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The SHAPE Guideline: Ahead of Its Time or Just in Time?

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Abstract In 2006, a grass roots movement called SHAPE (Screening for Heart Attack Prevention and Education) published a novel practice guideline for cardiovascular screening in the asymptomatic at-risk population. It suggested the use of noninvasive tests for subclinical atherosclerosis in cardiovascular risk assessment to target intensified preventive care to those at highest risk. The SHAPE guideline received much attention but not as much support from the "official" medical societies. However, subsequent studies published since 2006 have now provided strong supportive evidence for the strategy spearheaded by the SHAPE guideline. Indeed, the latest guidelines issued jointly by the American Heart Association and the American College of Cardiology have elevated recommendation levels for noninvasive imaging of subclinical atherosclerosis. This change is widely viewed as a significant step toward the SHAPE guidelines. The background for SHAPE and the evidence behind the recommendation to use coronary artery calcium score measured by computed tomography, carotid intima-media thickness and plaque measured by ultrasound, and ankle-brachial index in cardiovascular risk assessment is reviewed in this article.

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Introduction

Atherosclerosis with thrombosis superimposed, known as *atherothrombosis*, is the main cause of myocardial infarction, coronary death, heart failure, and large-artery stroke [1–3]. The development of thrombosis-prone atherosclerotic plaques, also known as high-risk or vulnerable plaques [4], in the coronary and carotid arteries is a leading cause of death and severe disability globally [5, 6]. Regrettably, sudden and unexpected death is still a common first manifestation of atherosclerotic cardiovascular disease (CVD) [7••]. Identifying individuals at risk for future cardiovascular events affords an opportunity for risk reduction and thus remains a major imperative for healthcare professionals [8–10].

Causal and modifiable risk factors for atherosclerotic CVD are well known (smoking, dyslipidemia, high blood pressure, diabetes, etc.) and account for most heart attacks in both sexes [11, 12••]. However, contrary to expectation, the risk factors causing atherosclerotic CVD are not very useful in identifying people at high risk of getting the disease because their predictive value is limited [13–16]. Most myocardial infarctions and strokes occur in individuals who would be misclassified as low or intermediate risk by the traditional risk factor–based approach, such as the Framingham risk scores [17]. For example, in the Framingham Heart Study [18], the Physicians' Health Study [19], the Women's Health Study [20], and the Northwick Park Heart Study [21], >75% of all hard coronary events occurred in people misclassified at low or intermediate risk and, consequently, not offered optimal preventive therapy. Conversely, others are misclassified as high

risk and advised to take risk factor–lowering drugs they don't need, and must stay on them for the rest of their life. These findings, as shown by Wald and Law [14] remind us that, although exposure to causal risk factors is necessary, the mere presence of risk factors is not sufficient for developing CVD. Perhaps more importantly, the level of susceptibility to these factors, and the presence or absence of unknown protective factors, play a crucial role in defining the outcome. Unfortunately, genetic testing for susceptibility, although potentially promising, has not proven useful for risk stratification [22•, 23] and cannot be recommended at this time [24••].

Better detection of at-risk individuals may be achieved by visualizing the diseased arterial wall rather than just assessing risk factors for getting the disease [25••]. Atherosclerosis develops silently over decades before symptoms occur, offering unique opportunities for early detection and personalized prevention. Subclinical atherosclerosis can be detected and quantified non-invasively, to show the cumulative effect of all known and unknown risk and susceptibility factors combined. Such a holistic approach to the primary prevention of atherosclerotic CVD constitutes the foundation of the Screening for Heart Attack Prevention and Education (SHAPE) paradigm.

SHAPE: Ahead of Its Time?

In 2006, the SHAPE Task Force introduced a risk assessment algorithm incorporating noninvasive tests for subclinical atherosclerosis to augment risk factor–based risk stratification in asymptomatic subjects between the ages of 45 to 75 years in men and 55 to 75 years in women, excluding those at very low risk or at high risk (Fig. 1) [10]. In June 2009, Texas Governor Rick Perry signed off on the Texas Heart Attack Prevention Bill introduced by Representative Rene Oliveira, mandating health-benefit plans to cover noninvasive screening for subclinical atherosclerosis. This bill grew out of the 2006 SHAPE Task Force guidelines and became effective September 1, 2009; an earlier version of the bill had been rejected in 2007. This generated a mixed reaction from health care professionals and others, much of which played out in the media. The critics argued that such an action is inappropriate because 1) the SHAPE guidelines were created by an ad hoc group and had not been explicitly endorsed by the American College of Cardiology (ACC) or the American Heart Association (AHA), and 2) SHAPE guidelines are not based on randomized controlled trials [26, 27]. However, the primary prevention guideline issued by the ACC and AHA in 2010 recommends sensible use of noninvasive tests for subclinical atherosclerosis [24••], in a manner largely similar to SHAPE, suggesting that SHAPE indeed was ahead of its time.

Ideally, legislative advocacy should not be the domain of ad hoc groups but is best achieved through the broader constituency of professional organizations. The Texas bill was not a SHAPE initiative, and SHAPE was not involved in lobbying efforts; on the contrary, it was Representative Oliveira who, after suffering a heart attack, reached out to SHAPE. Our professional organizations (ACC and AHA) have been slow in incorporating the wealth of data supporting the incremental value of imaging-guided risk assessment in specific subsets of patients. This fact, coupled with the reality of at-risk but yet unidentified and untreated subjects continuing to experience unheralded major cardiovascular events and reluctance of insurers to cover this service, provided an impetus for the SHAPE group to support the efforts of Representative Oliveira. Regrettably, some have chosen to ignore the evidentiary support and instead misconstrued the intensions of SHAPE. The SHAPE paradigm is the collective effort of many dedicated volunteers motivated by the best interests of their patients.

SHAPE: From Grass Roots to Society

SHAPE is a grass roots nonprofit organization with the mission of eradicating heart attacks. It grew from its predecessor, an Association for Eradication of Heart Attack, started by Dr. Morteza Naghavi, then on faculty at the Texas Heart Institute. The SHAPE Task Force comprises a diverse group of health care professionals from varied backgrounds who volunteer their time and expertise without any compensation; in fact many SHAPE members donated funds to support its mission. The SHAPE Task Force was galvanized into action because of the limitations of the current risk factor–based identification of asymptomatic individuals at risk for an unheralded acute cardiovascular event and because a large body of data supported the incremental prognostic value of subclinical atherosclerosis detection. One could reasonably argue that only the professional societies should develop practice guidelines because they provide the imprimatur of peer review and conflict-free evidence-based process. However, sensible guidelines developed by nonconventional groups such as the SHAPE Task Force should be judged on the merits of evidence base rather than on which group wrote the guidelines. It would be counterproductive to malign well-meaning volunteers who have assembled the evidence to support the proposed paradigm and are intent on improving cardiovascular prevention. Although some SHAPE Task Force members with imaging expertise could have a conflict of interest, many others, including the authors of this article, have no personal axe to grind and no conflict to disclose. Nevertheless, all potential conflicts of interest by

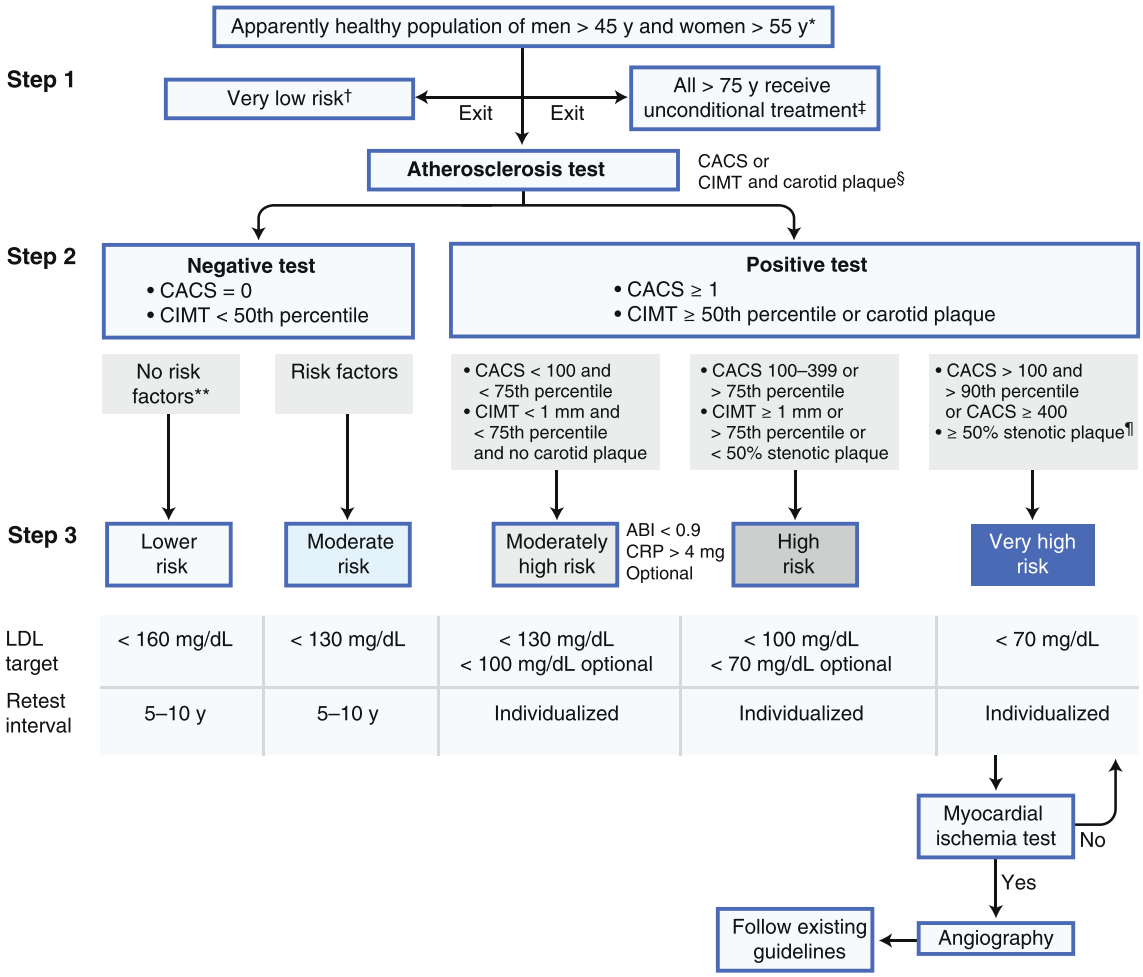

Fig. 1 Atherosclerosis test flow chart of the first SHAPE (Screening for Heart Attack Prevention and Education) guideline from 2006. ABI—ankle- brachial index; CACS—coronary artery calcium score; CIMT—carotid intima–media thickness; CRP—C-reactive protein; LDL—low-density lipoprotein. *No history of angina, heart attack, stroke, or peripheral arterial disease. †Must not have any of the following: total cholesterol level >200 mg/dL (5.18 mmol/L), blood pressure >120/80 mm Hg, diabetes mellitus, smoking, family history of coronary heart disease, or the metabolic syndrome. ‡Population aged >75 years is considered high risk and must receive therapy without testing for atherosclerosis. §Pending the development of standard practice guidelines. **High cholesterol, high blood pressure, diabetes, smoking, family history of coronary heart disease, or the metabolic syndrome. ¶For stroke prevention, follow existing guidelines. (*Data from* Naghavi et al. for SHAPE Task Force [10])

SHAPE members have been transparently disclosed [28]. After publication of the SHAPE Guideline in 2006 [10], a new structure was required, and SHAPE became the Society for Heart Attack Prevention and Eradication as we know it today.

Limitations of Risk Factors in Risk Assessment

Because the lifetime risk of cardiovascular events is quite high, one could consider the whole population at risk and implement preventive measures across the entire population. That makes sense for widespread promotion of a healthy lifestyle [12••]. However, at a practical level, that has proven to be an elusive goal for social, economic, and cultural reasons. Similarly, lifelong pharmacotherapy for all to manage dyslipidemia poses its own challenges of cost, accessibility, intolerance, and not to mention suboptimal adherence. If we had a uniformly effective, safe, easily available, and inexpensive intervention that would prevent most coronary heart disease (CHD) events, risk stratification would be unnecessary. Unfortunately, such an intervention does not exist. Furthermore, although the lifetime risk for CHD is quite high, it is far from 100%, and therefore unconditional treatment of all would expose a substantial number of individuals to the costs, inconvenience, and risks of lifelong pharmacotherapy without any benefit. Therefore, risk stratification to target aggressive prevention to those most at risk and avoid it in those with the least amount of risk makes sense.

The Framingham Heart Study has provided critical information about risk factors for CHD, many of them modifiable and targets of treatment [29]. The Interheart study showed that 90% to 95% of population-attributable risk of myocardial infarction is related to nine potentially modifiable risk factors all over the world [11]. However, what the study did not highlight is the fact that a large number of asymptomatic individuals who do not develop myocardial infarction (at least not in the next 5 to 10 years) also have risk factors [14] and, therefore, it is difficult to enforce intensive therapy and lifestyle modifications in the high-risk population based only on risk factors. Using simple and easily measurable risk factor variables, Framingham Risk Score can be determined that predicts the 10-year risk of CHD for a population, and subjects are divided into arbitrarily constructed low-risk (10-year risk <10%), intermediate-risk (10-year risk of 10% to 20%), and high-risk (10-year risk >20%) cohorts [29, 30]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines couple the intensity of treatment, predominantly focused on lipid modification and low-density lipoprotein cholesterol targets, to the magnitude of risk [30, 31]. Although these guidelines have never been validated through randomized controlled trials, their simplicity, low cost, and reasonable prognostic accuracy have made this approach the standard template for prevention. Further improvements in risk assessment could accrue from considering the family history and high-sensitivity C-reactive protein in what has become known as the Reynold's Risk Score; however, this too has not been validated in a randomized trial [19, 20].

The shortcomings of the Framingham/NCEP-ATP III risk assessment–management scheme need to be noted. This assessment rarely assigns a high risk score to women under the age of 70 years, making them ineligible for aggressive lipid modification even though their lifetime risk for CHD is nearly 40% [32]. There is considerable variability in the magnitude of atherosclerotic burden between individuals with similar level of risk factor exposure, presumably related to other known or unknown genetic and environmental risk factors [33], and this is relevant because the atherosclerotic burden impacts clinical outcome. Nasir et al. [34] reported that 79% of young men and women with a significant coronary atherosclerotic burden were not eligible for pharmacotherapy based on current NCEP-ATP III guidelines. A substantial number (60% to 75% in men and 90% in women) of unheralded cardiovascular events occur in low- and intermediate-risk groups that would not qualify for optimal preventive therapy under the current guidelines [17–21]. Akosah et al. [35] reported that 75% of previously asymptomatic subjects presenting with their first myocardial infarction had a Framingham risk score low enough that they would not have qualified for lipid-lowering therapy before their myocardial infarction. Recently, the AHA seems to have tackled this problem by lowering the threshold for high risk, implying more widespread use of risk-reducing drugs. However, although wider use of cheap, safe, and effective preventive medicine makes sense [36], we feel there is a more sensible way to deal with the problem.

Is Higher Sensitivity at the Expense of Specificity the Right Way to Go?

In 2001 and 2004, the NCEP-ATP III guidelines, which were endorsed by the AHA, defined high-risk individuals as having a 10-year risk of a hard CHD endpoint (myocardial infartion and coronary death) ≥20% [30, 31]. In a Scientific Statement on "Treatment of hypertension in the prevention and management of IHD" from 2007 [37], the AHA redefined high-risk patients as having ≥10% risk of a hard CHD endpoint, and this was repeated in an Expert Consensus Document from 2011 [38]. Then, in the 2011 updated guidelines from the AHA for the prevention of CVD in women, the ≥10% high-risk threshold was lowered further by changing the endpoint from "hard CHD" to the much more common endpoint "all CVD," which also includes coronary insufficiency, angina, stroke, transient ischemic attack, heart failure, and claudication [39•].

This arbitrary change in the definition of high risk will likely result in massive overtreatment and undue "high-risk" labeling of many otherwise healthy women. For example, a 65-year-old non-smoking, non-diabetic, non-hypertensive, non-obese woman with near ideal lipid levels (total cholesterol of 200 mg/dL and high-density lipoprotein cholesterol of 49 mg/dL) who lives an active lifestyle would now be classified as high-risk. In contrast, the same individual would be defined as low-risk by the 2010 American College of Cardiology Foundation (ACCF)/AHA [24••] and NCEP-ATP III guidelines [30, 31]. The new AHA women's guideline disregards the 2010 ACCF/AHA guidelines for assessment of cardiovascular risk in asymptomatic adults in whom testing for subclinical atherosclerosis such as coronary artery calcium (CAC) scoring by computed tomography (CT), carotid intima-media thickness (CIMT)/plaque by ultrasound, and ankle-brachial index (ABI) received a strong evidence-based (level IIa) recommendation [24••]. CAC scoring in risk assessment was also supported by the 2010 appropriate use criteria for cardiac CT released by nine professional medical organizations, including AHA and ACCF [40•]. Is it reasonable, cost-effective, and ethically acceptable to arbitrarily label millions of women as being "high-risk" for atherothrombotic cardiovascular events without testing them for subclinical atherosclerosis?

Testing for Subclinical Atherosclerosis

Although most of the population-attributable risk for myocardial infarction is related to several modifiable risk factors, their specificity is low because their prevalence is also high in those who never get CHD [41]. Intuitively, therefore, it makes sense to detect subclinical atherosclerosis, which is the anatomic substrate for all but a few CHD events, because its detection provides an integrated view of the cumulative exposure to known and unknown risk modifiers. The potential advantage of such an approach is that those without atherosclerosis could be spared risk factor–lowering drugs, whereas those with atherosclerosis could be recommended more aggressive risk factor modification, including pharmacotherapy. Subclinical atherosclerosis can be identified by noncontrast CT imaging of coronary arteries for calcification using the CAC score, B-mode ultrasound to measure CIMT and detect carotid plaque, and the ABI. CAC score serves as a noninvasive measure of coronary plaque burden in both genders and multiple ethnic groups [40•, 42••, 43••, 44]. The prognostic value of CAC score, independent of and incremental to that of Framingham Risk Scores, has been demonstrated in multiple studies, including ability to correctly reclassify a substantial number of people in the gray zone or intermediate-risk area [42••, 43]. Furthermore, a zero CAC score observed in 40% to 45% of asymptomatic subjects identifies a very low-risk cohort who can be spared aggressive pharmacotherapy (specifically, lipid-modifying therapy) and additional downstream testing for CHD [45]. Although a zero CAC score does not absolutely rule out coronary atherosclerosis, it identifies no or very low atherosclerotic burden. The major drawback of CAC scoring is radiation exposure, but with recent developments it can now be kept very low (<1.0 mSv).

B-mode ultrasound to measure CIMT and/or detect carotid plaque has the advantage of being risk free and could be more accessible for screening, but special technical expertise in performance and interpretation are required [46]. Prospective studies show that CIMT and plaque assessment provide incremental prognostic information to traditinal risk factor scoring, and improved risk classification has also been documented [47••, 48]. However, comparative studies in asymptomatic subjects have shown that CAC score provides a relatively greater incremental prognostic information compared to CIMT [49, 50].

An ABI<0.9 is considered diagnostic for lower extremity peripheral arterial disease (flow-limiting atherosclerosis) and associated with a high risk of developing other atherosclerotic manifestations. It is also true for the many asymptomatic individuals who live with a low ABI without knowing it. Asymptomatic ABI<0.9 provides predictive information beyond traditional risk factor scoring [51, 52••]. An ABI>1.4, indicating stiff and incompressible peripheral arteries and often associated with diabetes (medial arterial calcification), is also associated with increased cardiovascular risk but the exact mechanisms remain unclear [51, 52••].

To See Is to Understand–and Comply

Subclinical atherosclerosis detection has not been tested in randomized trials. However, observational data generally indicate that "seeing" subclinical atherosclerosis by the

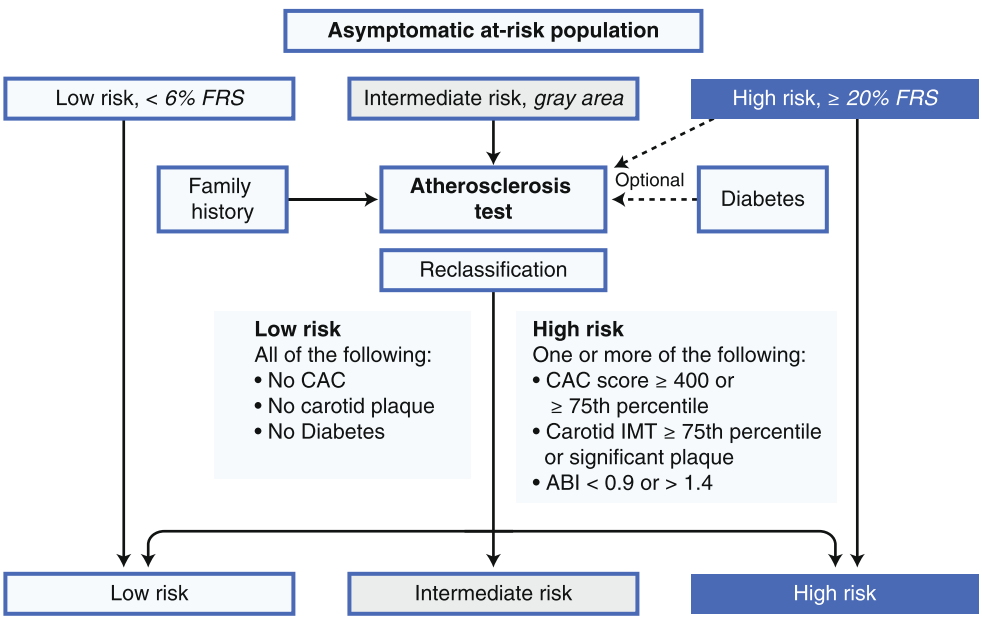

Fig. 2 Suggested conceptual approach to assessment of subclinical atherosclerosis. Inspired by SHAPE (Fig. 1), 2010 American College of Cardiology Foundation/American Heart Association cardiovascular risk-assessment guideline [24••], and 2010 appropriate-use criteria for cardiac computed tomography (CT) [40•]. ABI—ankle-brachial index; CAC—coronary artery calcium (measured by CT); IMT—intima-media thickness (measured by ultrasound); FRS—Framingham Risk Score

physician in charge as well as the patient in question could increase the use of and adherence with risk modifying interventions, which could be reasonably expected to improve outcomes; this is also a premise of Framingham risk assessment and NCEP-ATP III guidelines that has also not been tested in randomized trials [53]. Several observational studies have reported a significant association between the evidence of subclinical atherosclerosis and increased use of risk modifying behavior and pharmacotherapy among asymptomatic subjects, including the recent Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) trial [54••]. Thus, the totality of evidence supports a significant incremental prognostic value of subclinical atherosclerosis detection (in particular using CAC scoring) and potential favorable impact on the use and compliance with risk modifying interventions, making such testing a useful adjunct to Framingham risk assessment.

Recent Developments: The 2010 ACC/AHA Primary Prevention Guideline

The 2010 ACCF/AHA guideline for cardiovascular risk assessment recommends use of noninvasive tests for subclinical atherosclerosis (CAC scoring, CIMT/plaque, and ABI) in asymptomatic adults at intermediate risk according to traditional risk factor scoring (class IIa recommendation: reasonable to perform because benefit exceeds risk) [24••]. These tests can correctly reclassify a substantial number of people in the therapeutic gray area to lower-risk or higher-risk categories, for which treatments are better defined [40•, 42••, 43••, 47••, 51, 52••]. Tests for subclinical atherosclerosis might also be useful in the management of patients with diabetes and/or a family history of premature CVD [24••, 40•]. A flow chart of how noninvasive tests for subclinical atherosclerosis could be implemented in clinical practice is suggested in Fig. 2.

Conclusions

The time has come to change practice. In primary prevention of atherosclerotic CVD, we should strive to use the best methods to provide clinically meaningful prognostic information. Several ongoing studies are trying to refine and improve the predictive power of recommended tests and explore the incremental value of more advanced and costly technologies, such as magnetic resonance and nuclear imaging.

The burden of CVD is increasing despite falling mortality [55, 56]. We have inexpensive generic drugs to lower blood cholesterol concentrations and blood pressure that are of proven efficacy and safety. Their wider and sensible use will not only reduce the burden of disease but also save money because symptomatic CVD is extremely costly [57, 58]. On this background, noninvasive tests for subclinical atherosclerosis should be implemented to help to target medical prevention to those who need it, and thus limit both undertreatment and overtreatment.

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