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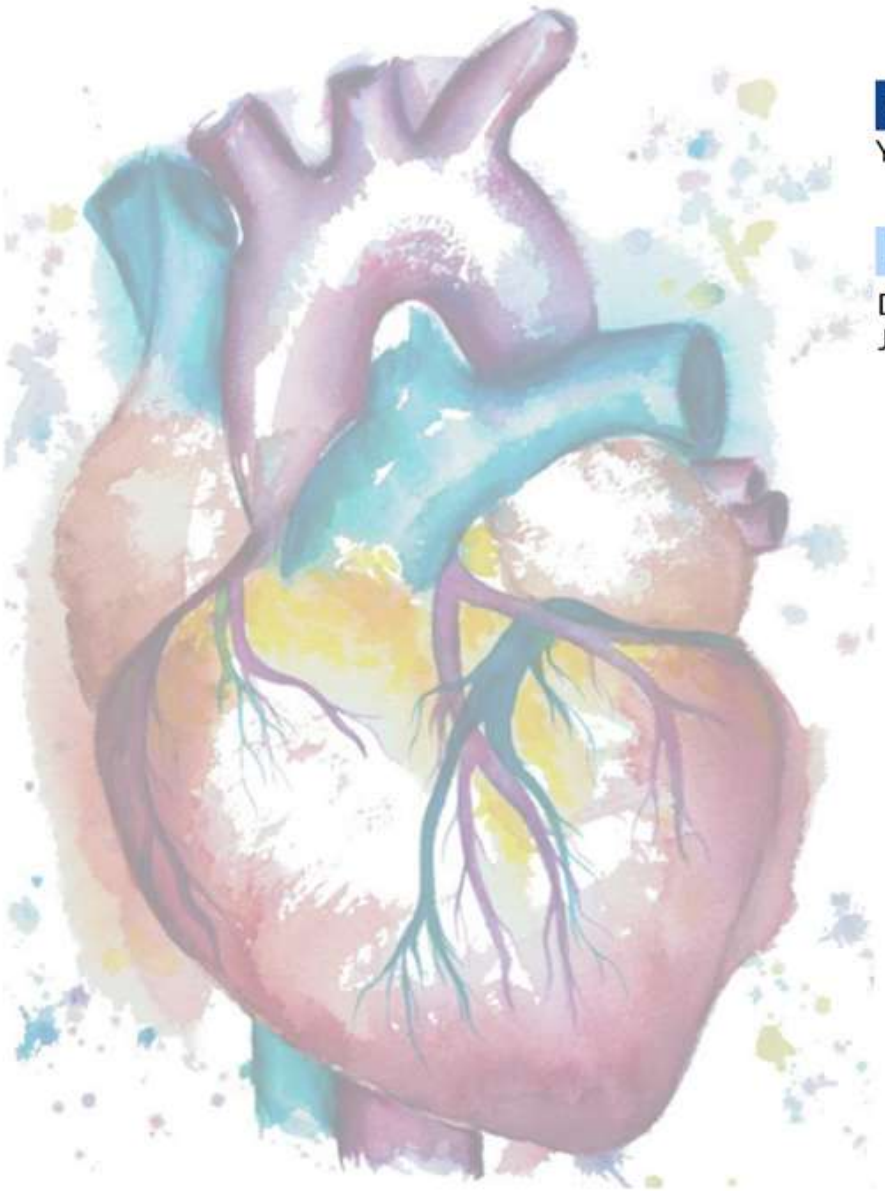

Original Research

Case Report

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Current Issue

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Original Research

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Andrianus Oktovianto [(1)], *Ni Putu Anggun Laksmi* [(2)], *Johanes Nugroho Eko Putranto* [(3)], *Raden Mohammad Yogiarto* [(4)]
(1) Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia ,
(3) Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, RSUD Dr. Soetomo, Surabaya, Indonesia ,
(4) Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya

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Moderate Cardiovascular Risk Factor among Indonesian: Do Carotid Intima-media Thickness (CIMT) Predict Further?

Rina Mawarti [(1)], *Denny Suwanto* [(2)], *Johanes Nugroho Eko Putranto* [(3)], *Djoko Soemantri* [(4)]
(1) Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia ,
(2) Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia ,
(3) Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia ,
(4) Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia

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(1) Faculty of Medicine, Mulawarman University, Samarinda, Indonesia

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(1) National Brain Centre, Jakarta Departmenet of Cardiology and Vascular Medicine, Gatot Soebroto Amry Hospital ,
(2) Tengku Rafi'an Hospital, Riau, Indonesia ,
(3) Department Cardiology and Vascular Medicine, Gatot Soebroto Army Hospital, Indonesia ,
(4) Department Cardiology and Vascular Medicine, Gatot Soebroto Army Hospital, Indonesia ,
(5) Cardiologist, Department of Cardiology and Vascular Medicine, Sebelas Maret University, Solo, Indonesia

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(1) Faculty of medicine, Universitas Muhammadiyah Prof. DR. Hamka, Tangerang ,
(2) Department Cardiology and Vascular Medicine, RSUP dr. Karyadi, Universitas Diponegoro, Semarang, Central Java ,

(3) Army Hospital Kesdam Jaya Cijantung, Jakarta

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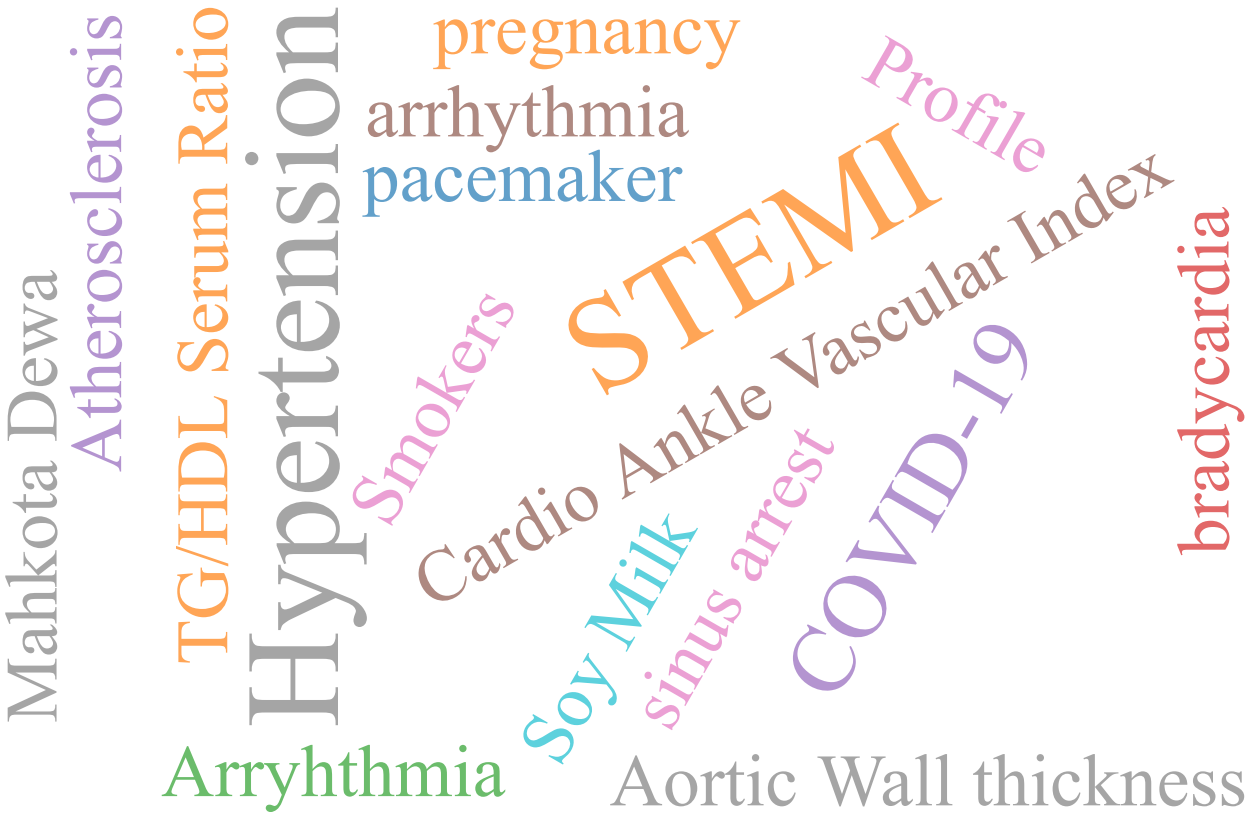

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Address

Department of Cardiology and Vascular Medicine
Faculty of Medicine, Universitas Airlangga
Jalan Mayjend Prof. Dr. Moestopo 6-8 Surabaya (60286) - East Java - INDONESIA

Contact Info:

Phone: +62-31-5501011
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Original Research

Moderate Cardiovascular Risk Factor among Indonesian: Do Carotid Intima-media Thickness (CIMT) Predict Further?

R. Mawarti[1], D. Suwanto[1], J. N. E. Putranto[1,2*], and D. Soemantri[1,2]
[1]*Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2]*Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia.*

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nugicardio1@yahoo.com

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ABSTRACT

Background. Determining management strategies in an individual with intermediate cardiovascular risk represent a great challenge. The impact of increased CIMT to improve estimated cardiovascular disease (CVD) risk score in individual at intermediate cardiovascular risk has not yet been fully elucidated. **Aims.** For this reason, we sought to determine the association between CIMT increment and incident of CVD. **Methods.** We conducted a longitudinal retrospective cohort study involving 28 patients with intermediate cardiovascular risk (Framingham risk score 10% - 20%). Subjects with criteria fulfillment had their data collected through history taking, physical examination, and CIMT re-measurement using echocardiography. **Results.** Bivariate analysis with regression logistic showed significant correlation between increased CIMT with CVD event (p= 0.016). CIMT measurement is a plausible noninvasive method to predict subclinical cardiovascular disease to further promote more aggressive management.

Introduction

Subclinical atherosclerosis may predict future CVD events. Therefore, the identification of subclinical atherosclerosis will provide benefits to prevent future CVD events [1]. Multiple methods and scoring system have been developed to predict cardiovascular diseases such as Framingham cardiovascular risk, high sensitivity C-Reactive Protein (hs-CRP), Ankle-Brachial Index (ABI), coronary artery calcium score [2], and Carotid Intima-Media Thickness (CIMT) [3]. The Framingham Risk Score (FRS) is a commonly used scoring system to estimate individual 10-year cardiovascular risk [4].

However, in those with low and intermediate-risk groups, the majority CVD event still manifest. Numerous studies have documented an association between atherosclerotic cardiovascular disease with the Carotid IntimaMedia Thickness (CIMT) and/or plaque [3, 5–8].

CIMT is a parameter to diagnose the extent of atherosclerotic vascular disease by measuring the

thickness of inner two (intima and media) layer of the carotid artery by B-mode ultrasonography, a noninvasive, reproducible, and sensitive examination technique to identify the extent of atherosclerotic vascular disease. CIMT measurement is useful for subclinical CVD identification and quantification.

CIMT as a parameter of asymptomatic vascular damage and an early marker of atherosclerosis, has been shown to be associated with various atherosclerotic cardiovascular disease in peripheral and coronary arteries [9]. CIMT measurement and carotid plaques identification can also be useful to improve risk estimation in individual at intermediate cardiovascular risk [10].

CIMT together with traditional cardiovascular risk factor can be used as a predictor for a future cardiovascular event in asymptomatic middle age and older adult [11]. A prospective study by Stein et al., in 1000 asymptomatic individual showed CIMT ability to predict future cardiovascular events such as myocardial infarction, stroke, and death from coronary artery disease [10]. It is utmost important to have an additional parameter to predict cardiovascular disease in moderate cardiovascular risk and subclinical cardiovascular disease to further promote aggressive lifestyle management and early pharmacotherapy. Therefore, we aimed to analyze the correlation between CIMT increment and CVD event in individual with moderate cardiovascular risk [10].

Methods

We performed an observational analytic study with retrospective cohort design at Dr. Soetomo General Hospital. Our study population consisted of 86 consecutive participants with previous CIMT measurement in 2010, following exclusion and inclusion criteria, 26 samples were obtained. Subjects voluntarily participated in our study. Those who had a history of valvular heart disease, cardiomyopathy were excluded. Cardiovascular risk factor, current, and previous medical history, and CIMT analysis were collected. Our study has been approved by Soetomo General Hospital and faculty of medicine Universitas Airlangga institutional review board.

a. Demographic and laboratory tests

We obtained baseline demographic and laboratory data for body mass index (BMI), fasting glucose, postprandial glucose, and lipid profile. Traditional modifiable risk factors include hypertension (defined according to the current guideline), diabetes, and smoker (current smoker and ex-smoker, with minimum of 3 years tobacco free period). Diabetes mellitus, coronary artery disease, cerebrovascular disease, and peripheral arterial disease were diagnosed based on medical history, patients' information, and laboratory data. Collected data were used to determine cardiovascular risk factor based on Framingham score 2008to predict 10 years risk of cardiovascular disease, which includes: sex category, age, total cholesterol, HDL cholesterol, systolic blood pressure, and diabetes.

b. CIMT Measurement

We use GE Medical Systems Vivid E-5 echocardiography machine Norway with the 9L probe as a measurement instrument. CIMT appropriate retrieval and interpretation techniques were based on the American Society of Echocardiography (ASE) Guidelines. Twelve semi-automatic CIMT measurements were taken along 100 mm at the distal part of each common carotid artery (CCA). CIMT mean calculated as the arithmetic mean of all measurements. CIMT max calculated as the maximum measurement results obtained from all measurement. We also obtained previous CIMT data in 2010.

B mode USG was used to measure CIMT by assessing tunica intima and tunica media thickness on carotid artery wall visible as double line pattern [12]. The ultrasound protocol to measure CIMT were made in a 1 cm segment in the distal CCA (1 cm proximal to dilation of the carotid bulb), 1 cm of the carotid artery bifurcation (1 cm proximal to the flow divider), and 1 cm in the proximal internal carotid artery (ICA) (1 cm section of the ICA immediately distal to the flow divider) of both right and left sides. Common carotid artery far wall lumen was used as a standard measurement location. We use electronic caliper software to trace the double line sign representing the intimal layer [2].

c. Cardiovascular event ascertainment

CVD events were identified through history taking, physical examination, patient-initiated reports of CVD event, and objective data including review of medical records. The cardiovascular event was defined based on Framingham Heart Study as coronary artery disease (stable angina pectoris or acute coronary syndrome), cerebrovascular incident (transient ischemic attack, thromboembolic or hemorrhagic stroke), peripheral arterial disease, and heart failure.

d. Statistical Analysis

Statistical analysis was performed using SPSS version 18. Categorical variables were summarized by counts and percentages, while continuous variables were summarized by means and standard deviation. Paired T-Test was used to compare means between the present and previous CIMT. Bivariate analysis between increased CIMT and cardiovascular outcome was evaluated by Chi-square. We constructed a regression logistic model with increased CIMT as the independent variable and cardiovascular outcome as the dependent variable. Statistical significance was considered when a p-value <0.05.

Results

Of 86 participants, 58 participants were excluded from analysis because the patient died (9.3%), being readmitted on another hospital (11.63%), or cannot be contacted (46,51%). Consequently, the analyses presented included 28 participants. Demographic, clinical, and laboratory as baseline characteristics of the population are shown in Table 1. The study population was dominated by a female (64.3%) with mean age of 67,96 ± 3,74 years-old. Mean serum creatinine was 1,004 ± 0,29 mg/dL, mean fasting blood glucose was 103,28 ± 17,44 mg/dL, mean cholesterol level was 186,10 ± 36,94 mg/dL, mean HDLCholesterol level was 49,75 ± 11,75mg/dL. Mean Framingham risk score was 16,25 ± 1,91%. Mean CIMT progression evaluation was 71,60 ± 1,13 months. Hypertension is the main modifiable risk factor in our subjects. Fifty-three point five seven percent was either dyslipidemic or on therapy. Twenty-six point one percent of our subjects were diabetes (or on antidiabetic therapy) and smoker.

Table 1. Baseline characteristic pattern.

Variable		N(%) Mean ±SD
Age	60-64	6(21.4)
	65-69	11(39.3)

	70-74	10(35.7)
	75-79	1(3.6)
Gender	Male	10 (35,7)
	Female	18 (64,3)
		23,78 ± 4,03
Body Mass Index	< 18,5	3 (10,7)
	18,5 – 24,9	15 (53,6)
	25,0 – 29,9	8 (28,6)
	≥ 30	2 (7,1)
Risk Factor	Hypertension	28 (100)
	On Antihypertension	28 (100)
	Diabetes Mellitus	6 (21,4)
	On Antidiabetic	6 (21,4)
	Dyslipidemia	15 (53,57)
	On Antidyslipidemic	11 (39,28)
	Smoker	6 (21,4)
Systolic Blood Pressure		134 ± 17,58
Diastolic Blood Pressure		76,42 ± 10,61
Heart Rate		72,71 ± 10,14
Serum Creatinin		1,004 ± 0,29
Fasting Blood Glucose (mg/dL)		103,28 ± 17,44
Total Cholesterol (mg/dL)		186,10 ± 36,94
HDL-Cholesterol (mg/dL)		49,75 ± 11,75
Framingham Risk Score (%)		16,25 ± 1,91
CIMT Measurement Interval (months)		71,60 ± 1,13

As shown in Table 2, the initial and re-evaluation CIMT showed significant increment in both mean and maximum CIMT value ($p < 0,0001$).

Coronary artery disease was the main complication (17.9%) on our cohort study, followed by heart failure (10.7%) and peripheral arterial disease (3.6%) (Table 3).

Table 2. Analysis of mean and max CIMT increment

Variable	***p***	**Mean ± Standard Deviation**
Mean Re-evaluation CIMT	<0,0001	0,079 ± 0,1046
Mean initial CIMT		
Max Re-evaluation CIMT	<0,0001	0,137 ± 0,1150
Max initial CIMT		

Table 3. Cardiovascular event

Variable	N (%)
Coronary Artery Disease	5 (17,9)
Heart Failure	3 (10,7)
Peripheral Artery Disease	1 (3,6)
Cerebrovascular Event	0 (0)

Table 4. Analysis mean CIMT increment with CV event

Variable	β	*p*	Adj OR	95%CI	
				Upper	Lower
Mean CIMT Increment	-16,741	0,016	0,0001	0,0001	0,044
Max CIMT Increment	-15,543	0,012	0,0001	0,0001	0,035

Bivariate analysis as in Table 4, showed significant association between CIMT mean and CIMT max with cardiovascular event. On contrary, multivariate analysis in our study failed to show correlation between traditional risk factor such as, diabetes [OR 1,7 (0,237-12,173)], dyslipidemia [0,563 (0,100- 3,168)] smoking [OR 0,533(0,051-5,554)], and age [OR 0,948 (0,747-1,202)] with cardiovascular event.

Discussion

Our study has shown that measurements of CIMT modestly improve the predictive ability of the Framingham risk score model in those without the incident disease. The similar result was found by Polak et al., in which CIMT increment by 0,0264 mm/year may increase the risk of stroke by two-fold.

A prospective study on 1000 asymptomatic samples, founded abnormal CIMT was correlated with myocardial infarction, stroke, and cardiovascular death. CIMT mean over 1.15 mm may increase the risk of coronary artery disease up to 94% [3, 10, 13].

Various algorithms and risk calculation has been developed based on common risk factor for cardiovascular disease to assess risk of specific atherosclerotic cardiovascular disease (CVD) events, i.e., coronary artery disease, stroke, heart failure, and peripheral vascular disease.

Framingham risk score is a gender specific algorithm used to estimate 10-year risk of cardiovascular disease in individual. Variables that are included in this algorithm are: gender, age, total cholesterol, HDL cholesterol, cigarette smoker, and systolic blood pressure. The result may classify an individual into low risk (10% or less CHD risk at 10 years), intermediate risk (10-20%), and with high risk(20% or more) [14].

Co-analysis of CIMT and Framingham risk factors in the Rotterdam study with a 10-year follow-up period in 3580 subjects, resulted in a Net Reclassification Improvement (NRI) of 8% for stroke and 8.2% for coronary heart disease 8.2% in older women, but similar improvement in older male was not found [9]. In IMPROVE trial involving of 3,703 subjects, Inter-adventitia Common Carotid Artery Diameter (ICCAD), together with several CIMT measurements, were associated with an NRI of 3-

12% (0.03-0.12) over and above Framingham Risk Score (FRS) [7].

In the Framingham Offspring Study cohort, 2.965 participants (mean age 58 years, 55% women) had increased NRI after adding internal carotid artery CIMT measurements to Framingham risk score (7.6% or 0.076, p<0.001), particularly in those without a history of CVD after an average of 7.2 years follow up period [15]. In another report from Cardiovascular Heart Study (CHS) reported, participants in the lowest quintile for CIMT demonstrated a 95% cumulative survival free of the acute coronary syndrome and a cerebrovascular incident in the lowest quintile CIMT compared to those in highest quintile CIMT (95% vs. 74%, *p*<0.001) [16].

However the limitation of our study was a small sample size without comparator group, this limitation was due to six years follow up period which will cause a large loss to follow up. Our findings suggest that CIMT assessment is valuable data to prevent under-classification (estimation), especially in individual at intermediate risk.

Conclusion

Nonetheless, our study has shown that CIMT measurement is a valuable and modestly improves 10-year risk prediction for clinical atherosclerotic cardiovascular disease beyond the capability of an FRS-type risk model, mainly to prevent under-classification (estimation), especially in individual at intermediate risk.

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There is no conflict of interest.

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