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

Nadim Shah *, Kean Soon, Chiew Wong, Anne-Maree Kelly

Western Health, Victoria, Australia

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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

* Corresponding author at: Department of Cardiology, Western Hospital, Footscray, 3011, Victoria, Australia. Tel.: +61 414 636 080; fax: +61 3 8345 7357.
E-mail address: nadim.shah@gmail.com (N. Shah).

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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