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Associations of common carotid intima-media thickness (IMT) with coronary heart disease risk factors and events vary with distance from the carotid bulb

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Abstract

Background—Common carotid artery (CCA) intima-media thickness (IMT) can be measured by ultrasound near to or below the carotid bulb. This might affect associations of IMT with coronary heart disease (CHD) risk factors and events.

Methods—We performed IMT measurements near and below the divergence of the CCA bulb, in 279 white individuals, aged 45–54 years, free of CHD at baseline and a subset of the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort composed of Whites, Blacks, Chinese and Hispanics. Participants were followed for an average of 8.2 years. Far wall mean of the maximum IMT (MMaxIMT) and mean of the mean IMT (MMeanIMT) of the right and left CCA were averaged. Framingham risk factors were used in multivariable linear regression models. Parsimonious Cox proportional regression models included first time CHD as outcome.

Results—MMeanIMT below the bulb was smaller than near the bulb (0.51 mm $\pm$ 0.078 mm versus 0.56 $\pm$ 0.088 mm; $p < 0.001$) and had similar associations with risk factors (model R^2 of 0.215 versus 0.186). MMaxIMT below the bulb was associated with risk factors (model R^2 : 0.211), MMaxIMT near to the bulb was not (R^2 : 0.025). MMeanIMT and MMaxIMT below the bulb were associated with CHD events (HR 1.67; $p = 0.047$ and 1.72; $p = 0.037$, respectively) but not when measured near the bulb.

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Conclusions—CCA IMT measurements made below the bulb are smaller but have more consistent associations with CHD risk factors and outcomes as compared to IMT measured near the bulb.

Keywords

risk factors; common carotid artery; ultrasound; coronary heart disease; intima media thickness; carotid artery bifurcation

Introduction

Carotid intima-media thickness (IMT) is defined as the distance between the lumen-intima and the media-adventitia interfaces seen on ultrasound images of the carotid artery wall¹.

The common carotid artery (CCA) is often used as a site to measure IMT. However, there are different approaches to measuring CCA IMT. One approach recommends using the common carotid artery lower than the carotid bulb, ideally in an area free of plaque². Another approach extends the site of measurement into the carotid bulb, the dilation seen before the origins of the internal and external carotid arteries³.

As pointed out by Lorenz et al, the location of the IMT measurement with respect to an anatomic landmark defined as the carotid bulb varies from study to study⁴.

We hypothesized that differences in the location of the common carotid IMT measurement might affect IMT measurements in two ways. Measurements made further away from the carotid bulb and lower in the neck may produce lower IMT values and may not have the same associations with risk factors as measurements made near to the carotid bulb. We study these two hypotheses in a subset of participants from the Multi-Ethnic Study of Atherosclerosis (MESA).

Materials and Methods

Population

MESA (Multi-Ethnic Study of Atherosclerosis) is an observational cohort study that includes a population of 6814 men and women aged 45–84 with no history of clinical cardiovascular disease enrolled between July 2000 and August 2002. The MESA cohort includes white, African-American, Hispanic-American, and Chinese participants determined by questionnaire. Participants were excluded if they had physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, atrial fibrillation or history of any cardiovascular procedure⁵. Participants with weight above 300 lbs, pregnancy, or any medical conditions that would prevent long-term participation were excluded. MESA protocols and all studies described herein have been approved by the Institutional Review Boards of all collaborating institutions and all participants gave informed consent.

We restricted our analyses to a subset of the MESA study of white ethnicity aged between 45 and 54 years. We selected this younger subset of the MESA population since they are likely to have a lower burden of atherosclerosis than older participants and the prevalence of

plaques likely to be the lowest. We sampled only one race/ethnicity to maintain homogeneity of our results given financial limitations.

Risk factors and anthropomorphic variables

Age, gender, race/ethnicity, and medical history were self-reported. Use of anti-hypertensive medications was also recorded. Current smoking was defined as self-report of one or more cigarettes in the last 30 days. Resting systolic and diastolic blood pressures (BP) were measured in a seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida).

Lipids were measured after a twelve-hour fast. Diabetes mellitus was determined using the 2003 ADA fasting criteria algorithm⁶. Total cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics), as was HDL after precipitation of non-HDL cholesterol with magnesium/dextran.

Carotid artery measures

The patients were imaged supine with their head rotated 45° towards the side opposite to the side being imaged. The common carotid artery was then imaged at 45 degrees from the vertical with the beginning of the bulb shown on the image (to the left). A matrix array probe (M12L, General Electric, Milwaukee, WI) was used with the frequency set at 13 MHz with two focal zones at a frame rate of 32 frames-per-second.

All carotid artery measurements were blinded and made at the ultrasound reading center in Boston, MA. Far wall common carotid IMT measurements were made on both sides of the neck at end-diastole (smallest carotid artery diameter). A continuous tracing was made of the far-wall intima-media and lumen-intima interfaces. An algorithm then calculated the mean distance between both interfaces as well as the maximum value⁷. The mean of the mean right and left IMT and the mean of the maximum right and left IMT values were averaged. Measurements were made at two common carotid artery locations over a distance of one cm. The first set of measurements was made near the bulb from where the lumen of the common carotid artery starts to dilate (Figure 1a). The second set of measurements was made below the bulb starting at the point where the outer wall (adventitia) of the artery begins to diverge (Figure 1b). Every attempt was made to measure the segments over a distance of 1 cm starting from these two fiduciary points. As such, there was partial overlap of the measurements.

We studied a random selection of 339 participants from the 723 white participants in this age range seen at baseline. Of these 339 participants, 60 participants with ultrasound studies where the dilation of the carotid bulb was not visible, where the lumen interfaces were parallel to the media-adventitia interfaces (Figure 1c), or with incomplete risk factor data were excluded.

We evaluated the consistency of our results by measuring images from a second study acquired at a different visit on the 279 participants. The correlation coefficient between both visits for mean of the mean IMT measurements starting next to the bulb was 0.83 and 0.85

for mean of the mean IMT below the bulb. The correlation coefficient between visits for mean of the maximum IMT was 0.51 for near to the bulb and 0.61 for below the bulb.

Events

Events were identified during follow-up examinations and by telephone interview conducted every 9 to 12 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Copies were obtained of all death certificates and of all medical records for hospitalizations and outpatient cardiovascular diagnoses. Two physicians from the MESA study events committee independently reviewed all medical records for end-point classification and assignment of incidence dates. The review process included all generated ICD definitions but the final adjudication of MESA endpoints was based on specific criteria applied to data obtained from medical records by two committee members or by the whole study events committee in case of disagreement. Coronary heart disease (CHD) events included myocardial infarction (MI), resuscitated cardiac arrest, definite or probable angina followed by coronary revascularization, and definite angina not followed by coronary revascularization. Cases of coronary artery revascularization that did not have a concurrent diagnosis of angina were not included.

Statistical analyses

The mean (and standard deviation) values of continuous variables and the distribution of dichotomous variables as % in each group are shown.

Four multivariable linear regression models were generated with IMT as the outcome: 1. mean of the maximum IMT near the bulb; 2. mean of the mean IMT near the bulb; 3. mean of the maximum IMT below the bulb; and 4. mean of the mean IMT below the bulb. Traditional Framingham risk factors were used in the models, including lipid lowering and blood-pressure lowering medications. The partial coefficient of determination between individual risk factors and IMT are reported as well as the global association of individual IMT measurements and risk factors.

We evaluated potential associations between CHD events and IMT measurements using unadjusted Cox proportional hazards models and forming minimally adjusted models for variables that were significantly associated with CHD as well as forcing age and sex into the models. We verified our findings by using forward selection in separate multivariable Cox proportional hazards models for all candidate variables and the respective IMT measurement. We used a cut-point of $p < 0.05$ for inclusion

We displayed the Kaplan-Meier curves for the respective IMT measurements using the respective median values as cut-points.

Statistical analyses were performed using STATA 11.2 (STATA Corporation, College Station, TX). Level of statistical significance was set at $p = 0.05$ (two-sided).

Results

Average age of the study population was 50.5 years with women making up 48.8% of participants (Table 1). The prevalence of diabetes was very low at 1.4%. Rate of use of blood pressure lowering therapy was relatively high at 22.6% whereas it was 11.8% for lipid lowering therapies. Mean HDL and total cholesterol levels were 51 and 198 mg/dL. About 18% of the participants were current smokers.

Mean of the mean IMT measurements (Table 1) near the bulb tended to be greater and show larger variance than that taken below the bulb (0.56 ± 0.088 mm versus 0.51 ± 0.078 mm; $p < 0.001$). The difference was more pronounced for mean of the maximum IMT values near to or below the bulb ($p < 0.001$).

The partial variance levels accounted for by selected risk factors (Table 2) with regard to IMT measurements were weakest for mean of the maximum IMT measurements near the carotid bulb. Risk factors tended to show stronger associations with the means of the mean IMT measurements than with the means of the maximum IMT measurements.

Multivariable linear regression models (Table 3) showed that both mean of the mean IMT and mean of the maximum IMT measured below the bulb had the strongest associations with risk factors than IMT measurements made near the bulb. The model coefficient of determination for mean of the mean IMT near the bulb was 0.186 as compared to 0.215 for measurements below the bulb. For mean of the maximum IMT, model R^2 was 0.025 for measurements near the bulb and 0.211 for measurements taken below the bulb.

Results of exploratory unadjusted Cox proportional hazards models with CHD as outcome (Table 4) showed that systolic blood pressure ($p = 0.011$), mean of the maximum IMT below the bulb ($p = 0.001$), mean of the mean IMT near the bulb ($p = 0.002$) and below the bulb ($p = 0.001$) were associated with events whereas mean of the maximum IMT near the bulb was not. Minimally adjusted Cox proportional hazards models (Tables 5 and 6) showed that IMT measurements made below the bulb were more consistently associated with CHD events than measurements made near to the bulb.

The Cox proportional hazards models for IMT measurements below the bulb using a forward stepwise strategy showed mean of the mean IMT ($p = 0.001$) and mean of the maximum IMT ($p = 0.001$) to be associated with CHD events. Results for IMT measurements near to the bulb showed mean of the mean IMT ($P = 0.002$) to be associated with CHD events but not the mean of the maximum IMT while the only variable to enter the model was systolic blood pressure ($p = 0.01$).

Discussion

We have found differences in two approaches to measuring common carotid artery IMT: starting within the divergence of the carotid bulb or starting slightly below. This difference applies to the two commonly used IMT measurements: mean of the mean IMT and mean of the maximum IMT. IMT measurements made near the bulb are larger, more weakly

associated with risk factors, and more weakly associated with events than measurements made below the bulb.

These results imply that careful attention should be given to the IMT measurement protocol when the results of various IMT studies are combined or when normative common carotid IMT measurements are used.

Our observation that the association of common carotid IMT with risk factors is affected by location where the measurement is made is novel. We used the overall goodness-of-fit (R^2) to evaluate the relative strength of the associations between IMT at these two locations and coronary heart disease risk factors. This represents the percent variability that can be explained by the risk factors in the models (Table 3). An implication of this observation is that change in IMT secondary to change in risk factors could also be different. One could therefore hypothesize that mean of the maximum IMT measurements near to the bulb would be less likely to detect the effects of an intervention than mean of the maximum IMT measured below the bulb since the percent variability explained by risk factors for each variable is 2.5% and 21.1% respectively. Use of the mean of the mean IMT is less influenced by location since near to the bulb 18.6% of the variability is explained by risk factors whereas below the bulb it is 21.5%. In addition, the partial coefficients R^2 goodness-of-fit values in Table 2 are a way estimating the variability explained by a risk factor on a specific IMT variable after taking into consideration the other risk factors. For example, the highest variability explained by a risk factor is 8.6% for the association of systolic blood pressure with the mean of the mean IMT below the bulb. None of the explained variability is significant for the mean of the maximum IMT near to the bulb whereas the strongest association with risk factors is for the mean of the mean IMT below the bulb. The relatively low contribution of age to overall variability might be due to the small number of participants and the 10-year span in participant age. The reproducibility of mean of the mean IMT was stronger, irrespective of location (0.83 near to the bulb, 0.85 below the bulb), than mean of the maximum IMT (0.51 near to the bulb, 0.61 below the bulb). This also suggests that mean of the mean IMT is less subject to variations due to slight differences in the site of CCA IMT measurements.

Our observation also has impact on reported associations between IMT and coronary heart disease events. They might, in part, shed some light on why certain studies do not show strong associations between common carotid IMT and events while others do. Meta-analyses that noted differences in the location where CCA IMT measurements were made also reported large differences in the associations of CCA IMT with cardiovascular events^{4, 8}.

Use of normative IMT measurements near the bulb would tend to underestimate risks for CHD events since IMT in this location is larger than IMT values taken lower in the common carotid artery. For example, the consensus guidelines for using IMT as a clinical risk prediction tool reference studies that can be used as the source of normative data⁹. The measurement process for CCA IMT varies between these studies and without careful attention to the protocol used the reference data might lead to inappropriate risk stratification of patients. For example, one of the references for IMT normative measurements is the

Atherosclerosis Risk in Communities (ARIC) study. The ARIC manual describing the IMT measurement process indicates that common carotid IMT measurements start at the “crest of the bulb”, corresponding to our near to the bulb measurements³. Conversely, the IMT measurements made in the Framingham Heart Offspring Study were made lower in the common carotid artery in the zone corresponding to the below the bulb location in the current study^{10,11}.

There have been a few studies on the differences between common carotid IMT measurements as a function of the location in the common carotid artery. One study evaluated changes in IMT as a function of distance from the carotid bulb and showed that IMT was larger closer to the bulb¹². Another study reported similar findings but linked this difference to variations in the shear rate of blood flow along the artery wall¹³. We expand to these findings by showing correlations with cardiovascular risk factors and events.

Limitations of our study include a restricted subset of the MESA study. Our results might therefore only apply to whites aged 45 to 54 years. This possibility should be considered given differences in the associations of coronary heart disease risk factors and events in individuals of different ethnicities¹⁴ despite similarities in the association of risk factors with IMT in Caucasian whites on different continents¹⁵.

We were also not able to measure wall shear-rates, the likely source of the differences in IMT due to the location of the measurement^{12, 13}. By using only one reader to perform the IMT measurements, we might have induced a systematic reader bias that we cannot control for, but limited inter-observer variability.

Although our study is underpowered with only 11 events having occurred during the follow-up period, we still show significant associations between events and systolic blood pressures as well as some of the IMT measurements. It is likely that as the number of events increases, the predictive value of other risk factors would improve and permit the development of multivariable models that could compensate for residual confounding. We further tested the validity of our findings by using a forward selection process in additional Cox proportional hazards models. We noted a consistent significant predictive value of mean of the mean IMT and mean of the maximum IMT measured below the bulb and, for measurements near to the bulb, a significant association with events for mean of the mean IMT and not for mean of the maximum IMT.

Our results were in part unexpected. We had hypothesized that IMT measurements made closer to the bulb might be better for risk assessment since these might include early plaque formation¹⁶. However, the near bulb measurements had weaker associations with events. It seems unlikely that this is simply due to the small sample size since positive associations are seen with measurements below the bulb. The mean of the maximum IMT measured near to the bulb also has the weakest associations with risk factors suggesting that this measurement is the least representative of carotid atherosclerosis. One possibility is that we are simply seeing the effects of a divergence in the blood flow near the bifurcation where the carotid walls are no longer parallel and not the effects of a purely atherosclerotic process. This divergence in blood flow decreases shear rates^{12, 13} and shear stress. The endothelium

might simply be inducing a local zone of intimal hypertrophy in order to normalize shear stress, in essence trying to extend the inner wall of the lumen in order to compensate for the divergence of the outer wall^{17, 18}. It is possible that in older individuals, as the likelihood of plaque formation progresses and extends from the bulb, mean of the maximum IMT might become more strongly associated with atherosclerotic plaque.

We observe that mean IMT measurements are less affected by the location of the measurements. This makes us propose that mean IMT measurements should probably be used in meta-analyses and for clinical risk assessment instead of the mean of the maximum unless the measurement location is clearly indicated.

Conclusions

We conclude that IMT measurements vary significantly with small changes in location with respect to the carotid artery bulb. These changes need to be accounted for when meta-analyses combine the results of carotid IMT studies and when normative data are used for risk assessment in patients. Overall, mean of the mean common carotid IMT measured below the bulb seems to offer slightly better predictive value for coronary heart disease events, modestly stronger associations with risk factors, and mildly better reproducibility than the other measurements we evaluated in this study.

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A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

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Figure 1.

Location of intima-media thickness (IMT) measurements The location of the near to the bulb IMT measurements (A) on the far wall of the artery is outlined by the white box on this composite image of a carotid bifurcation. The measurement zone extends 1 cm towards the body (right of the image) starting where the lumen starts to diverge from parallel. The location of the below the bulb IMT measurement is shown in figure 1B. The measurement zone also extends 1 cm towards the body (right of the image) but starts where the outer walls start to diverge. The zone of overlap is the length of the carotid artery between the divergence of the outer wall of the artery (adventitia) and the divergence of the lumen (intima). Cases where the lumen-intima and media-adventitia interfaces remained parallel to each other (arrows) near to the bulb (C) were not included in the analyses.

Figure 2.

Kaplan-Meier curves showing likelihood of not developing coronary heart disease (CHD) events during follow-up. Values greater than the median of the mean far wall intima-media thickness (IMT) measured further away from the bulb (A) are associated with a greater likelihood of incident CHD ($p = 0.032$; Log-Rank = 4.63) whereas mean of the maximum IMT measured in the same location (B) does not show a significant association ($p = 0.13$; Log-Rank = 2.35). Values greater than the median of the far-wall IMT nearer to the bulb (C) are also associated with CHD events ($p=0.033$; Log-Rank = 4.53) whereas mean of the maximum IMT measured at the same location (D) are not ($p = 0.77$; Log-Rank = 0.09).

Table 1

Demographics of the population studied (n = 279).

Variable	Value	Standard deviation or actual value
Age (years)	50.5	SD = 3.0
Sex (female)	48.8%	n = 136
Systolic blood pressure	113.1	SD = 16.6
HDL cholesterol (mg/dl)	50.6	SD = 14.4
Total cholesterol (mg/dl)	197.8	SD = 39.0
Diabetes (yes)	1.4%	n = 4
Current smoker (yes)	18.3%	n = 51
Blood pressure lowering medications (yes)	22.6%	n = 63
Lipid lowering medications (yes)	11.8%	n = 33
Mean maximum IMT* below bulb (mm)	0.58	SD = 0.092
Mean of the mean IMT* below bulb (mm)	0.51	SD = 0.078
Mean maximum IMT* near bulb (mm)	0.70	SD = 0.189
Mean of the mean IMT* near bulb (mm)	0.56	SD = 0.088

*
intima-media thickness

Table 2

Partial variance accounted for by respective risk factor with the selected common carotid artery intima-media (IMT) thickness variable used as outcome of adjusted multivariable models (total n = 279)

	Mean maximum IMT below bulb (mm)		Mean of the mean IMT below bulb (mm)		Mean maximum IMT near bulb (mm)		Mean of the mean IMT near bulb (mm)	
	Partial r ²	p-value	Partial r ²	p-value	Partial r ²	p-value	Partial r ²	p-value
Age (years)	0.025	0.009	0.015	0.043	0.002	0.45	0.0108	0.08
Sex (men)	0.051	0.0002	0.04	0.0009	0.0003	0.76	0.0225	0.014
HDL cholesterol (mg/dL)	0.001	0.58	0.001	0.59	0.004	0.31	0.001	0.61
Total cholesterol (mg/dL)	0.014	0.053	0.02	0.021	0.005	0.25	0.0336	0.002
Lipid lowering therapy (yes)	0.0	0.94	0.001	0.60	0.0	0.92	0.0023	0.43
Diabetes (yes)	0.002	0.47	0.0004	0.74	0.001	0.60	0.0026	0.40
Systolic pressure (mmHg)	0.066	< 0.0001	0.086	< 0.0001	0.004	0.32	0.0727	< 0.0001
Blood pressure lowering therapy (yes)	0.004	0.33	0.002	0.42	0.0	0.99	0.0016	0.51
Current smoker (yes)	0.0006	0.68	0.0006	0.69	0.005	0.26	0.0001	0.90

Table 3

Results of multivariable regression models with the selected common carotid artery intima-media thickness (IMT) variable used as outcome (total n = 279)

	Mean maximum IMT below bulb (mm)		Mean of the mean IMT below bulb (mm)		Mean maximum IMT near bulb (mm)		Mean of the mean IMT near bulb (mm)	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Age (years)	0.0045	0.009	0.0029	0.043	0.0029	0.45	0.0028	0.09
Sex (men)	0.0436	< 0.0001	0.0327	0.001	0.0079	0.76	0.0277	0.013
HDL cholesterol (mg/dL)	-0.0002	0.58	-0.0002	0.59	-0.0009	0.31	-0.0002	0.61
Total cholesterol (mg/dL)	0.0003	0.053	0.0003	0.02	0.0003	0.25	0.0004	0.002
Lipid lowering therapy (yes)	-0.0011	0.94	0.0072	0.60	0.0038	0.92	0.0122	0.43
Diabetes (YES)	0.0313	0.47	0.0120	0.74	0.0515	0.60	0.0351	0.4
Systolic pressure (mmHg)	0.0014	< 0.0001	0.0014	< 0.0001	0.0007	0.32	0.0015	< 0.0001
Blood pressure lowering therapy (yes)	0.0122	0.33	0.0086	0.42	0.0002	0.99	0.0080	0.51
Current smoker (yes)	0.0054	0.68	0.0044	0.69	0.0336	0.26	0.0016	0.9
Model R ²	0.211		0.215		0.025		0.186	

Table 4

Results of single variable Cox regression models with time to coronary artery disease events as outcome (n = 279 with 11 events)

	Hazard ratio [*]	Lower 95% CI	Higher 95% CI	p-value
Age (years)	1.19	0.95	1.50	0.14
Sex (men)	0.86	0.26	2.83	0.81
Hdl cholesterol (mg/dL)	0.97	0.92	1.02	0.24
Total cholesterol (mg/dL)	1.01	1.00	1.02	0.20
Lipid lowering therapy (yes)	1.64	0.35	7.60	0.53
Diabetes (yes)	Unstable [†]			
Systolic pressure (mmHg)	1.04	1.01	1.08	0.01
Blood pressure lowering therapy (yes)	0.78	0.17	3.61	0.75
Current smoker (yes)	2.57	0.75	8.77	0.13
Mean maximum IMT [‡] below bulb (mm)	1.97	1.33	2.92	0.001
Mean of the mean IMT [‡] below bulb (mm)	1.92	1.32	2.78	0.001
Mean maximum IMT [‡] near bulb (mm)	1.20	0.87	1.67	0.27
Mean of the mean IMT [‡] near bulb (mm)	1.89	1.25	2.85	0.002

* Hazard ratios for respective risk factors according to their units except for standardized hazard ratios for carotid artery intima-media thickness measures.

[†] small number of diabetics (n = 4)

[‡] intima-media thickness

Table 5

Parsimonious multivariable Cox proportional hazards models for CHD events: age, gender, systolic pressure and common carotid artery (CCA) intima-media thickness (IMT) variables below the bulb for 11 events.

Mean of the maximum intima-media thickness				Mean of the mean intima-media thickness					
		Low 95%		High 95%			Low 95%		High 95%
	Hazard ratio*	CI	p-value		Hazard ratio*	CI	p-value		
Age (years)	1.12	0.85	1.42	0.34	1.13	0.89	1.44	0.31	
Gender (men)	0.44	0.12	1.65	0.22	0.45	0.12	1.71	0.25	
Systolic Pressure (mmHg)	1.03	0.99	1.07	0.19	1.03	0.99	1.07	0.21	
CCA IMT variable	1.72	1.03	2.88	0.037	1.67	1.01	2.78	0.047	

* Hazard ratios for respective risk factors according to their units except for standardized hazard ratios for carotid artery intima-media thickness measures

Parsimonious multivariable Cox proportional hazards models for CHD events: age, gender, systolic pressure and common carotid artery (CCA) intima-media thickness (IMT) variable near to the bulb for 11 events.

Mean of the maximum intima-media thickness				Mean of the mean intima-media thickness			
	Hazard ratio *	CI	High 95%		Hazard ratio *	CI	High 95%
Age (years)	1.16	0.92	1.47	0.21	1.14	0.90	1.45
Gender (men)	0.62	0.18	2.11	0.44	0.50	0.13	1.81
Systolic Pressure (mmHg)	1.05	1.01	1.08	0.01	1.03	0.99	1.07
CCA/IMT variable	1.25	0.81	1.93	0.32	1.60	0.97	2.62
							0.07

* Hazard ratios for respective risk factors according to their units except for standardized hazard ratios for carotid artery intima-media thickness measures