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ORIGINAL ARTICLE

Screening for Premature Coronary Artery Disease (CAD) using Coronary Artery Calcium (CAC) Score: A Primary Prevention Pilot Study

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ABSTRAK

Penyakit Sindrom Koronari Akut (ACS) boleh dipercepatkan oleh faktor keluarga yang mempunyai sejarah penyakit koronari arteri (CAD). Kadangkala penilaian faktor risiko tidak berjaya untuk menjangkakan sindrom ini. Siasatan tambahan dengan menggunakan skor kalsium arteri koronari (CAC) boleh digunakan dalam pencegahan penyakit ini. Ini adalah kajian perbandingan secara terus yang merekrut ahli keluarga fasa pertama (FDR) asimptomatik bagi populasi muda berbanding dengan populasi muda yang tiada sejarah keluarga berpenyakit CAD yang bermula dari September 2017 hingga Mac 2018 di Klinik Kardiologi Pusat Perubatan Universiti Kebangsaan Malaysia. Sejumlah 36 peserta telah direkrut dengan bilangan yang sama bagi setiap kumpulan. Majoriti dalam setiap kumpulan adalah wanita dengan nilai peratusan 67%. Populasi keluarga yang mempunyai sejarah penyakit koronari adalah lebih muda [min (SD) umur 36.9 (4.9) berbanding 38 (3.8) dari populasi yang lain]. Kedua-dua kumpulan mewakili faktor risiko yang tinggi termasuk berat badan berlebihan dan obesiti, obesiti abdomen, serta dislipidemia. Dislipidemia yang baru dijumpai adalah signifikan bagi kumpulan dengan sejarah keluarga (83.3% berbanding 44.4%, P<0.01). Kedua-dua kumpulan yang disaring berada dalam kumpulan "Framingham Risk Score" berisiko rendah atau sederhana. Skor CAC lebih tinggi bagi kumpulan dengan sejarah keluarga (11.1% berbanding 0%, P>0.05). Kesimpulannya, CAC mungkin tidak relevan untuk pemeriksaan pada populasi yang lebih muda. Walau bagaimanapun, penemuan faktor risiko masih tahap membimbangkan dalam golongan muda.

Kata kunci: diagnosis, faktor risiko, penyakit koronari arteri, pencegahan awal

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ABSTRACT

Acute Coronary Syndrome (ACS) events can be accelerated by positive family history of young coronary artery disease (CAD). Risk factors assessment sometimes fail to predict ACS occurrence. Additional investigations with coronary artery calcium (CAC) score can be used independently in screening for primary prevention in some population. This was a cross-sectional study in asymptomatic population with first degree relatives (FDR) having premature CAD compared with a matched population with no family history of CAD from September 2017 to March 2018 at the Cardiology Clinic of Univeristi Kebangsaan Malaysia Medical Centre. A total of 36 subjects were recruited with equal number in each group. Female were the majority in each group (66.7%). The FDR group were slightly younger compared to the control group [mean (SD) age 36.9 (4.9) against 38 (3.8), respectively). Both groups represent high risk factors including overweight and obesity, abdominal obesity as well as dyslipidemia. Newly diagnosed dyslipidemia was significant in the group with family history (83.3% versus 44.4%, P<0.01). Both groups were screened either into the low or moderate risk Framingham Risk Score group. CAC score was higher in family history group (11.1% vs 0%, P>0.05). In conclusion, CAC may be irrelevant for screening in younger population. However, the yield of other risk factor is still alarming.

Keywords: coronary artery disease, diagnosis, primary prevention, risk factors

INTRODUCTION

Coronary artery disease (CAD) has caused significant morbidity and mortality in the world (Mendis et al. 2011; Donghee et al. 2015). Despite improvements in outcomes in recent years, prevalence of premature CAD seems to increase, particularly in developing countries. In Southeast Asia itself, cardiovascular disease (CVD) alone accounted for 45% of total non-communicable disease mortality and affects the younger age group (Dhillon et al. 2012). Acute coronary syndrome (ACS) patients in Malaysia that need percutaneous coronary intervention (PCI) represent a younger population with mean age of 57 years old; surprisingly, 24.4% of the total patients were aged below 50 years. This may be attributed to the rising prevalence of risk factors such as hypertension, dyslipidemia, diabetes and smoking (Ahmad & Sim 2011). Literature reviewed estimates prevalence of premature CAD at 3-10% among those aged of 45 years old and younger (Egred et al. 2005). The coronary score could be used to guide the treatment in the intermediate risk group to prevent CAD (Jana et al. 2020; Chua et al. 2020).

There are establish non-modifiable independent risk factors such as advance age, being male, some

ethnicity and a family history of premature CAD. Furthermore, it has been shown in some epidemiologic studies that family history can be more significant if it concerns first degree relative (FDR) (Nasir et al. 2004; Nasir et al. 2007). This may be explained by genetic predisposition and shared culture among family members as well as interplay among the multiple risk factors (Ties et al. 2012).

Young patient with CAD can have worst outcome during the first presentation of acute myocardial infarction (AMI) which includes mortality (Lerner & Kannel 1986). Studies have also managed to show a higher prevalence of single vessel CAD which may account for its rapid onset as opposed to the gradual progression seen in mature CADs (Muda et al. 2013; Ahmed Hussein 2012; Christus et al. 2011). As such, screening in the younger population is essential for early detection of CAD risk factor so early interventions can be taken to avoid catastrophic events. However, traditional risk algorithms such as the Framingham Risk Score (FRS) can miss FDR in the diagnosis of premature CAD (Sailam et al. 2008). Thus, multiple tools are continuously developed to better stratify risk in these cohorts. Coronary artery calcium (CAC) score has been widely studied to diagnose CAD in asymptomatic cohort with positive FDR, making it an interesting tool for primary prevention (Khera & Greenland 2018).

Atherosclerosis is the plaque in coronary arteries, where the calcium can be used as a marker for the disease (Blankenhorn & Stern 1959; Sonali et al. 2020). To detect this atheroma as a diagnosis of CAD, a computerised tomography (CT) scan that use Agatston score to classify calcium deposits in this area can be used as an effective tool. This would be referred to as the CAC score (Agatston et al. 1990). The value of calcium score represent the extensiveness of the disease (Budoff et al. 2001). Interestingly, CAC score has a high negative predictive value with good prognosis of 5 years period in individual with zero score (Haberl et al. 2001). There are no well-defined boundaries of risk levels or cut-off values. Instead, the calcium score and CAD risk relationship is a continuum, similar to hypertension. It is also widely used method with the association of CT angiography (CTA) for the evaluation of the subclinical coronary atherosclerosis burden compared to magnetic resonance angiography (MRA) (Sim et al. 2008).

CAC scores can be more valuable in terms of prognosis as compared to FRS in younger population (Sailam et al. 2008). In those of 45 years or younger, a very low CAC score can provide a clinical outcome for CAD as well as death (Carr et al. 2017). Primary prevention with CAC score can be used as an option in individual with premature FDR CAD (Sim et al. 2008; Goff et al. 2014). CAC also helps to illuminate the heterogeneity in the prevalence of CAD and outcomes among individuals with diabetes and metabolic syndrome. This further emphasise the role of CAC in improving CAD risk stratification over conventional risk factors in those with metabolic syndrome and diabetes.

This CAC scan is quick with maximum scan time of 5 minutes and also has low radiation exposure which is usually well tolerated (Carr et al. 2005; Messenger et al. 2016).

With the rising prevalence of CAD risk factors in Malaysia and development of newer risk factors, the number of premature CAD is expected to rise accordingly. Presence of CAC on younger individuals can be a marker of severity of CAD and be used effectively as a primary prevention.

The novelty element of this prospective pilot study is using CAC score as a risk stratification for primary prevention for patient with family history of young CAD in Malaysia (siblings with CAD). Currently there is no modality or guide on how to risk stratify this high-risk group. Usage of FRS for risk stratification in Malaysia does not include family history of young CAD as a weightage and may underestimate the risk. CAC scores can reclassify this group, allowing for stringent lifestyle modification and evidence-based therapeutic agents to be initiated.

Despite the consensus statement on utilisation of cardiac CT in 2008 (Sailam et al. 2008) and the proposed algorithm published in Medical Journal of Malaysia Feb 2014 Effarezan et al. (2014) state that there is a lack of proper guide on how to risk stratify the group in question. On the other hand, American College of Cardiology Foundation (ACCF), American Heart Association (AHA), National Cholesterol Education Programme (NCEP), Adult Treatment Panel (ATP) III and Canadian Cardiovascular Society (CCS) suggested a class IIa recommendation for asymptomatic adults with an intermediate FRS risk (10-20% 10-year risk) and a IIb recommendation for asymptomatic adults with a low to intermediate FRS risk (6-20% 10-year risk).

This is the first study examining asymptomatic individual with family history of young CAD. Previous conducted studies mainly explored either symptomatic or low to moderate risk patient, without specifically looking into this group of individual.

The primary objective of this study was to compare the value of CAC score for diagnosis of CAD in asymptomatic group that has family history of young CAD with the no family history of young CAD. While our secondary objective was to compare the different characteristic between these two groups which are group that has family history of young CAD and group that has no family history of young CAD with prevalence of classical risk factors (diabetes mellitus, hypertension, overweight/obesity, dyslipidemia)

MATERIALS AND METHODS

Patient Characteristics

This was comparative cross-sectional study for primary prevention screening in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) from September 2017 to March 2018. It utilised patient data obtained from the young CAD registry, UKMMC from the year 2014 to 2017 (unpublished). Patients were contacted to invite the family members aged 30 to 45

years to participate in the study. Participants without family history of young CAD were invited during Cardiology, UKMMC follow-up. All the participants were asymptomatic at the time of screening and those with target organ damage from any disease, such as hypertension or diabetes, liver cirrhosis and malignancy, or not consented were excluded. Women who were pregnant or potentially pregnant (based on last menstrual period) were also excluded. This study was approved by the UKMMC Ethics Committee (Project code: FF-2017-480). All participant signed a written informed consent form. Participants recruited were matched for age and gender.

Participants were categorised into 2 groups, those with positive or negative family history of premature CAD. Premature CAD was defined as occurrence of ACS with angiographic evidence of 50% stenosis or more of coronary vessel(s) at the age of 45 years or less (Egred et al. 2005; Doughty et al. 2002). The participants' ethnicity was based on their national identification card. Smoking status was based on the usage of tobacco actively or in the past (Ahmad & Sim 2011). FDRs were defined as siblings of the patients (Nasir et al. 2004).

An information sheet explaining the purpose of the study was distributed to the participant prior to the screening test. Participant's demographic data such as age, sex and smoking status were obtained. Blood pressure (BP) was obtained after participant was seated with last two mean measurement taken, after a total of three blood pressure measurement were taken. Diagnosis of hypertension was based on the current guideline of 140/90 mmHg (Malaysia Hypertension Guideline 2019). A standard local lab was used for analysis of total and high-density lipoprotein cholesterol and triglyceride. Low-density lipoprotein cholesterol was calculated from the above value. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured according to the standard procedure as in obesity guideline (Malaysia Obesity Guideline 2019). Diagnosis of diabetes was based on local guideline by the Malaysian Clinical Practice Guideline for Diabetes 2018, a usage of oral anti-diabetic agents or insulin. Dyslipidemia diagnosis was based on the definition outlined by the Malaysian CPG 2017 (Robaayah et al. 2017). Electrocardiogram (ECG) was performed as a baseline. A 10-year FRS was used to categorise FDRs into low (<10%), intermediate (10% to 20%), or high risk (20%) for diagnosis of CAD. (Wilson et al. 1998). Summary of this method is summarised in Figure 1.

Screening using Exercise Stress Test

Patients were advised to wear appropriate attire prior to the test. Exercise stress testing (EST) was conducted via treadmill. Patient medication list was verified prior to the test. Certain adjustment was needed prior to the test (e.g. insulin, oral anti-diabetic agents, asthma inhalers and anti-hypertensive). Continuous vital sign monitoring commenced prior

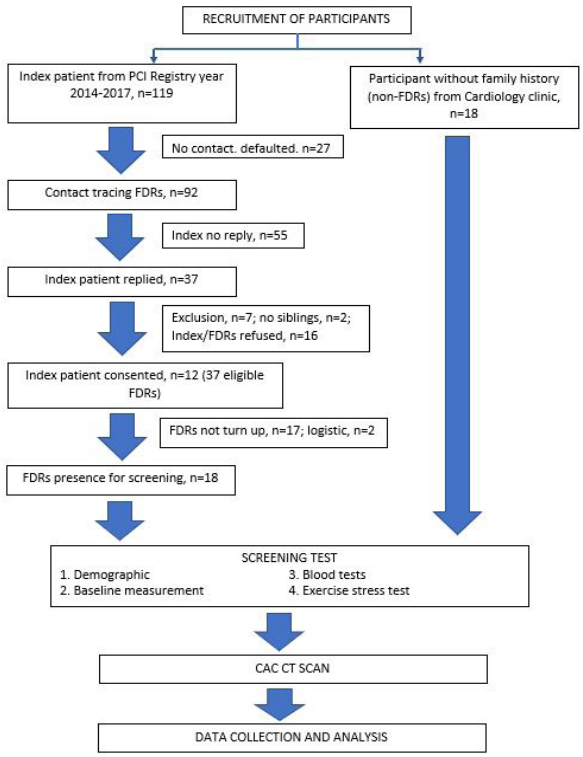

Figure 1: Flow chart of comparative cross-sectional study

and throughout the procedure by the attending staff and medical doctor. Evaluation of the procedure and termination of the test was conducted as per protocol.

Measurement of CAC by CT Scan

All data was acquired using the multi-detector computed tomography (MDCT) Toshiba Aquilion 600 slices. Patients were fasted for at least 6 hours before the CT procedure. Usual medications were allowed to be taken prior to the procedure, but caffeine and smoking were avoided for 4 hours prior to exam. In isolated cases where heart rate exceeded 80 beats/ minute, a titrated dose of metoprolol or verapamil was given prior to scan. Vitals parameter were closely monitored by experienced radiographer and medical officer throughout the procedure. Electrocardiograph (ECG) triggering signal was use to automatically turn the x-ray beam on or off. The sequential cardiac scan was done after a single breath hold at the end of inspiration. This helped to depress the diaphragm and liver to reduce attenuation of x-ray beam. The entire procedure was completed within 5 minutes. All 4 arteries were scanned and the image was read by the radiologist.

All calculation with age- and sex-matched was performed with computed Vitrea software 6.7.2 (Opus Parkway, Minnetonka, United

Table 1: Calcium score (Agatson score) and its implication.

Calcium score	Implication	Risk of CAD
0	No identifiable plaque	Very low, generally <5%
1-10	Minimal identifiable plaque	Very unlikely, <10%
11-100	Definite, at least mild atherosclerotic plaque	Mild or minimal coronary narrowings likely
101-400	Definite, at least moderate atherosclerotic plaque	Mild coronary artery disease highly likely, significant narrowing possible
401 or higher	Extensive atherosclerotic plaque	High likelihood of at least one significant coronary narrowing

State). The CT CAC images and score were then reviewed and verified by consultant radiologists that were blinded from the other parameters.. A total of four arteries were assessed to obtain CAC score. Any score >0 was considered as significant. Detectable calcium was defined as a CAC score >0. Table 1 illustrates the calcium score (Agatson score) and its implication.

Statistical Analysis

SPSS version 21.0 (SPSS, Chicago, IL) was used for statistical analysis. Normal distribution was described as

Table 2: Patients' baseline characteristics for participants with family history compared to participants without family history

Demographics	Family history of young CAD (n=18)	No family history of young CAD (n=18)	P value
Age (Yr) Mean (SD)	36.9 (4.9)	38.0 (3.8)	
Gender, n (%)			
Male	6 (33.3%)	6 (33.3%)	
Female	12 (66.7%)	12 (66.7%)	
Comorbidity, n (%)			
HPT	1 (5.6%)	6 (33.3%)	
DM	-	1 (5.6%)	
HPL	-	2 (11.1%)	
Medications, n (%)	0%	5 (27%)	
Anti HPT	-	3 (16.7%)	0.23
OHA/Insulin	-	1 (5.6%)	
Statin/ Anti HPL	-	1 (5.6%)	
Smoking status			
Former	2 (11.1%)	3 (16.7%)	0.64
Current	4 (22.2%)	2 (11.1%)	
BMI, kg/m^2, n (%)			
Overweight (≥25 to <30)	9 (50%)	12 (66.7%)	0.45
Obese (≥30)	6 (33.3%)	4 (22.2%)	
Blood pressure (mmHg) Mean (SD)			
Systolic	124.1 (15.3)	127.1 (15.8)	0.56
Diastolic	80.3 (11.5)	79.3 (10.7)	0.77
Waist circumference, n (%)			
(>85 cm men; >80 cm women)	13 (72.2%)	15 (83.3%)	0.69

Table 3: Baseline investigations for participants with family history compared to participants without family history

Investigations	Family history of young CAD (n=18)	No family history of young CAD (n=18)	P-value
Fasting blood sugar (mmol/L), Mean (SD)	4.7 (0.4)	5.0 (1.2)	0.98
Fasting lipid profile			
Total cholesterol, Median (IQR)	5.6 (1.79)	5.7 (2.04)	0.67
Triglycerides, Median (IQR)	0.9 (0.76)	1.0 (1.81)	0.74
LDL, Mean (SD)	4.0 (1.0)	3.8 (1.0)	0.48
HDL, Mean (SD)	1.3 (0.3)	1.3 (0.3)	0.90
Renal profile			
Urea, Mean (SD)	3.4 (1.1)	3.5 (0.9)	0.75
Creatinine, Median (IQR)	62.5 (25.4)	66.3 (24.2)	0.56
Liver profile			
ALT, Median (IQR)	17.5 (17)	25 (22)	0.12
Albumin, Mean (SD)	39 (1.3)	39 (2.1)	0.93

mean SD using standard Student t-test. If the distribution skewed, variables were described as median (IQR) using the Mann-Whitney test. Chi-square test or the Fisher exact test was used for categorical variables. P-value equal to or less than 0.05 was considered as significant.

RESULTS

Participants' Demographics and Anthropometric Measurements

A total of 119 index patients (defined as patients aged <45 with documented ACS and coronary stenosis of at least 50% on angiography) were screened initially from the Young PCI Registry UKMMC 2014-2017. Out of these 119 patients, 27 were uncontactable. A total of 37 of the index patients replied (55 did not reply) and 12 of them consented for their young CAD family to be screened. A total of 39 young CAD was available from this contact (2 were diagnosed with ACS and 1 was pregnant, hence excluded), in which 18 of them attended the appointment. The data of no family history of young CAD-those without family history of CAD, were obtained from the outpatient Cardiology Clinic. A total of 36 participants were recruited with 18 participants in each group, matched by age and gender. Figure 1 shows the flow chart of our comparative cross-sectional study design.

Mean age for family history with young CAD group was younger than their index patients, with 36.9 ($\pm$4.9) years and 39 ($\pm$1.1) years, respectively. 80% of the index patients were male while the majority of the FDRs were female (66.7%). More than half of the index patients had at least one comorbidity in contrast to their FDRs. The demographics and anthropometric measurements for family history with young CAD and no family history of young CAD are presented in Table 2. All of participants (n=36) were Malays and predominantly female (66.7%) in both groups. There was higher

Table 4: Newly diagnosed risk factors, FRS, EST and CAC for participants with family history compared to participants without family history

Risk factors	Family history of young CAD (n=18)	No family history of young CAD (n=18)	P-value
Newly diagnosed, n (%)			
Diabetes	-	-	
Hypertension	3 (16.7%)	3 (16.7%)	0.01
Dyslipidemia	15 (83.3%)	8 (44.4%)	
Framingham Risk Score			
Low risk	16 (88.9%)	16 (88.9%)	1.00
Moderate risk	2 (11.1%)	2 (11.1%)	
Exercise stress test			
Equivocal	1 (5.6%)	1 (5.6%)	1.00
Positive	1 (5.6%)	1 (5.6%)	
CAC score			
=0	16 (88.9%)	18 (100.0%)	0.49
>0	2 (11.1%)	-	

prevalence of comorbidities and medications prescription in the group with no family history of young CAD compared to the other group. (at 50% and 27% vs 5.6% and 0%), respectively. In terms of smoking, participants from the family history young CAD group had 10.1% more active smokers than other group; however, the prevalence of former smokers was higher by 5.6% in the latter. More than three quarter of participants in both groups were either pre-obese or obese. There was notable high percentage, 72.2% in family history of young CAD group while 83.3% in no family history of young CAD group.There were no statistical differences observed in waist circumference and mean blood pressure between the two groups.

Biochemical Investigations

TC and HDL-C in the no family of history young CAD group were slightly lower than those who has a family history young CAD with 5.4 (1.92) vs 5.6 (1.79) and 1.0 (±0.1) vs 1.3 (±0.3), respectively. Mean LDL-C in former group were lower than latter, with 3.6 (±0.3) and 4.0 (±1.0), respectively. The biochemical investigations of our study participants were showed in Table 3. Both groups, group has family history of young CAD and group no family history of young CAD showed considerably high median of TC with 5.6 mmol/L and 5.7 mmol/L, respectively. The mean (±SD) of LDL-C 4.0 (±1.0) was higher in the family history young CAD group. However, those with no family history of young CAD had higher triglycerides (TG) and fasting blood sugar (FBS) of 5.0 (±1.3) and 4.7 (±0.4), respectively. Both groups showed equal level of HDL-C of 1.3 (±0.3). Both groups also had normal renal and liver profile with no statistical differences.

Newly Diagnosed Risk Factors and Risk Stratification Tools

Table 4 show newly diagnosed risk

factors and risk stratification tools for both evaluated groups. The group with family history of young CAD had a higher percentage of newly diagnosed dyslipidemia with 38.9%. However, there were more participants from those with no family history of young CAD suspected to have familial hypercholesterolemia (4 vs 3, p=1.00). On the other hand, there was equal percentage of newly diagnosed hypertension in both groups (16.7%). No newly diagnosed diabetes was identified in both groups based on the FBS level. Both groups had equivalent percentage of participants with low and moderate risk for CAD based on the FRS. No participants in both groups were classified as having high or very high risk. Both groups had equal percentages of equivocal and positive EST. A majority of participants in both groups had normal EST. Positive CAC score were 11.1% higher in the group with family history with young CAD while all participants who did not have a family history young CAD had 0 CAC score. Those with CAC >0 were from the low-risk FRS and had normal EST. All participants with a moderate risk FRS, equivocal and positive EST group had CAC score of 0. The value for CAC >0 (present) and CAC=0 (absent) presented in Table 4.

DISCUSSION

Atherosclerosis is a sub clinical slow process before it become clinically significant. It can start during the teens with no clinical sign (Tuzcu et al. 2001). With rising cardiovascular risk factors in Malaysia, patients presented for ACS were at earlier age compare to Western countries (Ahmad & Sim 2011). As most of the young CAD patient presented with acute myocardial infarction (MI) which is often fatal (Muda et al. 2013). Early detection would be beneficial in reversing or halting the progression of the disease. Acute MI or sudden cardiac death (SCD) can be the first presentation of the coronary atherosclerosis or CAD. These individuals are usually asymptomatic or has been miss classified from during the risk factor assessment. Early detection of CAD can be done through CAC score, possibly playing a role in primary prevention. CAC has been used to detect the CAD in primary prevention (Han et al. 2015). However, in our study, due to the small number of samples, the positive result of the CAC was very low and may need to be validated with bigger sample.

The participants in the present study were all Malays. This might not accurately represent the overall multi-ethnic population of Malaysia, with the majority being Malay, Chinese and Indians. Majority (two-third) of the participants involved in this study were female, consistent with other primary prevention studies (Nasir et al. 2004; Sailam et al. 2008). The higher response rate from female participants could be possibly due to better awareness compared to male participants. The mean age for our participants were far younger than 40 years of age. Furthermore, due to the poor response rate, a fairly low number of participants were recruited (60% of target). The difficulty in recruitment was understandable as this was the first

ever attempt at recruiting the public by direct invitation (rather than voluntary screening which would require much bigger funding and longer time period). Nevertheless, these two groups, group that has family history of young CAD and group that has no family history of young CAD of participants represented what we are seeing in daily practice of screening or risk stratifying our patients for CVD.

As for those with family history of young CAD, there is no doubt many guidelines do recommend their screening for CVD risk as a Class I recommendation (Piepoli et al. 2016). Regardless of the result of this study, the screening of this group of participants is considered appropriate. However, most of the guidelines emphasises determination of common CVD risk factors and the usage of CVD risk prediction (e.g. FRS). Both American and European guidelines do state the role of CAC score in further reclassifying patients' CVD risk (Piepoli et al. 2016; Goff et al. 2014). In this study we attempted to implement this strategy in a group of participants who were at a younger cut off age (mean age <40) for FRS, EST and CAC scoring.

The analysis of conventional risk factors showed higher comorbidities in the group with no family history of young CAD, as most of them were recruited from the cardiology clinic that traditionally manages these group of patients with intermediate or high CVD risk profile. This also explained the lower cholesterol levels for those with no family history of young CAD compared to those with family history of young CAD as they were appropriately managed earlier, either by lifestyle modification or therapeutic treatments. This was in contrast to those with family history of young CAD, as most of them had never underwent routine medical screening except one. This provided an opportunistic screening to those with family history of young CAD, consistent with our Primary and Secondary Prevention Screening Guidelines 2017, which encourage early CVD risk screening for those with family history of premature CAD (Rajadurai et al. 2017). Early screening is crucial to identify conventional risk factors, allowing for lifestyle modifications to be implemented. There is notable in newly diagnosed conventional risk factors such as obesity and dyslipidemia in both groups. Newly diagnosed dyslipidemia is a significant risk factor among those with a family history of young CAD. This was consistent with the National Health and Morbidity Survey (NHMS 2015) which showed high prevalence of CVD risk factors in Malaysian adults' population, with 63.6% in men and 64.5% of women are either overweight or obese, 43% of men and 59% of women smoke, 43.5% of men and 52.2% of women having hypercholesterolemia and 30.8% of men and 29.7% of women have hypertension. Data from NHMS (2015) also showed that the prevalence of these CVD risk factors begin to increase from the age of 30 years. Apart from dyslipidemia and obesity, other risk factors were detected at much lower rate compared to that of NHMS V (2015) among those with a family

history of young CAD. Nevertheless, the presence of any CVD risk factors in this group of participants with strong family history would markedly increase their future risk, hence the importance of managing these risk factors early.

There was a high prevalence of newly diagnosed risk factors, suggesting that the age of onset at which patients typically develop multiple cardiac risk factors has probably shifted to a much earlier age in recent years. This is also reflected in the physical status of the young population in Malaysia. More than 80% of the participants from both groups were pre-obese or obese and have increased white cell (WC). The higher waist circumference seen among our study population is a good indicative of abdominal obesity, as it commonly precedes the development of hypertension, glucose intolerance and dyslipidemia. Several studies have shown a strong positive correlation between the degree of adiposity and fasting TG (Tanko et al. 2005). Plasma cholesterol was also positively correlated with BMI, although less strongly than TG, where HDL-C wasinversely correlated. Abdominal obesity accompanying glucose intolerance, hypertension, hypertriglyceridemia and low HDL-C has been termed the "metabolic syndrome" (Despres & Lemieux, 2006). All participants in both groups had normal renal and liver profile, showing that the target organ damage has not occurred yet. On the other hand, this also showed the possibility of good control by mean of lifestyle and medication among those with no family history of young CAD. However, prevalence of smoking was similar across the groups, which was somewhat lower than national figure. Cigarette smoking has long been recognised as one of the conventional risk factors in the development of atherosclerotic CAD. It has been persistently reported to be dominant and most significant risk factor in young CAD (Barbash et al. 1995).

The participants screened in our primary prevention via FRS scores classified as low and moderate risk group. Presence of CAC > 0 in FDRs, even in low-moderate risk, showed the possibility of CAC being used as risk modifier. This was consistent with findings from past studies (Nasir et al. 2004; Michos et al. 2005). In the Study of the Inherited Risk Factor for Coronary Atherosclerosis (SIRCA), 52% of women and 78% of men with family history of premature CAD and without CAD or diabetes had a positive CAC (Valdes et al. 2001). The mean age of men in SIRCA was 45 years while it was 50 for the women. Nasir et al. (2004) showed that age-, gender- and race-adjusted prevalence of CAC > 0 was significantly higher with the presence of any family history of premature CAD than those with no family history among individuals classified as low and moderate risk. Polonsky and Greenland (2012) also showed that addition of CAC to conventional risk factors improves risk prediction significantly compared to conventional risk factors alone. The protective value of a zero CAC score is also proven with 10-year event rate of about 1%, as consistently reported in a number of studies (Blaha et al. 2009; Detrano et al.

2008; Budoff et al. 2007). In this study, there were only two cases whose CAC score were higher than 0 (each having 1 and 3 CAC score each, still within the very low score group of <10). This very low CAC score may be explained partly by the very young mean age (<40) and predominance of women subjects (66.7%). Till this moment, there are no novel biomarkers or imaging that specific for this particular group of young people. Most of the guidelines emphasise on the detection of conventional risk factors and using the risk prediction to stratify the risk for these patients. There are other markers such as hs-CRP, urinary albumin, carotid intima media thickness (CIMT), pulse wave velocity (PWV) or finger photoplethysmography (Rajadurai et al. 2017; Goff et al. 2014). Hs-CRP had shown some promising roles in predicting future events, nevertheless, due to budget restriction we were unable to incorporate it in our study. The other markers were less specific for predicting coronary events and are still being used largely at the research level.

The pertinent question is how reliable and robust the result of CAC score in these two groups of participants. The robustness of CAC score had been established from literature and well recognised in all CVD prevention guidelines. Furthermore, our participants demonstrated low FRS score as well as very low rate of positive EST. Chang et al. (2015) demonstrated the ability of CAC score in predicting low CVD event among subjects with low FRS. In regard to EST, a study conducted at our centre demonstrated that among subjects with non-diagnostic EST, performing CAC score would further stratify their risk of having obstructive CAD (low calcium score had a 100% negative predictive value of the presence of CAD) (Ibrahim et al. 2013). Therefore, the findings of low FRS, mostly negative EST with low CAC score among our subjects in both arms were reassuring of their low probability of having obstructive CAD.

Some limitation in this study were thar index patients' data were collected directly from a single-centre, UKKMC PCI registry. Single-centre make the screening limited to UKMMC. Multi-centre studies may allow the recruitment of more participants with various ethnicities. Besides, comparison of the FDRs was made with the patient recruited from Cardiology Clinic, where comorbidities was diagnosed and treated earlier during the course of follow-up. Financial limitations restricted the numbers of participants involved and our initial plan to incorporate hs-CRP in this study.

CONCLUSION

There is high proportion of newly diagnosed risk factors among our young population especially in those with family history of young CAD. A significant number of participants have high BMI, abdominal waist circumference and dyslipidemia. Even though this study was unable to prove CAC score as additional risk factors in FDRs with family history of young CAD, they still needed to be screened for the risk factors assessment.

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