Are We Getting Nearer to Screening for Atherosclerosis?
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Case Presentation: A 48-year-old healthy man suffered a complex ankle fracture in a cross-country skiing accident that required orthopedic surgery. In the hospital, a routine 12-lead ECG showed a 1-mm ST depression in lead V5 to V6, which prompted a noninvasive coronary artery calcium test that had a high score. Therefore, a coronary arteriogram was done, disclosing 70% to 90% lesions in 3 major coronary arteries, which were balloon dilated. Thereafter, the ankle surgery was performed successfully. The patient admitted that he felt assured that, as a physically active nonsmoker with a normal total cholesterol value on a routine test years earlier, no need existed for medical or cardiac consultation despite his strenuous recreational activity.

General Considerations
In medicine, “screening” means to reach out actively to a certain segment of an apparently healthy population and recommend tests to detect the presence of a so-far undiagnosed disease at its earliest stage. This is in contrast to “preventing,” by which we mean advocating precautionary actions/tests/means to disclose factors that, if changed, may eventually prevent the disease.

Widespread, intensive, and very important activities that seek to reduce ischemic heart disease (IHD) incidence, prevalence, and mortality through risk factor prevention, detection, and control are being carried out by cardiologists all over the world and are endorsed and encouraged by all official scientific bodies of cardiologists and physicians in general. The same, however, cannot be said about screening, which should/could take place after the established risk factors already initiate the process of the “cardiovascular continuum” that leads to tissue damage but not necessarily to symptoms. Although in other fields of medicine efforts to screen asymptomatic adults to detect various maladies are encouraged, in cardiology, even recent guidelines fail to deal explicitly with the approach to apparently healthy middle-aged nondiabetic persons and to clarify whether we are obliged to screen or exempt from screening such individuals. An exception to this approach can be seen in the activities of the Screening for Heart Attack Prevention and Education Task Force, which published guidelines that called for screening for subclinical atherosclerosis of all asymptomatic middle-aged persons, “except those defined as very low risk,” ie, the persons without any traditional risk factor. This initiative was called by one of America’s leading cardiologists “original, ambitious, and provocative.”

The European guidelines for the prevention of IHD stress the “limited resources” and suggest giving priorities for preventive measures to high-risk patients with known multiple risk factors, to those with a markedly raised level of a single risk factor, and to those who are close relatives of patients with an early-onset atherosclerotic cardiovascular disease. These guidelines recommend the use of the Systematic Coronary Risk Evaluation system that takes into consideration the well-established risk factors (eg, systolic blood pressure, total cholesterol, and smoking status) that, together with age and gender, provide a composite coronary end point. The guidelines decreased the threshold of high risk to \( \geq 5\% \), instead of the former \( \geq 20\% \), for 10-year risk of a fatal event; however, no guidance is given as to the course to be taken with low-risk middle-aged individuals.

The prevalence of overt IHD in the United States is an estimated 13.2 million, but the number of middle-aged individuals who have never suffered from any heart-related symptoms but may harbor the disease can only be estimated. A basis for this estimation could be the well-known fact that, in a considerable number of persons in whom myocardial infarction was the...
first manifestation of IHD, postmortem examination indicated that severe coronary atherosclerosis must have existed before the infarction. Furthermore, among the estimated 164 000 victims of out-of-hospital cardiac arrests annually in the United States and a similar number in Europe, nearly two thirds occur without prior recognition of cardiac disease.8,10 Identifying these asymptomatic individuals before the event is the task before us. This can be accomplished only if a population-wide strategy educates the public to understand that, at a certain age, dangerous heart disease may already be present even if the person feels healthy.

**ECG as a Possible Diagnostic Tool for Screening**

A 12-lead ECG, beyond being invaluable for cardiac diagnosis,11 could be considered a relatively convenient tool for screening for atherosclerotic heart disease. However, to prove its sensitivity, specificity, and cost-effectiveness, we need to prospectively examine asymptomatic healthy individuals, and such studies are not numerous. Studying a cohort of ≈5000 healthy men and women ≥65 years of age, Rautaharju and coworkers12 found in 12-lead ECGs 5 variables that were significant predictors of mortality during a mean 9.1-year follow-up. Froelicher and coworkers13 followed up patients referred to the VA Health Care System for >10 years. The ECGs were performed in >30 000 outpatients, excluding medical, surgical, and emergency department patients; the 5-year survival for both male and female patients with a normal tracing was 99%. The authors cautiously suggested that the availability and the inexpensive nature of the 12-lead ECG “would seem to justify” its use as a screening tool in a similar population.

The incidental findings of a long-QTc14 or a short-QTc15 interval, the ECG characteristics of the Brugada syndrome,16 or even occasional ventricular premature beats in healthy subjects 45 to 64 years of age17 and 55 to 75 years of age18 were shown to increase the risk of cardiovascular mortality or sudden death. Cost-effectiveness of ECG screening of neonates for long-QT syndrome was demonstrated by Quaglini and coworkers,19 was criticized by Van Hare et al,20 and was rebutted by Schwartz and Quaglini.21 In adults, the incidental finding of a prolonged QTc interval on a digitized ECG in a large cohort of black and white healthy men and women who were followed up for >10 years was found to be a marker of subclinical atherosclerosis, supporting its value for risk stratification in the general population.14 Are these and many other recent studies convincing enough to change the opinion expressed by Sox et al22 in 1989 that the low prevalence of ECG abnormalities in asymptomatic, apparently healthy populations makes its use for routine screening of cardiovascular risk inappropriate?

Exercise testing as a screening tool was considered in the AHA Scientific Statement in 200023 and again in 2005.24 Despite agreeing with the prognostic capability of such screening in asymptomatic adults for risk assessment, especially if non-ECG parameters such as functional capacity, chronotropic response, heart rate recovery, and ventricular ectopy also are evaluated, these statements fall short of recommending it as a screening technique because results fail to demonstrate an improvement in long-term outcomes. The 2005 statement includes the suggestion that given the strong evidence linking exercise test findings to risk in asymptomatic subjects, priority should be given to implementing a large-scale randomized trial and including not only the clinical value but also the cost-effectiveness.

**Other Noninvasive Diagnostic Methods**

An increased carotid intima-media thickness was measured noninvasively by ultrasonography in persons without clinical cardiovascular disease. Over a 6.2-year follow-up, older individuals with an increased carotid intima-media thickness were shown to have an increased risk of infarction.25 Iglesias and coworkers26 reached similar results in the Rotterdam Study. Using carotid intima-media thickness testing, Davis and coworkers27 identified not only older adults but also children and young adults with premature atherosclerosis long before clinical signs and symptoms developed. The authors considered carotid intima-media thickness a surrogate marker of the degree of atherosclerotic process. A meta-analysis of 8 relevant studies28 summarized that carotid intima-media thickness is a strong predictor of future vascular events and contains information beyond the classic cardiovascular risk factors. Despite these studies, major health insurance bodies consider this test for use in clinically asymptomatic individuals investigational.29

Coronary artery calcium scoring had incremental prognostic value in asymptomatic unselected cohorts and in population samples.30–32 Similar results were obtained in a registry of >10 000 asymptomatic individuals with a 5-year follow-up for death from all causes.33 In the Shaw et al34 study, the prognostic value of coronary artery calcium scoring was accurate in identifying a high-risk cohort of asymptomatic smokers and nonsmokers. According to the authors, it may be useful in educating these individuals about their expected risk of dying over the next 5 years. The American College of Cardiology Clinical Expert Consensus Task Force/American Heart Association consensus document does not recommend coronary artery calcium measurement in patients with low risk (10-year risk of estimated IHD events of <10%); however, patients with atypical symptoms, even with low risk, may benefit from coronary artery calcium testing to help rule out the presence of IHD.34

Interestingly, the carotid intima-media thickness and coronary artery calcium tests are the ones for which insurance reimbursement is requested by a state bill introduced recently in
the Texas Legislature. This bill was called "a first legislative effort in the US" to encourage the identification of "apparently healthy individuals who are at risk of a near-future heart attack." Another recent laymen publication\textsuperscript{39} quotes the report of the Federal Agency for Health Care Research and Quality and concludes that Americans as a whole largely are not getting the tests, examinations, and advice from doctors that can lessen the burden from various diseases; the minorities, the poor, and the uninsured are especially missing out on the preventive screening and counseling they need.

Alternatively, is endothelial dysfunction the critical abnormality that should be assessed after a certain age in asymptomatic individuals? In asymptomatic, clinically healthy, normotensive subjects, endothelial dysfunction was shown to be present in the preclinical phase of vascular disease.\textsuperscript{37} Napoli and coworkers,\textsuperscript{38} discussing early detection for primary prevention, emphasized that endothelial dysfunction is an independent predictor of cardiovascular events beyond the known risk factors and may serve as an independent index of the success of primary prevention intervention. Bonetti et al\textsuperscript{39} cautiously remarked that targeting endothelial dysfunction to optimize risk reduction strategies "might become reality in the future."

The acute-phase plasma protein C-reactive protein, usually associated with generalized inflammation or infecion, if elevated is associated with future cardiovascular events independently of traditional risk factors\textsuperscript{40} but was found to have only limited clinical value in cardiovascular risk stratification in elderly people.\textsuperscript{41} Evidence suggests that lowering C-reactive protein levels reduces the rate of atherosclerosis progression.\textsuperscript{42}

In another important cardiovascular area, peripheral arterial disease, a previous "against screening" approach,\textsuperscript{43} was recently challenged.\textsuperscript{44} The opinion was that, on the basis of best available evidence, routine, targeted screening for this disease would increase the frequency of diagnosis, improve therapies, and reduce cardiovascular morbidity and mortality rates.

Will the advances in proteomics technologies, as summarized recently by Arab and coworkers,\textsuperscript{45} yield novel biomarkers reflecting cardiovascular disease to establish earlier detection strategies? This new science is gaining momentum in research and clinical application and may in the future provide a new window on the disease we strive to prevent or at least to detect at an early stage.

**An Important Symptom**

Because erectile dysfunction affects more than 50\% of men 40 to 70 years of age,\textsuperscript{46} it seems to be important to quote Mors and coworkers,\textsuperscript{47} who identified erectile dysfunction as a predictor of acute coronary syndromes with a prevalence of 49\% (147 of 300 patients); importantly, erectile dysfunction developed an average of 3 years before acute coronary syndromes. The Second Princeton Consensus Conference\textsuperscript{48} concluded that a man with erectile dysfunction even without any other cardiac symptom or sign is a "cardiac or vascular patient until proven otherwise." Because a time lag of 2 to 3 years was shown to be present between the start of erectile dysfunction and the time that IHD became symptomatic,\textsuperscript{49} the authors believed that this lead time could provide a golden opportunity to screen patients with erectile dysfunction for silent atherosclerotic heart disease. (Dr Jackson pointed out that ED, sometimes used for erectile dysfunction, also stands for endothelial dysfunction and for early detection.)

**Economic Considerations**

Despite the increasing number of noninvasive tests and techniques that help to diagnose cardiac disease at an early asymptomatic stage, screening remains controversial at the least, if not even contraindicated. Beyond the fear of overdiagnosis and overtreatment, the major concern is the economic impact of screening a large segment of the population with tests, even if noninvasive.

The economic burden of coronary artery disease, including healthcare expenditure and productivity losses, was calculated to be 45.6 billion euros (about $60 billion) annually in the European Union\textsuperscript{9} and $142.5 billion in the United States.\textsuperscript{51} It would, however, be much more difficult or even impossible to foresee the economic yield of preventing the disease or detecting it early through screening tests in a wide sector of the population, and estimating this is not within the scope of this article. The economic impact of reducing the morbidity and mortality from heart disease is not necessarily within our responsibilities. Maybe as doctors and cardiologists, our duty is to continue the basic research and clinical investigations aimed at finding the diagnostic tools for early detection, which could eventually lead to at least a decrease in if not a total eradication of heart disease. The public, through the national policy makers, will then decide whether the economic considerations allow the implementation of these tools.

**Conclusions**

Several noninvasive tests have been shown to have prognostic value for an increased risk of future cardiovascular events and mortality in asymptomatic middle-aged persons, but none of those was proven to reduce the rate of subsequent heart attacks. Although these tests are probably useful for individual patients being examined, their use for mass screening for atherosclerosis is presently not recommended. The search should go on for reliable tests for diagnosing IHD as its earliest, still asymptomatic, stage with an economically acceptable cost.

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**Disclosures**

None.
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