REVIEW

Screening for coronary artery disease in asymptomatic individuals: Why and how?

Pourquoi et comment dépister la maladie coronaire chez le sujet asymptomatique ?

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Summary Cardiovascular disease is still the main cause of death in the world, and coronary artery disease is the largest contributor. Screening asymptomatic individuals for coronary artery disease in view of preventive treatment is therefore of crucial interest. Apart from established risk scores based on traditional risk factors such as the Framingham or SCORE risk scores, new biomarkers and imaging methods have emerged (high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2 and secretory phospholipase A2, coronary artery calcium score,

Abbreviations: ABI, ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; BARI-2D, bypass angioplasty revascularization investigation 2 diabetes; CACS, coronary artery calcium score; CI, confidence interval; CIMT, carotid intima-media thickness; COURAGE, clinical outcomes utilizing revascularization and aggressive drug evaluation; ESC, European Society of Cardiology; FRS, Framingham risk score; hs-CRP, high-sensitivity C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2; MESA, Multi-Ethnic Study of Atherosclerosis.
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Coronary heart disease: the leading cause of death worldwide

Despite an important reduction in cardiovascular mortality in western countries [1,2], cardiovascular diseases are still the main causes of mortality in the world. In 2010, one in four deaths was attributable to ischaemic heart disease or stroke, compared to one in five in 1990 [3]. Likewise, in Europe, cardiovascular diseases were responsible for more than half of deaths in women and 42% of deaths in men, mainly due to coronary heart disease [4]. Data are similar in low-income countries, with more than 12 million deaths related to cardiovascular causes [5].

Why should we screen asymptomatic individuals for cardiovascular disease?

Atherosclerosis is a slowly progressing disease, characterized by a long asymptomatic period of several decades. Lipid-rich plaques develop in the arterial vessel walls and may be revealed by typical symptoms, such as angina pectoris or intermittent claudication, in stable patients. However, the disease can also be revealed by an acute event, such as an acute coronary syndrome or stroke, without any preceding symptoms and, in the worst case, by sudden death. It is therefore crucial to develop a screening strategy in asymptomatic individuals before potentially fatal events occur.

Cardiovascular screening in asymptomatic individuals aims at the identification of intermediate- or high-risk individuals. The objective is to initiate strategies that would reduce their incidence of ischaemic events (including myocardial infarction) and ultimately cardiovascular death. Different preventive strategies have been proposed.

First, cardiovascular risk can be reduced by optimal risk factor management and lifestyle changes. Smoking cessation is a cornerstone of cardiovascular disease prevention and represents a public health problem because of the effect of passive smoking [6]. All smokers should be encouraged to quit smoking by various smoking-cessation therapies [7]. Furthermore, a healthy diet and regular exercise are part of the general cardiovascular prevention measures applicable to the entire population [8,9]. Thus, around half of the reduction in deaths from coronary heart disease is attributable to better management of cardiovascular risk factors and the other half to advances in medical treatments [10].

Second, a preventive medical treatment can be considered before an acute cardiovascular event occurs. However, in a low-risk population, further risk assessment using novel biomarkers is not cost-effective. Furthermore, in a high-risk population, pharmacological treatment is usually mandatory for the majority of the patients and further risk assessment will not change this strategy. Conversely, in intermediate-risk individuals, further risk assessment by novel risk markers could refine cardiovascular risk and, in case of positive screening, indicate preventive pharmacological treatment. The effectiveness of statin treatment for primary prevention in a population with cardiovascular risk factors has been shown in large meta-analyses [11,12]. Statins reduce mortality and the risk of major cardiovascular and cerebrovascular events in people without known cardiovascular disease. Similarly, the effect of blood pressure reduction by antihypertensive drugs on cardiovascular disease prevention in a population without established cardiovascular disease has been demonstrated extensively, irrespective of the class of blood pressure lowering drugs used [13].

Another, more invasive, strategy could be ‘preventive’ coronary revascularization. However, most acute myocardial
Cardiovascular risk prediction by traditional risk factors

In 1948, a large, ongoing, longitudinal observational study was started in Framingham (USA) to study cardiovascular disease. Results allowed the definition of, among other things, the well-known Framingham risk score (FRS). Six easily available items, namely sex, age, cigarette smoking, blood pressure, lipid profile and diabetes mellitus, allow an estimation of the relative and absolute 10-year risk for coronary heart disease [18].

Cardiovascular risk is different across populations and a risk score is only applicable in the population it was validated in [19]. In fact, in Europe, mortality rates differ from North to South and from East to West, being higher in the Northeast part of Europe. This geographical gradient needs to be taken into account when assessing cardiovascular risk for primary prevention [20]. Thus, similarly to the FRS, the European Society of Cardiology (ESC) developed a risk score to predict the 10-year risk of fatal cardiovascular disease, stratified by high- or low-risk regions, called SCORE (Fig. 1 [22]). The ESC guidelines on cardiovascular disease prevention in clinical practice recommend the use of this score for total risk estimation in asymptomatic adults without evidence of cardiovascular disease [22]. Similarly, the QRISK2 score, an updated version of the QRISK score, should be used to estimate the 10-year risk of cardiovascular disease of the population in the United Kingdom, because of its good discriminative and calibration properties [23].

These risk scores are not, however, perfect prediction tools—the performance of the SCORE method is given by a receiver operating curve area of 0.81 (95% CI 0.80–0.82) in high-risk regions and 0.74 (95% CI 0.72–0.76) in low-risk regions, and should be further improved. Intense efforts are therefore being made to improve their discriminative performance, by the inclusion of novel biomarkers or developing new imaging techniques.

New methods for the assessment of cardiovascular risk

Several new methods for risk assessment, using either imaging or biomarkers, have been developed over the past decade, with variable success. We review below the evidence for the main methods in the context of the recently published Guideline on the Assessment of Cardiovascular Risk from the American College of Cardiology (ACC) and the American Heart Association (AHA) [24].

Ankle-brachial index

One of the simplest and most cost-effective markers of risk is the ankle-brachial index (ABI). The result is available immediately and can be interpreted at the patient’s bedside. In 2008, Fowkes et al. [25] reported, in a meta-analysis that included 16 population cohort studies with 48,294 healthy individuals, that a low ABI (≤ 0.9) was associated with increased 10-year cardiovascular mortality after adjusting for FRS (HR 2.9, 95% CI 2.3–3.7 for men and HR 3.0, 95% CI 2.0–4.4 for women). Nevertheless, the increase in c-statistics, compared with those using FRS alone, was only modest and not significant in men (from 0.646 to 0.655), but increased from 0.605 to 0.658 in women. Moreover, a recent double-blind randomized controlled trial that screened 28,980 asymptomatic participants without known cardiovascular disease on the basis of ABI for treatment with either low-dose aspirin or placebo did not find any improvement in outcomes after a mean follow-up of 8.2 years [26]. Guidelines agree that ABI has a class Iib (AHA/ACC) or class
Ila (ESC) indication in asymptomatic intermediate-risk individuals.

**High-sensitivity C-reactive protein**

One of the most studied emerging risk factors is probably high-sensitivity C-reactive protein (hs-CRP). A large meta-analysis [27] has shown that CRP concentration predicted vascular death in 160,039 individuals without known vascular disease after adjustment for age and sex. However, it predicted non-vascular death, for example death from cancer or respiratory disease, to the same extent. Thus, the actual value of higher CRP concentrations in the individual patient setting remains unclear and the recent ESC [22] and ACC/AHA [24] guidelines did not recommend hs-CRP measurement in asymptomatic low- or high-risk individuals (class III, level B), but suggested it might be useful for refining the risk in intermediate-risk individuals (class IIb, level B).

**Lipoprotein-associated phospholipase A2**

Lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme that is expressed by inflammatory cells in atherosclerotic plaques, plays a major role in the progression of the disease by producing pro-inflammatory and pro-apoptotic mediators via oxidized phospholipids hydrolysis. The result is a sustained inflammation at the plaque level with an expansion of the necrotic core. In 2006, Folsom et al. [28] reported a series of case-cohort studies including 15,792 participants followed up for 5 years for incident coronary heart disease. Several novel biomarkers were assessed as well as the traditional risk factors. Although Lp-PLA2 was associated with incident coronary heart disease after established risk factor adjustment (HR 1.17, P = 0.02), the c-statistic increment was only moderate, from 0.774 to 0.780. Another study indicated that Lp-PLA2 predicted survival free of coronary events in
a population of 1077 individuals without known coronary heart disease [29]. Similarly, Tsimikas et al. [30] published, in 2009, data from 765 subjects followed up prospectively for 10 years. They showed a significant relationship between Lp-PLA2 activity and incident cardiovascular disease, but only a modest increase in c-statistic, from 0.717 to 0.737 ($P=0.31$), compared to established risk factors alone. One of the largest meta-analyses summarized data from 79,036 individuals participating in 32 prospective studies [31]. After adjustment for conventional risk factors, risk ratios for incident coronary heart disease were 1.09 (95% CI 1.02–1.16) for Lp-PLA2 mass and 1.03 (95% CI 0.95–1.12) for Lp-PLA2 activity. Finally, a large randomized, double-blind trial assigned 15,828 patients with stable coronary heart disease to receive darapladib, a selective oral inhibitor of Lp-PLA2, or placebo [32]. After a median follow-up of 3.7 years, there was no significant difference in the primary endpoint, a composite of cardiovascular death, myocardial infarction or stroke (HR 0.94, 95% CI 0.85–1.03, $P=0.199$). These data meant that Lp-PLA2 assessment was only recommended for patients at high risk for a recurrent acute atherothrombotic event in the 2012 ESC guidelines [22] (class Ib, level B), and it was not included in the 2013 AHA/ACC guideline [24].

**Coronary artery calcium score**

The assessment of coronary artery calcium by ultrafast computed tomography and its quantification by a score was first described by Agatston et al. [33] in 1990. A coronary artery calciumification was defined as a hyper-attenuating lesion >130 Hounsfield units with an area ≥1 mm². A score for each region of interest is calculated by multiplying the lesion area (mm²) by a density factor (between 1 and 4). The total coronary artery calcium score (CACS) is determined by adding up each of these scores for 20 slices, with a slice thickness of 3 mm. Since then, several other scoring systems have been proposed: the volume score method and the calcium mass score. Two methods are used for the assessment: electron beam computed tomography and, more recently, multidetector computed tomography [34].

In 2005, Taylor et al. [35] published data from a non-referred cohort of 2000 healthy men and women aged between 40 and 50 years old and with a 3-year follow-up. Incident acute coronary syndromes and cardiac death occurred in 0.16% of the men without coronary calcium versus 1.95% of the men with coronary calcium ($P<0.0001$). This risk was incremental across increasing coronary artery calcium tertiles (HR 4.3 per quartile, $P=0.036$) after risk factor adjustment. Likewise, Detrano et al. [36] reported an increase in major cardiac events across different calcium score categories, in 6722 participants of different ethnic origins without known coronary artery disease at baseline, after a mean follow-up of 3.8 years ($P<0.001$). Raggi et al. [37] studied the prognostic value of CACS in 35,388 elderly asymptomatic participants without known coronary artery disease and a mean of 5.8 years of follow-up. Survival decreased across age decades and with higher CACS categories ($P<0.0001$). These data showed a relation between high CACS values and an increasing cardiovascular disease risk in healthy individuals, but do not demonstrate an added value of CACS over established risk factor scores.

In 2004, Greenland et al. [38] evaluated the additional prognostic value of CACS in 1312 asymptomatic participants without known coronary heart disease or diabetes after 7 years of follow-up. Eighty-four patients experienced myocardial infarction or death from coronary heart disease, and CACS predicted these events only in individuals with an FRS >10% ($P<0.001$), supporting its value for risk stratification within subjects at intermediate risk. Receiver operating curves showed an increase in area under the curve — and therefore in diagnostic performance — from 0.63 with FRS alone to 0.68 with FRS in combination with CACS ($P<0.001$). Similarly, a meta-analysis that included nine studies evaluated the value of adding CACS to established risk factors in asymptomatic subjects [39]. It showed an improvement in the c-statistic from 0.05 to 0.13 and a net reclassification improvement from 14 to 25%.

The subgroup deriving the highest value for CACS reclassification has been evaluated in a large population-based cohort of 5878 asymptomatic participants without known coronary heart disease or diabetes (mean follow-up of 5.8 years) [40]. The reclassification benefit after adding CACS to established risk factors was most evident in intermediate-risk categories (defined by a 3–10% 5-year risk of incident coronary heart disease), because 77% of the participants were classified in the extreme risk categories, compared to 69% with FRS alone. These data were confirmed in the Rotterdam study [41] that comprised 2028 asymptomatic participants evaluated after a median of 9.2 years of follow-up. In this study, 52% of the patients of the intermediate-risk group (10–20% by FRS) were reclassified after adding CACS evaluation. Finally, Erbel et al. [42] published, in 2010, the outcomes of 4129 individuals with no coronary artery disease at baseline. The net reclassification improvement for the intermediate-risk group (10–20% according to FRS) after the addition of CACS was 21.7% ($P=0.0002$); the receiver operating curve increased from 0.681 to 0.749 ($P=0.003$) with CACS, and CACS improved prediction of coronary death or non-fatal myocardial infarction when added to conventional risk scoring. A 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort has shown very low event rates in those with zero coronary artery calcium [43]. Ultimately, CACS may help match statin therapy to absolute cardiovascular disease risk [44].

**Coronary artery calcium score limitations**

CACS is assessed by computed tomography, which uses X-rays and exposes the patient to ionizing radiation. The average effective dose ranges from 0.7 to 1.8 mSv, around 10 times the effective dose of a chest X-ray, but it has recently been shown that low-dose scanning (0.37 mSv) can be as effective as the standard dose [45]. However, in cardiovascular risk assessment, a certain proportion of the screened individuals are healthy and this radiation exposure must be justified. Kim et al. [46] studied, in 2009, the lifetime excess cancer risk due to radiation exposure from a single examination at the age of 40 and showed that for a median dose of 2.3 mSv, this risk reached nine cancers per 100,000 men and 28 cancers per 100,000 women. Another issue concerns cost-effectiveness, because the cost of a computed tomography examination is approximately 100 US$. A recent cost-effectiveness study suggested that screening with CACS
in intermediate-risk men is superior to the current practice [47].

The ESC prevention guidelines [22] state that CACS ‘should be considered’ in intermediate-risk asymptomatic individuals for cardiovascular risk assessment (class IIa, level B). To the same extent, the AHA/ACC guideline [24] indicates a class IIb, level B for CACS use in this setting.

**Carotid intima-media thickness**

Recent evidence suggests that carotid intima-media thickness (CIMT) has a poor added value when combined with the FRS to refine cardiovascular risk assessment in asymptomatic individuals. A recent meta-analysis pooled data from 14 population-based cohorts with 45,828 individuals without known cardiovascular disease [48]. Overall, the net reclassification improvement was small (0.8%, 95% CI 0.1–1.6%), even when considering only intermediate-risk individuals (3.6%, 95% CI 2.7–4.6%). Thus, there is little reclassification benefit after adding CIMT to FRS for predicting the 10-year absolute risk for myocardial infarction or stroke, with c-statistics of 0.759 versus 0.757. Furthermore, CIMT measurement lacks standardization and there are concerns regarding interobserver variability [49]. As a consequence, the AHA/ACC guideline [24] advised against the use of CIMT in this setting (class III, level B).

**What is finally left of the new methods for risk assessment?**

Overall, the added value of emerging risk markers on top of standard risk score appears limited. A large head-to-head comparison of six novel risk markers has included 1330 intermediate-risk participants without diabetes of the MESA cohort [50]. Intermediate risk was defined by 5–20% risk according to FRS, and the primary outcome was incident coronary heart disease defined as myocardial infarction, angina followed by revascularization, resuscitated cardiac arrest or death from coronary heart disease. After a median 7.6-year follow-up, CACS, ABI, hs-CRP and family history were independently associated with incident coronary heart disease in multivariable analyses (HR 2.60, 95% CI 1.94–3.50; HR 0.79, 95% CI 0.66–0.95; HR 1.28, 95% CI 1.00–1.64 and HR 2.18, 95% CI 1.38–3.42, respectively). CIMT and brachial flow-mediated dilation were not associated with incident coronary heart disease in multivariable analyses (HR 1.17, 95% CI 0.95–1.45 and HR 0.95, 95% CI 0.78–1.14, respectively). To compare the added value of each marker to the FRS, areas under the curve were calculated for each of them: CACS showed the biggest increment in c-statistic, from 0.623 to 0.784 (P < 0.001). The five other markers showed only modest increments in c-statistics (Fig. 2) [50].

As a consequence, their systematic use is currently not recommended. The AHA/ACC guideline from 2013 [24] stated that if, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of one

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**Figure 2.** Receiver operator characteristic curves showing area under the curve for A. incident coronary heart disease; and B. incident cardiovascular disease, in intermediate-risk MESA participants. From Yeboah et al. [50] with permission. aC-statistics for FRS alone, 0.623; FRS plus coronary artery calcium, 0.784 (P < 0.001); FRS plus intima-media thickness, 0.652 (P = 0.01); FRS plus flow-mediated dilation, 0.639 (P = 0.06); FRS plus high-sensitivity C-reactive protein, 0.640 (P = 0.03); FRS plus family history, 0.675 (P = 0.001); and FRS plus ankle-brachial index, 0.650 (P = 0.01). bC-statistics for FRS alone, 0.623; FRS plus coronary artery calcium, 0.784 (P < 0.001); FRS plus intima-media thickness, 0.652 (P = 0.01); FRS plus flow-mediated dilation, 0.639 (P = 0.06); FRS plus high-sensitivity C-reactive protein, 0.640 (P = 0.03); FRS plus family history, 0.675 (P = 0.001); and FRS plus ankle-brachial index.
or more of the four markers (family history, hs-CRP, CACS, ABI) may be considered to inform treatment decision-making (class IIb, level B). Current ESC guidelines for cardiovascular disease prevention [22] globally agree with this statement and provide a class IIa, level B recommendation for CACS, ABI and CIMT and a class IIb, level B recommendation for hs-CRP and Lp-PLA2 in this setting.

Conclusions

Preventive treatment of coronary artery disease is effective and justifies screening for this frequent and potentially lethal disease in asymptomatic individuals. The major part of cardiovascular risk assessment can be readily performed using simple risk scoring systems based on established cardiovascular risk factors and requires simple biological measurements and clinical information. The added value of new clinical (ABI), biological (hs-CRP and Lp-PLA2) and imaging (CACS and CIMT) risk markers is limited and can only be recommended in intermediate-risk populations in order to further refine their cardiovascular risk and potentially change their treatment strategy. The most convincing data pertain to CACS, but we should keep in mind the costs and the radiation exposure of this technique and remember that identification of high-risk patients should not be equated with an indication for revascularization in otherwise stable asymptomatic individuals.

Disclosure of interest

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References


