Is there a Role for Routine Use of Calcium Scoring in Predicting Cardiovascular Event in Asymptomatic Adults in Primary Care?

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INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of premature death globally, both in developed and developing countries[1]. Despite a recent decline in CAD mortality in developed countries, the mortality rate continues to rise steadily in developing countries, contributing to more than 4.5 million deaths each year[2]. This phenomenon results from an escalating epidemic of cardiovascular (CV) risk factors, and there is no doubt that Malaysia is being confronted with this burden2. The recent National Health and Morbidity Survey (NHMS) 2011 showed that the prevalence of obesity among Malaysian adults > 18 years stood at a staggering 27.2%; and another 33.3% were found to be overweight3. Similar trends were shown with regards to the prevalence of hypercholesterolaemia (35.1%), hypertension (32.7%) and diabetes (15.2%)[3].

CAD has a long asymptomatic latent period that provides an opportunity for early preventive interventions in primary care. The risk prediction which uses multiple conventional CV risk factors is the mainstay of risk assessment in primary care and should be obtained for all asymptomatic adults without a clinical history of CAD[4]. These scores are useful for combining individual risk factor measurements into a single quantitative estimate of risk that can predict future CV events[5]. Some examples of risk prediction charts include the Framingham Risk Score (FRS), Prospective Cardiovascular Munster Score (PROCAM), Systemic Coronary Risk Evaluation (SCORE), risk score based on the Scottish Heart Extended Cohort (ASSIGN), CV disease risk score based on the British QRESEARCH database (QRISK), Joint British Societies Cardiovascular Risk Chart (JBS), and World Health Organization/International Society of Hypertension (WHO/ISH) Risk Chart[6-12]. The interpretation, customisation and application of these tools in clinical practice have been evaluated in a recent review[13].

Although many conventional risk factors have been well established as predictors of CAD, new risk markers are frequently being identified and evaluated as potential additions to the standard risk markers. Examples of these novel risk markers include natriureticuretic peptides, C-reactive protein (CRP), lipoprotein, apolipoprotein, microalbuminuria and calcium scoring. For any new risk marker to be considered as a useful candidate for risk prediction, it must, at the very least, have an independent statistical association with risk after being adjusted for the conventional risk markers[14]. This independent statistical association should be based on studies that include large numbers of outcome events[4,14]. Therefore, the aim of this paper is to review the evidence surrounding the role of calcium scoring to assess CV risk in asymptomatic adults in primary care.

REVIEW OF EVIDENCE

Coronary calcification occurs exclusively in the advanced stages of atherosclerosis hence it reflects the state of an individual's total atherosclerotic burden[15]. Histologically, it is the total atherosclerotic burden rather than the degree of luminal stenosis that predicts death following myocardial infarction[16]. Cardiac CT allows the detection and quantification of coronary calcification. The analysis involves a non-contrast scan using an ECG-triggered scanning mode with 2.5- to 3.0-mm thick axial images acquired through the heart[16].

Coronary calcification can be assessed quantitatively using three methods: (1) calcium volume score, (2) calcium mass and (3) the Agatston score. The calcium volume score is reproducible but prone to artefacts that may impair its accuracy. Calcium mass is accurate and has little variability, but it has a small database available to validate its use. The Agatston score is the most widely validated and commonly used method. The score is a product of the density factor and the area of calcium in the coronary artery, and it is correlated with total atherosclerotic burden and the severity of coronary stenosis[17-19].

The precise method for how to use the calcium score in clinical practice is still debatable. Two methods have been commonly used: (1) percentiles of age/sex with or without ethnicity and (2) absolute calcium score. The National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) recommended that patients with multiple risk factors and a calcium score above the 75th percentile for sex and age would benefit from aggressive preventive measures[20]. Using percentiles seems reasonable because they allow the comparison of the patient relative to his or her own age, sex and ethnicity. In addition, this method would allow physicians to treat those patients who are 'above' the curve. However, a study has noted that the percentile method tends

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Table I: Frequencies of abnormal myocardial perfusion imaging in asymptomatic subjects with different groups of calcium score

	Calcium score	<100	100-400	>400
Frequency of abnormal perfusion scan	Moser et al 26 (SPECT†)*	5%	24%	53%
	Rozanski et al27 (Scintigraphy)*	1.4%	4%	12.4%
	Chang et al28 (SPECT†)*	<2%	9.8%	31%

*These studies have used different myocardial perfusion imaging modalities. †Single-photon emission computed tomography (SPECT).

Table II: Summary of relative risk ratio and absolute risk for different calcium score cut-points

Calcium score	Relative risk ratio	Absolute risk	P value
1-101	1.9	0.7	0.001
101-400	4.3	2.1	<0.0001
401-999	7.2	4.6	<0.0001
>1000	10.8	7.1	<0.0001

to underestimate risk, especially in women21. The author of the study cited an example of a 50-year-old Hispanic woman with a calcium score of 25 would place her in the 95th percentile for her age/sex/ethnicity, on par with an 83-year-old white man with a calcium score of 1,572, which would place him in the 72nd percentile for his age/sex/ethnicity[21].

The absolute calcium score is an alternative. The commonly used calcium score cut-points are 1 to 100, 101 to 400 and more than 400. However, younger patients are at disadvantage with this method because they rarely achieve calcium scores of more than 100 and may benefit more from the percentile method[22].

Anatomically, calcium score correlates with the presence of obstructive CAD in invasive coronary angiography (ICA). A meta-analysis of 18 studies comprising a total of 10,355 symptomatic patients with suspected CAD underwent both calcium scoring and ICA23. The pooled sensitivity, specificity, negative predictive value and positive predictive value were 98%, 40%, 93% and 68%, respectively, for detecting >50% stenosis by ICA[23]. Calcium score also correlate with virtual histology intravascular ultrasound and histopathological analysis[24,25]. Functionally, an increased calcium score is associated with an increased frequency of myocardial ischaemia detected by perfusion imaging. Table I summarises the frequencies of abnormal myocardial perfusion imaging in asymptomatic subjects with different groups of calcium score. Asymptomatic individuals with a calcium score of less than 100 are less likely to have abnormal myocardial perfusion imaging results compared to those individuals with a calcium score of more than 100[26-28.]

Calcium score increases with age and the presence of other conventional CAD risk factors. The largest cross-sectional cohort study involving 30,908 asymptomatic men (mean age 50±9 years old) and women (mean age 54±9 years old) demonstrated that the mean calcium score increased proportionately with age and number of CAD risk factors[29]. In an age-adjusted multivariate regression analysis, cigarette smoking, hypercholesterolaemia, diabetes and hypertension were each significantly associated with the presence of calcium score[29].

Calcium score is also an independent predictor of future cardiac events. The ACCF/AHA clinical experts critically reviewed 6 studies published between 2003 and 2005 which investigated the prognostic value of various absolute calcium score cut-off points over a period of 3 to 5 years[30]. They confirmed an incremental relationship between calcium score and CHD death[30]. Table II summarises the relative risk ratios and absolute risk for different calcium score cut-points. A calcium score of 0 was associated with a very low rate of CHD death or MI (0.4%, n=49 events/11,815 individuals) over 3 to 5 years. Calcium scores of 1 to 100, 101 to 400, 401 to 999 and more than 1000 were associated with increased summary relative risk ratios of 1.9, 4.3, 7.2 and 10.8 and absolute risks of CHD death or MI of 0.7%, 2.1%, 4.6%, 7.1%, respectively, 3 to 5 years after calcium score scanning[30]. The annual rate of cardiac death by MI for a patient with an intermediate FRS risk and a calcium score of more than 300 is 2.8%[31]. This rate is roughly equivalent to a 10-year risk of 28%, which would be considered to be high.

Evidence continues to grow with more publications confirming the prognostic value of the calcium score in a variety of cohorts between 2005 and 2010. Two multi-ethnic prospective cohorts have shown that there are ethnic differences in calcium scores[32,33]. Non-Hispanic whites had significantly higher calcium scores compared to ethnic minorities (African Americans, Hispanics and Asians) and a lower prevalence of conventional risk factors[32]. In contrast, the ethnic minorities had lower calcium scores but a higher prevalence of risk factors[33]. The more extensive CAD burden has led to a sizeable increase in mortality risk, especially in African Americans. Two other cohorts added the prognostic values of the calcium scores in different ethnic groups. Both studies confirmed that increased calcium scores were associated with greater mortality in all ethnic groups regardless of risk factors, gender or age[34,35].

With regards to elderly patients, a cross-sectional study of 3750 subjects older than 70 years of age investigated the relationship between calcium score and all-cause mortality36. The annual mortality rate for a calcium score of 0 was 0.3% for subjects between 40 to 49 years of age and 2.2% for subjects older than 70 years of age. In all age groups, an increase in calcium score was associated with decreased survival. Among subjects with a calcium score of more than 400, the survival rate for subjects older than 80 years of age (88% for men, 95% for women) was lower than for those subjects younger than 40 years of age (19% for men, 44% for women)[36].

The role of calcium score in predicting CV events in asymptomatic type 2 diabetic patients has also been studied. Diabetes is associated with elevated overall mortality, and the NCEP considers diabetes a CAD equivalent. The PREDICT study, which involved a prospective cohort of 589 asymptomatic type 2 diabetes patients with a median follow-up of 4 years, showed that an increased calcium score is associated with an increased event rate. For the calcium score groups of 0 to 10, 11 to 100, 101 to 400, 401 to 1000 and more than 1000, the event rates were 1.4%, 8%, 14.6%, 15.7% and 26.2%, and the hazard ratios relative to calcium score 0 to 10 were 5.4, 10.5, 11.9 and 9.8, respectively[37]. The area under the ROC curve for the FRS and UKPDS of CHD risk improved when the calcium score was added but only with borderline significance (0.63 to 0.74, p=0.01 and 0.63 to 0.73, p=0.03, respectively37. Another study showed that when the calcium score was 0, the 5-year all-cause survival was similar for diabetics and non-diabetics[38]. These findings prove that even though diabetes is associated with an increased risk of CV events, the calcium score has the potential to improve the CV risk prediction. Importantly, patients without detectable coronary calcification are at low-risk of death over 4 to 5 years.

Due to the growing evidence supporting calcium scoring in predicting CV events, multiple studies have investigated its effect on the traditional FRS. The FRS fails to take the actual burden of atherosclerosis of an individual into account and thus a tendency to underperform particularly in those with a high suspicion of CAD, women and young individuals[39,40]. Since FRS is derived from American data, its applicability to other population is also uncertain. In fact several studies have demonstrated FRS can either underestimate or overestimate risk of initial CHD events in Japanese American, Hispanic men, Native American women as well as in European and Asian populations[5,41-44]. Whether these differences are real it is yet to be ascertained. It could be partly explained by the differences in research methodologies, adjudication procedures and time intervals utilised in these studies.

Consequently, whilst some countries have developed alternative models to better reflect their own population demographics such as the SCORE and QRISK2, others have proposed the concept of net reclassification improvement (NRI). NRI is a statistical model which explains the effect of enhancement in risk prediction when a novel marker is added to the standard risk prediction model[45]. Applying this concept, The St. Francis Heart Study found adding calcium score to the FRS improves the area under the receiver-operating characteristic curve from 0.69±0.03 to 0.79±0.03 (p<0.0006) in predicting CAD events[46]. Furthermore, adding calcium score to the FRS in the intermediate group has led to the reclassification to either lower or higher risk groups46. A mortality study has investigated the effect of individuals with discordant scores ("discordant low risk" = FRS ≤10% and calcium score ≥100, "discordant high risk" = FRS ≥20% and calcium score=0) and found individuals with discordant low risk had higher mortality rates than those individuals with discordant high risk[47]. Adding calcium score to the FRS also improves FRS classification in elderly people, where a similar trend was observed in which reclassification occurred mostly among the elderly in the intermediate risk group[36,48]. However, no prognostic data are available to investigate the effect of reclassification among the elderly.

Several studies have looked into the plausibility of monitoring progression of calcium score. A study which investigated the progression of calcium score in relation to traditional CV risk factors in asymptomatic patients found that only hypertension and diabetes were significantly associated with a progression of calcium score, whereas sex, age, hypercholesterolaemia, family history of premature heart disease, smoking and body mass index of more than 25 had limited relationship[49]. From a prognostic point of view, two retrospective and three prospective studies confirmed that subjects who developed MI had a higher progression rate from baseline compared to those subjects with a stable calcium score over 3 to 4 years of observation[38,40,50-52]. However, current published guidelines state that calcium score progression has a low positive predictive value due to the significant overlap among subjects with and without future events in these studies hence its value in refining risk prediction is questionable[31].

Progression of calcium score can be quantified via several methods which include absolute values, the percentage of relative change, log transformation or the regression method. However, these techniques are subjected to inter-scan variability. In the effort to improve image acquisition, mathematical transformations have been attempted. Hokanson proposed a square root transformation of the calcium volume score ≥2.5 mm^3 to signify a significant change[53]. A mortality study that followed 4,609 patients for a mean of 6 years showed that the change of calcium score progression measured using the Hokanson method is a useful predictor (p<0.0001) for mortality after controlling for baseline calcium score, age, sex and interval time between scans54.

Effect of treatment on calcium score

It seems intuitive to initiate pharmacological intervention to slow the progression of calcium deposition. This hypothesis was initially confirmed by several retrospective and prospective studies, but subsequent randomised controlled trials, using various types and doses of statins failed to show clinical significance[55-59]. Although statins did not reduce coronary calcification, they significantly reduced the non-calcified burden[60]. Pathological studies have shown that statins can induce microcalcification[61]. When statins reduce the soft lipid core of a calcified plaque, the overall effect could cause the density of the plaque and the Agatston score to increase and its volume to decrease[62].

Meta-analysis of clinical trials on the use of aspirin as a primary prevention in asymptomatic patients with CV diseases showed that its benefit is offset by the risk of bleeding[63,64]. Only one study to date investigated the effect of aspirin and statins on calcium score, and it failed to show a reduction in all CV events and in the progression of calcium score[65]. Other non-statin studies using calcium channel blockers, alpha-tocopherol, vitamin C, unopposed oestrogen therapy, garlic, folic acid and L-arginine also failed to demonstrate significant effects on reducing the progression of coronary calcification[64-67].

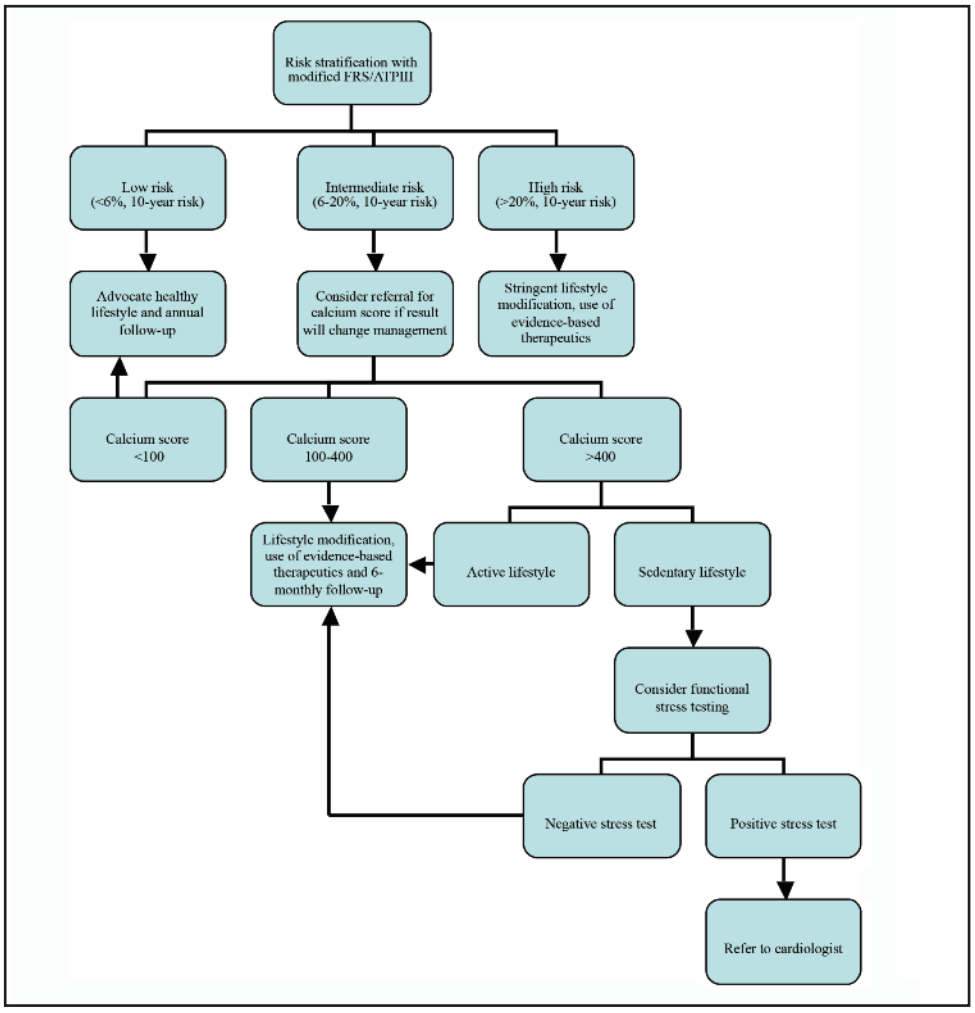

Fig. 1 : Proposed algorithm for utilization of calcium score in CV risk prediction for asymptomatic patients in primary care setting.

Economic evaluation of calcium score assessment

The rising costs of medical care and limited resources in low- and middle-income countries have increased the interest in documenting the economic effects of new tests and therapies. The most basic goal is to estimate the economic consequences of a decision to order a new test; the ultimate goal is to determine if performing the test provides sufficient value to justify its use. The EISNER study attempted to evaluate the cost-effectiveness of calcium score assessment[68]. This study randomised 2137 subjects into a calcium scan or non-calcium scan group and followed them for 4 years to track the changes of the CAD risk factor and FRS as the primary endpoints. There was a mean rise in the FRS score in the non-scan group, whereas it remained constant in the scan group[68]. In addition, resource utilisation was lower in patients with normal calcium scores and higher in those patients with calcium scores ≥400 [68]. Although there were favourable changes in systolic BP, LDL, triglyceride levels; the study failed to show net reductions in downstream testing and cost[68].

Translating calcium scoring into clinical practice

Many high-income countries with vast resources have issued clinical guidelines recommending the use of calcium scoring to improve CV risk stratification in asymptomatic adults. The ACCF/AHA, NCEP 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)[20,31,69]. However, the U.S Preventive Services Task Force (USPSTF) and the New Zealand Guideline Group (NZGG) found insufficient evidence to recommend calcium scoring even for the intermediate-risk population[70,71].

It is reassuring to learn that the risk of cardiac events at 3 to 5 years is very low in patients with an intermediate FRS risk and a calcium score of 0. The problem arises when there is detectable coronary calcification and clinicians are frequently vexed with the next therapeutic intervention following detectable calcium score. The ACCF/AHA has stated that those individuals with a calcium score of more than 100 would benefit from stringent lifestyle modification and evidence-based therapeutic agents[31]. Unfortunately, the writing committee has not stated which specific therapeutic agents should be used, given the lack of evidence that treatment will result in improved clinical outcomes. This ambiguity makes the management of patients with detectable calcium scores a grey area.

Guideline recommendation on the use of calcium score is still unavailable in the majority of Southeast Asian countries, including Malaysia. These could be explained by the paucity of evidence on calcium scoring involving Southeast Asian population. Most studies on calcium score were conducted in high-income countries, therefore the extrapolation of data to the Southeast Asian population should be made with caution. Calcium score is also more expensive compared to the conventional risk prediction such as the FRS, and the evidence on its cost-effectiveness is still scarce. Moreover, cardiac scanning facilities in Malaysia are limited, thereby limiting the use of calcium score.

Despite these limitations, there is still a need to develop some recommendations to guide the primary care physicians as to who should be referred for calcium scoring. Figure 1 shows the proposed algorithm based on the evidence presented in this paper. In the light of potential underperformance of FRS in Asian population, it is reasonable to recommend calcium score assessment of asymptomatic adults at intermediate risk (10%-20%, 10-year risk) by the modified FRS/ATP III when the result is expected to lead a change in management based upon reclassification to a lower or higher risk group. For asymptomatic patients in the low- (<6%, 10-year risk) and high- (>20%, 10-year risk) risk groups there is insufficient evidence to recommend the use of calcium score.

At present, the absolute cut-off rather the percentile method is recommended due to its ease of use and less study-specific. A cut off of 100 and 400 seems to perform well. Calcium score of less than 100 in asymptomatic individuals with intermediate risk portends good prognosis. However, the best approach in managing asymptomatic patients with calcium score of more than 400 is still uncertain. Question also lies in the management of asymptomatic patients at intermediate risk with calcium score within the range of 100-400. In addition to putting an emphasis on more stringent lifestyle modification, management of these patients should be individually tailored.

In line with the 2010 ACC/AHA recommendations, stress testing should be considered in sedentary individuals where absence of symptoms does not indicate absence of ischaemia[4]. The choice of stress testing should be of functional kind rather than anatomical, preferably stress myocardial perfusion imaging. However, this method is limited by its availability in the local setting, high cost and involves radiation involvement. Dobutamine stress echocardiography or exercise stress testing can be considered as an alternative.

There is also insufficient evidence to recommend calcium score as a screening tool to diagnose obstructive CAD due to its low specificity and may result in high false positive when the test is applied to low-risk population. The 2002 ACC/AHA guidelines have concluded that the efficacy of exercise stress testing in this cohort of patient is not well established[72]. These low risk patients should be stratified with the modified FRS/ATP III first before decision is made whether they would require calcium score. Routine serial measurement of calcium score progression is also not recommended as it is of unproven value. There is no evidence to show intervention slows down the progression of calcium score and routine serial measurement also involves inappropriate exposure to radiation.

CONCLUSIONS

The FRS is cheap and widely available for CV risk assessment in asymptomatic individuals. However, it is study-specific and has been shown to underperform in subgroups of individuals. Calcium score adds incremental prognostic value to the FRS and has gained moderate recommendation by the ACC/AHA, NCEP ATP III and CCS. Its strength lies in its negative predictive value. An absence of coronary calcification is associated with a very low incidence of cardiac events within 3 to 5 years. High-income countries may have enough resources to adhere to current guideline recommendations on calcium scoring. However, routine use of calcium scoring in predicting CV event in asymptomatic adults in Malaysia is still uncertain. Given the limited resources, local studies are needed to demonstrate the cost-effectiveness and the incremental prognostic value of calcium score over the conventional risk scores. At present, the FRS would probably be the best option for predicting CV event in asymptomatic adults in primary care. Until local evidence becomes available, recommendations to guide primary care physicians as to who should be referred for calcium scoring can be made by extrapolating existing published data. For individuals at intermediate risk and when the result is expected to lead a change in management based upon reclassification to a lower or higher risk group, primary care physicians could consider referring patients for calcium score if facilities are available. Prospective or randomized controlled-trials involving local population will be helpful to concretely determine the role of this imaging modality in Malaysia.

REFERENCES

1. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanisation. Circulation 2001; 104: 2746-53.
2. Okrainec K, Banerjee DK, Eisenberg MJ. Coronary artery disease in the developing world. Am Heart J 2004; 148: 7-15.
3. Institute for Public Health, Ministry of Health Malaysia. The National Health and Morbidity Survey (NHMS); Vol. II: Non-Communicable Diseases, 2011.
4. Greenland P, Alpert JS, Beller GA, *et al.* 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010; 122: 2748–64.
5. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P for the CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001; 286: 180-7.
6. D'Agostino RB, Vasan RS, Pencina MJ, *et al.* General cardiovascular risk profile for use in primary care. The Framingham Heart Study. Circulation 2008; 117: 743-53.
7. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) Study. Circulation 2002; 105: 310-5.
8. Conroy RM, Pyörälä K, Fitzgerald AP, *et al.* Estimation of ten year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24: 987-1003.
9. Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. BMJ 1997; 315: 722-29.

10. Hippisley-Cox J, Coupland C, Vinogradova Y, *et al.* Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ 2007; 335: 136.
11. Joint British Societies Cardiovascular Risk Chart [Internet]. British Hypertension Society. [updated 2012 Apr 23; cited 2011 Aug 13]. Available from: http://www.bhsoc.org/resources/cvd-risk-charts-and-calculators/
12. WHO/ISH cardiovascular risk prediction charts [internet]. World Health Organization [cited 2011 Aug 13]. Available from: http://www.who.int/cardiovascular_diseases/publications/Chart_predictions/en/
13. Chia YC. Review of tools of cardiovascular disease risk stratification: interpretation, customisation and application in clinical practice. Singapore Med J 2011; 52:116-23.
14. Hlatky MA, Greenland P, Arnett DK, *et al.* Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009; 119: 2408-16.
15. Stary HC. Natural history and histological classification of atherosclerotic lesions: an update. Arterioscler Thromb Vasc Biol 2000; 20: 1177-8.
16. Sangiorgi G, Rumberger JA, Severson A, *et al.* Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: A histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 1998; 31: 126-33.
17. Budoff JM, Kessler P, Gao YL, Qunibi W, Moustafa M, Mao SS. The interscan variation of CT coronary artery calcification score: analysis of the calcium acetate renagel comparison (CARE)-2 study. Acad Radiol 2008; 15: 58-61.
18. Baumgart D, Schmermund A, Goerge G, *et al.* Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. J Am Coll Cardiol 1997; 30: 57-64.
19. Rosen BD, Fernandes V, McClelland RL, *et al.* Relationship between baseline coronary calcium score and demonstration of coronary artery stenosis during follow-up: MESA (Multiethnic study of atherosclerosis). JACC Cardiovasc Imaging 2009; 2: 1175-83.
20. Third Report of the National Cholesterol Education Program (NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-421.
21. Budoff MJ, Nasir K, McClelland RL. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2009; 53: 345-52.
22. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 2005; 46: 807-14.
23. Sarwar A, Shaw LJ, Shapiro MD. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging 2009; 2:6 75-88.
24. Okabe T, Mintz GS, Weigold G. The predictive value of computed tomography calcium scores: a comparison with quantitative volumetric intravascular ultrasound. Cardiovasc Revasc Med 2009; 10: 30-5.
25. Rumberger JA, Simons DB, Fitzpatrick LA, *et al.* Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995; 92: 2157-62.
26. Moser KW, O'Keefe JHO, Bateman TM, *et al.* Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging. J Nucl Cardiol. 2003; 10: 590-98.
27. Rozanski A, Gransar H, Wong ND, *et al.* Clinical outcomes after both coronary calcium scanning and exercise myocardial perfusion scintigraphy. J Am Coll Cardiol 2007; 49:1352-61.
28. Chang SM, Nabi F, Xu J, *et al.* The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. J Am Coll Cardiol 2009; 54:1872-82.
29. Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrukov A, Kondos GT. Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30,908 healthy individuals. Ann Epidemiol 2003; 13: 163-9.
30. Greenland P, Bonow RO, Brundage BH, *et al.* ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007; 49: 378-402.
31. Greenland P, Alpert JS, Beller GA, *et al.* 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010; 56: e50-103.
32. Budoff MJ, Nasir K, Mao S, *et al.* Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis 2006; 187: 343-50.
33. Bild DE, Detrano R, Peterson D. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005; 111: 1313-20.
34. Nasir K, Shaw LJ, Liu ST, *et al.* Ethnic differences in the prognostic value of coronary artery calcification for all-cause mortality. J Am Coll Cardiol 2007; 50: 953-60.
35. Budoff MJ, Nasir K, McClelland RL. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol 2009; 53: 345-52.
36. Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw LJ. Coronary artery calcium to predict all-cause mortality in elderly men and women. J Am Coll Cardiol 2008; 52:17-23.
37. Elkeles RS, Godsland IF, Feher MD, Rubens MB, Roughton M, Nugara F for the PREDICT Study Group. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. Eur Heart J 2008; 29: 2244-51.
38. Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M. Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. Hypertension 2005; 46: 238-43.
39. Michos ED, Nasir K, Braunstein JB, *et al.* Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. Atherosclerosis 2006; 184: 201-6.
40. Ahmadi N, Hajsadeghi F, Blumenthal RS, Budoff MJ, Stone GW, Ebrahimi R. Mortality in individuals without known coronary artery disease but with discordance between the Framingham Risk Score and Coronary Artery Calcium. Am J Cardiol 2011; 107: 799-804.
41. Brindle P, Emberson J, Lampe F, *et al.* Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ 2003; 327: 1267.
42. Empana JP, Ducimetiere P, Arveiler D, Ferrieres J, Evans A, Ruidavets JB for the PRIME Study Group. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J 2003; 24: 1903-11.
43. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, *et al.* Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004; 291: 2591-9.
44. Khanna R, Kappor A, Kumar S, Tewari S, Garg N, Goel PK. Metabolic syndrome & Framingham Risk Score: observations from a coronary angiographic study in Indian patients. Indian J Med Res 2013; 137: 295-301.
45. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008; 27: 157-72.
46. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005; 46: 158-65.
47. Greenland P, LaBree L, Azen SP. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004; 291: 210-5.
48. Elias-Smale SE, Proença RV, Koller MT. Coronary calcium score improves classification of coronary heart disease risk in the elderly: The Rotterdam Study. J Am Coll Cardiol 2010; 56: 1407-14.
49. Shemesh J, Apter S, Stolero D, Itzchak Y, Motro M. Annual progression of coronary artery calcium by spiral computed tomography in hypertensive patients without myocardial ischemia but with prominent atherosclerotic risk factors, in patients with previous angina pectoris or healed acute myocardial infarction, and in patients with coronary events during follow-up. Am J Cardiol 2001; 87: 1395-7.
50. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004; 24: 1272-7.
51. Raggi P, Cooil B, Shaw LJ, *et al.* Progression of coronary calcium on serial electron beam tomographic scanning is greater in patients with future myocardial infarction. Am J Cardiol 2003; 92: 827-9.
52. Motro M, Shemesh J. Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. Hypertension 2001; 37: 1410-13.
53. Hokanson JE, MacKenzie T, Kinney G, *et al.* Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. Am J Roentgenol 2004; 182: 1327-32.

54. Budoff MJ, Hokanson JE, Nasir K, *et al.* Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010; 3: 1229-36.
55. Budoff MJ, Yu D, Nasir K, *et al.* Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 2005; 149: 695-700.
56. Achenbach S, Ropers D, Pohle K, *et al.* Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. Circulation 2002; 106:1077-82.
57. Raggi P, Davidson M, Callister TQ, *et al.* Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation 2005; 112: 563-71.
58. Schmermund A, Achenbach S, Budde T, *et al.* Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation 2006; 113: 427-37.
59. Houslay ES, Cowell SJ, Prescott RJ, *et al.* Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. Heart 2006; 92: 1207-12.
60. Terry JG, Carr JJ, Kouba EO, *et al.* Effect of simvastatin (80 mg) on coronary and abdominal aortic arterial calcium (from the coronary artery calcification treatment with zocor [CATZ] study). Am J Cardiol 2007; 99: 1714-7.
61. Burgstahler C, Reimann A, Beck T, *et al.* Influence of a lipid-lowering therapy on calcified and noncalcified coronary plaques monitored by multislice detector computed tomography: results of the New Age II Pilot Study. Invest Radiol 2007; 42: 189-95.
62. Stary HC. The development of calcium deposits in atherosclerotic lesions and their persistence after lipid regression. Am J Cardiol 2001; 88: 16E-19E.
63. Seshasai SRK, Wijesuriya S, Sivakumaran R, *et al.* Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012; 172: 209-16.
64. Belch J, MacCuish A, Campbell I, *et al.* The prevention and progression of arterial disease and diabetes (POPADAD) trial: factorial randomized placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008; 337: a1840.
65. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol 2005; 46: 166-72.
66. Budoff MJ, Chen GP, Hunter CJ, *et al.* Effects of hormone replacement on progression of coronary calcium as measured by electron beam tomography. J Womens Health 2005; 14: 410-17.
67. Budoff MJ, Ahmadi N, Gul KM et al. Aged garlic extract supplemented with B vitamins, folic acid and L-arginine retards the progression of subclinical atherosclerosis: a randomized clinical trial. Prev Med 2009; 49: 101-7.
68. Rozanski A, Gransar H, Shaw LJ, *et al.* Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol 2011; 57: 1622-32.
69. Genest J, McPherson R, Frohlich J, *et al.* 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol 2009; 25: 567-79.
70. U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009; 151: 474-82.
71. Assessment and management of cardiovascular risk by NZ Guidelines group New Zealand Guideline Group [Internet]. New Zealand Ministry of Health. [updated 2013 Oct 2; cited 2011 Aug 15]. Available from http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk-summary
72. Gibbons RJ, Balady GJ, Bricker JT, *et al.* ACC/AHA 2002 guideline update for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to Update the 1997 exercise testing guidelines). Am Coll Cardiol 2002; 40: 1531-40.

Multiple Choice Questions

1. Which of these are associated with coronary calcification?
   A. Increasing age
   B. Diabetes
   C. Intake of calcium supplement
   D. Hypertension
   E. Smoking

2. Calcium score:
   A. Increased calcium score is associated with increased likelihood of ischaemia on functional testing.
   B. Increased calcium score is associated with increased likelihood of obstructive coronary artery disease.
   C. Calcium score of zero excludes presence of coronary artery disease.
   D. Measurement of calcium score involves no radiation.
   E. Serial measurement of calcium score is indicated to measure the effectiveness of treatment.

3. In patients with intermediate FRS risk:
   A. All patients would require further risk stratification with calcium score
   B. A calcium score of zero confers mortality benefit
   C. Patients with calcium score of 100-400 may benefit from stringent lifestyle modification
   D. Asymptomatic patients with calcium score of 100-400 should receive aspirin
   E. Sedentary patients with high calcium score may benefit from additional functional testing even though they are asymptomatic

4. Which of these asymptomatic patients would benefit from further risk stratification with calcium score?
   A. A 25 year-old male smoker with no known medical illness
   B. A 50 year old non-smoker male with blood pressure of 160/85, total cholesterol of 6mmol/L and HDL cholesterol of 0.9mmol/L
   C. A 50 year old male with history of coronary angioplasty
   D. A 65 year-old obese female on treatment for diabetes, hypertension and dyslipidaemia
   E. A 65 year-old male smoker with history of peripheral vessel disease