02. Carotid Intima-Media Thickness in Indonesian

by Rinambaan W. M. Kaligis

Carotid Intima-Media Thickness in Indonesian Subjects with Cardiovascular Disease Risk Factors Who Were Not Receiving Lipid-Lowering Agents

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Abstract

Carotid intima-media thickness (CIMT) is frequently utilized for detection of subclinical atherosclerosis. This study aims to investigate the association between the CIMT values and demographic characteristics, cardiovascular disease (CVD) risk factors, lipid biochemistry profiles, and high-sensitivity C-reactive protein (hs-CRP) levels among the Indonesian population. Subjects who had two or more CVD risk factors but were not receiving lipid-lowering therapy were recruited from six hospitals of Indonesia. Measurements of CIMT are obtained by ultrasonography of 12 sites within the common carotid artery. CVD risk factors, lipid and glucose profiles, and hs-CRP values were analyzed with respect to distribution of CIMT. The mean–max CIMT was 0.805 ± 0.190 mm (minimum, 0.268 mm; maximum, 1.652 mm) and the mean–mean CIMT was 0.614 ± 0.190 mm (minimum, 0.127 mm; maximum, 1.388 mm). Multivariate analyses confirmed an independent association between increasing CIMT and increasing age (regression coefficient = 0.004; $p = 0.004$). Our data show normative mean–mean CIMT data for Indonesian subjects with two or more CVD risk factors who are not receiving lipid-lowering therapy, which may guide CVD risk stratification of asymptomatic individuals in Indonesia.

Keywords

- intima-media thickness
- atherosclerosis
- cardiovascular diseases risk factors
- Indonesia
- common carotid artery
- lipid-lowering therapy
- asymptomatic individuals

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Like many countries undergoing socioeconomic transition, Indonesia is struggling with a fast-growing burden of noncommunicable diseases such as diabetes and cardiovascular diseases (CVDs). CVD is one of the main causes of death in Indonesia, contributing for 31.9% of all deaths in the country and 11.2% of all deaths in hospitals.[1] Data from the Indonesia Basic Health Research conducted by the Ministry of Health in 2007showed that among people older than 18 years the prevalence of hypertension was 29.8% and that of heart diseases was 7.2%.[2] Risk factors such as smoking, poor diet, and lack of exercise are growing in importance and further contributing to the incidence of these diseases.

Atherosclerosis is the underlying cause of the majority of CVDs. It has been known that atherosclerosis starts in the early years and develops over decades as a clinically silent disease, thus providing the opportunity for identification of high-risk individuals in preclinical stage and early initiation of preventive strategies. Early identification of subclinical atherosclerosis by noninvasive measures such as ultrasonic measurements of intima-media thickness (IMT) is often used as a surrogate end point of CVD and coronary artery disease, with increased carotid IMT (CIMT) having been associated with both the presence and extent of coronary artery disease.[3,4]

Although extensive studies on the use of CIMT have been conducted in the last two decades, data among Asian population have been growing just recently. One study of atherosclerotic disease involving eight Asian countries has reported the distribution of CIMT values in Asian population with at least two CVD risk factors who were not receiving any lipid-lowering treatment.[5] The study has established that age, male gender, low high-density lipoprotein cholesterol (HDL-C) levels, and elevated fasting blood glucose levels are associated with the increase of mean–mean CIMT. However, the Asian population consisted of diverse ethnic groups, and the study found a significant variation of mean–mean CIMT across countries.

As the third-largest country in Asia and the largest in the Southeast Asia, the Indonesian population represents an important proportion of Asian people who might have distinct CVD profile, risk associations, and different levels of genetic–environmental interactions.

This study aim to investigate the association between the CIMT values and demographic characteristics, CVD risk factors, lipid biochemistry profiles, and high-sensitivity C-reactive protein (hs-CRP) levels among the Indonesian cohort in the Asian study.

Methods

Study Subjects

The methods of this study have been published elsewhere.[5] In summary, the study participants were people aged 30 to 69 years with at least two CVD risk factors who had not received lipid-lowering treatment within the 3 months prior to study entry. CVD risk factors included age (males ≥45 years and females ≥55 years), cigarette smoking (any cigarette smoking in the past month), hypertension (arterial blood pressure ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic or taking antihypertensive medication), low HDL-C (<40 mg/dL, corresponding to 1.0 mmol/L), and family history of premature coronary heart disease (CHD) (clinical CHD or sudden death in the father or another first-degree male relative <55 years of age; CHD in the mother or another first-degree female relative <65 years of age). Exclusion criteria were a history of CHD or any condition that affects hs-CRP levels, including malignancy or chronic inflammation.

This study was performed in accordance with the ethical principles of the Declaration of Helsinki, and is consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The study protocol and informed consent forms were approved by the Ethics Committee for Medical Research, Harapan Kita National Cardiovascular Centre.

Data Collection

Data collection for each subject was performed during one or two visits, depending on the availability of a sonographer at the study site. The time between visits was not more than 3 months and eligibility criteria were reassessed at the second visit. Subjects' informed consent was taken, physical examination and measurement of vital signs (including weight, height, waist circumference, and blood pressure) were conducted, and demographic data were collected.

Subjects' fasting blood samples were taken for analyses of total cholesterol, triglyceride, low-density lipoprotein cholesterol, HDL-C, fasting blood glucose, and hs-CRP levels, which were performed at a single central laboratory for consistency.

Subjects were asked to complete a questionnaire which recorded information regarding prevailing knowledge of CVD risk factors, cholesterol management, and physician visit frequency.

CIMT Measurement

Measurements of CIMT in all subjects were conducted using a SonoSite MicroMaxx high-resolution, digital, portable ultrasound system with standard accessories and SonoCalc-embedded IMT software by a certified sonographer. Measurements were taken in the left and right distal common carotid artery (CCA) of both the near and far wall at each location from three positions: anterior, lateral, and posterior. Using all 12 measurements taken, the SonoCalc software calculated for each subject the mean (mean–mean CIMT), minimum, and maximum for the average values of the 12 measurements and the mean (mean–max CIMT), minimum, and maximum for the maximum values of the 12 measurements.

Statistical Analysis

The distribution of CIMT measurements was described in terms of mean, standard deviation (SD), median, minimum, and maximum values. The associations between CIMT measurements and demographic characteristics, CVD risk factors, and lipid and hs-CRP values were analyzed using one-way analysis of variance (ANOVA) models (for categorical variables) and univariate linear regression models (for continuous variables). The effects of identified explanatory variables were further explored using a general linear model approach by stepwise inclusion of explanatory variables into a multivariate model, based on a significance level of 1%. Log-transformed hs-CRP values were used for statistical analyses except for calculating descriptive statistics. The per protocol analysis set (PPS) from available data was used for analysis. It included subjects who did not violate inclusion and exclusion criteria and whose CIMT values were available. The SAS package, version 9.2 (SAS Institute Inc., Cary, NC), was used for all statistical analysis.

Results

Subject Characteristics

A total of 374 patients from six hospitals in Indonesia enrolled in this study. Of those, 356 were included in the PPS. The subjects included more male (236/356, 66.3%), with the mean (SD) age of the subjects being 56 (7.2) years. ►**Table 1** shows the demographic characteristics, CHD risk factors, presence of CHD risk equivalence, and metabolic syndrome of the Indonesian subjects included in the PPS. The most common CHD risk factors were older age (332/356 subjects; 93.3%) and hypertension (259/356 subjects; 72.8%), while the most common metabolic syndrome present was high blood pressure (230/355; 64.8%), followed by abdominal obesity (198/355; 55.9%).

Overall, 287 (80.6%) subjects had never received any lipid-lowering treatment. Of those who had previously received lipid-lowering therapy, statins were the most commonly administered lipid-lowering agent and were taken for a mean of 4.6 months (minimum and maximum treatment duration of 1 and 48 months, respectively). Treatment was stopped at least 3 months prior to study entry.

CIMT Measurements

The overall mean (SD) of the average CIMT measurements (mean–mean CIMT) was 0.614 (0.19) mm (►**Table 2**). The minimum and maximum values of mean–mean CIMT measurements were 0.127 and 1.388 mm, respectively. Of the 356 Indonesian subjects in the PPS, 209 (58.71%) had a mean–mean CIMT value of 0.6 or higher (►**Fig. 1**).

The mean (SD) of maximum region CIMT values (mean–max CIMT) was 0.805 (0.19) mm (►**Table 2**). The minimum and maximum values of mean–max CIMT measurements were 0.268 and 1.652 mm, respectively. Of the 356 Indonesian subjects in the PPS, 186 (52.24%) had a mean–max CIMT value of 0.8 or higher (►**Fig. 2**)

We found only two subjects with carotid plaque.

Association of Mean–Mean CIMT with Demographic and CVD Risk Factors

Linear regression analysis (►**Table 3**) found that factors which have positive association with mean–mean CIMT were age (regression coefficient = 0.003; $p = 0.026$) and log (hs-CRP) (regression coefficient = 0.020; $p = 0.029$), while triglyceride level was negatively associated with mean–mean CIMT (regression coefficient = −0.0002; $p = 0.022$). Other demographic and CVD risk factors were found to be not associated with mean–mean CIMT based on ANOVA analysis. Further multivariate analysis using general linear model found that no factors could be included in the final model at $\alpha = 0.01$ level.

Association of Mean–Max CIMT with Demographic and CVD Risk Factors

Linear regression analysis (►**Table 3**) found that factors that have positive association with mean–max CIMT were age (regression coefficient = 0.004; $p = 0.004$) and log (hs-CRP) (regression coefficient = 0.022; $p = 0.021$), while triglyceride level was negatively associated with mean–max CIMT (regression coefficient = −0.0003; $p = 0.012$). Other demographic and CVD risk factors were found to be not associated with mean–mean CIMT based on ANOVA analysis. Further multivariate analysis using general linear model found age as the only independent risk factor for the increase of mean–max CIMT (regression coefficient = 0.004; $p = 0.004$).

Discussion

Our study found that the average mean CIMT and average max CIMT of Indonesian patients with two or more CVD risk factors were 0.614 and 0.805 mm, respectively. The only independent association found was between age and average max CIMT.

This result is quite similar with a study among healthy middle-age population in Korea, which found the average mean CIMT of 0.60 among men and 0.53 among female.[6] However, our study found no significant difference on the average mean CIMT between male and female. The average mean CIMT of the Indonesian cohort is also lower compare with normotensive middle age and elderly population in southern China with the average mean of 0.71 mm.[7]

Analysis of the healthy individuals younger than 45 years from the six cohorts that are part of the USE-Intima Media Thickness project found higher average mean CIMT of 0.63 mm. This analysis of the USE-IMT project included population from Germany, Canada, Finland, Japan, Norway, and the United States.[8]

The overall mean–mean CIMT of the eight Asian countries in the original study was higher (0.662 ± 0.16 mm).[5] In this study, the Indonesian cohort has the third lowest mean–mean CIMT after Thailand (0.567 ± 0.120 mm) and the Philippines (0.583 ± 0.117 mm). However, it was also reported that the participants from Thailand and the Philippines were relatively younger compare with Indonesian participants (48.8 ± 12.5 and 52.2 ± 7.6 years vs. 0.56.0 ± 7.2 years).A significant correlation between increasing age and mean CIMT has been consistently observed in diverse populations, including the Asian.[5,6,9,10]

Besides older age, low HDL-C, elevated fasting blood glucose, and male gender were independent predictor of the mean–mean CIMT increase in the overall Asian population. Yet,

Table 1 Subjects' demographic characteristics, CHD risk factors, presence of CHD risk equivalence, and metabolic syndrome ($n = 356$)

Factors		
Age (y)	Mean (SD)	56.0 (7.2)
	Median (min/max)	57 (32/69)
Age	30 to 39 y	5 (1.40)
	40 to 49 y	68 (19.10)
	50 to 59 y	160 (44.94)
	60 to 69 y	123 (34.55)
Gender	Male	236 (66.29)
	Female	120 (33.71)
Weight (kg)[a]	Mean (SD)	63.9 (11.7)
	Median (min/max)	64 (26/111)
Height (cm)[a]	Mean (SD)	160.2 (8.2)
	Median (min/max)	160 (134/180)
BMI (kg/m^2)[a]	Mean (SD)	24.8 (3.9)
	Median (min/max)	25 (12.89/36.59)
BMI (kg/m^2)[a]	Normal weight (<25)	194 (54.80)
	Overweight (25 to 30)	122 (34.46)
	Obese (>30)	38 (10.73)
Waist circumference (cm)[a]	Mean (SD)	87.9 (10.9)
	Median (min/max)	89 (58/117)
Sitting SBP (mm Hg)[a]	Mean (SD)	135.4 (21.4)
	Median (min/max)	130 (100/220)
Sitting DBP (mm Hg)[a]	Mean (SD)	83.4 (12.0)
	Median (min/max)	80 (53/140)
CHD risk factors	Age (men ≥ 45 y; women ≥ 55 y)	332 (93.3)
	Cigarette smoking (any cigarette smoking in the past month)	152 (42.7)
	Hypertension	259 (72.8)
	Low HDL-C	18 (5.1)
	Family history of premature CHD	32 (9.0)
	High HDL-C (negative risk factor if ticked "yes")	2 (0.6)
Presence of CHD risk equivalents[b]	Diabetes	38 (10.7)
	Abdominal aortic aneurysm	1 (0.3)
	Carotid artery disease	7 (2.0)
Presence of metabolic syndrome[b]	Abdominal obesity: (men ≥ 90 cm; women ≥ 80 cm)[a]	198 (55.9)
	Triglyceride (TG ≥ 150 mg/dL)	16 (4.5)
	HDL-C: (men < 40mg/dL; women < 50 mg/dL)	22 (6.2)
	Blood pressure (≥130/85 mm Hg)	230 (64.8)
	Fasting glucose (≥100 mg/dL)	20 (5.6)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure.
[a] $n = 354$.
[b] $n = 355$.

in Indonesian cohort, age is only associated independently with mean–max CIMT and not mean–mean CIMT. One study among Iranian population of 35 to 64 years old without history of cardiovascular event also found that age (odds ratio [OR], 1.11; 95% confidence interval [CI], 0.56–4.34; $p < 0.01$) and male gender (OR [95% CI], 1.14 [0.63–2.23]; $p < 0.05$) were the only significant independent predictors of the mean–max CIMT of ≥0.8 mm.[11]

Table 2 CIMT and hs-CRP values of the Indonesian subjects ($n = 356$)

	Mean	SD	Median	Minimum	Maximum	95% CI	
						Lower	Upper
Mean–mean CIMT (mm)	0.614	0.1885	0.627	0.127	1.388	0.595	0.634
Mean–max CIMT (mm)	0.805	0.1945	0.805	0.268	1.652	0.785	0.825
	G-mean	CV%					
hs-CRP (mg/dL)[a]	0.172	179.76	0.180	0.020	9.240		

Abbreviation: CIMT, carotid intima-media thickness; hs-CRP, high-sensitivity C-reactive protein.
Note: G-mean is the geometric mean. CV is the coefficient variation calculated as SQRT([exp(s^2) − 1] x100, where s is a standard deviation on a log-transformed scale.
[a]$n = 349$.

Although hs-CRP and triglyceride level were found to be associated during bivariate linear regression analysis with both the mean–mean CIMT and mean–max CIMT in the Indonesian cohort, both failed to stand as independent predictor of CIMT during multivariate analysis. Several studies have shown that hs-CRP is positively correlated with increased risk of CVD. Yet, in the study among Asian population, hs-CRP level did not correlate directly with CIMT values.[5]

Our study has been the first to show the application of the CIMT measurements among Indonesian subjects, which

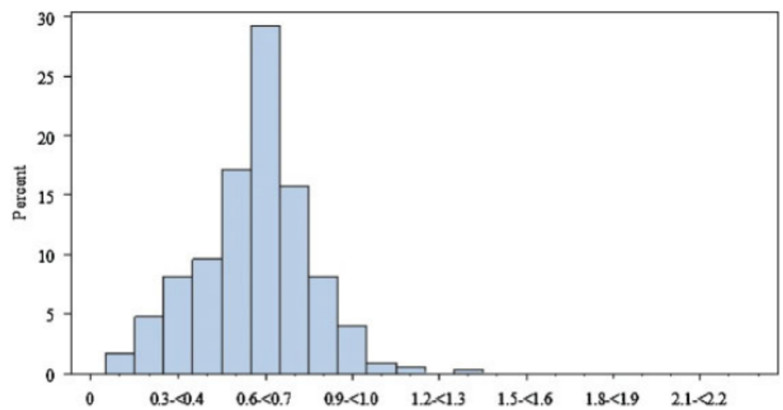

Fig. 1 Distribution of CIMT in PPS population of Indonesia ($n = 356$) based on the average of the mean region values (mean–mean CIMT). CIMT, carotid intima-media thickness; PPS, per protocol analysis set.

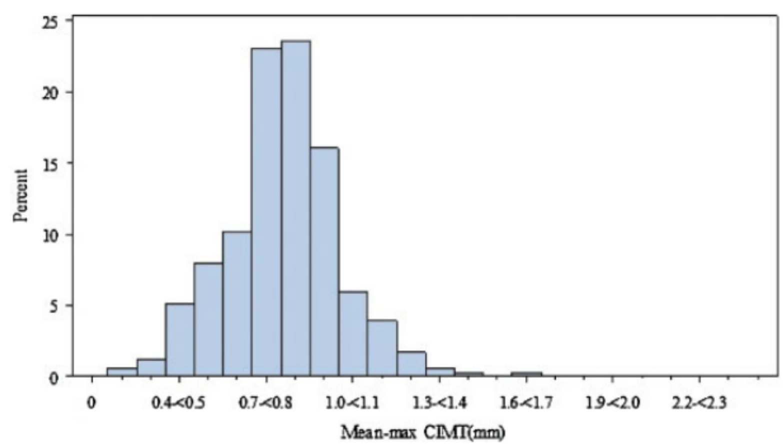

Fig. 2 Distribution of CIMT in PPS population of Indonesia ($n = 356$) based on the average of the maximum region values (mean–max CIMT). CIMT, carotid intima-media thickness; PPS, per protocol analysis set.

Table 3 Association of mean–mean CIMT and mean–max CIMT with demographic and CVD risk factors

Factors	Regression coefficient estimate	SE	95% CI		*p*-Value
			Lower	Upper	
Mean–mean CIMT					
Age (y)	0.003095	0.001384	0.000372	0.005817	0.0260
Weight (kg)	−0.000840	0.000857	−0.002524	0.000845	0.3277
BMI (kg/m^2)	−0.003017	0.002564	−0.008060	0.002026	0.2402
Waist circumference (cm)	−0.000143	0.000928	−0.001968	0.001681	0.8772
TC (mg/dL)	0.000203	0.000242	−0.000273	0.000678	0.4024
LDL-C (mg/dL)	0.000494	0.000291	−0.000078	0.001065	0.0903
HDL-C (mg/dL)	−0.000876	0.000916	−0.002676	0.000925	0.3395
TG (mg/dL)	−0.000244	0.000106	−0.000452	−0.00036	0.0218
Glucose (mg/dL)	0.000203	0.000278	−0.000343	0.000750	0.4648
Log (hs-CRP)	0.020103	0.009183	0.002042	0.038164	0.0293
Mean–max CIMT					
Age (y)	0.004138	0.001421	0.001343	0.006933	0.0038
Weight (kg)	−0.000822	0.000884	−0.002560	0.000917	0.3531
BMI (kg/m^2)	−0.002635	0.002647	−0.007841	0.002571	0.3202
Waist circumference (cm)	−0.000111	0.000957	−0.001993	0.001771	0.9073
TC (mg/dL)	0.000242	0.000250	−0.000249	0.000733	0.3332
LDL-C (mg/dL)	0.000581	0.000300	−0.000009	0.001171	0.0537
HDL-C (mg/dL)	−0.000714	0.000947	−0.002577	0.001149	0.4516
TG (mg/dL)	−0.000276	0.000109	−0.000491	−0.000061	0.0120
Glucose (mg/dL)	0.000285	0.000287	−0.000280	0.000850	0.3216
Log (hs-CRP)	0.021917	0.009488	0.003257	0.040577	0.0215

Abbreviations: BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
Note: Only the continuous variables are presented. Analysis was done by linear regression.

shows the values among those with at least two CVD risk factors who were not receiving any lipid-lowering treatment. As the CIMT measurement is often used in the identification of subclinical atherosclerotic disease, information on the baseline value is important.

Limitation of our study includes its cross-sectional nature, which is not the strongest design to prove causal associations. In addition, our examination was limited to the CCA, which may not have detected the presence of atherosclerosis in other vascular beds or more distal segments of the carotid artery. Since our study involved subjects with at least two CVD risk factors which possibly have higher risk of CAD, measurement of healthy subjects is necessary to establish the normative CIMT value among Indonesian subjects. A longitudinal study is further needed for a better evaluation of the relationships between cardiovascular risk factors, subclinical atherosclerosis, and the risk of cardiovascular events in this population.

Conclusion

The findings of this study have important implications for CVD screening and the identification of asymptomatic, high-risk patients and the consequent implementation of CVD prevention strategies in Indonesia.

Acknowledgment
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