Impact of Intima–Media Thickness Progression in the Common Carotid Arteries on the Risk of Incident Cardiovascular Disease in the Suita Study

Yoshihiro Kokubo, MD, PhD, FAHA, FACC, FESC, FESO; Makoto Watanabe, MD, PhD; Aya Higashiyama, MD, PhD; Yoko M. Nakao, MD, PhD; Fumiaki Nakamura, MD, PhD; Yoshihiro Miyamoto, MD, PhD

Background—No prospective study of the relationship between intima–media thickness (IMT) progression and incident cardiovascular disease (CVD) has been performed.

Methods and Results—We studied 4724 participants (mean age: 59.7±11.9 years; without CVD at the baseline) who had carotid ultrasonographic measurement of IMT on both sides of the entire carotid artery area (ie, the entire scanned common carotid artery [CCA], carotid artery bulb, internal carotid artery, and external carotid artery areas for both sides) between April 1994 and August 2001. Carotid ultrasonographic follow-up was performed every 2 years between April 1994 and March 2005 in 2722 of these participants, newly revealing 193 CCA plaques (maximum IMT in the CCA >1.1 mm). We followed up for incident CVD until December 2013. Statistical analyses were performed using a Cox proportional hazards regression model, evaluated using C statistics, and net reclassification improvement. During the 59 909 person-years of follow-up, we observed 221 strokes and 154 coronary heart disease events. CCA plaque and maximum IMT in the whole carotid artery area >1.7 mm were risk factors for CVD. CCA plaque presented an increased risk of CVD based on C statistics and the reclassification improvement of the current risk prediction model. After adding the new incident CCA plaques, during the 23 702 person-years of follow-up, 69 strokes and 43 coronary heart disease events occurred. The adjusted hazard ratios for incident CCA plaque were 1.95 (95% confidence interval, 1.14–3.30) in CVD and 2.01 (95% confidence interval, 1.01–3.99) in stroke.

Conclusions—Maximum IMT in the CCA contributed significantly but modestly to the predictive power of incident CVD used in calculating traditional risk factors. This study provides the first demonstration that new progression of incident CCA plaque is a CVD risk. **(*J Am Heart Assoc*. 2018;7:e007720. DOI: 10.1161/JAHA.117.007720.)**

Key Words: atherosclerosis • cardiovascular disease • carotid intima–media thickness • epidemiology • progression of carotid atherosclerosis • prospective cohort study

The carotid intima–media thickness (IMT) is a noninvasive intermediate marker that can be used for the prediction of stroke[1] and coronary heart disease (CHD).[2,3] The carotid IMT is also a surrogate marker for cardiovascular risk factors[4] and atherosclerosis.[5,6] For preventive medicine, it would be useful to determine whether carotid IMT can be used to supplement traditional cardiovascular risks to increase the probability of predicting cardiovascular disease (CVD). The ARIC (Atherosclerosis Risk in Communities) study showed that adding the carotid IMT to traditional risk factors improved CHD risk prediction.[2] In the Framingham Offspring Study, maximum internal carotid artery (ICA) IMT and mean common carotid artery (CCA) IMT both predicted CVD outcomes, but only maximum ICA IMT slightly but significantly improved the classification of risk of CVD.[7] In contrast, carotid IMT did not consistently improve the risk classification of individuals in a general[8] or hypertensive population[9] in meta-analyses, although carotid IMT was predictive of CVD events. These inconsistent results may have been due to the use of the mean or maximum IMT or to differences in age range, ethnicity, and background of participants, such as the presence of hypertension between studies.

From the Departments of Preventive Medicine (Y.K., M.W., A.H., Y.M.) and Preventive Medicine and Epidemiologic Informatics (A.H., Y.M.N., F.N., Y.M.), National Cerebral and Cardiovascular Center, Suita, Japan.

Accompanying Data S1 and Tables S1 through S6 are available at http://jaha.ahajournals.org/content/7/11/e007720/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Yoshihiro Kokubo, MD, PhD, FAHA, FACC, FESC, FESO, Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. E-mail: ykokubo@ncvc.go.jp

Received January 2, 2018; accepted April 30, 2018.

Clinical Perspective

What Is New?

- High mean intima–media thickness (IMT) and carotid plaque in the common carotid artery (CCA) and the entire carotid artery area were risk factors for cardiovascular disease (CVD) in a general Japanese population.
- Maximum IMT in the CCA and the in the entire carotid artery area predicted CVD, but only maximum IMT in the CCA contributed significantly but modestly to the predictive power of the risk factors for CVD used in calculating the current risk prediction model and improved risk classification, providing the first such evidence in a non-Western population.
- This study provides the first evidence that new progression of incident carotid plaque (maximum IMT in the CCA >1.1 mm) is associated with an increased risk of later CVD.

What Are the Clinical Implications?

- In medical examinations and outpatient clinics, carotid ultrasonography at the CCA can be easily measured both to screen for and to evaluate carotid plaque (maximum IMT in the CCA >1.1 mm) as a risk factor for future CVD.
- We plan to develop a risk score for carotid atherosclerosis in the Suita Study cohort for use in medical examinations and outpatient clinics without the need for carotid ultrasonography, with the ultimate goal of preventing carotid atherosclerosis.

A meta-analysis of the PROG-IMT Collaborative Project (individual progression of carotid intima media thickness as a surrogate of vascular risk) revealed a strong association between carotid IMT and CVD events, but the association between individual carotid IMT progression and CVD in the general population is still unproven.[10] Almost all studies of the association between carotid IMT and incident CVD were conducted in Western countries; moreover, no prospective study on the association between carotid IMT progression and incident CVD has been performed. We conducted this study (1) to analyze the relationship between various carotid IMT values at baseline and incident CVD and (2) to evaluate the association between carotid IMT progression and the risk of CVD in a general urban Japanese population.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The study population consisted of members of the Suita Study, an epidemiological study of CVD and cerebrovascular diseases that was based on a random sampling of 15 200 participants in Suita City, stratified by sex and age in 10-year increments from 1989. For these participants, we set the baseline of the present study as the medical examination held between April 1994 and August 2001. Of the 6590 people examined during their visit to the National Cerebral and Cardiovascular Center (NCVC; located in Suita City), we excluded 352 individuals who had a past or present history of CVD, 1008 who had not undergone a medical examination that included ultrasonography, and 506 who could not be followed up to the end of 2013. A total of 4724 individuals had interpretable carotid ultrasonography images. Missing data (n=1008) were due to scheduling issues or unavailability of the ultrasonography device. The baseline characteristics of the current and excluded participants are shown in Table S1. Details of the original Suita Study design have been published elsewhere.[11,12] Supplemental methods are shown in the expanded methods (Data S1). All participants in our study provided written informed consent, and the NCVC institutional review board approved our study.

Risk Factors and Anthropomorphic Variables

Well-trained physicians measured each participant's blood pressure (BP) 3 times using a mercury column sphygmomanometer, an appropriately sized cuff, and a standard protocol.[11] Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. BP values were taken as the average of the second and third measurements, which were recorded >1 minute apart. At the time of the baseline examination, each participant was classified into 1 of 3 categories of systolic and diastolic BP alone: *normal* (<120/80 mm Hg), *systolic/diastolic prehypertension* (120–139/80–89 mm Hg), and *systolic/diastolic hypertension* (≥140/90 mm Hg), respectively. Categories of body mass index, calculated as weight (kg) divided by height (m^2), were defined as *underweight* (<18.5), *normal weight* (18.5 to <25), and *overweight* (≥25).[13] The prevalence of obesity among all participants was <1.6%, and obese participants were included in the overweight category.

At the baseline examination, we performed routine blood tests that included serum total and high-density lipoprotein cholesterol and glucose levels. An individual's non–high-density lipoprotein cholesterol level was calculated by subtracting the high-density lipoprotein cholesterol from the total cholesterol. Glucose categories were defined as *diabetes mellitus* (fasting plasma glucose levels [FPG] ≥126 mg/dL, non-FPG ≥200 mg/dL, or use of diabetes mellitus medication), *impaired fasting glucose* (FPG 100–125 mg/dL and non-FPG 140–199 mg/dL), and *normal glucose tolerance* (FPG <100 mg/dL and non-FPG <140 mg/dL). The glomerular filtration rate (shown as GFR; mL/min per 1.73 m^2) of each participant was calculated using the Modification of Diet in

Renal Disease equation modified by the Japanese coefficient (0.881), as follows[14]:

$$GFR = 0.881 \times 186 \times (\text{age})^{-0.203} \times (\text{serum creatinine})^{-1.154} (\times 0.742 \text{ for women})$$

Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

Physicians and nurses administered a questionnaire that assessed each participant's habits and illness status at the time. Smoking and drinking habits were classified as *current, quit*, or *never*. We defined excessive alcohol consumption as ≥48 g/d ethanol (≥2 goes/d for Japanese sake). The questionnaire asked the participant about his or her past and present history of stroke (cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage) and CHD (myocardial infarction, angina pectoris, and coronary intervention).

Carotid IMT Measures

Details of the carotid ultrasonic examination methods have been published previously.[4,15,16] Briefly, for this examination, the participant was in a supine position on a bed. We used a high-resolution B-mode ultrasound system (SSA-250A; Toshiba) with a 7.5-MHz transducer (SMA-736S; Toshiba). Carotid atherosclerosis was evaluated by high-resolution ultrasonographic measurement with atherosclerotic indexes of IMT on both sides of the CCA, carotid artery bulb, ICA, and external carotid artery. All measurements were made at the time of scanning with an electronic caliper and were recorded as photocopies. The same well-trained physician performed all examinations.

Mean IMT was defined as the mean of the IMT of the proximal and distal walls for both sides of the CCA on a longitudinal scan at a point 10 mm proximal from the beginning of the dilation of each carotid artery bulb. The procedure has been described in detail previously.[16] The maximum IMT in the CCA (max-CIMT) was defined as the maximum measurable IMT in the scanned CCA areas, and the maximum IMT in the entire area (max-IMT) was defined as the maximum measurable IMT in the entire scanned CCA, bulb, ICA, and external carotid artery areas for both sides.

The intrareader reproducibility of the measurements was assessed for the IMT in the CCA of 50 participants just before the start of this study. IMT was examined twice with a 1-month interval in a blinded manner to obtain the correlation coefficient between the first and second IMT measurements (r=0.87, P<0.001). A paired t test showed no significant difference between the 2 measurements. The mean difference and standard deviation between the 2 measurements of the IMT was 0.02±0.08 mm.[4]

Confirmation of Stroke and CHD

Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the US National Survey of Stroke criteria.[17] For each stroke subtype (ie, cerebral infarction [thrombotic or embolic], intracerebral hemorrhage, and subarachnoid hemorrhage), a definite diagnosis was established based on the examination of computed tomographic scans, magnetic resonance images, or autopsies. Definite and probable myocardial infarctions were defined according to the criteria set out by the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project.[18] The criteria for a diagnosis of CHD included first-ever acute myocardial infarction, sudden cardiac death within 24 hours after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty. In the present study, we defined CVD as stroke or CHD.

Follow-up Survey

For the detection of CHD and stroke occurrences, each participant's health status was checked during clinical visits to the NCVC every 2 years. Yearly questionnaires by mail or telephone were also completed by all participants. In addition, to complete our surveillance for fatal strokes and CHD, we conducted a systematic search for death certificates. All data were checked against medical records to confirm the incidence of CVD. When informed consent could not be obtained for a medical records survey (19.5%), we identified possible strokes or CHD using information from (1) questionnaires for verifying stroke and CHD at the health examination and/or (2) death certificates bearing a diagnosis of probable stroke or CHD. The end point of the follow-up period for each participant was whichever of the following occurred first: (1) the date of the first diagnosis of CHD or stroke event; (2) the date of death; (3) the date of leaving Suita City; or (4) December 31, 2013. For each participant, the person-years of follow-up were calculated from the date of baseline survey to the first end point.

For all participants who attended the baseline carotid ultrasonographic survey between April 1994 and August 2001, carotid ultrasonographic follow-up was performed every 2 years between April 1998 and March 2005. After the baseline survey, we performed carotid ultrasonography an average of 2.1±0.9 times (range: 1–6 times) using the same protocol. During the follow-up for carotid ultrasonography measurement, we excluded the following participants: those with plaques at baseline (n=1156 for max-CIMT >1.1 mm, n=1088 for max-IMT >1.7 mm); those lost to follow-up (n=804 for max-CIMT >1.1 mm, n=822 for max-IMT >1.7 mm); and those with incident CVD during echocardiography examination at follow-up (n=42 for max-CIMT >1.1 mm, n=46 for max-IMT >1.7 mm). Finally, we could follow up participants (n=2722 for max-CIMT >1.1, n=2768 for max-IMT >1.7 mm) and observed new developing plaques (n=193 for max-CIMT >1.1 mm, n=153 for max-IMT >1.7 mm; Figure). The end point of the plaque follow-up period for each participant was whichever of the following occurred first: (1) the date of the first developing plaque; (2) the date of the last carotid ultrasound examination; or (3) March 31, 2005 (censored). Subsequently, after the follow-up of developing plaques, we set the end point of plaque follow-up as the baseline of the CVD follow-up. The end point of the follow-up period for incident CVD was whichever of the following occurred first: (1) the date of the first diagnosis of a CHD or stroke event; (2) the date of death; (3) the date of leaving Suita City; or (4) December 31, 2013. For each participant, the person-years of follow-up for incident CVD were calculated from the end point of the plaque follow-up and the incident CVD.

Statistical Analysis

We used ANOVA and χ^2 tests to compare the mean values and frequencies according to incident CVD. We examined the associations between the quartiles of carotid IMT indexes and the risk of incident CVD and its subtypes using a sex- and age-adjusted and multivariable-adjusted Cox proportional hazards regression model. Multivariate analyses used age, sex, body mass index (overweight, normal weight, underweight), systolic/diastolic normal BP, prehypertension, and hypertension, total cholesterol (<160, 160–239, 240–279, >280 mg/dL), high-density lipoprotein cholesterol (<35, 35–49, 50–59, >60 mg/dL), glomerular filtration rate (>60, 45–59, <45 mL/min per 1.73 m^2), antihypertensive and antihyperlipidemic drug use, diabetes mellitus, impairment of fasting glucose, current smoking, and excessive drinking.

The current risk prediction model was directly calculated by employing each variable of the Suita Risk Score[19] in the Cox regression model using the current data. After adding

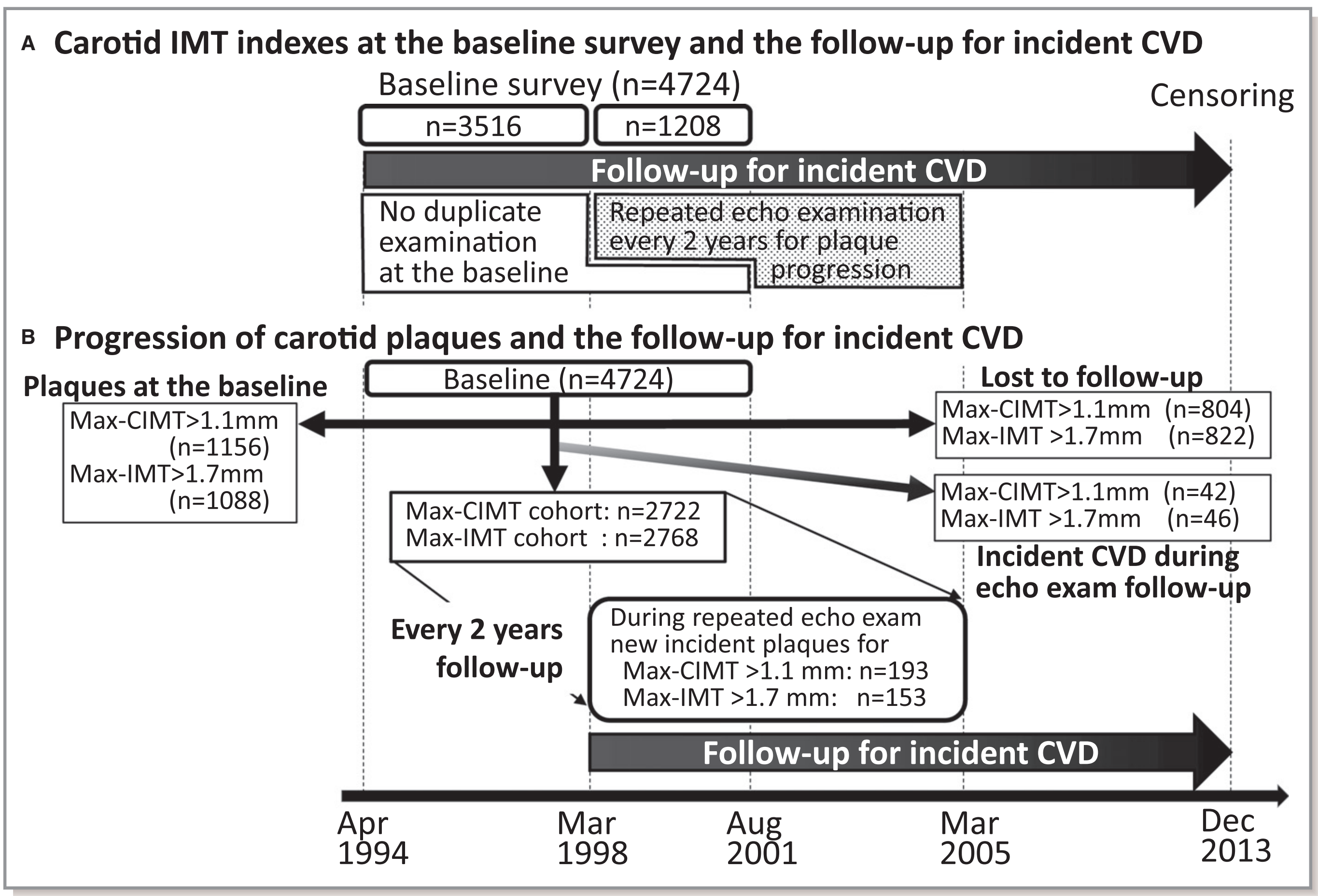

Figure. A schematic flow of 2 prospective study designs for carotid ultrasonography in the Suita Study. (A) Carotid IMT at the baseline survey and at follow-up for incident cardiovascular disease. (B) Progression of carotid plaques (max-CIMT >1.1 mm or max-IMT >1.7 mm) and follow-up for incident CVD. CVD indicates cardiovascular disease; IMT, intima–media thickness; max-CIMT, maximum intima–media thickness in the common carotid arteries; max-IMT, maximum intima–media thickness in the entire carotid artery area.

carotid plaques (max-CIMT >1.1 mm or max-IMT >1.7 mm) to the current risk model, we conducted statistical analysis to assess whether max-CIMT or max-IMT significantly improved 3 metrics used to determine CVD prediction: the C statistic, the net reclassification index, and the integrated discrimination index for the current risk model. Discrimination was assessed by Harrell C statistics, which were interpretable as the area under a receiver operating characteristic curve for comparing predictions in 2 outcome groups. A value of 1.0 indicates perfect predictive discrimination, whereas a value of 0.5 indicates no ability to discriminate. The 95% confidence intervals (95% CIs) of the C statistic were estimated using 200 bootstrap samples, then the standard error for the difference in the C statistics between each model was estimated from the bootstrap samples and used to calculate a *z* score and a *P* value for the difference. To compare the calibration that is the ability to estimate the accuracy of the model's prediction, we used the log-likelihood ratio test and the Bayesian information criterion. Lower values for the Bayesian information criterion suggest better calibration of the model. We also examined the associations between the progression of carotid plaques per 5 years and the risk of incident CVD and its subtypes using sex- and age-adjusted and multivariable-adjusted Cox proportional hazards regression models.

Results

A total of 4724 participants with a mean age (±SD) of 59.7±11.9 years and no history of CVD at the baseline were followed for an average of 12.7 years; 2566 (54.3%) were women. The baseline characteristics of the study participants by incident CVD during follow-up are summarized in Table 1. On average, the participants with CVD were older and had higher systolic and diastolic BP, body mass index, and prevalence of antihypertensive drug use, diabetes mellitus, and current smoking compared with participants without CVD during follow-up.

During the 59 909 person-years of follow-up, 375 incident CVD events (221 incident stroke and 154 incident CHD events) occurred. Table 2 provides the age- and sex-adjusted and multivariable-adjusted hazard ratios (HRs) for CVD and its subtypes according to quartiles of various IMT values. Compared with the first quartile of mean IMT, the age- and sex-adjusted HRs for CVD and stroke indicated that the third and fourth quartiles of mean IMT values presented an increased risk of CVD and stroke and that those HRs for the fourth quartile of mean IMT values presented an increased risk of CHD; however, after multivariable adjustment, only the fourth quartile of mean IMT values presented an increased risk of CVD.

Regarding the quartiles of max-CIMT, an increased risk of incident CVD was indicated by the third and fourth quartiles, an increased risk of stroke was indicated by the fourth quartile, and an increased risk of CHD was indicated by the second to fourth quartiles of max-CIMT. After multivariable adjustment, the third and fourth max-CIMT quartiles presented an increased risk of CVD and CHD, and the fourth Max-CIMT quartile presented an increased risk of stroke. The third and fourth quartiles of max-IMT showed increased risks of incident CVD and CHD. Mean CIMT >0.95 mm, max-CIMT >1.1 mm, and max-IMT >1.7 mm were all significantly associated with the risk of CVD in the multiple adjustment models.

Table 3 provides the various multivariable-adjusted models values (mean IMT >0.95 mm, max-CIMT >1.1 mm, and max-IMT >1.7 mm) associated with CVD, stroke, and CHD and the difference of C statistics. When those cutoff points were added to the current risk prediction model, the differences of C statistics for CVD were all significantly increased. Moreover, when max-CIMT >1.1 mm and max-IMT >1.7 mm were added to the current risk prediction model, the difference of C statistics for stroke and CHD increased.

Table 1. Baseline Characteristics of the 4724 Participants Without Evidence of CVD on Carotid Ultrasonography, According to CVD Status at Follow-up

Characteristic	No CVD at Follow-Up (n=4349)	CVD at Follow-up (n=375)
Duration of follow-up, y	13.1	8.1
Age, y	59.0±11.8	66.6±9.6
Sex (male), %	44.5	59.5
Body mass index, kg/m^2	22.6±3.1	23.1±3.2
Systolic BP, mm Hg	126.3±19.4	137.4±19.4
Diastolic BP, mm Hg	78.2±10.8	81.8±10.5
Total cholesterol, mg/dL	209.1±33.2	215.9±32.3
HDL cholesterol, mg/dL	60.4±15.7	56.7±16.0
GFR, mL/min/1.73 m^2	80.9±19.6	75.5±31.0
Antihypertensive drug use, %	14.6	27.2
Antihyperlipidemic drug use, %	5.2	5.3
Diabetes mellitus, %	4.0	10.1
Current smoking, %	23.2	29.1
Excessive drinking, %	8.2	9.3
IMT		
Mean CCA thickness, mm	0.86±0.13	0.96±0.15
Maximum CCA thickness, mm	1.04±0.38	1.25±0.44
Maximum carotid artery thickness, mm	1.41±0.68	1.84±0.81
CCA thickness >1.1 mm, indicating plaque, %	19.6	44.5

Data are shown as mean±SD except as noted. To convert the values for cholesterol to mmol/L, multiply by 0.02586. BP indicates blood pressure; CCA, common carotid artery; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; intima–media thickness.

Table 2. Age- and Sex-Adjusted and Multivariable-Adjusted HRs for CVD and Subtype According to Quartiles of Various IMTs, Plaques, and per 1-SD Increase in IMT

Mean IMT in the CCA	≤0.75 mm	0.76–0.85 mm	0.86–0.95 mm	>0.95 mm	>0.95 mm vs ≤0.95 mm	Per 1-SD Increase
Participants at baseline, n	1042	1224	1337	1021	. . .	. . .
Person-years	15 446	16 423	16 890	11 151	. . .	. . .
CVD, n	26	59	123	167	. . .	. . .
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.33 (0.83–2.13)	1.92 (1.21–3.04)	3.08 (1.90–4.97)	1.95 (1.56–2.44)	1.50 (1.35–1.67)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.07 (0.67–1.72)	1.37 (0.86–2.18)	1.93 (1.18–3.13)	1.58 (1.26–1.98)	1.31 (1.17–1.48)
Stroke, n	14	34	78	95		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.30 (0.69–2.45)	1.96 (1.06–3.62)	2.74 (1.44–5.22)	1.84 (1.38–2.46)	1.40 (1.21–1.62)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.06 (0.56–2.00)	1.47 (0.79–2.74)	1.88 (0.98–3.61)	1.55 (1.16–2.07)	1.25 (1.07–1.46)
CHD, n	12	25	45	72		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.37 (0.67–2.79)	1.88 (0.94–3.79)	3.86 (1.88–7.95)	2.25 (1.58–3.20)	1.68 (1.44–1.97)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.05 (0.52–2.15)	1.19 (0.59–2.42)	2.04 (0.98–4.25)	1.71 (1.20–2.44)	1.45 (1.22–1.72)
Max-CIMT	≤0.85 mm	0.86–0.95 mm	0.96–1.10 mm	>1.10 mm	>1.1 mm vs ≤1.1 mm	Per 1-SD Increase
Participants at baseline, n	1060	1050	1458	1156	. . .	. . .
Person-years	14 135	13 973	18 791	13 010	. . .	. . .
CVD, n	19	48	126	182	. . .	. . .
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.64 (0.96–2.81)	2.19 (1.31–3.64)	3.69 (2.20–6.20)	1.93 (1.56–2.39)	1.17 (1.11–1.23)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.42 (0.83–2.44)	1.68 (1.01–2.80)	2.44 (1.44–4.12)	1.55 (1.25–1.93)	1.11 (1.05–1.18)
Stroke, n	13	27	76	105		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.35 (0.64–2.44)	1.69 (0.90–3.15)	2.67 (1.41–5.05)	1.79 (1.36–2.36)	1.13 (1.04–1.23)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.08 (0.55–2.12)	1.33 (0.71–2.50)	1.91 (1.00–3.64)	1.53 (1.16–2.03)	1.06 (0.96–1.17)
CHD, n	6	21	50	77		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	2.54 (1.01–6.37)	3.40 (1.40–8.27)	6.54 (2.67–16.04)	2.26 (1.61–3.15)	1.20 (1.13–1.27)
Multivariable-adjusted HR (95% CI)	1 (Ref)	2.21 (0.88–5.53)	2.45 (1.01–5.97)	3.78 (1.53–9.33)	1.67 (1.19–2.34)	1.16 (1.08–1.25)
Max-IMT	≤0.9 mm	0.91–1.20 mm	1.21–1.70 mm	>1.7 mm	<1.7 mm vs ≤1.7 mm	Per 1-SD Increase
Participants at baseline, n	1183	1260	1193	1088	. . .	. . .
Person-years	15 640	16 954	15 375	11 940	. . .	. . .
CVD, n	27	73	108	167	. . .	. . .
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.41 (0.90–2.22)	1.93 (1.24–3.00)	2.97 (1.90–4.63)	1.73 (1.40–2.14)	1.27 (1.18–1.37)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.25 (0.79–1.96)	1.57 (1.01–2.45)	2.24 (1.44–3.50)	1.50 (1.21–1.85)	1.20 (1.10–1.30)
Stroke, n	19	49	64	89		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.22 (0.71–2.11)	1.45 (0.84–2.48)	1.96 (1.14–3.37)	1.45 (1.10–1.91)	1.18 (1.05–1.32)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.10 (0.64–1.90)	1.21 (0.71–2.07)	1.57 (0.91–2.70)	1.30 (0.98–1.71)	1.12 (0.99–1.26)
CHD, n	8	24	44	78		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	1.85 (0.82–4.18)	3.24 (1.48–7.09)	6.05 (2.77–13.23)	2.31 (1.66–3.22)	1.38 (1.25–1.52)
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.59 (0.70–3.59)	2.51 (1.15–5.49)	4.22 (1.92–9.23)	1.92 (1.37–2.68)	1.31 (1.17–1.46)

Multivariable-adjusted for age, sex, body mass index (overweight, normal weight, underweight), BP (normal, prehypertension, hypertension), total cholesterol (<160, 160–239, 240–279, ≥280 mg/dL), high-density lipoprotein cholesterol (<35, 35–50, 50–59, ≥60 mg/dL), glomerular filtration rate (≥60, 45–59, <45 mL/min/1.73 m^2), antihypertensive and antihyperlipidemic drug use, diabetes mellitus, impairment of fasting glucose, current smoking, and excessive drinking. The cutoff values of plaques for mean IMT at CCA, max-CIMT, and max-IMT were >0.95, 1.1, and 1.7 mm, respectively. CCA indicates common carotid artery; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IMT, intima–media thickness; max-CIMT, maximum intima–media thickness in the common carotid arteries; max-IMT, maximum intima–media thickness in the entire carotid artery area; Ref, reference.

Table 3. Differences of C Statistic Values for the Current Risk Prediction Model of CVD, Stroke, and CHD by Various IMT Plaques

	C Statistic Difference*	*P* Values	*z* Score
CVD			
Risk model	0		
Risk model+mean IMT in the CCA >0.95 mm	0.0192 (0.0081–0.0304)	0.001	3.37
Risk model+max-CIMT >1.1 mm	0.0178 (0.0065–0.0291)	0.002	3.08
Risk model+max-IMT >1.7 mm	0.0233 (0.0112–0.0355)	<0.001	3.76
Stroke			
Risk model	0		
Risk model+mean IMT in the CCA >0.95 mm	0.0118 (−0.0009 to 0.0246)	0.069	1.82
Risk model+max-CIMT >1.1 mm	0.0115 (0.0024–0.0206)	0.014	2.47
Risk model+max-IMT >1.7 mm	0.0112 (0.0019–0.2050)	0.019	2.35
CHD			
Risk model	0		
Risk model+mean IMT in the CCA >0.95 mm	0.0107 (−0.0014 to 0.0229)	0.084	1.73
Risk model+max-CIMT >1.1 mm	0.0120 (0.0010–0.0231)	0.032	2.14
Risk model+max-IMT >1.7 mm	0.0199 (0.0051–0.0347)	0.008	2.65

CCA indicates common carotid artery; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima–media thickness; max-CIMT, maximum intima–media thickness in the common carotid arteries; max-IMT, maximum intima–media thickness in the entire carotid artery area.
*C statistic differences and the standard error between risk score model with and without each of the 3 IMT plaques were estimated from the bootstrap samples and used to calculate a *z* score and a *P* value for the difference.

Table 4 shows the reclassification of the current categories in the risk prediction model after the addition of carotid plaques. According to the current risk prediction model, which were calculated in these cases for the risk of CVD by max-CIMT >1.1 mm and max-IMT >1.7 mm, low risk indicated a risk of <6%, intermediate risk was 6% to 20%, and high risk was >20%. The net reclassification indexes for the current risk prediction model in max-CIMT >1.1 mm and max-IMT >1.7 mm were 4.8% (18/375) and 4.3% (16/375) for the participants with events, 1.1% (50/4349) and 1.6% (71/4349) for the participants without CVD events, and 6.0±2.0% and 5.9±2.1% overall, respectively. Further statistical analyses are shown in Table S2.

After the new incident plaques in the CCA (max-CIMT >1.1 mm) and the entire CA (max-IMT >1.7 mm), we observed 112 and 117 incident CVD events (69 and 79 strokes and 43 and 38 CHDs) during 23 702 and 24 062 person-years of follow-up, respectively. Table 5 shows that after the new incident plaques (max-CIMT >1.1 mm), the multivariable-adjusted HRs for CVD and stroke were 1.95 (95% CI, 1.14–3.32) and 2.01 (95% CI, 1.01–3.99), respectively.

As shown in Table 6, compared with the first quartile of 5-year progression of max-CIMT, the multivariable-adjusted HRs for incident CVD and stroke were 2.80 (95% CI, 1.54–5.11) and 2.30 (95% CI, 1.14–4.63) in the fourth quartile, respectively. The multivariable-adjusted HRs for max-CIMT 1 mm per 5 years were 2.89 (95% CI, 1.40–5.95) for CVD and 3.06 (95% CI, 1.19–7.87) for stroke. There was no association between progression of max-IMT and CVD (data not shown). Supplemental results are expressed in Data S1.

Discussion

Our findings demonstrated that carotid artery IMT, measured noninvasively with the use of carotid artery ultrasonography,

Table 4. Reclassification of the Current Risk Prediction Model Categories After Addition of Carotid Atherosclerosis

Original Risk Category	Current Risk Model Reclassification		
	Low Risk	Intermediate Risk	High Risk
Max-CIMT >1.1 mm			
Participants with CVD events			
Low risk, n	65	10	
Intermediate risk, n	10	192	26
High risk, n		8	64
Participants without CVD events			
Low risk, n	2204	99	
Intermediate risk, n	174	1559	85
High risk, n		60	168
NRI±SE, %	6.0±2.0%, *P*=0.003		
Max-IMT >1.7 mm			
Participants with CVD events			
Low risk, n	63	12	
Intermediate risk, n	11	191	26
High risk, n		11	61
Participants without CVD events			
Low risk, n	2205	98	
Intermediate risk, n	196	1539	83
High risk, n		56	172
NRI±SE, %	5.9±2.1%, *P*=0.005		

CCA indicates common carotid artery; CVD, cardiovascular disease; IMT, intima–media thickness; max-CIMT, maximum intima–media thickness in the common carotid arteries; max-IMT, maximum intima–media thickness in the entire carotid artery area; NRI, net reclassification index.

Table 5. HRs for Incident CVD, Stroke, and CHD by IMT Progression of Max-CIMT (>1.1 mm) and Max-IMT (>1.7 mm)

	Max-CIMT			Max-IMT		
	≤1.1 mm	>1.1 mm	*P* Value	≤1.7 mm	>1.7 mm	*P* Value
Person-years	21 771	1931		22 501	1561	
CVD, n	90	22		106	11	
Age- and sex-adjusted HR (95% CI)	1 (Ref)	2.00 (1.20–3.35)	0.008	1 (Ref)	1.15 (0.57–2.32)	0.705
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.95 (1.14–3.32)	0.014	1 (Ref)	1.08 (0.53–2.22)	0.837
Stroke, cases	58	11		72	7	
Age- and sex-adjusted HR (95% CI)	1 (Ref)	2.04 (1.06–3.95)	0.034	1 (Ref)	1.20 (0.50–2.87)	0.676
Multivariable-adjusted HR (95% CI)	1 (Ref)	2.01 (1.01–3.99)	0.047	1 (Ref)	NA	
CHD, cases	32	11		34	4	
Age- and sex-adjusted HR (95% CI)	1 (Ref)	2.05 (0.90–4.66)	0.088	1 (Ref)	1.03 (0.31–3.39)	0.967
Multivariable-adjusted HR (95% CI)	1 (Ref)	1.80 (0.74–4.35)	0.195	1 (Ref)	NA	

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IMT, intima–media thickness; max-CIMT, maximum intima–media thickness in the common carotid arteries; max-IMT, maximum intima–media thickness in the entire carotid artery area; NA, not assessed (incalculable value given the small sample size); Ref, reference.

is an independent predictor of new-onset CVD events in a general Japanese population without a history of CVD at baseline. We observed that the max-CIMT and max-IMT, but not mean IMT, slightly but significantly improved classification for the prediction of incident CVD; this is the first such finding in a non-Western country. In addition, the new progression of incident carotid plaque (max-CIMT >1.1 mm) was shown to be associated with increased risks of CVD and stroke. To the best of our knowledge, this study is the first to reveal that new progression of incident carotid plaque is significantly associated with increased risk of incident CVD.

In the ARIC study, adding plaque and IMT to CHD risk prediction based on traditional risk factors improved CHD prediction, but the definition of plaque and IMT were not simple[2]; the IMT was defined as the mean of both the right and left sides of the distal CCA, the carotid artery bifurcation,

Table 6. HRs of Incident CVD, Stroke, and CHD by the Quartiles of Progression of Max-CIMT for 5 Years (Highest vs Lowest Quartiles) and Progression of Max-CIMT per 1 mm at for 5 Years

	Quartiles of 5-Year Progression of Max-CIMT		5-Year Progression of Max-CIMT per 1 mm	
	Lowest Quartile (< −0.12 mm/5 y)	Highest Quartile (>0.02 mm/5 y)	HR (95% CI)	*P* Value
CVD				
Person-years	5691	5124		. . .
Cases, n	19	39	. . .	. . .
Age- and sex-adjusted HR (95% CI)	1 (Ref)	2.80 (1.55–5.08)	2.92 (1.48–5.78)	0.002
Multivariable-adjusted HR (95% CI)	1 (Ref)	2.80 (1.54–5.11)	2.89 (1.40–5.95)	0.004
Stroke				
Cases, n	15	22		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	2.32 (1.16–4.64)	3.00 (1.24–7.24)	0.015
Multivariable-adjusted HR (95% CI)	1 (Ref)	2.30 (1.14–4.63)	3.06 (1.19–7.87)	0.020
CHD				
Cases, n	4	17		
Age- and sex-adjusted HR (95% CI)	1 (Ref)	5.14 (1.46–10.06)	2.81 (0.94–8.36)	0.064
Multivariable-adjusted HR (95% CI)	1 (Ref)	NA	2.61 (0.79–8.63)	0.114

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; max-CIMT, maximum intima–media thickness in the common carotid arteries; NA, not assessed (incalculable value given the small sample size; Ref, reference.

and the proximal ICA, and plaque was defined as meeting 2 of the following 3 abnormal criteria: wall thickness (IMT >1.5 mm), shape, and wall texture. This measurement method seems to be complicated by screening of high risk for the development of CHD.

In the Framingham Offspring Study, the mean CCA IMT and the maximum ICA IMT were independent predictors of CVD events, but only the maximum ICA IMT (>1.5 mm) significantly improved the classification of CVD risk prediction.[7] It can be said that the measurement method in the Framingham Offspring Study is simpler than that in the ARIC study. In the Framingham Offspring Study, Cox models were used by comparing the respective C statistics for the Framingham Risk Score[20] before and after the addition of the variables for ICA IMT. In our present study, ICA IMT could not be evaluated in ≈10% of the participants. Compared with Western patients, the carotid bifurcation in Japanese patients is higher by ≈1 cervical vertebra.[21] Consequently, we could not measure ICA IMT by carotid ultrasonography for ≈10% of our participants and could not use ICA IMT; instead, we used max-IMT. Our analyses revealed that max-CIMT >1.1 mm could be used to predict the incidence CVD, which significantly improved the classification of CVD risk prediction. Among the previous relevant Japanese population studies, there is a single study of the association between carotid IMT ≥1.1 mm (the highest quartile) and incident stroke.[22] The US guidelines emphasize CVD risk as a high-risk indicator when CCA IMT is >75th percentile.[23,24]

To our knowledge, our study is the first to show that the progression of max-CIMT >1.1 mm can be used to predict incident CVD, stroke, and CHD after that. In the PROG-IMT Collaborative Project, there was no evidence of an association between individual IMT progression and the risk of subsequent CVD events,[10] but the mean follow-up periods for the scan interval of carotid ultrasonography and the mean CVD follow-up periods after the second scan were only 3.7 and 6.9 years on average, respectively, which are shorter durations than that of our follow-up study, at 5.1 years for the scan interval and 10.3 years for incident CVD. Our follow-up period was not long enough; we believe that, empirically, the minimum follow-up period for incident CVD is >10 years.

Compared with Western patients, Japanese patients have higher prevalence of hypertension, smoking, and excessive alcohol use,[25] which are risk factors for incident stroke and CHD. The slope of the association between BP and CVD is steeper among Asian patients than Australasian patients.[26] Systolic BP and smoking are more strongly associated with IMT in Asian patients.[27] These characteristic backgrounds may have accentuated the association between the progression of plaque and incident CVD in our study.

Pathologically, IMT represents mainly hypertensive medial hypertrophy and thickening of smooth muscles in the media, which seem to be related to changes in local shear stress and represent partial arterial remodeling at the early stages of atherosclerosis.[28] In contrast, carotid plaque is largely associated with traditional risk factors, namely, endothelial dysfunction, oxidative stress, smooth muscle cell proliferation, and an intimal process (with deposition of cholesterol, inflammation, and cell infiltration) at a later stage of atherogenesis.[29–32] Epidemiologically, mean IMT is more predictive of stroke than of CHD, and the reverse is true for carotid plaque,[28,29,33] which is compatible with our data (Table 2).

This study has several strengths. First, this study was the first to investigate whether the development of carotid plaque is associated with incident stroke and CHD. The previous studies reported no association between the development of carotid plaque and incident stroke and CHD. Our present study covered a relatively long period and a relatively large sample size. Second, the same cohort of participants was examined by carotid ultrasonography every 2 years during follow-up. Third, the same followed cohort members were randomly selected from the population registry of Suita City and stratified into groups by sex and 10-year age increments in a premeditated manner. This cohort is representative of Japan's urban population, which composes >70% of the country's population. Fourth, the Suita Risk Score for CHD has just been adopted in the Japan Atherosclerosis Society "Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases" in Japan, 2017 version.[34] We use this guideline to evaluate the relationship between atherosclerosis and CVD prevention in Japan. The Suita Study is representative of CVD cohort studies in Japan. Fifth, the average number of follow-up years for incident CVD after the progression of carotid plaque exceeded 10 years of follow-up. The mean follow-up period in the PROG-IMT Collaborative Project was 6.9 years.[10]

There were also several study limitations. As mentioned, we did not use ICA IMT in this study because we could not measure all IMTs at the ICA, but we measured max-IMT in the entire area as much as possible. Second, our data were obtained in a Japanese urban population, and although our findings might be useful for Asian communities, they might not be helpful for individuals of other ethnicities and racial backgrounds. Nonetheless, we observed that the progression of carotid plaque is associated with future CVD events. Our data showed that carotid plaque was more predictive of CHD than of stroke, as in previous studies.[28,29,33] Further studies are needed to elucidate whether the progression of incident plaque at the CCA is associated with an increased risk of incident CVD. Third, the IMT values could not be divided into quartiles precisely because of the discrete values of IMT. For the evaluation of the relationship of quantity reactivity, we also examined the association of risks per 1 mm and 1 SD of IMT values with CVD. Fourth, we could not recruit both ≈23%

of the attendees at medical examinations during the baseline survey (Table S1) and the carotid ultrasonographic follow-up after the baseline survey (Tables S3 and S4). We found similar but slightly significant differences in clinical background between the study participants and nonparticipants at both the baseline and carotid ultrasonographic follow-up. The main reasons for exclusion from this study were scheduling issues and unavailability of the ultrasonographic device by 1 specific physician rather than health problems. The participants in this study were randomly extracted at medical examination visits, but those who were not subjects for carotid ultrasonography were encouraged to be examined every 2 years during follow-up. It is possible that high-risk participants may have dropped out during follow-up of cardiovascular events; therefore, it is possible that the association may be underestimated. Fifth, we do not have any standardized tools such as an arc when we measure carotid IMT. Although measurement errors cannot be avoided, a specific well-trained physician performed the examinations and good reproducibility was obtained. Sixth, defining max-CIMT values >75th percentile as plaque may be premature even though evidence shows that CVD risk increases with >75th percentile values. Incidental findings that may require further evaluation should be described such as a soft plaque, calcification finding, and meandering of the carotid artery. Seventh, we did not use the Suita Risk Score in this study because the risk score is based on a risk model for CHD events. Consequently, we directly conducted analyses by using each variable of the Suita Risk Score[19] in the Cox regression model with the current data. Finally, we did not examine the types of antihypertensive and statin agents used by the participants. We put antihyperlipidemic drug use in the statistical models, and we did not observe an association with carotid atherosclerosis. When divided into 2 groups, whether controlled by taking antihyperlipidemic drugs or not, incident CVD and CHD were higher in the uncontrolled group (Table S5). Most antihyperlipidemic drugs used were statins, but they were not classified by type of statin agent, and the current study started at the same time as statin use in the early 1990s. Because the rate of statin use rose during the follow-up periods (Table S6), it is necessary to analyze the time dependency of statins, but that is a subject for future research.

Conclusions

High mean CIMT and carotid plaque in the CCA and entire carotid artery area were risk factors for CVD in a general Japanese population. Among the carotid ultrasonographic indexes, max-CIMT >1.1 mm was revealed to be associated with increased risks of CVD, stroke, and CHD by the C statistic improvement and the reclassification of the current risk prediction model. New progression of incident carotid plaque (max-CIMT >1.1 mm) was shown to be associated with an increased risk of CVD. In medical examinations and outpatient clinics, carotid ultrasonography at the CCA is easily measured at screening, and thus carotid plaque (max-CIMT >1.1 mm) could be evaluated to help prevent increased risk of future CVD. We plan to develop a risk score for carotid atherosclerosis using the Suita Study population shortly, with the ultimate goal of using this score in medical examinations and outpatient clinics as a preventive screening measure for carotid atherosclerosis without the requirement of carotid ultrasonography.

Acknowledgments

We thank Dr Katsuyuki Kawanishi, the president of the Suita Medical Association, for his support of the Suita Study. We also thank the members of the Suita City Health Center, the Suita Medical Association, and all the researchers and staff of the Department of Preventive Cardiology for performing the medical examinations and the follow-up; and Satsuki-Junyukai, the volunteers involved in the administration of the Suita Study. We thank Drs Kazuyuki Nagatsuka, Masatoshi Koga, and Michikazu Nakai for the valuable discussions.

Sources of Funding

This study was supported by grants-in-aid from the Ministry of Health, Labor, and Welfare of Japan: Challenging Exploratory Research (grant no. 17K19873) and a Grant-in-Aid for Scientific Research B (no. 16H05252), and the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-1-2) in Japan.

Disclosures

None.

References

1. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:3017–3021.
2. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607.
3. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467.
4. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita Study. *Stroke*. 1997;28:518–525.
5. Tran LT, Park HJ, Kim HD. Is the carotid intima-media thickness really a good surrogate marker of atherosclerosis? *J Atheroscler Thromb*. 2012;19:680–690.
6. Koivistoinen T, Virtanen M, Hutri-Kahonen N, Lehtimaki T, Jula A, Juonala M, Moilanen L, Aatola H, Hyttinen J, Viikari JS, Raitakari OT, Kahonen M. Arterial pulse wave velocity in relation to carotid intima-media thickness, brachial flow-mediated dilation and carotid artery distensibility: the Cardiovascular Risk in

Young Finns Study and the Health 2000 Survey. *Atherosclerosis*. 2012;220:387–393.

7. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365:213–221.
8. van den Oord SC, Sijbrands EJ, ten Kate GL, van Klaveren D, van Domburg RT, van der Steen AF, Schinkel AF. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. *Atherosclerosis*. 2013;228:1–11.
9. Bots ML, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Ikram MA, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Franco OH, Peters SA, den Ruijter HM. Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. *Hypertension*. 2014;63:1173–1181.
10. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Volzke H, Tuomainen TP, Sander D, Plichart M, Catapano AL, Robertson CM, Kiechl S, Rundek T, Desvarieux M, Lind L, Schmid C, DasMahapatra P, Gao L, Ziegelbauer K, Bots ML, Thompson SG; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet*. 2012;379:2053–2062.
11. Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita Study. *Hypertension*. 2008;52:652–659.
12. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kobayashi T, Watanabe T, Okamura T, Okayama A, Miyamoto Y. Interaction of blood pressure and body mass index with risk of incident atrial fibrillation in a Japanese urban cohort: the Suita Study. *Am J Hypertens*. 2015;28:1355–1361.
13. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i–xii, 1-253.
14. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol*. 2007;11:41–50.
15. Inamoto N, Katsuya T, Kokubo Y, Mannami T, Asai T, Baba S, Ogata J, Tomoike H, Ogihara T. Association of methylenetetrahydrofolate reductase gene polymorphism with carotid atherosclerosis depending on smoking status in a Japanese general population. *Stroke*. 2003;34:1628–1633.
16. Mannami T, Baba S, Ogata J. Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: the Suita Study. *Arch Intern Med*. 2000;160:2297–2303.
17. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981;12:I13–I44.
18. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation*. 1994;90:583–612.
19. Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the Framingham Risk Score: the Suita Study. *J Atheroscler Thromb*. 2014;21:784–798.
20. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
21. Toyota A, Shima T, Nishida M, Yamane K, Okada Y, Csiba L, Kollár J, Sikula J. Angiographical evaluation of extracranial carotid artery: comparison between Japanese and Hungarian. *No To Shinkei*. 1997;49:633–637.
22. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, Kiyama M, Tanigawa T, Yamagishi K, Shimamoto T. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke*. 2004;35:2788–2794.
23. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK; American College of Cardiology Foundation/American Heart Asscoiation Tasl Force on Practice G. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:2748–2764.
24. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS; American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189–190.
25. Kokubo Y. Prevention of hypertension and cardiovascular diseases: a comparison of lifestyle factors in Westerners and East Asians. *Hypertension*. 2014;63:655–660.
26. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S; Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707–716.
27. Gijsberts CM, Groenewegen KA, Hoefer IE, Eijkemans MJ, Asselbergs FW, Anderson TJ, Britton AR, Dekker JM, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Holewijn S, Ikeda A, Kitagawa K, Kitamura A, de Kleijn DP, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Pasterkamp G, Peters SA, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Bots ML, den Ruijter HM. Race/ethnic differences in the associations of the Framingham Risk Factors with carotid IMT and cardiovascular events. *PLoS One*. 2015;10:e0132321.
28. Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. *Curr Cardiol Rep*. 2009;11:21–27.
29. Spence JD. Technology insight: ultrasound measurement of carotid plaque—patient management, genetic research, and therapy evaluation. *Nat Clin Pract Neurol*. 2006;2:611–619.
30. Spence JD, Hegele RA. Noninvasive phenotypes of atherosclerosis: similar windows but different views. *Stroke*. 2004;35:649–653.
31. Hegele RA. The pathogenesis of atherosclerosis. *Clin Chim Acta*. 1996;246:21–38.
32. Roquer J, Segura T, Serena J, Cuadrado-Godia E, Blanco M, Garcia-Garcia J, Castillo J, Study ARTICO. Value of carotid intima-media thickness and significant carotid stenosis as markers of stroke recurrence. *Stroke*. 2011;42:3099–3104.
33. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. 2012;220:128–133.
34. *Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases*. Tokyo, Japan: Japan Atherosclerosis Society; 2017.

Supplemental Material

Data S1.

Expanded Methods

Study Participants

As a baseline, 12,200 and 3,000 participants (age 30–79 years) were randomly selected in 1989 and 1996, respectively, from the municipality population registry of Suita City and stratified into groups by sex and age in 10-year increments. Of these, participants attending the baseline examination of the original (n=6,485) and the second cohort (n=1,329) were eligible for the present investigation from 1989–1996 and 1996–1998, respectively. In the present study, the baseline examination of a volunteer group (n=546, in 1992–2006) was also included. Informed consent was given by all participants.

We compared the baseline characteristics of the three cohort groups (original, secondary, and volunteer). [1] Although the prevalence of hyperlipidemia and overweight were higher in the volunteer group, lifestyle habits (i.e., smoking and drinking) and the mean systolic and diastolic blood pressures (SBP and DBP) were similar among the three groups.

Carotid Intra-Medial Thickness Measures

The subject was in a supine position on a bed, and the extracranial carotid arteries were scanned bilaterally along three different longitudinal axes and a cross-sectional axis in the following manner. First, the CCA, internal (ICA), and external carotid artery (ECA) were examined along a cross-sectional plane with the subject lying with jaw upright and turning his or her head to the other side while under examination.

Second, the CCA, ICA, and ECA were examined along three different longitudinal plane axes, i.e., the anterior-oblique, lateral, and posterior-oblique planes. Each measurement was made primarily in the lateral plane, and the evaluation of stenosis was made in the cross-sectional plane. Third, the carotid artery of the other side was examined in the same way, with the subject lying with jaw upright and turning his or her head to the side under examination.

The IMT was measured on a longitudinal scan of the CCA at a point of 10 mm proximal from the beginning of the dilation of the bulb. IMT was defined as the mean of the IMT of the near and far walls at the point of measurement. Its scan pattern is characterized by two echogenic lines separated by a hypoechoic or anechoic space. The outer line corresponds to the medial-adventitial border and the inner line to the luminal-intimal border. Thus, the distance between the two parallel lines represents the IMT.

Expanded Results

The baseline characteristics of the current and excluded subjects were shown in **Table S1**. We have included a table on the baseline characteristics of the subjects of the current study, excluded from the present study, and with past illness of cardiovascular disease as a Supplement Table 1. The subjects (n=1,514) who were excluded from this study consisted of 1,008 who had not undergone a medical examination that included ultrasonography and 506 who could not be followed-up to the end of 2013. Compared with the current subjects, means age, systolic blood pressure, total cholesterol, and HDL cholesterol and the prevalence of cigarette smoking were significantly but slightly different from the subjects excluded from this study.

IDI showed improvements of discrimination (Supplement Table 2). Results of Bayesian information criterion and likelihood ratio test showed the improvement of calibration by adding max-CIMT >1.1 mm or max-IMT >1.7 mm to the current risk prediction models.

Our plaque definitions (CIMT>1.1 mm and IMT>1.7 mm) were based on above the 75 percentile of the study population. The Japanese Carotid Ultrasound Examination Guideline shows that plaque is defined as IMT>1.1 mm.[2] However, this guideline lack evidence of the association between IMT>1.1 mm and cardiovascular disease event.

During the follow-up of carotid ultrasonographic measurement, we excluded the subjects with plaques at the baseline (Max-CIMT >1.1 mm n=1,088 for Max-IMT >1.7 mm), lost to follow-up subjects, and subjects with incident CVD during follow-up carotid echo examination. **Tables S3** and **S4** showed the baseline characteristics of the Max-CIMT and Max-IMT followers, lost to follow-up subjects, and subjects with incident CVD during follow-up of carotid ultrasonographic measurement, respectively. Compared with carotid ultrasonographic followers, age, sex, systolic and diastolic blood pressure, glomerular filtration rate, antihypertensive drug use, diabetes, and prevalence of cigarette smoking were significantly but slightly different in Lost to follow-up subjects. The Max-CIMT and Max-IMT differences between carotid plaque followers and lost to follow-up subjects due to follow-up of the Max-CIMT and Max-IMT were not significant (P= 0.067 and 0.302), respectively.

Table S5 showed the cross-sectional study for the risks of plaques and the prospective study for the risks of CVD according to the non-HDL cholesterol levels and antihyperlipidemic drug use. The cross-sectional study showed that uncontrolled non-

HDL cholesterol was increased risks of carotid plaques (Max-CIMT>1.1 mm and Max-IMT>1.7 mm). Similarly, the prospective study showed that uncontrolled non=HDL cholesterol was increased risks of incident cardiovascular disease and coronary heart disease, and that controlled non-HDL cholesterol was not increased risks of CVD, stroke, and coronary heart disease.

Antihyperlipidemic drug user did not become statistically significant with carotid plaque (IMT-CMax>1.1mm) when the antilipidemic drug was put into the Cox model independently of total cholesterol categories. The hazard ratios for carotid plaque (IMT-CMax>1.1 mm) in categories of total cholesterol and HDL cholesterol levels on covariates were as follows. Compared with total cholesterol levels <160 mg/dL, multivariable HRs (95% CI) for carotid plaque were 1.69 (1.24-2.21) and 2.03 (1.31-3.15) in total cholesterol (240-279 mg/dL and 280- mg/dL), respectively. Compared with HDL cholesterol (35-50 mg/dL), multivariable HRs (95% CI) for carotid plaque were 0.83 (0.72-0.97) and 0.75 (0.65-0.87) in HDL cholesterol levels (35-49 mg/dL and 50-59 mg/dL), respectively. Therefore, antilipidemic drug uses were not independent risk of arteriosclerosis, but were found to be related to arteriosclerosis via TC and HDL levels (data not shown).

Carotid ultrasonographic follow-ups were performed every two years between April 1998 and March 2005. During the follow-ups, we divided the 5-yeart progression of Max-CIMT by quartiles. Compared with the highest (fourth) quartile group (the progression Max-CIMT >0.02 mm/5 years), mean value of diastolic blood pressure and excessive drinking rate decreased and antihyperlipidemic drug use increased in the lowest (first) quartile group (the progression Max-CIMT <-0.12 mm/5 years), although we observed the increasing antihypertensive drug use and diabetes and the decreasing of cigarette smoking rates in both the lowest and highest progression Max-CIMT (**Table S6**).

Table S1. Baseline Characteristics of the Subjects of the Current Study, Excluded from This Study, and with Past Illness of CVD.

Characteristic	The current subjects (n=4,724)	The subjects excluded from this study* (n=1,514)	P value	The subjects with past illness of CVD (n=352)	P value
Age, year	59.6±11.8	58.6±14.3	0.008	69.8±8.8	<0.001
Sex (Men, %)	45.7	46.1	0.785	64.7	<0.001
Body mass index, kg/m^2	22.6±3.1	22.6±3.2	0.686	23.0±3.1	0.022
Systolic blood pressure, mmHg	127.2±19.6	128.7±22.6	0.016	136.9±20.5	<0.001
Diastolic blood pressure, mmHg	78.5±10.8	78.9±12.1	0.121	80.0±10.8	0.012
Total cholesterol, mg/dL	209.6±33.1	206.7±36.1	0.003	201.6±33.5	<0.001
HDL cholesterol, mg/dL	60.1±15.7	58.5±14.8	<0.001	55.1±15.1	<0.001
Glomerular filtration rate, mL/min/1.73m^2	80.5±20.8	77.8±20.4	<0.001	69.2±19.5	<0.001
Antihypertensive drug use, %	15.6	17.0	0.200	45.7	<0.001
Antihyperlipidemic drug use, %	5.2	4.5	0.297	12.5	<0.001
Diabetes, %	4.5	6.2	0.650	10.8	<0.001
Cigarette smoking, %	23.7	28.8	<0.001	21.3	0.322
Excessive drinking, %	8.3	8.8	0.500	7.1	0.434
Intima-media thickness					
Mean CCA thickness, mm	0.86±0.14	-		0.97±0.14	<0.001
Maximum CCA thickness, mm	1.06±0.39	-		1.34±0.54	<0.001
Maximum carotid artery thickness, mm	1.44±0.70	-		2.05±0.98	<0.001
CCA thickness>1.1 mm, indicating plaque, %	21.6	-		56.9	<0.001

*The subjects consisted of 1,008 who had not undergone a medical examination that included ultrasonography and 506 who could not be followed-up to the end of 2013.

Plus-minus values are means ±standard deviations. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Analyses of variances and chi-square tests were used to compare mean values and frequencies (the current subjects vs. the subjects excluded from this study or with past illness of cardiovascular disease). CCA, common carotid artery; HDL, high-density lipoprotein; CVD, cardiovascular disease.

Table S2. Comparison of Risk Prediction Models with Max-CIMT >1.1 mm or Max-IMT >1.7 mm in the Current Study.

	Risk prediction model	Risk prediction model + Max-CIMT >1.1 mm	Risk prediction model + Max-IMT >1.7 mm
Discrimination			
Absolute IDI	-	0.0094, p<0.001	0.0084, p<0.001
Calibration			
Likelihood ratio test, p value	-	p<0.001	p=0.004
Bayes information criterion	5.849 x 103	5.818 x 103	5.811 x 103

IDI, integrated discrimination index; NRI, net reclassification index; Max-CIMT, maximum intima-medial thickness of common carotid artery; Max-IMT, maximum intima-medial thickness of whole carotid artery

Table S3. Baseline Characteristics of the Max-CIMT Followers, Lost to Follow-up Subjects, and Subjects with Incident CVD During Follow-up of Max-CIMT.

Characteristic	Max-CIMT Followers (n=2,722)	Lost to Follow-up Subjects* (n=804)	P value	Subjects with Incident CVD During Follow-up of Max-CIMT* (n=42)	P value
Age, year	56.6±10.8	57.7±13.1	0.011	64.1±7.5	<0.001
Sex (Men, %)	40.6	46.0	0.007	54.8	0.065
Body mass index, kg/m^2	22.5±3.0	22.4±3.4	0.836	22.7±2.3	0.648
Systolic blood pressure, mmHg	123.3±18.0	125.7±18.9	0.001	130.2±18.8	0.015
Diastolic blood pressure, mmHg	77.5±10.4	78.5±11.5	0.021	80.7±9.9	0.052
Total cholesterol, mg/dL	207.8±32.5	206.1±33.3	0.199	214.3±34.1	0.204
HDL cholesterol, mg/dL	61.4±15.6	60.3±16.2	0.067	59.7±16.5	0.488
Glomerular filtration rate, mL/min/1.73m^2	83.2±21.4	80.8±19.9	0.004	74.8±20.2	0.011
Antihypertensive drug use, %	10.0	14.6	<0.001	14.2	0.374
Antihyperlipidemic drug use, %	4.4	4.4	0.882	7.1	0.409
Diabetes, %	3.0	5.4	0.002	2.4	0.826
Cigarette smoking, %	22.1	25.4	0.047	19.0	0.644
Excessive drinking, %	8.3	9.7	0.225	14.3	0.175
Intima-media thickness					
Mean CCA thickness, mm	0.808±0.093	0.813±0.101	0.185	0.858±0.069	<0.001
Maximum CCA thickness, mm	0.917±0.116	0.925±0.120	0.067	0.993±0.078	<0.001
Maximum carotid artery thickness, mm	1.238±0.496	1.281±0.573	0.037	1.576±0.833	<0.001

*The lost to follow-up subjects consisted of 804 who had not attended a medical examination that included ultrasonography and 42 who had cardiovascular disease events during the follow-up of carotid artery ultrasonography period.

Plus-minus values are means ±standard deviations. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Analyses of variances and chi-square tests were used to compare mean values and frequencies. CCA, common carotid artery; HDL, high-density lipoprotein; CVD, cardiovascular disease; Max-CIMT, maximum of common carotid intima-medial thickness.

Table S4. Baseline Characteristics of the Max-IMT Followers, Lost to Follow-up Subjects, and Subjects with Incident CVD During Follow-up of Max-IMT.

	Max Carotid Plaque Followers	Lost to Follow-up Subjects		Subjects with Incident CVD During Follow-up of Max-IMT	
Characteristic	(n=2,768)	(n=822)	P value	(n=46)	P value
Age, year	56.9±10.9	57.9±13.0	0.030	64.2±7.5	<0.001
Sex (Men, %)	39.5	44.9	0.006	50.0	0.150
Body mass index, kg/m^2	22.6±3.0	22.7±3.4	0.379	23.0±2.4	0.341
Systolic blood pressure, mmHg	124.0±18.4	126.5±19.3	<0.001	127.5±16.8	0.211
Diastolic blood pressure, mmHg	77.7±10.6	78.6±11.3	0.025	79.2±9.2	0.320
Total cholesterol, mg/dL	208.8±33.0	207.4±33.0	0.290	213.1±31.7	0.382
HDL cholesterol, mg/dL	61.3±15.5	59.9±16.3	0.030	58.1±16.3	0.178
Glomerular filtration rate, mL/min/1.73m^2	83.0±21.4	80.7±20.5	0.006	77.8±19.3	0.102
Antihypertensive drug use, %	10.8	15.0	<0.001	15.2	0.353
Antihyperlipidemic drug use, %	4.0	4.5	0.520	8.7	0.116
Diabetes, %	3.2	6.0	<0.001	2.2	0.715
Cigarette smoking, %	21.1	2.6	0.002	19.5	0.799
Excessive drinking, %	7.3	8.8	0.157	13.0	0.147
Intima-media thickness					
Mean CCA thickness, mm	0.824±0.112	0.833±0.126	0.044	0.888±0.098	<0.001
Maximum CCA thickness, mm	0.960±0.181	0.977±0.196	0.017	1.063±0.137	<0.001
Maximum carotid artery thickness, mm	1.138±0.283	1.149±0.282	0.302	1.276±0.232	0.001

*The lost to follow-up subjects consisted of 822 who had not attended a medical examination that included ultrasonography and 46 who had cardiovascular disease events during the follow-up of carotid artery ultrasonography period.

Plus-minus values are means ±standard deviations. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Analyses of variances and chi-square tests were used to compare mean values and frequencies. CCA, common carotid artery; HDL, high-density lipoprotein; CVD, cardiovascular disease; Max-IMT, maximum of carotid intima-medial thickness in the entire area.

Table S5. Cross-sectional Study for the Risks of Plaques and Prospective Study for the Risks of Cardiovascular, Stroke, Coronary Heart Disease According to the Non-HDLC Categories.

	Non-HDLC categories			
	Non-antilipidemic drug use		Controlled	Uncontrolled
	<160 mg/dL	160-189 mg/dL	non-HDLC	non-HDLC
Cross-sectional study				
Number of subjects, n	2,627	1,851	265	647
Cases of plaque (Max-CIMT>1.1 mm), n	450	515	74	217
Multivariable adjusted-odds ratios (95% CIs)	1 (reference)	1.61 (1.36-1.90)	1.12 (0.82-1.55)	2.25 (1.80-2.83)
Cases of plaque (Max-IMT>1.7 mm), n	460	449	86	162
Multivariable adjusted-odds ratios (95% CIs)	1 (reference)	1.36 (1.15-1.61)	1.71 (1.26-2.33)	1.51 (1.20-1.91)
Prospective study				
Number of subjects, n	2,503	1,770	247	613
Person-years	31,286	21,907	2,865	7,629
Cardiovascular disease, n	147	168	19	66
Multivariable adjusted-hazard ratios (95% CIs)	1 (reference)	1.33 (1.05-1.67)	0.99 (0.61-1.61)	1.53 (1.13-2.08)
Stroke, n	97	96	9	35
Multivariable adjusted-hazard ratios (95% CIs)	1 (reference)	1.19 (0.89-1.60)	0.63 (0.31-1.25)	1.32 (0.88-1.98)
Coronary heart disease, n	50	72	10	31
Multivariable adjusted-hazard ratios (95% CIs)	1 (reference)	1.60 (1.10-2.31)	1.83 (0.91-3.66)	1.98 (1.24-3.16)

HDLC, high density lipoprotein cholesterol; Non-HDLC=total cholesterol-HDLC. Controlled non-HDLC was defined as taking anti-hyperlipidemic drugs to control non-HDLC to less than 190 mg/dL. Uncontrolled non-HDLC was defined as non-HDLC over 190 mg/dL irrespective of taking antihyperlipidemic drug use. Multivariable adjusted for age, sex, body mass index (overweight, normal weight, underweight), blood pressure (normal blood pressure, prehypertension, grade I or II+III hypertension), high density lipoprotein cholesterol (<35, 35-50, 50-59, 60- mg/dL), glomerular filtration rate (≥60, 45-59, <45 mL/min/1.73m^2), antihypertensive drug uses, diabetes, impairment of fasting glucose, current smoking, and excessive drinking. Max-CIMT, maximum intima-media thickness at the common carotid arteries; Max-IMT, maximum intima-media thickness of the whole carotid arteries; Ref, Reference; CIs, confidence intervals.

Table 6. Characteristics of the Participants at the Baseline and Endpoint Survey During Carotid Echo and Changes of Characteristics by 5-year Follow-up Periods.

	The lowest quartile group (n=691)			The highest quartile (n=565)		
Characteristic	Baseline survey of carotid echo	Endpoint survey of carotid echo	Changes by 5-year follow-up	Baseline survey of carotid echo	Endpoint survey of carotid echo	Changes by 5-year follow-up
Age, year	59.2±10.7	64.5±10.9	-	57.8±10.9	62.5±11.0	-
Body mass index, kg/m^2	22.5±2.9	22.6±3.1	0.10 (0.06)	22.8±3.2	22.9±3.3	0.16 (0.07)*
Systolic blood pressure, mmHg	125.0±18.3	125.3±19.5	1.14 (0.83)	126.7±18.7	127.5±19.1	1.17 (0.91)
Diastolic blood pressure, mmHg	78.5±10.0	75.7±10.7	-2.77 (0.52)†	78.8±10.6	78.5±10.2	-0.13 (0.57)
Total cholesterol, mg/dL	209.8±32.9	208.8±33.5	-0.59 (1.37)	208.2±32.6	209.8±32.0	2.68 (1.50)
HDL cholesterol, mg/dL	62.9±16.0	61.8±15.4	-0.68 (0.52)	58.9±15.8	59.5±15.8	0.65 (0.56)
Antihypertensive drug use, %	12.3	19.4	6.3†	12.0	16.4	3.9*
Antihyperlipidemic drug use, %	5.6	9.8	3.6*	5.1	7.4	2.0
Diabetes, %	3.5	5.7	2.3*	4.2	5.8	2.7*
Cigarette smoking, %	20.6	16.2	-4.2†	25.7	21.5	-5.1†
Excessive drinking, %	9.6	7.1	-2.4*	9.9	8.0	-2.0

Plus–minus values are means ±SD. The parentheses indicate the 5-year follow-up adjusted means and standard errors. The differences are the values per five years of the differences between the values at baseline and endpoint. HDL, high-density lipoprotein. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. *p<0.05 and †p<0.001 differences between baseline and endpoint surveys by 5-year follow-up period.

Supplemental References:

1. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kobayashi T, Watanabe T, Okamura T, Okayama A, Miyamoto Y. Interaction of Blood Pressure and Body Mass Index With Risk of Incident Atrial Fibrillation in a Japanese Urban Cohort: The Suita Study. *Am J Hypertens*. 2015;28:1355-1361

2. The Joint Committee of The Japan Academy of Neurosonology and The Japan Society of Embolus Detection and Treatment on Guideline for Nuerosonology. Carotid Ultrasound Examination Guideline. *Neurosonology*. 2006;9:49-69. (Japanese)