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A Comparison of Segment-Specific and Composite Measures of Carotid Intima-Media Thickness and their Relationships with Coronary Calcium

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Aims: The utility of carotid intima-media thickness (cIMT) as a marker for coronary heart disease is under heavy debate. This is predominantly due to the lack of a standard definition of cIMT, leading to inconsistent results. We investigated and compared the relationships of five different measures of cIMT with coronary calcium.

Methods: Japanese men aged 40-79y (n=869) from Shiga Epidemiological Study of Subclinical Atherosclerosis were examined. Mean cIMT was measured in three segments of the carotid arteries: common carotid artery (CCA_{mean}), internal carotid artery (ICA_{mean}) and bifurcation (Bif_{mean}). Mean cIMT of average values (Mean cIMT) and mean cIMT of maximum values (Mean-Max cIMT) of all segments combined were assessed. Coronary calcium was assessed as coronary artery calcification (CAC). Ordinal logistic regression was used to determine the odds ratio (OR) of higher CAC per 1 standard deviation higher cIMT measure. Analyses were adjusted for cardiovascular covariates and stratified by age quartiles.

Results: All cIMT measures had positive associations with CAC ($p<0.001$): [OR, 95% Confidence Interval]: ICA_{mean} [1.23, 1.07-1.42], CCA_{mean} [1.27, 1.08-1.49], Bif_{mean} [1.33, 1.15-1.53], Mean cIMT [1.42, 1.22-1.66], and Mean-Max [1.50, 1.28-1.75]. In age-stratified analyses, only Mean-Max cIMT maintained a significant relationship with CAC in every age quartile ($p<0.05$), while CCA_{mean} had some of the weakest associations among age quartiles.

Conclusions: Mean-Max cIMT had consistently stronger associations with coronary calcium, independent of important confounders, such as age. The most oft-used measure, CCA_{mean}, was no longer associated with coronary calcium after age-adjustment and stratification.

Key words: Carotid intima-media thickness (cIMT), Coronary artery calcification (CAC), Coronary atherosclerosis, Carotid atherosclerosis, Carotid artery

Introduction

Carotid intima-media thickness (cIMT) is a measure of the thickness of the intimal and medial layers of the carotid arteries[1)] and is representative of generalized atherosclerosis in the body[2)]. Not only is higher cIMT associated with higher risk of incident coronary heart disease (CHD)[3-5)], but it has been found to improve risk prediction beyond traditional cardiovascular risk factors[6)]. These findings highlight the potential for cIMT to be used as a surrogate for CHD events in epidemiological studies[7)] or as an early

screening tool for CHD prevention in the general population[4].

The availability, affordable cost, and ease of use of ultrasound equipment has resulted in the widespread use of cIMT in CHD- and cardiovascular disease (CVD)-related studies worldwide[8]. Unfortunately, this has led to poor standardization of methodology and an inconsistent definition of cIMT[9]. Different research groups have used different segments of the carotid artery and their combinations, either out of convenience or out of discrepancies in knowledge or experience, to represent cIMT[1]. This in part has led to inconsistent findings with regards to improved cardiovascular risk prediction in the general population[10].

Since different cIMT definitions may reflect distinct underlying pathophysiology, a thorough assessment of their characteristics and relationships with CHD and coronary atherosclerosis are needed. However, few studies have compared the different segments and definitions of cIMT in relation to their associations with CHD risk[11-13]. Uncovering which measures of cIMT are most related to CHD and its risk factors will help determine whether specific cIMT definitions provide more useful information beyond traditional and well-known CHD risk factors, a possible guide for epidemiological research and future screening with cIMT.

Aim

We propose to look at different intima-media thickness (IMT) measures of the carotid arteries that are often defined as "cIMT" and compare their relationships with coronary artery calcification (CAC), a manifestation of coronary atherosclerosis and a strong surrogate marker for CHD[5]. Although both cIMT and CAC can independently predict CHD and CVD events, CAC has been found to be the better predictor for both[14].

Methods

Study Participants

We studied participants enrolled in the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), who were randomly selected from Kusatsu City, Shiga, Japan in 2006-2008[15, 16]; a total of 1094 men aged 40-79 years old. Participants who had history of myocardial infarction (n=29) or stroke (n=40), on lipid medication (n=168) or had missing information on cIMT or CAC (n=33) were excluded from this present study. A total of 225 men were excluded (some participants fell in more than one category for exclusion criteria). Individuals on lipid medication were excluded since the use of lipid medication, such as statins, has been found to reduce cIMT progression[17, 18]. Thus, a total of 869 Japanese men were analyzed. All participants provided written informed consent. This study conforms to the Declaration of Helsinki and was approved by the Institutional Review Board of Shiga University of Medical Science, Japan.

Participants completed a questionnaire involving medical history, use of medication, smoking and drinking behavior, as well as other lifestyle traits. Smoking amount was defined in pack-years. Alcohol intake was defined as grams of alcohol per week (g/week). Trained technicians reviewed answers to the completed questionnaire with each participant individually.

A physical examination was performed to collect data on height, weight, blood pressure and other physical measurements. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Blood pressure was measured using an automated sphygmomanometer (BP-8800, Omron Colin, Japan) after participants were motionless in a seated position for 5 minutes. The mean of two consecutive measurements of the right arm was used to estimate blood pressure.

Hypertension was defined as a systolic blood pressure (SBP) of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg or use of anti-hypertensive medication. Diabetes was defined as a fasting glucose ≥ 6.99 mmol/L (≥ 126 mg/dL) or hemoglobin A1c of ≥ 6.1 % measured by Japanese Diabetes Society (JDS) criteria; equivalent to ≥ 6.5% with National Glycohemoglobin Standardization Program (NGSP) criteria[19].

Blood Samples

Blood was drawn from all participants after a 12-hour fast. Blood samples were centrifuged at 4℃ and serum was collected and stored at −80℃. Serum total cholesterol was measured using enzymatic techniques and high-density lipoprotein cholesterol (HDL-C) was measured using heparin-calcium

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precipitation. US Center for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network (CDC/CRMLN) protocol was followed for standardization of measurements. Friedewald equation was used to estimate low-density lipoprotein cholesterol (LDL-C) levels [LDL-C = total cholesterol (mg/dL) – HDL-C (mg/dL) – triglyceride (mg/dL) / 5] in participants with triglycerides ≤ 4.52 mmol/L (≤ 400 mg/dL) (n = 857). Non-HDL-C was calculated as Total cholesterol (mg/dL) – HDL-C (mg/dL). Blood plasma samples were collected into tubes containing sodium fluoride for the enzymatic measurements of fasting blood glucose. Hemoglobin A1c (HbA1c) was measured by latex agglutination inhibition assay following the standardized methodology of JDS and converted into NGSP values with the formula recommended by JDS: HbA1c (NGSP) (%) = 1.02 x HbA1c (JDS) (%) + 0.25 [19]. C-reactive protein (CRP) was measured using BN Analyzer nephelometry, with a threshold of 0.16mg/L.

Carotid Intima-Media Thickness

A standardized protocol from the Ultrasound Research Laboratory at the University of Pittsburgh was followed for the measurement of IMT of the carotid arteries [15, 20]. In brief, a high-resolution ultrasound scanner (Toshiba ZarioSSA-660A, Toshiba Medical Systems, Japan) with a 7.5 MHz linear-array imaging probe was used to scan both right and left carotid arteries of participants in a supine position. B-mode ultrasound images of the common carotid artery (CCA), internal carotid artery (ICA) and the carotid bifurcation (Bif) were captured at end diastole phase (upstroke of R wave) by trained technicians for later reading. IMT of the near and far walls of the CCA 1 cm proximal to the Bif, far wall of ICA 1cm proximal to the Bif, and far wall of the Bif **(Supplementary Fig. 1)** was measured by trained readers using semi-automated computerized image reading program AMS (Chalmers University of Technology, Gotenburg, Sweden).

The mean IMT of CCA (CCA_{mean}), ICA (ICA_{mean}) and Bif (Bif_{mean}) of left and right carotid arteries were measured and defined as "segment-specific" cIMT. The average of these segment-specific measurements was defined as Mean cIMT. The maximum IMT measured in each carotid segment was averaged and defined as Mean-Max cIMT. Mean and Mean-Max cIMT were defined as "composite" cIMT measurements as they incorporated IMT values from a combination of the three segments. All cIMT measurements include IMT values of areas with plaques.

Coronary Artery Calcification

Electron-beam computed tomography (EBCT) with a C-150 scanner (Imatron South San Francisco, USA) or a 16-channel multidetector-row computed tomography (MDCT) with an Aquilion scanner (Toshiba, Tokyo, Japan) was used to image coronary artery calcification (CAC). A total of 603 (69.4%) participants had CAC measured by EBCT and 266 (30.6%) had it measured by MDCT. For EBCT, images were taken with a scan time of 100 milliseconds and for MDCT, images were taken every 320 milliseconds, every 3 mm slice starting from the root of the aorta. With the aid of electrocardiogram triggering, images were obtained at 70% of the cardiac cycle during one breath-hold. AccuImage software (AccuImage Diagnostics, South San Francisco, USA) was used to quantify CAC. This software used a minimum area of 1 mm^2 (3 contiguous pixels) with a density of ≥ 130 Hounsfield units per computed tomography (CT) image to identify calcified lesions [1]. Peak density and area were measured at each calcified lesion and used to calculate CAC as Agatston score [21]. CT images were assessed by one physician who was trained in CT reading at the Cardiovascular Institute at the University of Pittsburgh. The physician was blinded to participant information. Reproducibility of CAC score among participants with non-zero score had an intraclass correlation of 0.98 [22].

Statistical Analysis

Characteristics were displayed as mean ± SD or median [25^{th}–75^{th} percentile] for continuous variables or as percentages for categorical variables. Values for p-trend along age were determined per 1-year higher age using linear regression when the response variable was continuous or logistic regression when it was categorical.

CAC was stratified into groups according to the following Agatston scores found to be related to very low to low, moderate, moderately high, and high CVD risk: 0-10, >10-100, >100-400, >400, respectively [23].

Ordinal logistic regression was used to determine the odds ratio (OR) of higher CAC group (as described above) per 1 SD higher cIMT measure. Regression models were adjusted for Model 1: CT machine used (EBCT/MDCT), Model 2: Model 1 + age, Model 3: Model 2 + cardiovascular risk factors: BMI, SBP, hypertension medication (yes/no), non-HDL-C, HbA1c, diabetes (yes/no), drinking status (yes/no), alcohol intake, smoking status (yes/no), and smoking amount. To avoid collinearity, LDL-C was excluded from the covariates as it is a calculated value involving HDL-C (Friedewald equation). Model 4

Table 1. Segment-specific and composite carotid intima-media thickness measures of left and right carotid arteries in SESSA men aged 40-79 years (n=869)

cIMT	Definition	Mean ± SD (μm)	Median (μm)	25th - 75th percentile (μm)
ICA_{mean}	Mean IMT of 1cm segment of far wall of ICA proximal to the bifurcation	736 ± 290	670	568-819
CCA_{mean}	Mean IMT of 1cm segments of near and far walls of CCA proximal to the bifurcation	813 ± 164	799	696-910
Bif_{mean}	Mean IMT of far wall of bifurcation	981 ± 311	918	765-1125
Mean	Mean of ICA_{mean}, CCA_{mean} and Bif_{mean}	835 ± 183	807	705-940
Mean-Max	Mean of maximum IMT values in ICA, CCA and Bif	1105 ± 259	1066	923-1242

cIMT = carotid intima-media thickness, ICA = internal carotid artery, CCA = common carotid artery, Bif = bifurcation, SD = standard deviation. All cIMT values were from both left and right carotid arteries.

covariates included Model 3 variables and all segment-specific cIMTs in one model (ICA_{mean}, CCA_{mean}, and Bif_{mean}). Adjustments for composite cIMTs (Mean and Mean-Max) were not included in Model 4 due to high collinearity as they are derived from segment-specific cIMTs. ORs of higher CAC per 1 SD higher cIMT measure were also determined according to quartiles of age. All models met the Proportional Odds Assumption for ordinal logistic regression (Score test). No interactions were identified with CT machine used (EBCT vs MDCT) in any of the models. Data are presented as OR, 95% Confidence Interval (95% CI) and χ^2 p-values.

Sensitivity analyses of ordinal logistic regression were performed for inclusion of individuals on lipid medication (n=995), for individuals with history of CVD and on lipid medication (n=1060), and for quintiles of age (5 age groups). A sensitivity analysis for the relationship of cIMT and CAC as continuous variables were performed with linear regression modelling. As CAC Agatston score has values of 0 and a positively skewed distribution, it was transformed to log (CAC+1) to investigate linear relationships with cIMT.

Two-tailed p values of <0.05 were considered significant and SAS version 9.4 was used for all analyses.

Results

Measures of central tendency and dispersion for segment-specific and composite measures of cIMT are displayed in **Table 1**. Of the three segment-specific cIMT measures, ICA_{mean} was the thinnest at 736 μm ± 290 μm SD, while Bif_{mean} was the thickest at 981 μm ± 311 μm. CCA_{mean} had the least variability, as evidenced by its lower SD (164 μm) and narrow interquartile range (25^{th}–75^{th} percentile: 696 μm - 910 μm) values. For composite measures, mean value of Mean cIMT was 835 μm ± 183 μm and Mean-Max cIMT was 1105 μm ± 259 μm. A schematic of the carotid artery segments measured can be found in **Supplementary Fig. 1**.

Characteristics of SESSA men aged 40-79 years according to quartiles of age groups are shown in **Table 2**. With higher age, there was a trend of higher SBP and HbA1c (p-trend <0.001). Whereas BMI, total cholesterol, LDL-C and non-HDL-C appeared to have inverse relationships with age (p-trend: <0.001, <0.001, 0.048, and 0.002, respectively). With higher age, a greater proportion of participants were hypertensive, on hypertension medication, and were diabetic (p-trend <0.001). There was a lower prevalence of current drinking and current smoking with higher age (p-trend <0.001). CAC score and all cIMT measures had positive associations with age (p-trend <0.001).

The relationships of cIMT measures with select cardiovascular disease risk factors are displayed in **Table 3**. Different cIMT measures had different strengths of correlations with the cardiovascular risk factors investigated. With the exception of smoking amount, CCA consistently had the highest Spearman correlation coefficients with the cardiovascular risk factors investigated: age, BMI, SBP, HDL-C, LDL-C, non-HDL-C, HbA1c and alcohol intake.

Fig. 1 shows the OR for higher CAC score per 1 SD higher cIMT measure. All cIMT measures were significantly positively associated with CAC in Models 1 through 3. Among the cIMT measures, ICA_{mean} had the lowest strength of association in Model 1 (OR [95% CI]: 1.55 [1.35-1.78]) and in subsequent models. CCA_{mean} and Bif_{mean} appeared to have similar strengths of associations with CAC in Model 1 (1.70 [1.49-1.94] for CCA_{mean} and 1.69 [1.48-1.93] for Bif_{mean}). However, after adjustments in Models 2 and

Table 2. Characteristics of SESSA men along quartiles of age (n=869)

Characteristic	Quartiles of age				
	1 40.2 to 57.7y (n=217)	2 57.9 to 64.1y (n=217)	3 64.1 to 71.5y (n=218)	4 71.5 to ~80.0y (n=217)	p-trend
Age (y)	49.6±5.6	61.3±1.8	67.4±2.2	75.2±2.4	-
BMI (kg/m^2)	24.1±3.1	23.4±3.0	23.1±2.9	22.9±2.9	<0.001
SBP (mmHg)	128±17	136±19	140±20	140±19	<0.001
Total cholesterol (mg/dL)	213±32	212±36	209±33	203±33	<0.001
HDL-C (mg/dL)	59.6±16.8	59.8±18.5	59.9±17.9	57.8±16.0	0.196
LDL-C (mg/dL)*	128±30	126±34	126±31	124±30	0.048
Non-HDL-C (mg/dL)†	154±35	152±38	149±33	145±33	0.002
HbA1c (%)‡	5.4±0.6	5.6±0.6	5.8±0.9	5.7±0.7	<0.001
Hypertension (%)	28.1	50.7	62.8	63.6	<0.001
Hypertension drug (%)	9.7	26.3	29.8	33.6	<0.001
Diabetes (%)	8.8	17.1	24.8	22.6	<0.001
Current drinker (%)	83.9	82.0	73.4	71.4	<0.001
Current smoker (%)	45.6	34.6	32.1	21.7	<0.001
Alcohol intake (g/week)	98 [15-294]	153 [22-350]	98 [0-255]	70 [0-191]	<0.001
Smoking amount (pack-year)	21.5 [5-35]	26.3 [8-43]	23.0 [2-45]	26.3 [8-45]	<0.001
CRP (μg/L)	0.4 [0.2-0.7]	0.5 [0.2-0.8]	0.4 [0.2-0.8]	0.5 [0.3-1.1]	0.030
CAC score (Agatston)	0 [0-4]	5 [0-47]	15 [0-112]	31 [0-174]	<0.001
ICA$_{mean}$ cIMT (μm)	639±158	707±203	740±266	856±418	<0.001
CCA$_{mean}$ cIMT (μm)	697±120	801±168	846±147	906±141	<0.001
Bif$_{mean}$ cIMT (μm)	816±211	943±259	1032±348	1133±317	<0.001
Mean cIMT (μm)	712±119	813±159	866±168	950±191	<0.001
Mean-Max cIMT (μm)	951±178	1069±235	1131±223	1270±280	<0.001

Data are presented as mean±standard deviation, median [25$_{th}$ - 75$_{th}$ percentile], or as percentages (%) as indicated. Values for p-trend were obtained using linear regression (for continuous variables) or logisitc regression (for categorical variables) per 1 year higher age.
*LDL-C was calculated using Friedewald's formula [LDLC=Total Cholesterol - HDL-C - (Triglycerides/5)].
†Non-HDL-C was calculated as Total cholesterol– HDL-C.
‡Measured as Japan Diabetes Society (JDS, %). To convert to National Glycohemoglobin Standardization Program (NGSP) values, use the formula: HbA1c (NGSP) (%)=1.02 x HbA1c (JDS) (%)+0.25.
BMI=bodymass index, SBP=systolic blood pressure, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, HbA1c=hemoglobin A1c, CRP=c-reactive protein, CAC=coronary arterty calcification, cIMT=carotid intima-media thickness, ICA=internal carotid artery, CCA=common carotid artery, Bif=bifurcation, SD=standard deviation.

Table 3. Spearman correlation coefficients of cIMT measures with select cardiovascular risk factors.

cIMT (μm)	Age (y)	BMI (kg/m^2)	SBP (mmHg)	Total-C (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)†	Non-HDL-C (mg/dL)‡	HbA1c (%)	Alcohol intake (g/week)	Smoking amount (pack-year)
ICA$_{mean}$	0.28	0.06	0.20**	0.02	-0.06	0.04	0.05	0.12**	-0.07*	0.11*
CCA$_{mean}$	0.53**	0.19**	0.31**	0.06	-0.21**	0.15**	0.16**	0.26**	-0.14**	0.13**
Bif$_{mean}$	0.45**	0.01	0.20**	0.04	-0.08*	0.10*	0.08*	0.19**	-0.10*	0.14**
Mean	0.52**	0.10*	0.28**	0.04	-0.15**	0.12**	0.12**	0.24**	-0.08*	0.16**
Mean-Max	0.50**	0.08*	0.25**	0.05	-0.14**	0.12*	0.12**	0.23**	-0.07*	0.17**

*p<0.05, **p<0.001
†LDL-C was calculated using Friedewald's formula [LDLC = Total Cholesterol - HDL-C - (Triglycerides/5)].
‡Non-HDL-C was calculated as Total cholesterol – HDL-C.
BMI=bodymass index, SBP = systolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, HbA1c = hemoglobin A1c, cIMT = carotid intima-media thickness, ICA = internal carotid artery, CCA = common carotid artery, Bif = bifurcation, SD = standard deviation.

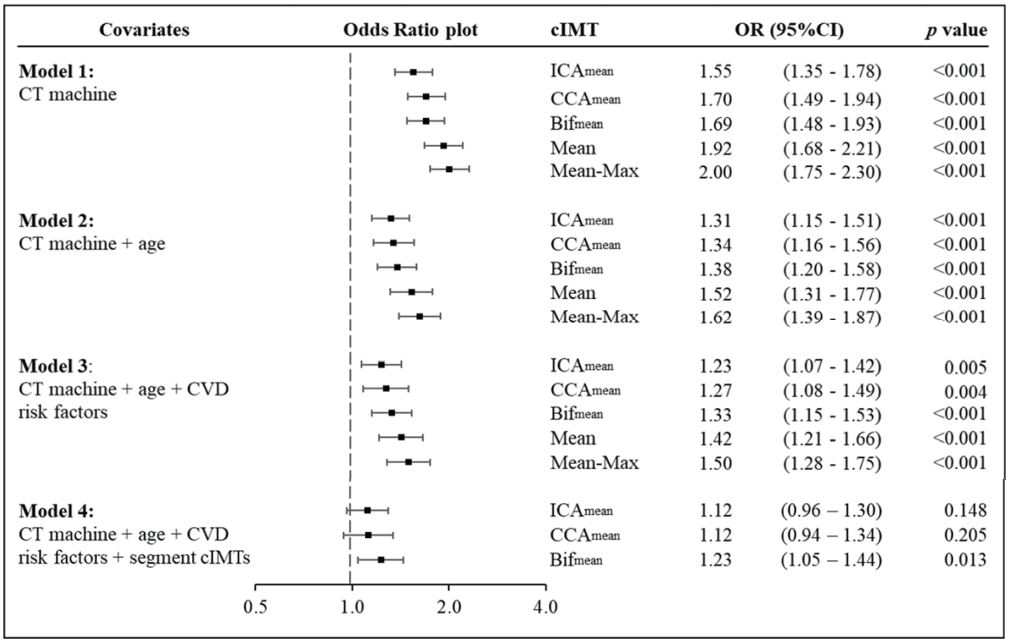

Fig. 1. Odds ratio for higher CAC score with a 1 standard deviation higher cIMT measure

Odds Ratios (OR) were determined using ordinal logistic regression for higher CAC grouping: 0-10, >10-100, >100-400, and > 400 Agatston score. Covariates in Model 1: Computed tomography (CT) machine used (EBCT/MDCT); Model 2: CT machine + age; Model 3: CT machine + age + cardiovascular disease (CVD) risk factors (body mass index, systolic blood pressure, hypertension medication (yes/no), non-high-density lipoprotein cholesterol, hemoglobin A1c, diabetes (yes/no), current drinker (yes/no), drinking amount, current smoker (yes/no), and smoking amount; Model 4: Model 3 + ICA_{mean}, CCA_{mean}, and Bif_{mean}.

3, Bif_{mean} had higher ORs with CAC than did CCA_{mean}. Furthermore, inclusion of all segment-specific cIMTs in one regression model (Model 4) has shown that Bif_{mean} is associated with higher CAC score, independent of the other segment cIMTs: 1.23 [1.05-1.44], whereas ICA_{mean} (1.12 [0.96-1.30]) and CCA_{mean} (1.12 [0.94-1.34]) were no longer significantly associated with CAC.

Composite measures of cIMT had higher adjusted ORs with CAC in Model 1 (1.92 [1.68-2.21] for Mean and 2.00 [1.75-2.30] for Mean-Max) in comparison to segment-specific measures. This pattern persisted in Models 2 and 3. Of all measures of cIMT, Mean-Max had the highest adjusted ORs for higher CAC score consistently in all models. Similar results were observed in the sensitivity analysis of CAC as a continuous variable (log (CAC+1)) and cIMT under linear regression **(Supplementary Table 1)**.

In the age-stratified analysis, composite measures generally had higher ORs for higher CAC compared to segment-specific ones in each quartile of age **(Fig. 2)**. Interestingly, only Mean-Max maintained a significant positive relationship with CAC in all age quartiles, which was also observed in a sensitivity analysis of age quintiles **(Supplementary Table 2)**. In sensitivity analyses including individuals on lipid medication, similar patterns of associations were observed, although the relationships of cIMT with coronary calcium in the youngest quartiles were attenuated to the null **(Supplementary Fig. 2)**. For analyses including those on lipid medication and those with history of CVD, a similar pattern of results was observed (data not shown).

Discussion

Summary

We found that of all the cIMT measures investigated, Mean-Max cIMT consistently had the strongest associations with coronary calcium. Moreover, Mean-Max cIMT maintained this association even after accounting for age, a major confounder. Strikingly, the most oft-used measure of cIMT, CCA_{mean}, lost most associations with coronary calcium after age stratification.

Segment-Specific Measures of cIMT

The most often-utilized segment-specific measure of cIMT is CCA[24], as formerly, IMT measurements in this segment were easier to image and are more reproducible compared to ICA and Bif segments[25, 26]. In our study, we found that cIMT of CCA had similar

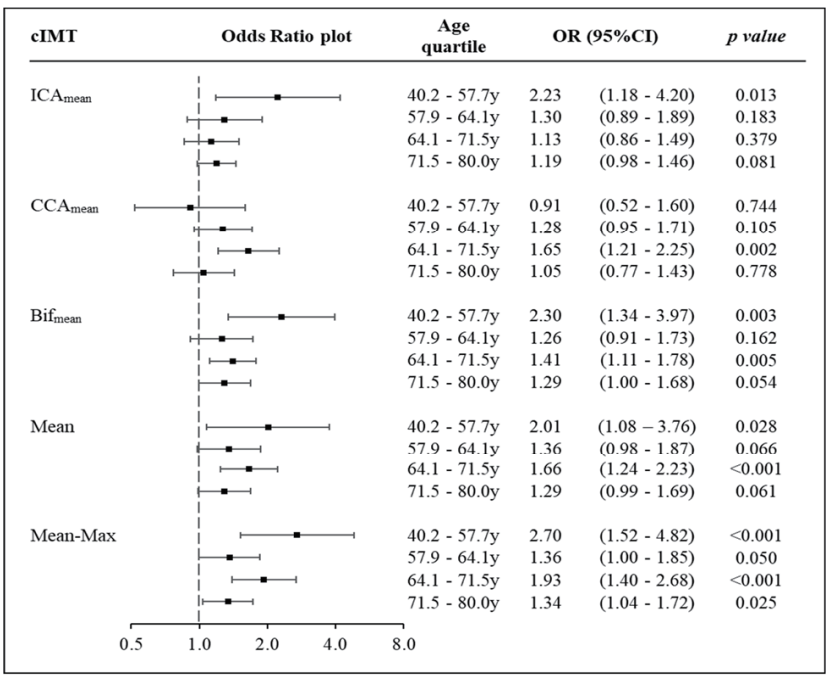

Fig. 2. Odds ratio for higher CAC score with a 1 standard deviation higher cIMT measure

Odds Ratios (OR) were determined using ordinal logistic regression for higher CAC grouping: 0-10, >10-100, >100-400, and >400 Agatston score. Covariates in the model were computed tomography machine used (EBCT/MDCT), age, and cardiovascular disease (CVD) risk factors (body mass index, systolic blood pressure, hypertension medication (yes/no), non-high-density lipoprotein cholesterol, hemoglobin A1c, diabetes (yes/no), current drinker (yes/no), drinking amount, current smoker (yes/no), and smoking amount). Age quartiles were (1) 40.2-57.7 y, (2) 57.9-64.1 y, (3) 64.1-71.5y, (4) 71.5- ~80 y.

strengths of associations as did Bif with subclinical coronary calcium, yet greater than those of ICA. We also found that CCA cIMT, compared to other cIMT measures, was most strongly and positively associated with well-known cardiovascular risk factors, such as age, BMI, SBP, LDL-C, and HbA1c. Although relationships of all cIMT measures with CAC were attenuated with adjustment for cardiovascular risk factors, they did not appear to be attenuated to the same extent as CCA cIMT. Our results suggest that the relationship of CCA with subclinical coronary calcium can be partially explained by these cardiovascular risk factors. Polak *et al.* have found that CCA cIMT was more strongly associated with traditional CVD risk factors, such as age, SBP, and BMI, and that these factors can explain a great proportion of the variability in CCA[27]. Model adjustment for cardiovascular risk factors is important in determining whether a cIMT measure can provide information beyond these risk factors and, hence, whether there is further benefit in measuring cIMT for the purpose of CHD risk assessment.

When comparing segment-specific cIMT measures, we found that only Bif_{mean} was significantly associated with higher CAC score, independent of the other segment-specific cIMTs. Since most plaques are found within the Bif[24], it suggests that plaques are more pertinent to coronary atherosclerosis than are vascular hypertrophy, blood pressure, and hypertension, general characteristics associated with measuring CCA[12, 28].

In our age-stratified analysis, we found that Bif_{mean} and ICA_{mean} were indicative of higher coronary calcium in younger adults. Since age alone leads to the vascular wall hypertrophy and intimal hyperplasia[29], cIMT may represent the change and damage inflicted by a combination of ageing of the arterial system and presence of cardiovascular risk factors over time in the elderly. Whereas in younger adults, higher cIMT in Bif and ICA, is more indicative of atherosclerotic plaques. The actual occurrence of CVD events are likely closely related to plaque rather than general carotid artery wall thickening as plaques are physical manifestations of atherosclerosis[30].

Composite Measures of cIMT

In our study, Mean and Mean-Max cIMT had the strongest associations with subclinical coronary calcium, largely independent of age. Although studies on comparisons of the different cIMT segments and

their relationships with CHD are rare, a study by Baldassarre *et al.* has found that Mean and Mean-Max cIMT are better predictors of combined cardiovascular events and cerebrovascular events, compared to segment-specific ones[11]. Composite measures can evaluate the general burden of atherosclerosis in the carotid arteries. Mean cIMT provides an overview of wall thickening, reflecting both presence of atherosclerotic plaques and hypertension-related stress[25], while Mean-Max cIMT is more likely to identify plaque presence[9], but also can be indicative of plaque severity, where higher cIMT represents a larger degree of arterial stenosis. The rationale in utilizing CCA cIMT in preference to composite measures in cardiovascular risk assessment is questionable, especially when composite measures are more representative of actual atherosclerosis.

Standardization Issues of cIMT

The usefulness of cIMT to improve risk estimation beyond traditional risk factors in populations with low or intermediary CHD risk is heavily debated[9]. In fact, ACC/AHA Prevention Guidelines for assessment of cardiovascular risk do not recommend the use of cIMT in routine clinical practice for risk assessment of first atherosclerotic cardiovascular disease event[31]. Problems in the standardization and definition of cIMT were highlighted as a major challenge[31]. We have identified that even within a study that employs standardized protocol, different segments and definitions of cIMT have differing degrees of association with coronary calcium. Measurements of different carotid segments and different combinations of these segments and their lengths, among other technical variations, lead to descriptions of different phenotypes.

Limitations

Due to the cross-sectional design of this study, temporality of the cIMT and CAC relationship cannot be assessed. However, our goal was not to determine causality, rather to compare associations of different cIMT measures with CAC. Secondly, although we had adjusted for and stratified by age in our analyses, residual confounding from age cannot be ruled out. Other limitations include generalizability of our findings to women and other non-Japanese populations. Importantly, our methods and protocol for assessing the different cIMT measures are just one set among many. The method of scanning and its philosophy can significantly affect the phenotype portrayed by "cIMT" and our results should be interpreted with this in mind.

Strengths

We provide a thorough comparison of segments and definitions of cIMT often used in other epidemiological studies, including composite mean and maximum measures. Our analyses included adjustments for known CVD risk factors, covariates and other strong confounders, especially age. We attempted to control for confounding by age through model adjustment and stratification. A very limited number of studies have assessed different cIMT measures and compared their associations with coronary atherosclerosis or coronary calcium. Importantly, we show cIMT associations in asymptomatic individuals of a Japanese general population who are generally healthy and one can only assume that such findings will be more striking in higher risk populations.

Conclusion

Overall, Mean-Max cIMT appeared to have consistently stronger associations with coronary calcium, independent of important confounders such as age. The most oft-used measure, CCA_{mean} , was largely not independent of age. The utility of Mean-Max cIMT and CCA_{mean} as surrogate measures for CHD risk need to be determined and compared by comprehensive longitudinal studies with standardized protocol.

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Conflict of Interest

None.

Author Contributions

M.Z. conducted analyses of data, collected part of the data, interpreted the data, and drafted the article. A.F. collected part of the data, interpreted the data, drafted the article and provided critical revision of the article. T.H., A.K., S.K., and A.Sa., collected part of the data and provided critical revision of the article. A.Se., E.B-M, M.H., K.M. and H.U., interpreted the data and provided critical revision of the article.

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Appendix

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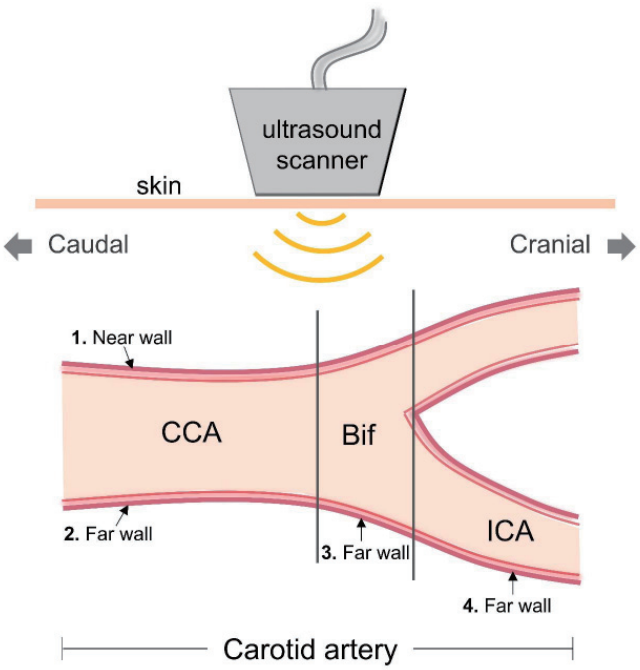


Supplementary Fig. 1. A schematic of the carotid artery segments and the walls used for the measurement of carotid intima-media thickness (cIMT)

CCA=common carotid artery, Bif=bifurcation, ICA=internal carotid artery. Of each segment, near walls are the carotid walls closest to ultrasound scanner and far walls are the farthest. A total of four walls of the artery were measured (indicated by numbers 1-4). With the exception of the far wall of the bifurcation, all near and far walls were measured with lengths of 1cm proximal to the bifurcation. Vertical lines indicate distinction between the segments.

Supplementary Table 1. Estimated linear relationship between log (CAC +1) and each cIMT measure

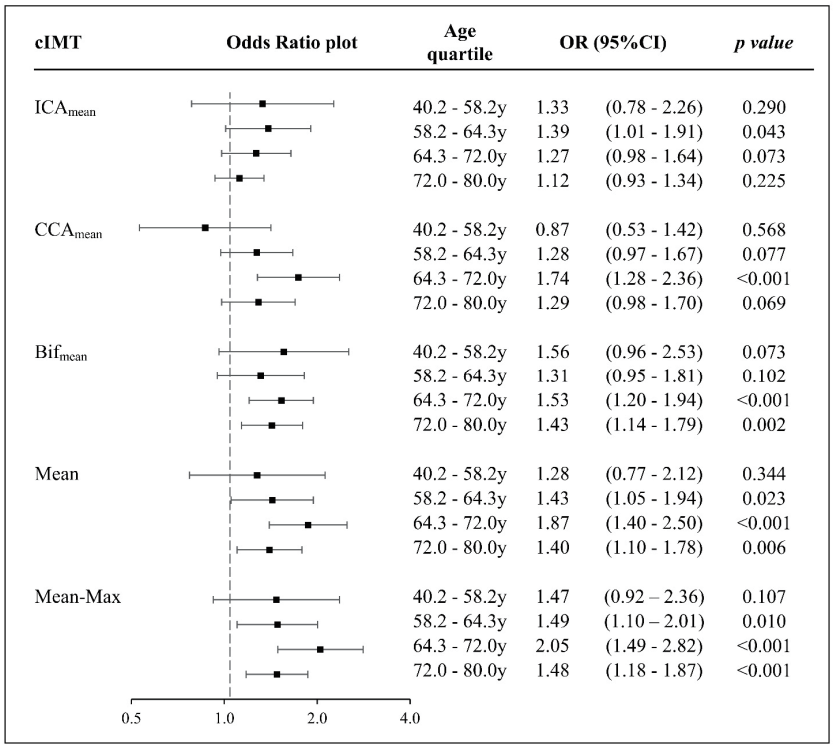
Covariates	cIMT	Estimate	95% CI		*p* value
Model 1	ICA_{mean}	0.50	0.35	0.65	<0.001
	CCA_{mean}	0.67	0.52	0.81	<0.001
	Bif_{mean}	0.64	0.49	0.79	<0.001
	Mean	0.77	0.63	0.91	<0.001
	Mean-Max	0.81	0.67	0.96	<0.001
Model 2	ICA_{mean}	0.30	0.16	0.45	<0.001
	CCA_{mean}	0.35	0.19	0.51	<0.001
	Bif_{mean}	0.37	0.22	0.53	<0.001
	Mean	0.48	0.32	0.64	<0.001
	Mean-Max	0.55	0.40	0.71	<0.001
Model 3	ICA_{mean}	0.21	0.06	0.36	0.005
	CCA_{mean}	0.24	0.07	0.41	0.006
	Bif_{mean}	0.31	0.16	0.46	<0.001
	Mean	0.36	0.20	0.53	<0.001
	Mean-Max	0.43	0.27	0.59	<0.001
Model 4	ICA_{mean}	0.11	-0.05	0.27	0.164
	CCA_{mean}	0.10	-0.09	0.28	0.318
	Bif_{mean}	0.24	0.06	0.41	0.007

Estimates and 95% CI are from linear regression of higher log (CAC + 1) per 1 standard deviation higher cIMT measure.
1 standard deviation ICA_{mean} = 290 μm , CCA_{mean} = 164 μm, Bif_{mean} = 311 μm , Mean = 183 μm and Mean-Max = 259 μm.
Model 1 = CT machine.
Model 2 = Model 1 + age.
Model 3 = Model 2 + bodymass index, systolic blood pressure, hypertension medication (yes/no), non-high-density lipoprotein cholesterol, hemoglobin A1c, diabetes (yes/no), current smoker (yes/no), smoking amount, current drinker (yes/no), and drinking amount.
Model 4 = Model 3 + ICAmean, CCAmean, and Bifmean.
cIMT = carotid intima-media thickness, CI = confidence interval, ICA = internal carotid artery, CCA = common carotid artery, Bif = bifurcation.

Supplementary Table 2. Odds ratios of higher CAC score stratified by quintiles of age

cIMT	Quintiles of age				
	1 (*n* = 173) 40.2 to 55.8 y OR (95% CI)	2 (*n* = 174) 55.8 to 62.2 y OR (95% CI)	3 (*n* = 174) 62.2 to 66.8 y OR (95% CI)	4 (*n* = 174) 66.8 to 72.8 y OR (95% CI)	5 (*n* = 174) 72.8 to ~80.0 y OR (95% CI)
ICA_{mean}	1.87 (0.79 - 4.41)	1.30 (0.81 - 2.08)	1.68 (1.17 - 2.42)**	1.03 (0.77 - 1.37)	1.20 (0.96 - 1.50)
CCA_{mean}	0.66 (0.31 - 1.41)	1.27 (0.88 - 1.83)	1.69 (1.23 - 2.33)**	1.46 (0.99 - 2.13)	1.02 (0.72 - 1.43)
Bif_{mean}	1.60 (0.73 - 3.49)	1.74 (1.16 - 2.63)**	1.38 (1.06 - 1.80)*	1.22 (0.90 - 1.65)	1.26 (0.95 - 1.67)
Mean	1.26 (0.53 - 2.99)	1.56 (1.03 - 2.37)*	1.85 (1.34 - 2.56)**	1.33 (0.94 - 1.87)	1.26 (0.94 - 1.69)
Mean-Max	1.40 (0.59 - 3.30)	1.78 (1.21 - 2.56)**	1.82 (1.29 - 2.56)**	1.50 (1.06 - 2.12)*	1.34 (1.01 - 1.78)*

Data are presented as Odds Ratios (95% Confidence Interval).
p values * < 0.05, ** < 0.01.
Adjusted for CT machine, age, bodymass index, systolic blood pressure, hypertension medication (yes/no), non-high-density lipoprotein cholesterol, hemoglobin A1c, diabetes (yes/no), current drinker (yes/no), drinking amount, current smoker (yes/no), smoking amount.
SD = standard deviation, OR = odds ratio, CI = confidence interval, cIMT = carotid intima-media thickness, ICA = internal carotid artery, CCA = common carotid artery, Bif = bifurcation.



Supplementary Fig. 2. Odds ratio for higher CAC score with a 1 standard deviation higher cIMT measure in SESSA men aged 40 to ~80 years, (including those on lipid medication), $n=995$

Odds Ratios (OR) were determined using ordinal logistic regression for higher CAC grouping: 0-10, >10-100, >100-400, and >400 Agatston score. Covariates in the model were computed tomography machine used (EBCT/MDCT), age, and cardiovascular disease (CVD) risk factors (body mass index, systolic blood pressure, hypertension medication (yes/no), non-high-density lipoprotein cholesterol, hemoglobin A1c, diabetes (yes/no), current drinker (yes/no), drinking amount, current smoker (yes/no), smoking amount and lipid medication (yes/no)). Age quartiles were (1) 40.2-58.2 y ($n=248$), (2) 58.2-64.3 y ($n=249$), (3) 64.3-72.0y ($n=249$), (4) 72.0- ~80 y ($n=249$).