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Screening for asymptomatic coronary heart disease in the young 'at risk' population: Who and how?

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ABSTRACT

Deaths due to coronary heart disease (CHD) remain high worldwide, despite recent achievements. An effective screening strategy may improve outcomes further if implemented in a high or 'at risk' cohort. Asymptomatic CHD in the young maybe underappreciated and applying an effective screening strategy to a young cohort may lead to improved outcomes due to significant socioeconomic impact from the consequences of CHD in this sub-group. A positive family history of CHD, which is known to be associated with an increased risk of future myocardial events, could aid in identifying the 'at risk' young cohort.

Traditional cardiovascular risk scoring systems are in wide use but lack the sensitivity or specificity required to estimate risk in an individual. Rather their use is limited to predicting population attributable risk. Functional studies such as exercise stress tests are readily available and cost effective but do not have the required sensitivity required to suggest their use as part of a screening protocol. Coronary CT angiography has been demonstrated to have high sensitivity for the detection of CHD and therefore may be suitable for screening purposes but there are concerns regarding radiation exposure.

Here we review the evidence for the use of potential screening strategies and the suitability of using such strategies to estimate risk of CHD in a young 'at risk' population.

1. Background

Coronary heart disease (CHD) remains the primary cause of death worldwide [1]. There is general agreement regarding the need for investigation of symptomatic patients suspected of CHD and subsequent instigation of therapies [2,3]. Screening asymptomatic individuals, however, is controversial but potentially allows early detection and more accurate risk estimation [4]. Estimating risk in any one individual is important not only for implementation of effective management strategies but also for reassurance and psychosocial security. In some cases, the first presentation of CHD maybe myocardial infarction (MI) or worse, sudden cardiac death (SCD) [5]. Screening may allow detection of occult CHD prior to such catastrophic events. That said, while these catastrophic events are often associated with CHD, silent or asymptomatic ischemia may account for more than 75% of ischemic episodes [6].

Identifying asymptomatic disease is only useful if disease progression can be altered [7]. Dietary and pharmacological interventions have been shown to reduce morbid cardiovascular events in asymptomatic individuals [8–11] although the published data did not specifically focus on a young cohort. Both the PREDIMED and the JUPITER studies enrolled participants without known CHD and were able to demonstrate a reduction of major cardiovascular events with administration of a Mediterranean diet and a statin respectively [8,10]. Screening of the general population is not cost effective [7], hence a mechanism is required to identify 'at risk' individuals.

Risk of CHD can be estimated in any individual via risk scores, and this can be further refined with functional and non-functional investigations. Here we review existing risk estimation tools, potential screening modalities and the appropriateness of implementing them in estimating risk of CHD in the young.

1.1. CHD in the 'young'

20% of men as young as 34 has been shown to have advanced coronary artery lesions [12]. The Framingham Heart Study demonstrated a rate of MI in men and women between the ages of 30–44 of 51.1/1000 and 7.4/1000 respectively [13]. A higher rate of MI of between 4% and 10% among those aged ≤45 years was reported in other studies with the vast majority of them being male [14–16]. 20% of MI has been demonstrated to occur in the young in an urbanized Australian population [17]. It of course stands to reason that the prevalence of asymptomatic CHD in the young is higher. There is some evidence to suggest that the prevalence may be even higher in a socioeconomically deprived area

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[18]. Despite this there is paucity of data on the prevalence of CHD and MI of the young.

The manifestation of developing heart disease at a young age can be psychologically and economically challenging not only for the individual but also for family members and especially siblings who may fear for their own health. Family history of premature CHD is known to be a risk factor for CHD [19,20] but is lacking in the widely accepted risk scores. The prevalence of family history of CHD in young MI patients has been reported as high as 64% [16,21,22]. In the Framingham Offspring Study, presence of sibling CHD increases the risk of a cardiovascular event in young adults by almost two fold [23]. It can therefore be hypothesized that siblings of patients who experience MI at a young age maybe at increased risk of asymptomatic CHD and future premature MI. Yusuf et al [20] demonstrated the importance of family history as a risk factor for MI particularly in young patients. With the aid of an effective screening tool premature CHD could potentially be identified in these individuals.

Screening asymptomatic patients for subclinical CHD could be equally important in young and old populations at risk. This paper, however, specifically focuses on a younger population because of significant socioeconomic impact from the consequences of CHD in this sub-group. The application of an effective screening strategy to the young is likely to lead to large clinical and social successes due to their increased potential life expectancy. As we have already discussed, screening an entire population to identify this group is neither cost effective nor feasible. Hence identification of the 'at risk' group is paramount in implementation of any screening tool.

2. Estimating risk

The contemporary "gold standard" for detection of CHD is the catheter-based coronary angiogram. Catheter based selective coronary angiography, however, is an invasive procedure that is associated with a small but significant risk of life threatening complications such as stroke, bleeding and MI [24]. Hence, catheter-based coronary angiography is not suitable as a screening tool or a method of estimating risk of CHD.

The concept of screening requires not only a cost-effective strategy but also clearly established treatment or disease modifying tools for the pathology being screened for [7]. It must also be safe and accurate, with high sensitivity in order to detect disease [7]. Screening must be targeted at disorders with high prevalence [7], and CHD appears to be perfectly positioned in this respect. Existing screening programs such as strategies aimed at detecting colorectal carcinoma via fecal occult blood testing (FOB) [25] and breast carcinoma via mammography [26] demonstrate many of these qualities. Controversies do exist regarding the use of FOB and mammography, however, overall they are regarded beneficial and potentially helpful in mitigating the risk of late detection and its consequences.

2.1. Risk scores

Risk scores are based on the premise that an individual's total burden of risk factors for CHD is more predictive than the level of any one particular risk factor. They predict a statistical population attributable risk but lack sensitivity or specificity in identifying an individual's risk [27].

Perhaps the most well known risk scoring system in the field of CHD originated from the Framingham Heart Study [28]. This study utilized observational data to formulate a risk estimation system based upon categorical variables where an individual's risk of having a CHD event is predicted at 10 years. The variables incorporated are age, presence of diabetes, smoking, blood pressure and total and LDL cholesterol. The receiver-operating characteristic (ROC) curve c-statistic of the model (using total cholesterol as a variable) is 0.73 and 0.76 in men and women respectively. A c-statistic of greater than 0.7 typically suggests a reasonable model [29]. There are a number of factors associated with this tool that may not necessarily make it universally applicable however. It was a single center study, based in the United States of America, and focused on a middle-aged white cohort with data from the early 70s.

The contemporary Interheart study sought to overcome some of these limitations [20,30]. It was a large case-control study of acute MI in 52 countries that attempted to represent every inhabited continent. The risk factors required for estimation of risk are age, apolipoprotein B:A1 ratio, smoking, passive smoking, presence of diabetes and hypertension. Validation of the score was demonstrated across an international population with consistent results across ethnic groups and geographic regions [30]. An area under the ROC curve c-statistic of 0.71 was established.

A risk scoring system developed specifically for Europe was published in 2003. The Systemic Coronary Risk Evaluation (SCORE) project was established due to concerns of applying the Framingham Risk Score to a European cohort [31]. Data were derived from 12 European countries and comprised over 200,000 people. Variables of the score are age, sex, blood pressure, smoking and either total cholesterol or cholesterol/HDL ratio. Contrary to the other two risk factors described above, SCORE aims to predict fatal cardiovascular risk rather than CHD risk. Areas under the ROC curve for this risk scoring system are between 0.71 and 0.84 [31] over the differing geographical locations studied.

2.2. Exercise stress test

The simple exercise stress test (EST) or exercise electrocardiograph (ECG) is a mainstay of investigating patients suspected of CHD, but it has also been utilized as a screening tool due to the correlation demonstrated between asymptomatic or silent ischemia and CHD mortality [32,33]. Rautaharju et al [32] and Ekelund et al [33] showed the potential of a positive EST to predict the risk of cardiac death. It appears, however, that the exercise capacity of an individual during exercise rather than ST changes, which is usually the factor used to discriminate between a normal and abnormal test, maybe the better discriminator of outcome [34].

Presence of risk factors strongly affects the pretest probability of an EST [35,36]. The relative risk of CHD mortality if an individual has 3 or more risk factors and an abnormal EST is 80 [35] with a 5.9 fold increased in CHD mortality for a smoker with silent ischemia [36]. EST can predict CHD death with high specificity of 89%, but this is countered against relatively poor sensitivity of 61%, as demonstrated by Gibbons et al [35].

The published literature is biased when describing the diagnostic accuracy of EST as most of the studies include symptomatic rather than asymptomatic individuals. The EST studies discussed above focus on mortality and hence cannot be used to evaluate the sensitivity and specificity of EST in detecting asymptomatic CHD. For this one would require all patients with a negative EST to undergo coronary angiography. A review suggests specificity and sensitivity of approximately 80% and 50% respectively of EST in an asymptomatic cohort [37]. Data from a meta-analysis, not exclusively looking at asymptomatic individuals, report wide variability with sensitivity and specificity of 68 $\pm$ 16% (SD) and 77 $\pm$ 17% (SD) respectively [38].

EST is usually only viable if the underlying ECG is normal and is dependent on an individual being able to exercise. Hence it is not suitable for all individuals.

2.3. Exercise myocardial perfusion imaging

Radionuclide myocardial perfusion imaging (MPI) may be utilized for the detection of CHD and thereby to estimate individual risk. The uptake of tracer by the myocardium can be detected and acts as a surrogate for the presence and magnitude of CHD. It can therefore also be used to identify ischemia of specific myocardial territories. Similar to

EST, however, the ability of MPI to detect ischemia is dependent on an adequate level of exercise and therefore heart rate being achieved [39]. Also, as with EST, certain ECG abnormalities can impair the predictive value of MPI. In particular left bundle branch block can provide false positives indicating myocardial ischemia of the septum [40].

Meta-analysis of weighted pooled results has demonstrated 87% (95% CI, 86%–88%) sensitivity of MPI for diagnosis of CHD but relatively poor specificity of 64% (95% CI, 60%–68%) [41]. This could potentially lead to further unnecessary invasive investigations due to false positives. If one restricts the positive definition of this modality to multiple myocardial distributions rather than single territories then the specificity increases to 87% (95% CI, 85%–89%) but at the cost of a much lower sensitivity of 44% (95% CI, 38%–49%) [41]. Conversely however the accuracy of MPI in detecting left main and triple vessel coronary artery disease is low [42]. Kwok et al [43] demonstrated that 26% of patients had triple vessel or left main coronary artery disease where the MPI was abnormal in only a single coronary territory.

The balance of evidence for the usefulness of MPI is weighted in the direction of symptomatic rather than asymptomatic individuals due to lack of data. Blumenthal et al [44] however conducted a study concentrating on asymptomatic siblings of persons with documented CHD. They demonstrated a high false positive rate of MPI with only 25% of participants who had a positive MPI having angiographically significant disease as defined by coronary stenosis greater than 70%.

As with any modality utilizing radiation, the exposure to the patient always needs to be taken into consideration. This is of particular importance with the cumulative exposure of repeated studies. Radiation doses between 8 mSv and 30 mSv have been reported for MPI [45] depending on the isotope and protocol choices.

2.4. Exercise stress echocardiography

CHD may be detected by demonstration of wall motion abnormalities with the aid of two-dimensional stress transthoracic echocardiography. Myocardial stress is typically induced with exercise or pharmacotherapy using agents such as adenosine, dipyridamole or dobutamine. Use of dobutamine has been associated with achieving the optimum combination of sensitivity and specificity [46].

Meta-analysis data, not exclusively concentrating on asymptomatic patients, suggest sensitivity and specificity of 85% (95% CI, 83%–87%) and 77% (95% CI, 74%–80%) respectively [41]. Marwick et al [47] have validated a high positive predictive value of 89% for stress echocardiography, but this was offset with a relatively low negative predictive value of 61%. In addition Marwick et al [47] reported reduced sensitivity of stress echocardiography in patients unable to tolerate dobutamine and therefore unable to reach target heart rate. The negative predictive value of stress echocardiography for prediction of MI and cardiac death however appears to be better at 98% [48].

Once again data on the asymptomatic cohort is lacking. In a small study conducted by Bacci et al [49], on 35 asymptomatic patients with type 2 diabetes mellitus, the sensitivity and specificity of stress echocardiography was demonstrated to be 21% and 94% respectively. This may not be applicable to a non-diabetic cohort however, and the diagnostic accuracy of stress echocardiography in an all comer asymptomatic cohort is unknown.

Unlike MPI which can be semi-automated, the interpretation of stress echocardiography is subjective and dependent on the experience of the clinician [50]. Certain patient characteristics such as presence of left ventricular hypertrophy, left bundle branch block and high body mass index may be associated with erroneous results and therefore preclude its use in certain patient groups [47].

The use of stress echocardiography as a screening test for CAD may be appropriate given the relative high sensitivity and specificity that have been demonstrated. Also it has been shown to be at least as cost effective as MPI [51] but without the added potential risk of radiation that would be associated with MPI.

2.5. Coronary artery calcium scoring via computer tomography (CT)

Currently 64-detector multidetector row computer tomography (MDCT) can be used to quantify coronary artery calcification (CAC) and allow representation via the Agaston score [52]. The sensitivity of CAC for detection of coronary stenosis ≥50% has been demonstrated to be as high as 91% but with a high variance of between 68 and 100% [53]. Specificity in the literature is reported to be as low as 49% but again with a wide range between 21 and 100% [53]. Similarly high negative predictive values of up to 100% and 97% with low positive predictive values of 66% and 62% in females and males respectively have been reported although this was for a low threshold score of between 0 and 20 [54]. As with many modalities the sensitivity drops with increasing threshold cut off CAC scores, and Budoff et al [55] have shown a sensitivity of 98% for CAC score > 0 and as low as 60% for CAC score of >400. There is a correlation between age and degree of coronary calcium with higher CAC scores found in higher age groups [54]. Haberl et al [54] demonstrated an area under the ROC curve of >0.75 for all age groups for coronary stenosis ≥50%.

CAC has been shown to predict CHD events in an asymptomatic cohort with a relative risk of 10.5 and 2.6 in men and women respectively [56]. The accuracy of prediction for future CHD events appears to be related to the degree of coronary calcification with a sensitivity of 89% and 53% for CAC threshold cut off score of 100 and 680 respectively [57]. CAC appears a better predictor of mortality over the traditional risk scores described above and is also able to accurately reclassify risk from intermediate to low and high risk [58,59].

2.6. Coronary CT angiography (CCTA)

CT can be utilized not only to determine the amount of calcium burden but also allows indirect visualization of the coronary arteries and therefore filling defects. Although MDCT scanners have high temporal resolution image acquisition, and therefore quality, it is still dependent on achieving a low enough heart rate, typically around 60–70 beats/min. It involves injection of iodinated contrast and therefore maybe contraindicated in certain individuals such as those with history of contrast allergy.

When considering the sensitivity and specificity of CCTA it is common for the literature to include evaluation at the patient level (i.e. patient has significant CHD or not) and at the segment level (accuracy of identifying site of CHD). For asymptomatic patients, the literature concentrates on patient level evaluation. With respect to patient level evaluation, Budoff et al demonstrated high sensitivity for CCTA of 95% (95% CI, 85%–99%) with modest specificity of 83% (95% CI, 76%–88%) for detection of ≥50% coronary artery stenosis [60]. Positive and negative predictive values were 64% and 99% respectively. Miller et al however established a lower sensitivity of 85% (95% CI, 79%–90%) with a higher specificity of 90% (95% CI, 83%–94%) [61]. Meanwhile Meijboom et al revealed the highest sensitivity of 99% (95% CI, 98%–100%) but with a correspondingly low specificity of 64% (95% CI, 55%–73%) [62]. A systemic review published in 2008 confirms the high sensitivity of CCTA at 98% with comparatively low specificity of 88% [63].

CCTA has been utilized to detect asymptomatic CHD in young adults. Ha et al demonstrated CHD in a population of adults under the age of 40 years with a prevalence of >10% [64]. They also illustrated increasing prevalence in higher risk groups that were determined via a risk scoring tool.

The utility of CCTA extends beyond the detection of ≥50% coronary artery stenosis as even the detection of nonobstructive (≤50% coronary artery stenosis) plaque allows risk to be predicted due to the relationship between nonobstructive coronary plaque and increased mortality [65,66]. Other imaging modalities such as intravascular ultrasound and optical coherence tomography have been demonstrated to be useful in predicting the vulnerability of these mild plaques and thereby allow prediction of future acute coronary syndromes [67,68]. These

complementary imaging modalities are, however, invasive and therefore not suitable for screening.

Limitations of this modality include patient factors such as tachycardia, arrhythmias and inability to breath hold. As with many modalities increasing age can reduce the effectiveness and in the case of CCTA severe coronary calcification, which often coexists in the elderly, can interfere with image reconstruction. Radiation dose was an initial concern in the previous generations of MDCT scanners with effective doses up to 10.5 mSv [69]. With contemporary technology, however, the radiation dose can be reduced to well below 2 mSv, which approximates to the Australian annual background radiation dose [70]. That level of radiation exposure is estimated to result in an excess lifetime cancer risk of approximately 42/100 000 men and 62/100 000 women [69].

3. Current practice guidelines

3.1. American College of Cardiology Foundation/American Heart Association (ACC/AHA)

The ACC/AHA Task Force Practice Guidelines discuss screening for asymptomatic cardiovascular disease using the modalities described above [71]. The use of EST is suggested for intermediate-risk (6–10% 10 year risk) adults but only with a class IIb recommendation, and importance is given to non-ECG markers as a surrogate for a positive test such as exercise capacity. Stress echocardiography is not recommended, and the use of MPI is suggested only for those with diabetes or for those with a strong family history of CHD but again with a relatively weak class IIb recommendation. They suggest CAC to guide risk assessment in individuals at intermediate (10–20% 10-year risk) risk (class IIa recommendation) and low to intermediate (6–10% 10-year risk) risk (class IIb recommendation) but not for low (<6% 10-year risk) risk. CCTA was not recommended as a screening tool due, mainly, to a lack of evidence.

3.2. European Society of Cardiology (ESC)

The recommendation for the use of EST in cardiovascular risk assessment by the ESC is comparable to that of the ACC/AHA with a class IIb recommendation and similar emphasis focused on non-ECG markers [72]. The ESC suggests use of CAC for cardiovascular risk assessment in asymptomatic adults at moderate (SCORE risk assessment 1— < 5% 10-year risk) risk with a grade IIa recommendation and alludes to the use of CCTA in the same group [72].

4. Discussion

Here we have presented various potential modalities and tools that can be used to estimate the risk of CHD and related mortality of an individual. Most of the data discussed however were not derived from studies aimed at screening asymptomatic patients and concentrates on patients aged over 50 years of age. As a result of this lack of data it is difficult to objectively review the modalities discussed above when considering their use for potential risk estimation in an asymptomatic cohort, and therefore if the aim is to define the risk of CHD in a young 'at risk' group the application of these data to formulate a screening tool may not be appropriate.

If we hypothesize that a substantial number of patients with a strong family history of MI have significant CHD despite being asymptomatic then early detection of disease by imaging and non-invasive functional tests may have a significant role in primary prevention and thereby lead to improved long term outcome. Currently available risk predictive algorithms may not be accurate in predicting the presence of CHD as detected on CCTA. Risk scores are a good tool in predicting population attributable risk but poor at demonstrating individual risk.

The anxiety associated with discovering premature CHD in a sibling should not be underestimated. Nor should the reassurance of knowing one does not have critical CHD. In order to do this however a screening modality is required which has a high sensitivity and hence a low false negative rate but at the same time must also have sufficient specificity and therefore a low false positive rate. As we have illustrated above CCTA appears to be well positioned in this respect with very high sensitivity and negative predictive value, but without sacrificing specificity.

EST remains the most widely used and accessible non-invasive preliminary investigation but due to the poor relative sensitivity, with a wide variability, warrants further scrutiny. In any case it is usually performed as part of exercise stress echocardiography and exercise MPI. The high sensitivity of MPI appears to lend itself well to screening purposes, but it exposes the individual to radiation without the benefit of the high specificity of CCTA. Stress echocardiography has a comparable sensitivity to MPI, at least in a symptomatic cohort, but has the advantage of a lack of radiation.

Currently CCTA does not have a strong recommendation by the AHA or ESC for the purposes of CHD screening, but there is increasing momentum for its use in this cohort which is likely being driven by reducing radiation exposure and costs. As a result there are varying practices with the use of CCTA. In the past, screening via CCTA or CAC was discouraged in view of concern regarding the radiation dose. As discussed above, however, the radiation dose of this modality has decreased significantly in recent times due to advances of CT technology and better scanning protocols making it more attractive as an investigational tool.

5. Summary

The prevalence of CHD in the young is not insignificant and is higher among those with a family history of MI. Assessing these individuals further with risk score estimation and screening investigations may allow the identification of a high risk group in whom the risk can be modified and future adverse events prevented. The screening tools chosen for this task should abide by the requirements of a suitable screening strategy. Currently available clinical risk score lacks specificity and sensitivity while functional stress tests lack strong clinical data for its sensitivity and specificity. CAC has emerged as a more reliable risk predictor in comparison with conventional risk assessment modality. CCTA is also a potential screening tool, but it lacks clinical data, and it comes with ionizing radiation, which has been a concern in the past.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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