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

Maryam Zaid1, 2, Akira Fujiyoshi3, 4, Takashi Hisamatsu5, Aya Kadota2, Sayaka Kadowaki3, Atsushi Satoh6, Akira Sekikawa7, Emma Barinas-Mitchell7, 8, Minoru Horie8, Katsuyuki Miura2, 3 and Hirotugu Ueshima2, 3, for the SESSA Research Group

1 Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China
2 Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Shiga, Japan
3 Department of Public Health, Shiga University of Medical Science, Shiga, Japan
4 Department of Hygiene, Wakayama Medical University, Wakayama, Japan
5 Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan
6 Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
7 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, USA
8 Clinical Translational Science Institute, University of Pittsburgh, Pittsburgh, USA
9 Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Shiga, Japan

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 (CCAmean), internal carotid artery (ICAmean) and bifurcation (Bifmean). 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]: ICAmean [1.23, 1.07-1.42], CCAmean [1.27, 1.08-1.49], Bifmean [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 CCAmean 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, CCAmean, 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 arteries1) and is representative of generalized atherosclerosis in the body2). Not only is higher cIMT associated with higher risk of incident coronary heart disease (CHD)3), but it has been found to improve risk prediction beyond traditional cardiovascular risk factors4). These findings highlight the potential for cIMT to be used as a surrogate for CHD events in epidemiological studies5) or as an early...
screening tool for CHD prevention in the general population.

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. Unfortunately, this has led to poor standardization of methodology and an inconsistent definition of cIMT. 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. This in part has led to inconsistent findings with regards to improved cardiovascular risk prediction in the general population.

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. 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. Although both cIMT and CAC can independently predict CHD and CVD events, CAC has been found to be the better predictor for both.

**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, 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. 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/m²). 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.

**Blood Samples**

Blood was drawn from all participants after a 12-hour fast. Blood samples were centrifuged at 4°C and serum was collected and stored at −80°C. Serum total cholesterol was measured using enzymatic techniques and high-density lipoprotein cholesterol (HDL-C) was measured using heparin-calcium
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 \([\text{LDL-C}=\text{total cholesterol (mg/dL)} - \text{HDL-C (mg/dL)} - \text{triglyceride (mg/dL)} / 5]\) in participants with triglycerides \(\leq 4.52 \text{mmol/L (} \leq 400 \text{mg/dL)} (n=857)\). 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 measured by Agatston software (AccuImage Diagnostics, South San Francisco, USA) 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 mm² (3 contiguous pixels) with a density of \(\geq 130\) 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\(^21\).

**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 mm² (3 contiguous pixels) with a density of \(\geq 130\) 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\(^21\).

**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<sub>mean</sub> | Mean IMT of 1 cm segment of far wall of ICA proximal to the bifurcation     | 736 ± 290     | 670         | 568-819                     |
| CCA<sub>mean</sub> | Mean IMT of 1 cm segments of near and far walls of CCA proximal to the     | 813 ± 164     | 799         | 696-910                     |
|                    | bifurcation                                                                 |               |             |                             |
| Bif<sub>mean</sub> | Mean IMT of far wall of bifurcation                                         | 981 ± 311     | 918         | 765-1125                    |
| Mean               | Mean of ICA<sub>mean</sub>, CCA<sub>mean</sub> and Bif<sub>mean</sub>       | 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<sub>mean</sub>, CCA<sub>mean</sub>, and Bif<sub>mean</sub>). 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 $\chi^2$ 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<sub>mean</sub> was the thinnest at 736 µm ± 290 µm SD, while Bif<sub>mean</sub> was the thickest at 981 µm ± 311 µm. CCA<sub>mean</sub> had the least variability, as evidenced by its lower SD (164 µm) and narrow interquartile range (25<sup>th</sup>–75<sup>th</sup> 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 ($\chi^2$ < 0.001). Whereas BMI, total cholesterol, LDL-C and non-HDL-C appeared to have inverse relationships with age ($\chi^2$ < 0.001, 0.048, and 0.002, respectively). With higher age, a greater proportion of participants were hypertensive, on hypertension medication, and were diabetic ($\chi^2$ < 0.001). There was a lower prevalence of current drinking and current smoking with higher age ($\chi^2$ < 0.001). CAC score and all cIMT measures had positive associations with age ($\chi^2$ < 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, LDL-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<sub>mean</sub> had the lowest strength of association in Model 1 (OR [95% CI]: 1.55 [1.35-1.78]) and in subsequent models. CCA<sub>mean</sub> and Bif<sub>mean</sub> appeared to have similar strengths of associations with CAC in Model 1 (1.70 [1.49-1.94] for CCA<sub>mean</sub> and 1.69 [1.48-1.93] for Bif<sub>mean</sub>). However, after adjustments in Models 2 and...
Table 2. Characteristics of SESSA men along quartiles of age (n=869)

| Characteristic          | 1          | 2          | 3          | 4          | p-trend |
|-------------------------|------------|------------|------------|------------|---------|
| Age (y)                 | 49.6 ± 5.6 | 61.3 ± 1.8 | 67.4 ± 2.2 | 75.2 ± 2.4 | -       |
| BMI (kg/m²)             | 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  |
| ICAmean cIMT (µm)       | 639 ± 158  | 707 ± 203  | 740 ± 266  | 856 ± 418  | <0.001  |
| CCAmean cIMT (µm)       | 697 ± 120  | 801 ± 168  | 846 ± 147  | 906 ± 141  | <0.001  |
| Bifmean 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 [25th - 75th percentile], or as percentages (%) as indicated. Values for p-trend were obtained using linear regression (for continuous variables) or logistic regression (for categorical variables) per 1 year higher age.

*LDL-C was calculated using Friedewald’s formula [LDL-C = Total Cholesterol - HDL-C - (Triglycerides/5)].
†Non-HDL-C was calculated as Total cholesterol – HDL-C.
‡HbA1c (%) was calculated using Friedewald’s formula [LDL-C = Total Cholesterol - HDL-C - (Triglycerides/5)].
§Mean ± SD (standard deviation).

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

| cIMT (µm) | Age (y) | BMI (kg/m²) | 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) |
|-----------|---------|-------------|------------|-----------------|---------------|---------------|-----------------|-----------|------------------------|--------------------------|
| ICAmean   | 0.28    | 0.06        | 0.20**     | 0.02            | -0.06         | 0.04          | 0.05            | 0.12**    | -0.07*                 | 0.11*                    |
| CCAmean   | 0.53**  | 0.19**      | 0.31**     | 0.06            | -0.21**       | 0.15**        | 0.16**          | 0.26**    | -0.14**                | 0.13**                   |
| Bifmean   | 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

[1] LDL-C was calculated using Friedewald’s formula [LDL-C = Total Cholesterol - HDL-C - (Triglycerides/5)].
[2] Non-HDL-C was calculated as Total cholesterol – HDL-C.

BMI = body mass 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.
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, CCAmean, lost most associations with coronary calcium after age stratification.

Segment-Specific Measures of cIMT

The most often-utilized segment-specific measure of cIMT is CCA34), as formerly, IMT measurements in this segment were easier to image and are more reproducible compared to ICA and Bif segments25, 26). In our study, we found that cIMT of CCA had similar

---

**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 + ICAmean, CCAmean, and Bifmean.
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 Bifmean 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 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 Bifmean was significantly associated with higher CAC score, independent of other segment-specific CIMTs. Since most plaques are found within the Bif (20), 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).

**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) 64.1-71.5 y, (4) 71.5-80 y.
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\(^1\). 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\(^2\), while Mean-Max cIMT is more likely to identify plaque presence\(^3\), 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\(^4\). 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\(^3\). Problems in the standardization and definition of cIMT were highlighted as a major challenge\(^4\). 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\(_{\text{mean}}\), was largely not independent of age. The utility of Mean-Max cIMT and CCA\(_{\text{mean}}\) as surrogate measures for CHD risk need to be determined and compared by comprehensive longitudinal studies with standardized protocol.

**Acknowledgements**

Authors would like to thank members of the SESSA Research Group (See Appendix).

**Notice of Grant Support**

This study has been supported by Grants-in-aid for Scientific Research (A) 13307016, (A) 17209023, (A) 21249043, (A) 23249036, (A) 25253046, (A) 15H02528, (B) 26293140, (B) 18H03048 and (B)17K15826 from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, by National Institutes of Health in USA [R01HL068200], and by Glaxo-Smith Kline GB. The present study was initiated and analyzed by the authors. The funding sources listed above have no role in the study design, collection, analyses, and interpretation of the results.

**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.

References
1) Zaid M, Fujiyoshi A, Kadota A, Abbott RD, Miura K. Coronary Artery Calcium and Carotid Artery Intima Media Thickness and Plaque: Clinical Use in Need of Clarification. J Atheroscler Thromb, 2017; 24: 227-239
2) Iwakiri T, Yano Y, Sato Y, Hatakeyama K, Marutuka K, Fujimoto S, Kitamura K, Kario K, Asada Y. Usefulness of carotid intima-media thickness measurement as an indicator of generalized atherosclerosis: findings from autopsy analysis. Atherosclerosis, 2012; 225: 359-362
3) Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation, 1997; 96: 1432-1437
4) 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
5) Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb, 1991; 11: 1245-1249
6) O’Leary DH, Polak JE, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med, 1999; 340: 14-22
7) Nambi V, Brunner G, Ballantyne CM. Ultrasound in cardiovascular risk prediction: don’t forget the plaque! J Am Heart Assoc, 2013; 2: e000180
8) Nambi V, Chambless L, Folsom AR, Mosley T, Boerwinkle E, Ballantyne CM. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J, 2012; 33: 183-190
9) Ravani A, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, Ballantyne CM. Lipoprotein-associated phospholipase A2 is related to risk of subclinical atherosclerosis but is not supported by Mendelian randomization analysis in a general Japanese population with an estimated 10-year absolute risk of CAD death according to the Japanese Atherosclerosis Society (JAS) guidelines 2012: the Shiga Epidemiological Study of Atherosclerosis (SESSA). J Atheroscler Thromb, 2013; 20: 755-766
10) Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavoussi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O’Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rossell M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA, 2012; 308: 796-803
11) Baldassarre D, Hamsten A, Végla F, de Faire U, Humphries SE, Smit AJ, Giral P, Kurl S, Rauramaa R, Mannarino E, Grossi E, Paolleti R, Tremoli E, Group IS. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. J Am Coll Cardiol, 2012; 60: 1489-1499
12) Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J, 2002; 23: 934-940
13) Nambi V, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, Ballantyne CM. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J, 2012; 33: 183-190
14) Folsom AR, Kronmal RA, Detrano RC, O’Leary DH, Bild DE, Bluemke DA, Budoff MJ, Liu K, Shea S, Szklo M, Tracy RP, Watson KE, Burke GL. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med, 2008; 168: 1333-1339
15) Kadota A, Miura K, Okamura T, Fujiyoshi A, Ohkubo T, Kadowaki T, Takashima N, Hisamatsu T, Nakamura Y, Kasagi F, Maegawa H, Kashiwagi A, Ueshima H, Group SR, Group NDR. Common carotid intima-media thickness and plaque in apparently healthy Japanese individuals with an estimated 10-year absolute risk of CAD death according to the Japan Atherosclerosis Society (JAS) guidelines 2012: the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). J Atheroscler Thromb, 2013; 20: 755-766
16) Ueshima H, Kadowaki T, Hisamatsu T, Fujiyoshi A, Miura K, Ohkubo T, Sekikawa A, Kadota A, Kadowaki S, Nakamura Y, Miyagawa N, Okamura T, Kita Y, Takashima N, Kashiwagi A, Maegawa H, Horie M, Yamamoto T, Kimura T, Kita T, Access, Groups SR. Lipoprotein-associated phospholipase A2 is related to risk of subclinical atherosclerosis but is not supported by Mendelian randomization analysis in a general Japanese population. Atherosclerosis, 2016; 246: 141-147
17) Bedi US, Singh M, Singh PP, Bhuriya R, Bahaker A, Molnar J, Kholis S, Arora R. Effects of statins on progression of carotid atherosclerosis as measured by carotid intimal--medial thickness: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol Ther, 2010; 15: 268-273
18) Crouse JR, 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O’Leary DH, Grobbee DE, Bots ML, Group

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: November 26, 2020 Published online: February 5, 2021
19) Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, Tominaga M, Oikawa S, Noda M, Kawamura T, Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y, Ohashi H, Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes S. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Investig, 2012; 3: 39-40

20) Sutton-Tyrrell K, Wolfson SK, Jr., Thompson T, Kelsey SF. Measurement variability in duplex scan assessment of carotid atherosclerosis. Stroke, 1992; 23: 215-220

21) Zaid M, Miura K, Fujiyoshi A, Abbott RD, Hisamatsu T, Kadota A, Arima H, Kadowaki S, Torii S, Miyagawa N, Suzuki S, Takashima N, Ohkubo T, Sekikawa A, Maegawa H, Horie M, Nakamura Y, Okamura T, Ueshima H, Group SR. Associations of serum LDL particle concentration with carotid intima-media thickness and coronary artery calcification. J Clin Lipidol, 2016; 10: 1195-1201 e1191

22) Sekikawa A, Ueshima H, Kadowaki T, El-Saed A, Okamura T, Takamiya T, Kashiwagi A, Edmundowicz D, Murata K, Sutton-Tyrrell K, Maegawa H, Evans RW, Kita Y, Kuller LH. Less subclinical atherosclerosis in Japanese men in Japan than in White men in the United States in the post-World War II birth cohort. Am J Epidemiol, 2007; 165: 617-624

23) Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. Mayo Clin Proc, 1999; 74: 243-252

24) O’Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J, 2010; 31: 1682-1689

25) Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens, 2002; 20: 159-169

26) O’Leary DH, Polak JF, Wolfson SK, Jr., Bond MG, Bommer W, Sheth S, Psaty BM, Sharrett AR, Manolio TA. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. CHS Collaborative Research Group. Stroke, 1991; 22: 1155-1163

27) Polak JF, Person SD, Wei GS, Godreau A, Jacobs DR, Jr., Harrington A, Sidney S, O’Leary DH. Segment-specific associations of carotid intima-media thickness with cardiovascular risk factors: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Stroke, 2010; 41: 9-15

28) Espeland MA, Tang R, Terry JG, Davis DH, Mercuri M, Crouse JR, 3rd. Associations of risk factors with segment-specific intimal-medial thickness of the extracranial carotid artery. Stroke, 1999; 30: 1047-1055

29) Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. Arterioscler Thromb Vasc Biol, 2010; 30: 177-181

30) 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

31) Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D’Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O’Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler J, Sellke FW, Shin WK, Smith SC, Jr., Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014; 129: S49-73
Appendix

Members of the SESSA Research Group.

Chairpersons: Hirotsugu Ueshima and Katsuyuki Miura (Department of Public Health and Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga)

Research members: Minoru Horie, Yasutaka Nakano, Takashi Yamamoto, Hideki Hayashi (Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Shiga), Emiko Ogawa (Health Administration Center, Shiga University of Medical Science, Otsu, Shiga), Hiroshi Maegawa, Itsuko Miyazawa (Division of Endocrinology and Metabolism, Department of Medicine, Shiga University of Medical Science, Otsu, Shiga), Kiyoshi Murata (Department of Radiology, Shiga University of Medical Science, Otsu, Shiga), Kenichi Mitsunami (Shiga University of Medical Science, Otsu, Shiga), Kazuhiko Nozaki (Department of Neurosurgery, Shiga University of Medical Science, Otsu, Shiga), Ikuo Toyama, Akihiko Shiino, (Molecular Neuroscience Research Center, Shiga University of Medical Science, Otsu, Shiga), Teruhiko Tsuru (Department of Urology, Shiga University of Medical Science, Otsu, Shiga), Hisakazu Ogita, Akio Shimizu (Division of Medical Biochemistry, Department of Biochemistry and Molecular Biology, Shiga University of Medical Science, Otsu, Shiga), Naomi Miyamatsu (Department of Clinical Nursing Science Lecture, Shiga University of Medical Science, Otsu, Shiga), Toru Kita (Kyoto University, Kyoto), Takeshi Kimura (Department of Cardiovascular Medicine, Kyoto University, Kyoto), Yoshihiko Nishio (Department of Diabetology, Metabolism, and Endocrinology, Kagoshima University, Kagoshima), Yasuyuki Nakamura (Department of Food Science and Human Nutrition, Faculty of Agriculture, Ryukoku University, Otsu, Shiga), Tomonori Okamura (Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo), Akira Sekikawa, Emma JM Barinas-Mitchell (Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA), Daniel Edmundowicz (Department of Medicine, Section of Cardiology, School of Medicine, Temple University, Philadelphia, PA, USA), Takayoshi Ohkubo (Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo), Atsushi Hozawa (Preventive Medicine, Epidemiology Section, Tohoku University, Tohoku Medical Megabank Organization, Sendai, Miyagi), Yoshitaka Murakami (Division of Medical Statistics, Department of Social Medicine, Toho University, Tokyo), Nagako Okuda (Department of Health and Nutrition, University of Human Arts and Sciences, Saitama), Hisatomi Arima (Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka), Yoshikuni Kita (Faculty of Nursing Science, Tsuruga Nursing University, Tsuruga, Fukui), Takashi Hisamatsu (Department of Environmental Medicine and Public Health, Faculty of Medicine, Shimane University, Izumo, Shimane), Aya Higashiyama (Research and Development Initiative Center, National Cerebral and Cardiovascular Center, Suita, Osaka), Shinya Nagasawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa, Ishikawa), Koichiro Azuma (Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo), Masahiko Yanagita (Department of Health and Sports Science, Doshisha University, Kyotanabe), Robert D. Abbott (Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga), Akira Fujiyoshi (Department of Public Health, Shiga University of Medical Science, Otsu, Shiga), Aya Kadota (Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga), Naoyuki Takashima (Department of Public Health, Shiga University of Medical Science, Otsu, Shiga), Seiko Ohno (Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga), Takashi Kadowaki, Sayaka Kadowaki, Naoko Miyagawa, Keiko Kondo, Sayuki Torii, Maryam Zaid, Yoshino Saito, Sentaro Suzuki, Takahiro Ito, Atsushi Sato, Masahiro Yamazoe (Department of Public Health, Shiga University of Medical Science, Otsu, Shiga).
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\text{mean} | 0.50   | 0.35  | 0.65 | <0.001 |
|            | CCA\text{mean} | 0.67 | 0.52  | 0.81 | <0.001 |
|            | Bif\text{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\text{mean} | 0.30 | 0.16  | 0.45 | <0.001 |
|            | CCA\text{mean} | 0.35 | 0.19  | 0.51 | <0.001 |
|            | Bif\text{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\text{mean} | 0.21 | 0.06  | 0.36 | 0.005 |
|            | CCA\text{mean} | 0.24 | 0.07  | 0.41 | 0.006 |
|            | Bif\text{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\text{mean} | 0.11 | -0.05 | 0.27 | 0.164 |
|            | CCA\text{mean} | 0.10 | -0.09 | 0.28 | 0.318 |
|            | Bif\text{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\text{mean}=290 \, \mu m, CCA\text{mean}=164 \, \mu m, Bif\text{mean}=311 \, \mu m, Mean=183 \, \mu m and Mean-Max=259 \, \mu m. 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+ICA\text{mean}, CCA\text{mean}, and Bif\text{mean}. 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 |  |  |  |  |  |  |
|------|----------------|---|---|---|---|---|---|
| ICA\text{mean} | 1 (n=173) | 2 (n=174) | 3 (n=174) | 4 (n=174) | 5 (n=174) |  |
| 40.2 to 55.8 y | 1.30 (0.81 - 2.08) | 1.68 (1.17 - 2.42)** | 1.03 (0.77 - 1.37) | 1.20 (0.96 - 1.50) |  |
| OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |  |
| CCA\text{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\text{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 smoker (yes/no), smoking amount, current drinker (yes/no), and drinking 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).