Original Article

Low or Even Zero CAC may not be Warranted as Safe in Thai Officers: A 10-year prospective cohort study

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Abstract

OBJECTIVES: CAC has been widely accepted as a strong independent event predictor in asymptomatic moderate risk in the western population. However, the role of coronary artery calcium (CAC) has not been established in the Thai population yet. Thus, we conducted a 10-year prospective study to verify the predictive role of CAC in asymptomatic Thai participants.

MATERIAL AND METHODS: A total of 239 asymptomatic officers were voluntarily enrolled and consented to take part. We excluded participants aged < 35 or > 60 years, prior cardiovascular diseases (CVD), pregnant and those not willing to sign an informed consent of participation. The population underwent an exercise stress test (EST) to screen for occult coronary artery disease (CAD). Coronary angiography was performed if there is an evidence of exercise-induced myocardial ischemia within 7 METS. All the studied population underwent a 256-slide multidetector computed tomography (MDCT) scan to obtain a CAC scoring. CAC volume was measured by Agaston method which defines CAC as a mass of HU 130 or more. The studied population were divided into two groups, CAC = 0 and CAC > 0. All of them received medication, education for lifestyle modification and were followed up annually for ten consecutive years (2006-2016). **Primary end points** were fatal or non-fatal acute coronary syndrome (ACS) and any types of stroke. **Secondary end point** was all causes of mortality. Student t test and Pearson's Chi-square were used to compare the difference and the p value of < 0.05 was considered statistically significant.

RESULT: Most candidates were men (96.7%) and had a mean age of 52.4 ± 4.8 years. The common coronary risk factors were elevated low density lipoprotein cholesterol (LDL-C) >130 mg/dl (66.9%), elevated triglyceride (TG) > 150 mg/dl (53.1%), systolic blood pressure (SBP) > 140 mmHg (39.7%), impaired fasting glucose > 100 mg/dl (34.5%), cigarette smoking (32.2%) and low high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl, (12.6%).

Ten cases (4.2%) had ischemic exercise test (EST) response and 50% of them had severe coronary stenosis requiring revascularization or aggressive medication. The other half also had documented causes of exercise-induced ischemia including coronary slow flow, vasospasm and myocardial bridging. Thus, all of these cases were excluded for outcome measurement, therefore we had total of 229 cases, half (51.5%) of them had no detectable calcified coronary plaque using the Agaston-130 method (CAC = 0). There was no statistical difference in age, gender, SBP, fasting blood sugar (FBS), total serum cholesterol (T. Chol), serum TG, HDL-C and cigarette smoking between candidates with absent or present CAC, except the mean LDL-C which was statistically significantly higher in the group with no CAC, 154.7 vs 143.7 mg/dl, $p = 0.036$.

After ten years, there were 23 CVD events including 3 ACS cases, 9 strokes (all ischemic type) and 11 deaths (91% were non-CVD causes). There was no statistically significant difference between these events in the two groups, CAC = 0 (n = 121) vs CAC > 0 (n = 108) regarding to; ACS 0.8% vs 1.9% ($p = 0.603$), stroke 5% vs 2.8% ($p = 0.506$), death 2.5% vs 7.4% ($p = 0.121$) and the combined outcome (ACS + stroke + death): 8.3% vs 12% ($p = 0.384$). The mean CAC in CVD victims was quite low, 32.76 (0 - 53.1) for three ACS cases and 23.75 (0 - 180.9) for nine strokes.

CONCLUSION: While the small number and the prominent male gender of candidates were the major limitations and precluded extrapolation to others, this study was the first 10-year cohort that reported different results from western studies, low or even zero CAC might not be safe in asymptomatic Thai people. Thus, we should be skeptical to use CAC as a CVD risk predictor in our population. Whether or not Thai men had low prevalence of calcified coronary plaque or had a different pathophysiologic mechanisms, further study in a larger population is mandatory.

Keywords: coronary calcium score, CAC zero, CVD risk assessment

Cardiovascular diseases (CVD) remained the leading causes of death worldwide and accounted for one-third of the global death.[1] In 2016, 17.9 million people died from CVDs and 85% of deaths were from heart attack and stroke.[2] In China, stroke and coronary artery disease (CAD) are the first and second leading cause of CVD death.[3,4] In Thailand, reports from the Ministry of Public Health indicated that more Thai people had died from CVD than in the previous decade. From 2007-2014, the rate of sickness from CAD and stroke rose 24% and 41% respectively.[5] The mortality rate of CVD increased from 21.3 to 28.9:100,000 (2008-2014) for CAD and from 20.8 to 31.7:100,000 (2008-2012) for stroke.[5,6] It is clear that the population at risk needs to be identified to prevent future CVD events.

CVD risk assessment by traditional risk factors has been generally recommended to predict the 10-year CVD risk by current practice guidelines.[7,8] However, the predictive accuracy for the future CVD events by traditional risk score i.e. Framingham score, was only modest, in the range of 50-65%.[9] Coronary artery calcium (CAC) is the consequence of atherosclerotic healing process so it can be used to quantify the amount of calcified plaque for risk stratification. Several research studies have verified the role of CAC in predicting hard CVD events in asymptomatic patients and following the progression of the atherosclerotic process. CAC is proven to be a better risk estimator, beyond systemic risk scores, in predicting coronary events, stroke, and heart failure.[10-16] However, all of these evidences come from western population studies and the role of CAC remains undocumented in Thai people. Thus, we conducted a 10-year prospective study in asymptomatic Thai officers who underwent CAC screening in 2006 and followed their CVD events through 2016.

Material and Methods

After receiving approval by the hospital ethical committee, this study was initiated in 2006 during the annual physical check-up. Only asymptomatic candidates aged between 35-60 years were voluntarily enrolled. (see Figure 1). We excluded officers who had prior CVD, were not willing to sign the informed consent for participation and pregnant candidates. The family history of premature atherosclerosis, dyslipidemia, cigarette smoking, blood pressure, lipid profiles and blood glucose were obtained.[17,18] To rule out pre-existing CAD, all participants underwent exercise stress test by the standard Bruce protocol. Candidates who had ischemic response within 7 METS would be referred for coronary angiography (CAG). Coronary revascularization or medication were justified based upon the result of individual angiographic results. Candidates with documented CAD were later excluded for outcome measurements. The study flow is illustrated in Figure 1.

CAC study: CAC volume is obtained by using 256 – slice MDCT, Philips system and measured by Agaston method

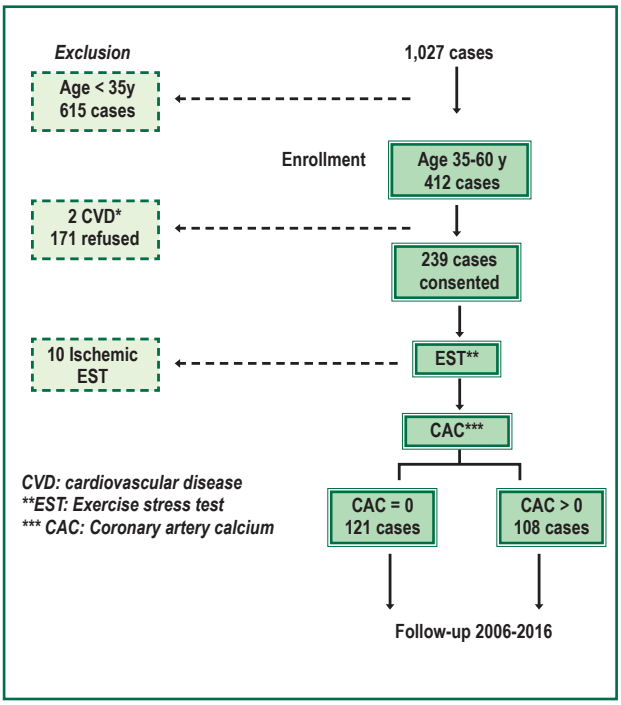

Figure 1: The study flow chart is illustrated. After exclusion, a total of 229 cases underwent CAC scan.

which defines 130 HU or more for threshold to identify CAC. CT scan for CAC is operated by non-contrast technique at tube current 55 -80 mAs with tube voltage of 120 kVp. Based upon the CAC volume, the population studied is divided into two groups, CAC = 0 versus CAC > 0. The occurrence of CVD events in all candidates were followed up annually for consecutive ten years (2006-2016)

Clinical end points: Candidates who had positive EST were excluded. The primary end points were fatal and non-fatal ACS and any types of stroke. Secondary end point was all causes of mortality.

Statistical analysis: The Student t test and the Pearson's Chi-square were used to compare the different outcomes between candidates with and without CAC, and $p < 0.05$ was considered statistically significantly different.

Results

Of a total of 412 officers, 239 candidates (58%) consented voluntarily. The majority of participants were men (96.7%) and had the mean age of 52.4 ± 4.8 years. As shown in Table 1, the common coronary risk factors were elevated LDL-C >130 mg/dl (66.9%), elevated TG >150 mg/dl (53.1%), systolic blood pressure (SBP) >140 mmHg (39.7%), impaired FBS > 100 mg/dl (34.5%), cigarette smoking (32.2%) and HDL-C < 40 mg/dl (12.6%).

By CT CAC with Agaston-130 method, half of candidates (51.5%) had no detectable calcified plaque, CAC = 0. The

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demographic of candidates between zero CAC score (CAC = 0) and more than zero (CAC > 0) was shown in Table 1. There was no statically significant difference in gender, age, mean values SBP), FBS, T.Chol, TG), HDL-C and present-day cigarette smoking. However, the mean LDL-C of candidates with zero CAC was significantly higher than that of the CAC > 0 candidates, 154.7 vs 143.7 mg/dl, $p = 0.036$.

Exercise stress test (EST) result: Ten cases (4.2%) had ischemic EST response within 7 METS and underwent coronary angiography. All of them had explainable causes of exercise induced myocardial ischemia. Two cases from CAC absent group had myocardial bridging and coronary slow flow (CSF). Eight cases were from the CAC present group (CAC > 0), five cases (62.5%) had severe CAD and one of each other three cases had coronary spasm, myocardial bridging and CSF. In five cases with severe CAD, three cases had percutaneous coronary stent implantation, one case had bypass surgery and another one needed aggressive medication. (Figure 3). The calcified plaque distribution and coronary angiographic findings are illustrated in Table 2. Since severe CAD, coronary spasm, CSF and myocardial bridging could result in either ACS or sudden death, all of these ten positive EST tests were excluded for outcome calculation.

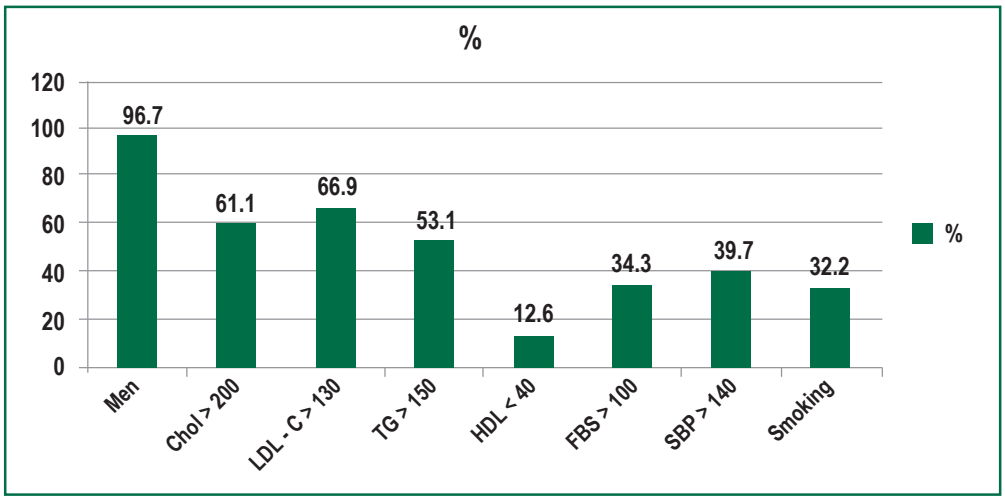

Figure 2: The prevalence of conventional coronary risk factors in 239 candidates.

Abbreviation: Chol = total serum cholesterol, LDL-C = Low density lipoprotein cholesterol, TG = serum triglyceride, HDL = High density lipoprotein cholesterol, FBS = fasting blood sugar, unit in mg/dl, SBP = systolic blood pressure. (mmHg)

Table 1: Demographic data and conventional risk factors of candidates with detectable calcified plaque (CAC > 0) and absent calcified plaque (CAC=0) are displayed in proportion (%) and mean ± standard deviation in mg/dl. There was no statistically significant difference except the mean LDL-C which was significantly higher in candidates with absent CAC.

Conventional risk factors	CAC = 0 (n = 123)	CAC > 0 (n = 116)	*p*
Age years	51.9 ± 5.2	53.0 ± 4.4	0.107
Men (%)	116 (94.0)	115 (99.1)	0.067
SBP (mmHg)	138.7 ± 19.9	138.9 ±18.1	0.930
FBS (mg/dl)	100.0 ± 24.0	103.2 ± 34.2	0.404
T. Chol (mg/dl)	220.6 ± 40.0	210.9 ± 43.6	0.076
TG (mg/dl)	171.1 ± 105.8	187.8 ± 110.8	0.251
HDL-C (mg/dl)	57.3 ± 16.5	53.6 ± 13.6	0.063
LDL-C (mg/dl)	154.7 ± 38.4	143.7 ± 42.2	0.036*
Smoking (%)	39 (31.7)	38 (32)	0.862

Abbreviation: SBP = Systolic blood pressure, FBS = Fasting blood sugar, T.chol = total serum cholesterol, TG = serum triglyceride, HDL-C = High density lipoporotein cholesterol, LDL-C = Low density lipoprotein cholesterol, *$p < 0.05$

Table 2 : The amount of calcified plaque was shown in 10 ischemic EST cases. The mean CAC was 116.74 and the mean age was 54.7 years. All of them were excluded.

Case	CAC Agaston	Detected Age (years)	Findings	Treatment
SD	0	56	M. Bridging	Medication
SS	0	49	Slow Flow	Medication
AS	5	59	Slow Flow	Medication
TC	11.4	50	>80% RCA	PCI
YS	42.1	53	Ostial RCA spasm	Medication
TB	46.4	58	Mod. Severe LAD/Dg	Medication
TY	59.5	54	Slow Flow	Medication
JD	180.9	58	99% Mid RCA	PCI
WK	286.2	51	Severe LAD, Cx	CABG
NA	535.9	59	Severe RCA, Cx	PCI
Mean	116.74	54.7		

Abbreviation; EST = Exercise Stress Test, RCA = Right coronary artery, LAD = Left anterior descending coronary, Dg = Diagonal branch, Cx = Circumflex artery, PCI = Percutaneous Coronary Intervention, CABG = Coronary Bypass Graft Surgery, mCRC = modified Coronary Risk Chart

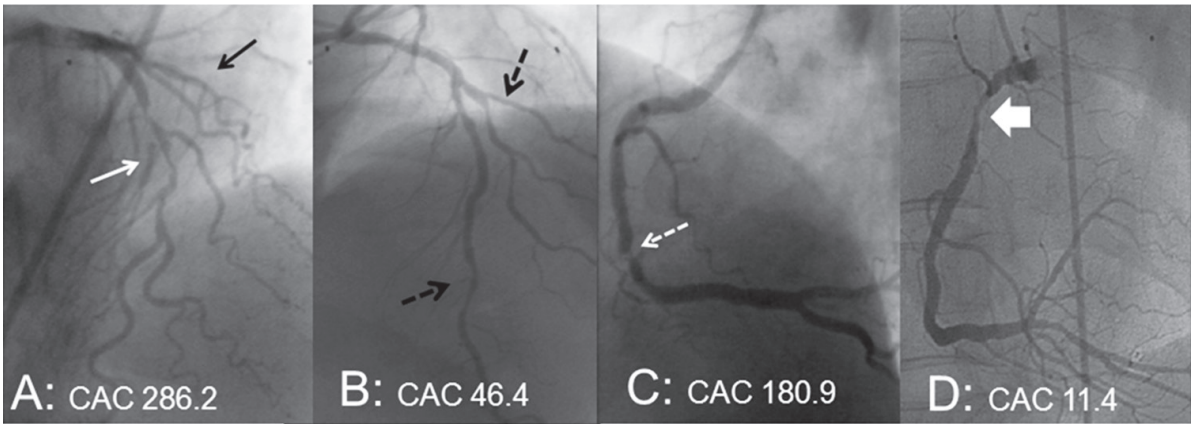

Figure 3: Coronary angiograms of four positive EST cases with severe epicardial coronary stenosis are illustrated. **A:** WK (CAC of 286.2) had severe stenosis of left anterior descending (LAD) and circumflex (Cx) arteries. **B:** TB had low CAC of 46.4 but had moderately severe diffuse lesions in both LAD and diagonal arteries. **C:** JP (CAC of 180.) had subtotal mid right coronary (RCA) stenosis. **D:** TC had low CAC, 11.4, but had severe proximal RCA stenosis.

Clinical end points: after ten years, there were a total of 23 events including 3 ACS cases, 9 ischemic strokes and 11 deaths, see Table 3. The three ACS cases appeared at the mean duration of six years and their average age was 57.7 years. Their angiographic findings are illustrated in Figure 4. Stroke cases appeared later than ACS, within 7.5 years, and they were older (mean age was 61.8 years). Eleven cases (mean age was 55.3 years) had died with the average time of 6.45 years. The major causes of death were non-CVD death (91%), including cirrhosis 36.4%, cancer 18.2% and the rest, 9.1% (one of each expired from immune deficiency, sepsis, drowning and accident). Only one CVD death case occurred at age 63 years. He had acute basal ganglia infarction and later expired from heart failure within a few weeks.

Regarding all clinical outcomes, there were no statistically significant differences observed between the absent CAC group (CAC = 0, n = 121) vs the present CAC group (CAC > 0, n = 108); ACS 0.8% vs 1.9% ($p = 0.603$), stroke 5% vs 2.8% ($p = 0.506$), death 2.5% vs 7.4% ($p = 0.121$) and the combined outcome (ACS + stroke + death): 8.3% vs 12%, $p = 0.384$. (Table 3).

The amount of calcified plaque (CAC), measured by the Agaston method of ≥ 130 HU, is displayed in range, from 0, 1-100, 101-200, 201-300, 301-400 and > 400, and correlated with the clinical outcomes in Table 4. It was noted that calcified plaque burden, CAC < 100, was detected in 100% of ACS cases, 89% of stroke victims and 54.5% of death patients. There was no statistical difference between events and CAC severity.

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Table 3 : Clinical outcome between candidates without (CAC = 0) and with calcified coronary plaque (CAC > 0). There was no statistically significant difference between the two groups.

Clinical Outcome After Exclude EST +	CAC = 0 (n = 121), n (%)	CAC > 0 (n = 108), n (%)	*p*
ASC (%)	1 (0.8)	2 (1.9)	0.603
Stroke (%)	6 (5)	3 (2.8)	0.506
Death (%)	3 (2.5)	8 (7.4)	0.121
ACS + Stroke + Death (%)	10 (8.3)	13 (12)	0.384

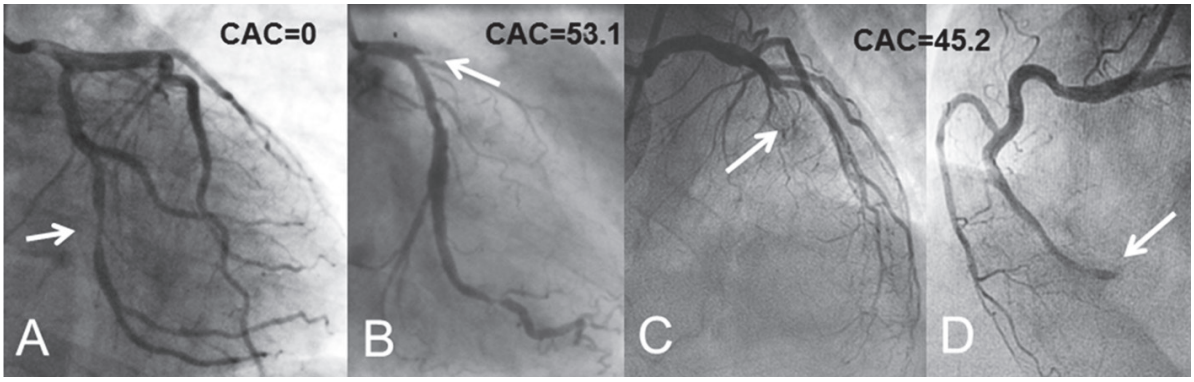

Figure 4: Angiograms of all three ACS cases with CAC are illustrated. **A:** NT (CAC=0) had non-ST segment elevation myocardial infarction (NSTEMI) from tight circumflex artery stenosis within five years. **B:** SK (CAC = 53.1) developed acute anterior ST segment elevation (STE) myocardial infarction (MI) from proximal left anterior descending artery (LAD) occlusion within three years. **C&D:** RS (CAC = 45.2) had aborted ventricular fibrillation arrest from acute inferior STEMI within ten years. He had total occlusion of the proximal LAD (C) and the distal RCA (D).

Table 4 : Calcium distribution in various clinical CVD events is illustrated. Low calcified plaque burden, CAC < 100, was detected in 100% of ACS cases, 89% of stroke victims and 54.5% of death patients. There was no statistical difference between events and CAC severity.

Variable	CAC = 0	CAC 1 - 100	CAC 101 - 200	CAC 201 - 300	CAC 301 - 400	CAC > 400
ACS	1 (0.8%)	2 (2.5%)	0	0	0	0
+ EST	2 (1.6%)	5 (6.3%)	1 (7.1%)	1 (16.7%)	0	1 (8.3%)
ACS + EST	3 (2.4%)	7 (8.9%)	1 (7.1%)	1 (16.7%)	0	1 (8.3%)
Stroke	6 (4.9%)	2 (2.5%)	1 (7.1%)	0	0	
ACS + EST+ Stroke	9 (7.3%)	9 (11.4%)	2 (14.3%)	1 (16.7%)	0	1 (8.3%)
Death	3 (2.4%)	3 (3.8%)	1 (7.1%)	1 (16.7%)	1 (20%)	2 (16.7%)
ACS + Stroke + Death	10 (8.1%)	7 (8.9%)	2 (14.3%)	1 (16.7%)	1 (20%)	2 (16.7%)

Table 5 : The absence of CAC and clinical events compared with other CVC studies.

Study, Year	Size / Type	CAC = 0 n (%)	Mean follow-up (years)	Outcome	Event rate
Sarwar et al.,2009[19]	71,595 Pooled Data	29,312 (41)	4.2	CVD Events	0.5%
Blaha et al.,2009[20]	44.052 Retrospective	19,898 (45)	5.6	All-Cause mortality	0.5%
MESA,2009[10]	6,809 Prospective	3,414 (50)	4.1	CHD Events, (Hard)	0.3%
Heinz-Nixdorf, 2010[11]	4,219 Prospective	1,322 (32)	5.0	CHD Events, (Hard)	0.8%
Valenti, et al.,2009[21]	9,715 Prospective	4,864 (50)	14.6	All-Cause mortality	4.7%
Lee, et al.,2009[41]	48,215 Prospective	30,605 (63.5)	4.4	All-Cause mortality	0.5%
This Study	**229 Prospective, Treated**	**121 (51.4)**	**10**	**ACS Stroke All-Cause mortality**	**0.8% 5.0% 2.5%**

CAC = Coronary artery calcium, CVC = Central venous catheter, CAD = Cardiovascular disease, CHD = Coronary heart diseases, ACS = Acute coronary syndrome

Discussion

CAC Zero is safe in western population

Calcified coronary artery plaque burden, so-called CAC, is a well-established independent marker for predicting cardiovascular events and death in western population.[11-16,19-21] The absence of CAC, zero CAC, has been associated with a very low risk of having CVD events[13,14,22] and all causes mortality.[23] (Table 5). In the longest prospective study of 14.6 years, involving 9,715 individuals, the overall mortality of 4,864 individuals with CAC = 0 group was three times lower than that of CAC > 0 group, (4.7% vs 14.6%).[24] Thus, the author concluded that CAC was the strongest mortality predictor with the hazard ratio of 2.67 (95% CI 2.39-3.11, $p < 0.05$).[24] Currently, CAC had been recommended by ACC/AHA preventive guideline for individual risk assessment[11,25] and guiding statin therapy.[26] From the American Heart Association (AHA)/American College of Physician (ACC) recommendation in 2018, adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥ 70 to 189 mg/dL, at a 10 - year ASCVD risk score of ≥ 7.5% to 19.9%, treatment with statin therapy may be withheld or delayed if CAC is zero, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.[26]

Exclusion of occult CAD in asymptomatic candidates

Since the predictive role of CAC had not been documented in the Thai population, CAC screen was performed in 239 volunteered officers who had no history of CVD. To further exclude occult CAD, EST was performed in all candidates and ten cases (4.2%) had ischemic exercise response. Half of them, five cases, had occult severe coronary stenosis that required either revascularization (four cases) or aggressive medication in another (Table 2 and Figure 3), so these cases were excluded. The other half (five cases) had potential causes of myocardial ischemia including coronary slow flow in three cases, vasospasm in one case and myocardial bridging in another. Since life-threatening arrhythmias, myocardial infarction or even sudden death had been previously reported with CSF[27-29], vasospasm [30-32] and myocardial bridging[33-38] cases, we also excluded them from statistical analysis in order to prevent confounding clinical outcomes.

CAC Zero may not be safe in Thais

Despite providing healthy life style education and medication, 21 events still appeared overall within ten years. There was no statistically significant difference between candidates of CAC 0 vs CAC > 0, regarding ACS: 0.8% vs 1.9% ($p = 0.603$), stroke: 5% vs 2.8% ($p = 0.506$), total death: 2.5% vs 7.4 % ($p = 0.121$) and the combined outcome (ACS + stroke + death): 8.3% vs 12%, $p = 0.384$, see Table 3. Our study did show different results from western data that CAC zero might not have definite power to protect ACS, stroke and overall death in our population. Thus, CAC zero, only by itself, could not yet be proven as a sole protective indicator for low CVD risk in asymptomatic Thai patients. From Table 4, there is no statistically significant difference in CAC severity and clinical outcome including EST results. In addition, the mean CAC in all vascular cases was quite low; 32.76 (0 - 53.1) for three ACS cases and 23.75 (0 - 180.9) for nine stroke patients. By AHA/ACC guidelines[11,25], all ACS cases and 88.9% of stroke victims would be classified as low risk candidates since their calcified plaque burden was low, below 100.

How to explain the low CAC and events

Racial difference in CAC has been addressed in previous studies.[36-40] The first autopsied study that showed racial difference of calcification in major coronary arteries was reported in 1965.[39] Of a total of 777 autopsied cases that died from non-coronary causes, the prevalence of calcified coronary arteries was three times less in black patients, in comparison to white cases, 20% vs 75% .[40] In a MESA study, the highest

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CAC was observed among asymptomatic white subjects and the lowest value was also found in the black candidates.[40] In the elderly, Chinese American men (age >70 years) and women (aged >75 years) had the lowest CAC.[41] From a large Korean population study, involving 86,165 adults who underwent a CAC study from 2002-2014, a logistic regression analysis indicated that the severity of coronary calcification of adult Koreans was significantly lower than in US adults of the same age group.[41] In comparison with US adults, the odds of a severe CAC in 65- to 74-year- old Korean adults were 0.66 (95%CI: 0.48 – 0.91), 0.78 (95%CI: 0.52 – 1.19), and 0.50 (95%CI: 0.29–0.86) overall, for men, and women, respectively. In addition, attenuation of CAC differences between US and Korean adults was observed with advancing age.[44] The high prevalence of zero CAC was also noted in another Korean cohort study. Lee et al,[45] studied the warranty period of zero CAC in 48,215 Korean patients with the mean follow up of 4.4 years. The CAC absent CAC group was 63.5% and they had statistically significant less CVD risk factors. With no conventional risk factors, the overall mortality of CAC zero group was low, only 0.5%, but the CAC did not show the power of protection, and there was a 95% CI of incidence per 1,000 person-year at 1.0 (0.7-1.3).[45] These studies [44,45] supported our findings that the Asian population tends to have lower coronary calcified plaque burden than Caucasian populations. It also suggested that, without a population-based study or adjusting the CAC cut point, low risk candidates (CAC = 0), by the western guideline, may not be simply applicable to the Thai population. There are several possible causes of low CAC in Asian populations including genetic, behavioral or cultural factors (food, exercise etc.), and all of these remain to be verified.

It is worth mentioning that zero CAC does not mean the absence of calcified plaque since the cut-off point is an arbitrary limit set by the Agaston-130 method.[11] A negative test (score 0) does not exclude the lipid rich plaque that might be prone to rupture in the presence of a low and undetected calcified healing process. In the final MESA study, involving 3,923 asymptomatic cases, no detected CAC was found in 3,415 cases (87%) and there were 28 CVD events (0.82%) which was three-fold lower than those in the CAC positive group.[46] The associated risk factors in the negative CAC were prior smoking (HR = 3.57; 1.08-11.77), current smoking (HR = 4.93; 1.20-20.30), and diabetes (HR=3.09; 1.07 - 8.93) (43). None of our three ACS cases were diabetic but all of them were current smokers and had a high LDL-C, mean LDL-C of 182.67 mg/dl. One case with zero CAC not only smoked cigarettes, but also had premature atherosclerosis in a family member. These factors have been known to be associated with an athero-thrombotic process[47-49] and all negative CAC cases should be looked for these condition before justifying a future CVD risk.

Conclusion

Several limitations existed in our study, first, the small number of cases from a single center which might have less statistical power to justify the predictive role of CAC. Second, the population study was Thai officers, aged 35-60 years, and the majority of them were men, which precluded application to other population groups. Third, all of them were medically treated and educated for lifestyle modification. However, all candidates were voluntarily recruited without compensation, so this study should have less selection bias in this regard. Based on this result, patients with low or even zero CAC could not be viewed as low risk cases and zero CAC did not warrant as a safety marker at least in Thai officers. Further study in a larger population is mandatory to accurately determine the predictive role of CAC in our population.

As mentioned in discussion section, the cut-off point of CAC is set by the Agaston-130 method. To reduce CAC detection threshold to detect microcalcification (which is undetected with cutoff point Agaston 130) may be possible. However, reducing CAC detection threshold would make the CAC scoring susceptible to image noise which may affect to the accuracy in CAC scoring. In addition, no available supporting data of improvement risk prediction yet by improved microcalcification detection method.[50]

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