min per 1.73 m^2	97.8 ± 9.6	94.5 ± 11.6*
Uric acid, mg/dL	5.05 ± 1.24	5.22 ± 1.19
FPG, mg/dL	95.2 ± 12.2	98.4 ± 15.4*
LDL cholesterol, mg/dL	125.8 ± 26.4	121.7 ± 30.1
HDL cholesterol, mg/dL	61.0 ± 13.5	58.9 ± 14.0
Triglyceride, mg/dL	101.8 ± 55.9	105.2 ± 63.0
Hemoglobin, g/dL	13.5 ± 1.4	13.6 ± 1.3
IMT, mm	0.73 ± 0.14	0.83 ± 0.19†
Yearly increase in SBP, mm Hg/year	−0.36 ± 5.66	6.98 ± 11.1†
Yearly increase in DBP, mm Hg/year	−0.52 ± 4.10	2.63 ± 8.00†
Diabetes mellitus, n (%)	45 (6.6%)	17 (9.2%)
Dyslipidemia, n (%)	302 (44.2%)	76 (41.3%)
Current smoking status, n (%)	86 (12.6%)	26 (14.1%)
Family history of HT, n (%)	154 (22.5%)	55 (29.9%)*

Values are mean ± standard deviation, the number (%) of participants.
DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.
* $P < .05$.
† $P < .001$ vs "without future HT" (unpaired Student *t* test, Chi-square test [gender, diabetes mellitus, dyslipidemia, current smoking status, family history of HT]).

hypertension (21.2%, 76.9 per 1000 person-years), with a higher incidence in males (24.7%, 90.8 per 1000 person-years) than in females (18.5%, 66.1 per 1000 person-year; $P < .05$). By retrospective analysis, carotid IMT was greater in subjects with (0.83 ± 0.19 mm) than without future hypertension (0.73 ± 0.15 mm; $P < .001$), although most variables at baseline were different between subjects with and without future hypertension (Table 2).

Univariate analysis and multivariate Cox-hazard regression analysis adjusted for age, gender, body mass index, SBP, heart rate, serum creatinine, uric acid, FPG, LDL-cholesterol, HDL-cholesterol, current smoking habit, and family history of hypertension at baseline revealed that carotid IMT measured at baseline was an independent predictor of future hypertension (Table 3). The cut-off value, area under the curve (AUC), sensitivity, and specificity for new onset of hypertension was 0.75 mm, 0.667, 59.8, and 66.5, respectively, based on receiver operating characteristics (ROC) curve analysis. Then, subjects were divided into 2 groups using the cut-off value obtained from the ROC curve analysis to compare the risk of future hypertension (see Table 1); by multivariate Cox-hazard regression analysis, those subjects with increased IMT had a 63% increase in risk (Table 4, Model A). The incidence of hypertension in the low and high IMT groups was 47.1 and 103.5 per 1000 person-years, respectively. Subjects were then divided into tertiles according to the carotid IMT value and the incidence of hypertension was analyzed by the Kaplan–Meier method. The IMT value in the first, second, and third tertiles was 0.59 ± 0.06, 0.75 ± 0.04, and 0.95 ± 0.15 mm, respectively, and the incidence of hypertension was increased across the tertiles (39.6, 70.0, and 134.5 per 1000 person-years in the first, second, and third tertiles, respectively, $P < .001$ by log-rank test; Fig. 1). Multivariate Cox-hazard regression analysis demonstrated that HR (95% CI) was increased with increasing carotid IMT values (Table 4, Model B). In addition, the carotid IMT value at baseline significantly correlated with yearly increases in SBP during the follow-up period by univariate and multivariate liner regression analyses ($r = 0.176$, $P < .001$ and $r = 0.192$, $P < .001$, respectively) (Table 5).

4. Discussion

The present study demonstrated that carotid IMT assessed by ultrasound sonography is a significant determinant of future

Table 3

Cox proportional hazard regression analyses for future development of hypertension.

	Univariate		Multivariate	
Variable at baseline	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, y	1.039 (1.020–1.057)	<.001	1.022 (1.001–1.044)	.036
Gender, male	1.387 (1.038–1.853)	.027	0.957 (0.631–1.452)	.838
Body mass index, kg/m^2	1.079 (1.028–1.133)	.002	1.054 (0.994–1.116)	.080
SBP, mm Hg	1.060 (1.044–1.076)	<.001	1.051 (1.034–1.067)	<.001
DBP, mm Hg	1.067 (1.045–1.090)	<.001	—	—
Heart rate, bpm	1.019 (1.002–1.036)	.024	1.010 (0.993–1.028)	.259
Serum creatinine, mg/dL	3.737 (1.774–7.874)	.001	3.358 (1.324–8.497)	.011
Uric acid, mg/dL	1.129 (1.004–1.269)	.042	1.012 (0.870–1.177)	.879
FPG, mg/dL	1.016 (1.006–1.026)	.002	1.006 (0.995–1.017)	.324
LDL cholesterol, mg/dL	0.995 (0.989–1.000)	.067	0.994 (0.988–1.000)	.039
HDL cholesterol, mg/dL	0.989 (0.978–1.000)	.057	1.002 (0.990–1.015)	.698
Triglyceride, mg/dL	1.001 (0.999–1.003)	.497	—	—
Current smoking status	1.123 (0.742–1.700)	.584	1.456 (0.933–2.273)	.098
Family history of HT	1.382 (1.008–1.894)	.045	1.687 (1.214–2.345)	002
IMT, mm	13.38 (6.770–26.43)	<.001	7.080 (3.058–16.39)	<.001
IMT, 0.1 mm	1.296 (1.211–1.387)	<.001	1.216 (1.118–1.323)	<.001

All variables included in the multivariate analysis are listed in the table.
CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.

Table 4

Multivariate Cox proportional hazard regression analyses for future development of hypertension.

Variable at baseline	Model A		Model B	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, y	1.028 (1.007–1.050)	.009	1.019 (0.998–1.041)	.083
Gender, male	1.036 (0.684–1.570)	.868	1.016 (0.670–1.542)	.939
Body mass index, kg/m^2	1.057 (0.997–1.121)	.062	1.055 (0.996–1.119)	.069
SBP, mmHg	1.051 (1.034–1.068)	<.001	1.050 (1.034–1.067)	<.001
Heart rate, bpm	1.009 (0.992–1.027)	.284	1.013 (0.996–1.031)	.139
Serum creatinine, mg/dL	3.253 (1.302–8.127)	.012	3.482 (1.384–8.759)	.008
Uric acid, mg/dL	0.983 (0.846–1.141)	.817	0.993 (0.857–1.151)	.929
FPG, mg/dL	1.008 (0.997–1.019)	.146	1.007 (0.996–1.018)	.206
LDL cholesterol, mg/dL	0.995 (0.989–1.001)	.100	0.995 (0.989–1.000)	.071
HDL cholesterol, mg/dL	1.001 (0.989–1.013)	.884	1.003 (0.991–1.016)	.634
Current smoking status	1.471 (0.942–2.297)	.090	1.421 (0.911–2.214)	.121
Family history of HT	1.655 (1.191–2.300)	.003	1.658 (1.194–2.304)	.003
High IMT (vs. Low IMT)	1.629 (1.149–2.304)	.006	—	—
IMT-first tertile	—	—	1 (reference)	—
IMT-second tertile	—	—	1.600 (1.029–2.490)	.037
IMT-third tertile	—	—	2.636 (1.654–4.201)	<.001

Model A: Subjects were divided into 2 groups according to the cut-off value obtained from receiver operating characteristics curve analysis.
Model B: Subjects were divided into tertiles.
All variables included in the multivariate analysis are listed in the table.
CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.

development of hypertension in normotensive subjects. Since yearly increases in blood pressure are also independently correlated with carotid IMT, this index is also strongly associated with the process by which the future hypertension might develop.

In the present study, although retrospective analysis indicated a significant increase in carotid IMT in subjects with future hypertension, most variables investigated at baseline were different between subjects with and without future hypertension. Conversely, prospective analysis taking carotid IMT as a continuous variable after adjustment for important variables identified this carotid index as an independent predictor of new-onset hypertension. To confirm and explore these initial results, we performed further analyses after dividing the subjects into 2 or 3 groups according to the carotid IMT value to find that the risk of developing hypertension increased even within the normal range of carotid IMT (below 1.1 mm).[9] The cutoff value obtained from ROC curve analyses in general (0.75 mm; that is also the median carotid IMT value in the present study) is not considered to indicate hypertensive organ damage, but our subjects with carotid IMT >0.75 mm had an increased risk of future hypertension. Although the AUC, sensitivity, and specificity was not sufficiently high to propose this value as a cutoff for predicting hypertension per se, the predictive value of carotid IMT for future hypertension was relatively high based on the analysis of subjects divided into tertiles. The concept that carotid IMT is an independent predictor of new-onset hypertension is further supported by the present analysis showing an

Table 5

Univariate and multivariate regression analyses demonstrating the relationship between baseline variables and yearly increase in systolic blood pressure.

Variable at baseline	Univariate		Multivariate	
	β	*P*	β	*P*
Age, y	0.095	.006	0.058	.124
Gender, male	0.043	.129	−0.115	.022
Body mass index, kg/m^2	−0.001	.974	0.035	.345
SBP, mm Hg	−0.253	<.001	−0.317	<.001
DBP, mm Hg	−0.142	<.001	—	—
Heart rate, bpm	0.009	.803	0.075	.029
Serum creatinine, mg/dL	0.042	.227	0.071	.117
Uric acid, mg/dL	0.043	.221	0.044	.301
FPG, mg/dL	0.132	<.001	0.121	.001
LDL cholesterol, mg/dL	−0.050	.147	−0.073	.032
HDL cholesterol, mg/dL	−0.066	.056	−0.042	.237
Triglyceride, mg/dL	0.001	.997	—	—
Current smoking status	0.100	.004	0.099	.004
Family history of HT	0.020	.563	0.041	.220
IMT, mm	0.176	<.001	0.189	<.001

All variables included in the multivariate analysis are listed in the table.
DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.

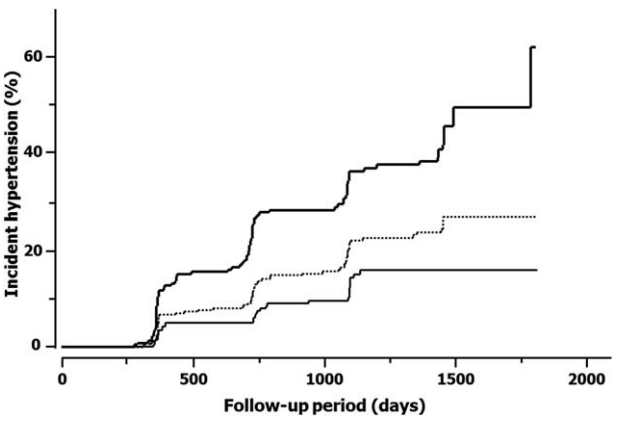

Figure 1. Plots of hypertension incidence rates. Participants were divided into the tertiles according to their carotid IMT levels at baseline. The straight, dotted, and bold straight lines indicate the first, second, and third tertiles, respectively. $P < .0001$ by log-rank test.

independent correlation with changes in SBP and baseline IMT. However, it should be noted that several other factors have also been associated with the development of hypertension, including increased blood pressure within the normal range, family history of hypertension, obesity, impaired glucose tolerance, reduced glomerular filtration rate, urinary albumin, and left ventricular hypertrophy assessed by electrocardiography,[10–13] and carotid IMT is not the only predictor of hypertension.

The causal relationship between an increased carotid IMT and the development of hypertension was not proved by the present observational study and the mechanisms possibly underlying such an association remain unclear. Carotid IMT is also considered to predict hypertensive organ damage and is thus used for risk stratification in patients with hypertension.[4] Since IMT is representative of systemic atherosclerosis, an increase suggests the presence of atherosclerotic risk factors such as aging, smoking, hypertension, diabetes mellitus, and dyslipidemia. This was partially confirmed in the cross-sectional analysis at baseline that correlated carotid IMT with age, male gender, body mass index, SBP, FPG, LDL-cholesterol, and HDL-cholesterol. The results thus indicate that individuals with increased carotid IMT might have other, closely associated risk factors, as suggested in the fundamental principles of the metabolic syndrome. Thus, normotensive subjects with increased carotid IMT might have atherosclerotic risk factors other than hypertension and a fundamental abnormality (e.g., insulin resistance or visceral fat accumulation) that causes both increased blood pressure and disorders in lipid or glucose metabolism. Such a scenario could underlie the present finding of carotid IMT as a significant predictor of future hypertension. Alternatively, the increased carotid IMT at baseline might have reflected a mild or transient increase in blood pressure because in the early phase of developing hypertension, blood pressure gradually increases with fluctuations. Indeed, individuals with white-coat hypertension who show transient increases in blood pressure often go on to develop a sustained hypertension.[14] An increase of carotid IMT may have indicated hypertensive organ damage in some participants.

IMT measured by ultrasound is a useful marker of cardiovascular events,[15–17] although slowing or preventing a progressive increase in IMT by intensive medical treatment is not directory related to a reduced incidence of cardiovascular events.[18] Moreover, guidelines for the management of arterial hypertension (2013 ESH/ESC) noted the modest effect of antihypertensive medication on carotid IMT and recommended limiting IMT evaluation as an index of clinical management.[19] Since the present study did not prove a causal relationship between IMT and the risk of hypertension, it remains unclear whether medically inhibiting increased IMT, such as by the use of statins, might reduce an individual's risk of hypertension and, thereby, cardiovascular disease. Further study will be necessary to determine the effects of such interventions to reduce carotid IMT.

The interpretation of the present results is limited by the following points. First, the study subjects were participants in our annual physical checkup program, so blood pressure was measured only once a year. Data on ambulatory blood pressure monitoring or home blood pressure measurement were not available and white coat hypertension cannot be excluded from our study. Moreover, follow-up data on blood pressure were not available in all participants and, thus, the diagnosis of hypertension may have not been definite. Second, IMT was measured manually by a number of different trained technicians and the presence or absence of plaque was not evaluated in this study. Third, effects of medications such as antidiabetic or antidyslipidemic drugs could have affected the results.

In conclusion, the index of carotid IMT is significantly associated with both the development of hypertension and yearly increases in blood pressure in normotensive subjects. Carotid IMT is a novel predictor of future hypertension as well as a marker of hypertensive organ damage.

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