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Improving Coronary Heart Disease Risk Assessment in Asymptomatic People

Role of Traditional Risk Factors and Noninvasive Cardiovascular Tests

Philip Greenland, MD; Sidney C. Smith, Jr, MD; Scott M. Grundy, MD, PhD

At least 25% of coronary patients have sudden death or nonfatal myocardial infarction without prior symptoms.¹ Therefore, the search for coronary patients with subclinical disease who could potentially benefit from intensive primary prevention efforts is critically important. The American Heart Association's (AHA) Prevention V Conference, "Beyond Secondary Prevention: Identifying the High Risk Patient for Primary Prevention," addressed ways to identify more patients who are asymptomatic and clinically free of coronary heart disease (CHD) but at sufficiently high risk for a future coronary event to justify more intensive risk reduction efforts.² In this report, we amplify on key findings and recommendations of the AHA Prevention V conference, highlight new research since the conference, and propose an approach to the use of office-based testing and additional noninvasive procedures in selected patients to better define their coronary event risk. The recommendations are concordant with the recently released approach to risk assessment and management from the third report of the Adult Treatment Panel of the National Cholesterol Education Program (ATP-III).³

Enthusiasm for primary prevention and risk assessment in asymptomatic people has been spurred by recent advances in prevention research. Lipid-lowering trials demonstrated that primary prevention of coronary events is feasible, evidenced by the West of Scotland Coronary Primary Prevention Study (WOSCOPS) trial⁴ of hypercholesterolemic men and by the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial⁵ in average or typical risk men and women with only moderate lipid abnormalities. Aspirin⁶ or ACE inhibitors⁷ can also reduce risk in selected asymptomatic, high-risk people. Emerging coronary risk factors have been described including inflammatory, infectious, and thrombotic markers,⁸ and there has been a steady flow of reports that focus attention on potential new ways of predicting coronary risk.⁹ In addition, noninvasive tests for subclinical atherosclerotic disease are available and becoming widely promoted for risk assessment in asymptomatic patients. Accordingly, the Prevention V Conference examined

whether current techniques or a combination of tests can optimize or improve risk assessment for primary prevention of CHD.

A primary recommendation of the Prevention V Conference was that risk assessment begins in the physician's office, where all adults should undergo an office-based risk assessment as the initial step in predicting risk to identify those needing more intensive risk reduction. Numerous approaches (Table) are available for office-based risk assessment,⁹⁻¹¹ but none is yet considered ideal.^{9,12} However, as a first approximation of risk prediction, office-based measures are essential to begin the process of selecting patients for further intervention or additional testing. One approach endorsed by both the AHA and the American College of Cardiology (ACC) is a determination of "global risk" as measured by a multifactorial statistical model such as the Framingham Risk Score.¹³ Well-established risk factors including age, sex, smoking history, blood pressure, total serum cholesterol, HDL cholesterol, and blood glucose (or history of diabetes) are measured and entered into a risk calculation model. The procedure can be paper-based^{3,14} or computer-based^{3,13} and results in an estimation of relative risk and absolute risk of a cardiac event in the near term (eg, 10 years). The AHA offers materials to assist physicians in the performance of this task,¹³ and "global risk assessment" by these methods is more quantitative than use of categorical risk factors alone.¹⁵ Newer risk factors not included in standard office-based tools, such as homocysteine, C-reactive protein, and lipoprotein (a), were considered at the Prevention V Conference^{2,8}; however, none emerged as a convincing means of improving office-based risk assessment. Advice to perform an initial risk assessment in all patients is consistent with current clinical practice guidelines including ATP-III³ and Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)-VI,¹⁶ with European Guidelines¹¹ and with AHA/ACC recommendations.¹³

After a patient has been assessed for absolute coronary risk in the doctor's office, the next step is to use this information to determine appropriate interventions including reassurance

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Examples of Approaches to Risk Assessment With Multiple Coronary Heart Disease Risk Factors*

- National Cholesterol Education Program Guidelines (NCEP)
- European Societies of Cardiology, Atherosclerosis, and Hypertension
- Framingham Risk Score
- British Regional Heart Study (BRHS) Risk Score
- Sheffield Coronary Risk Tables
- GREAT (General Rule to Enable Atheroma Treatment)
- Munster Heart Study (PROCAM) Risk Score
- Dundee Coronary Risk Disc
- National Heart Foundation of New Zealand Guidelines
- West of Scotland Cardiovascular Event Reduction Tool (CERT)

*Derived from References 9 and 34.

of low-risk patients or further testing when estimated risk level does not provide clear clinical direction. We propose that asymptomatic patients fall into 3 reasonably distinct categories at this point in assessment (Figure 1). In one category are patients who have a low Framingham risk score and no identifiable CHD risk factors (nonsmoking, total cholesterol ≤ 200 mg/dL, HDL cholesterol >40 mg/dL, systolic blood pressure <120 mm Hg, diastolic blood pressure <80 mm Hg, no evidence of glucose intolerance, body mass index <25 kg/m², and no family history of premature atherosclerotic vascular disease). These people are at low risk of coronary events both short-term¹⁰ and long-term¹⁷ and can be reassured about their risk status without further risk assessment testing. We estimate that this “low-risk” group constitutes approximately 35% of the US adult population 20 years of age and over.¹⁸ In the short-term, they can be offered general public health recommendations, and they can usually avoid further risk assessments for approximately 5 years.³ On the basis of Framingham data,¹⁰ these patients have an absolute risk for “hard CHD” of less than 5% to 6% in 10 years. Hard CHD is defined in the Framingham Heart Study as recognized and unrecognized myocardial infarction, coronary insufficiency, and coronary heart disease death.¹⁰

At the other end of the risk spectrum, following office-based assessment in asymptomatic people, a second category of patients can be identified as “high-risk.” These patients can have established CHD, other clinical forms of atherosclerotic disease, type 2 diabetes, or are older patients with multiple other CHD risk factors. Some patients may be at high risk because of extreme elevations of serum cholesterol or blood pressure. In accordance with ATP-III³ or JNC-VI¹⁶ guidelines, high-risk asymptomatic people should have all CHD risk factors treated to reduce CHD and total cardiovascular disease risk. On the basis of a recent analysis of National Health and Nutrition Examination Survey (NHANES) III data, approximately 25% of US adults belong in this “high-risk” category.¹⁸ Thus, at the 2 ends of the spectrum (low risk or definitely high risk), we estimate that approximately 60% of the US adult population can be risk-stratified and further treated without additional assessments beyond an office-based risk analysis. According to Framingham data,¹³ high-risk patients would typically have a risk for “hard CHD” events greater than 2% per year and frequently greater than 3% per year, similar to that seen in patients with prior CHD events.^{10,19} In concert with new ATP-III guidelines, risk factor targets should be identical in these patients to the AHA’s secondary prevention guidelines.²⁰ Such patients either have CHD or are considered to have a CHD risk equivalent.³

The third category of patients following the office-based assessment falls in a risk zone intermediate between the categories described above. This is a sizable group, judging from NHANES III data, roughly 40% of the US adult population.¹⁸ Patients in the intermediate risk group do not currently qualify for the most intensive risk factor interventions,²⁰ yet they have 1 or more risk factors that exceed desirable levels. Such patients should be counseled about their intermediate CHD risk and offered general dietary and life habit advice that might influence them to change behaviors and achieve low-risk status in the future. Some intermediate-risk patients also will be candidates for cholesterol-lowering drugs. Intermediate-risk patients could benefit

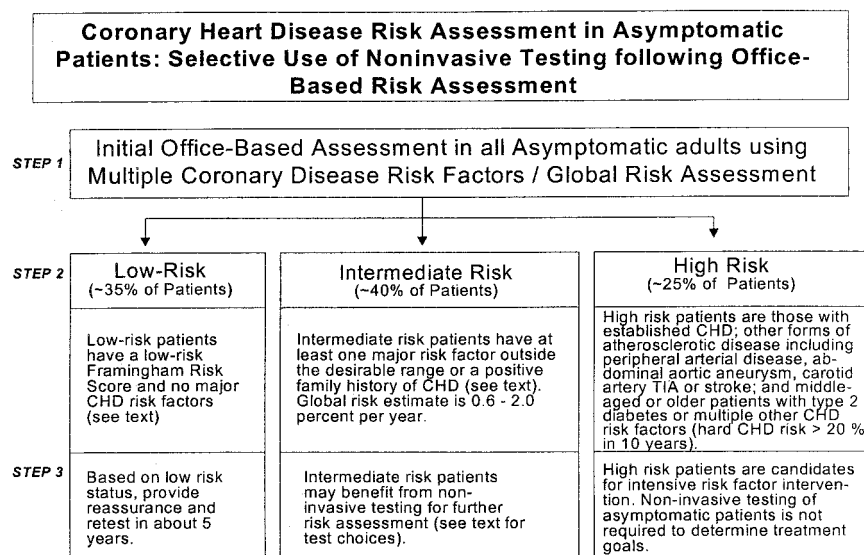


Figure 1. Flow chart.

most from further risk stratification testing, if such testing is feasible, practical, targeted, and effective at further defining risk or in motivating effective behavioral changes.

There is evidence to support the use of various noninvasive tests of silent ischemia and/or of subclinical vascular occlusive disease in the intermediate-risk population. Relevant literature was reviewed in the Prevention V Conference,^{21,22} and it was concluded that “selected patients” should have further testing if initially found to be at intermediate risk. Boundaries for selecting such patients were not clearly defined in the Prevention V Conference. New research results published since the Prevention V Conference add support to this approach to selective use of noninvasive testing to enhance risk assessment.

Ankle-brachial index (ABI), the ratio of systolic blood pressure in the ankle arteries to the systolic blood pressure in the brachial arteries, provides incremental prognostic utility over traditional risk factors, at least in patients older than 60 years of age. The ABI is considered a reliable sign of peripheral arterial disease when it is <0.90 . Patients with symptomatic peripheral arterial disease, that is, those with intermittent claudication, are well known to have markedly increased risks of CHD events and of other cardiovascular disease (CVD) events (up to 15-fold increased in one study²³). In population studies, asymptomatic individuals with low ABI also have been found to have markedly increased CHD and total-CVD risks. For example, in a long-term, prospective study, primarily asymptomatic men and women with an average age of 66 years and a low ABI value (<0.90) had a relative risk of 6.3 for all cardiovascular disease mortality, 4.8 for coronary disease mortality alone, and 3.1 for all-cause mortality. High relative risks persisted after adjustment for standard CVD risk factors considered in the Framingham Risk Score.²³ These relative risks are similar, in the primary prevention setting, to relative risks seen in secondary prevention.^{19,20} We judge this level of risk to be considerable enough to move a patient with apparent “intermediate risk,” based on office risk assessment to high-risk status. An abnormal ABI, in an otherwise asymptomatic patient, provides incremental prognostic information, especially in people older than 60 years of age or in smokers. The ABI could therefore be useful in refining risk prediction in these categories of intermediate-risk patients. It is inexpensive but not yet widely available outside of vascular laboratories. It could potentially be used, in selected patients, in the office setting.

Carotid B-mode ultrasound, with emphasis on intima-media thickness (IMT), can also yield incremental risk stratification information. The examination is performed bilaterally on the distal straight 1 cm of the extracranial common carotids, the carotid bifurcations, and the proximal 1 cm of the internal carotids. Several carefully conducted studies^{24–26} in asymptomatic people older than 50 years of age demonstrated that abnormal IMT values result in relative risks as high as 5.0, over and above traditional coronary risk factors, for occurrence of future cardiovascular (stroke or myocardial infarction) events. Again, this level of relative risk is similar to that seen in secondary prevention and has therefore been termed “a coronary risk equivalent” to signify

that the risk for future events is similar to that seen in the coronary patient.^{3,19} Thus, carotid ultrasonography may also improve risk assessment in intermediate-risk patients, especially in those older than 50 years of age. However, one caveat must be stated. The carotid ultrasound examination for IMT measurement is not routinely performed in clinical ultrasound examinations, and the best-validated predictive value of carotid IMT derives exclusively from highly quality-controlled research laboratories. It is not clear that a similar quality of IMT measurements can be derived in the majority of clinical ultrasound laboratories.

Recent work suggests that electron-beam tomography (EBT) can also improve risk prediction in intermediate-risk patients.²⁷ In a cohort of 1172 asymptomatic men and women (mean age, 53 years) who were self-referred for EBT, with average follow-up 3.6 years, 39 subjects had a coronary event, including 3 coronary deaths, 15 nonfatal myocardial infarctions, and 21 coronary artery revascularizations. For a coronary calcium score of ≥ 80 , sensitivity for prediction of one of these coronary events was 0.85 with specificity 0.75. Thus, with a prior probability of a coronary event in the intermediate range ($>6\%$ in 10 years but $<20\%$ in 10 years), a calcium score ≥ 80 would yield a posttest probability in virtually all such patients greater than 2% per year, that is, a level similar to that in secondary prevention, or a “coronary risk equivalent.” Therefore, positive EBT test results could be useful in further risk stratification for the intermediate-risk patient. Figure 2 demonstrates how a pretest-estimated risk of 6% in 10 years (derived from initial office-based testing) can move up to a posttest probability of $>20\%$ in 10 years when the EBT calcium score is at least 80 (per data from Arad et al).²⁷

Despite conventional teaching to the contrary, exercise stress testing in asymptomatic men can also yield prognostic information that permits refined risk stratification in intermediate-risk patients.²⁸ A recent report illustrates this point in a population of 25 927 healthy men (mean age, 42.9 years) free of clinical cardiovascular disease who underwent maximal exercise stress testing in the context of a preventive health evaluation.²⁸ With an end point of CHD death, an abnormal maximal exercise stress test yielded an age-adjusted relative risk of 21 in patients with no major coronary risk factors. Relative risks ranged from 8 to 10 in patients with 1, 2, or 3+ coronary risk factors compared with similar patients with normal exercise test results. Similarly useful prognostic results have been reported in at least 2 other studies of asymptomatic men with coronary risk factors.^{29,30} Thus, in a manner similar to that seen with EBT, carotid ultrasound, or ABI, an abnormal exercise stress test can advance a patient’s risk status from intermediate to high risk. Conversely, a negative test in the intermediate-risk male patient can lower the patient’s risk status to a level at which greater reassurance can be provided and less intensive risk factor intervention more confidently advised. Exercise stress testing can therefore be considered as another means of further risk-stratifying the intermediate-risk male patient after an office-based assessment. Unfortunately, similar data are not available in women.²

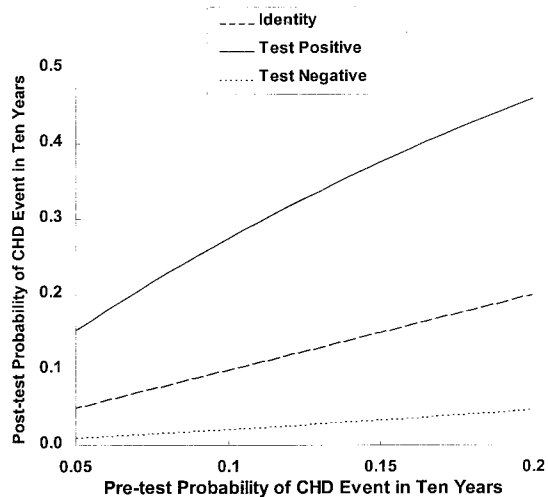


Figure 2. Example of how a noninvasive test result could substantially modify probability estimates of a CHD event. Pretest probability (x-axis) is estimated (see References 9 and 12) by standard CHD risk factor measurements and one of the available multivariate models for quantification of probability of a future CHD event (pretest probability). Posttest probability (y-axis) is different from pretest estimate whenever sensitivity and specificity are not each 50% (line of identity shown as hatched line). In this example, post-test probability is different from pretest probability, and values differ markedly, depending on whether the noninvasive test result is positive (solid line) or negative (dashed line). On the basis of sensitivity and specificity data from Arad et al,²⁷ test sensitivity is assumed to be 0.85 and test specificity is assumed to be 0.75. Similar graphs can be plotted for each of the noninvasive tests reviewed here by sensitivity and specificity data from the literature. Note that a threshold of 20% in 10 years (see text) is crossed in this example when pretest probability is >6% in 10 years and noninvasive test result is positive. On the other hand, a negative test result markedly reduces predicted CHD risk estimate within the pretest range of probabilities shown (intermediate pretest risk).

A few patient examples illustrate these points. Consider a 52-year-old asymptomatic male smoker with a blood pressure level of 155/90, total serum cholesterol of 240 mg/dL, HDL cholesterol of 37 mg/dL, and normal fasting blood glucose. The first step is to perform an office-based risk assessment with these data. With the use of the AHA Risk Calculator,¹³ this person's risk falls into the high-risk category (by AHA risk calculator, risk is estimated at 20% in 10 years for hard CHD). He is therefore a candidate for intensive risk factor modification, and further noninvasive assessment is not required to define the need for preventive therapies or the goals of such treatment.

A second case illustrates how noninvasive testing could influence patient treatment in an intermediate-risk patient. Consider a 50-year-old asymptomatic man who does not smoke, who has a blood pressure level of 140/85, total cholesterol of 210 mg/dL, LDL cholesterol of 137 mg/dL, HDL cholesterol of 32 mg/dL, a negative family history of vascular disease, and a normal fasting blood glucose. On the basis of Framingham risk assessment scoring,¹³ this man's risk falls into the "intermediate" zone with a 9% estimated 10-year risk of hard CHD (refer to Figure 1). Although he does not fall into the high-risk category requiring intensive intervention,²⁰ his LDL cholesterol level is not optimal, and blood pressure is also not optimal. If further testing were done in this person, for example EBT, and a coronary calcium

score of ≥ 80 were found, the physician would be able to reassign him to a higher risk category (at least 20% in 10 years) and justifiably proceed more aggressively to reduce his risk factors that are present. Specifically, given that this hypothetical patient's estimated risk is equivalent to that of a typical coronary patient, we propose the need for intensive intervention.²⁰ If the calcium score were zero (as it would be in 35% of men his age), the physician should still counsel the patient about trying to control his risk factors for the long term, but one would not be justified to intervene with costly lipid-lowering or blood pressure-lowering drugs at this time, based on a revised (posttest) risk estimate of approximately 1.9% in 10 years. Although this illustration used EBT, an alternative test might have been a stress ECG²⁸; however, because of his relatively young age, this 50-year old man would not be an exceptionally good candidate for carotid ultrasound or ABI because of the relatively low likelihood of positive tests in this age group.

A prominent feature of risk estimation by means of the Framingham equation is the progressive increase in absolute risk with advancing age. Undoubtedly, this increase reflects the cumulative nature of atherosclerosis. The powerful effect of age in risk prediction denotes the higher risk for major coronary events present in persons with more advanced atherosclerotic disease. Nonetheless, a single age score will mask the extent of variability in risk resulting from differences in plaque burden in older individuals. To apply average risk scores for age to individual patients may lead to miscalculation of true risk, particularly because Framingham applies so much weight to age as a risk factor. Especially in older persons, Framingham-based risk estimates could lead to inappropriate selection of patients for aggressive risk-reduction therapies. This fact points to the need for flexibility and the application of clinical judgment in adapting treatment guidelines for persons 65 years of age and older. The use of noninvasive testing for subclinical atherosclerotic disease appears to be promising for risk assessment in older persons. The extent of atherosclerotic plaque burden, or presence of subclinical ischemia, may be a better way to select such persons for aggressive risk factor intervention than measures of risk factors, some of which have diminished power to predict CHD in this age range.³¹

The goal of improved risk assessment is a more selective approach to the use of noninvasive cardiovascular studies and of preventive interventions such as lipid lowering, aspirin, or ACE inhibition. It must be understood clearly that an abnormal noninvasive test result in an intermediate-risk, asymptomatic person should be interpreted as yet another risk factor for a future cardiovascular event and not as a mandate for diagnosis of the presence or absence of angiographic coronary artery disease. Test results in an asymptomatic person must not be confused with apparently similar test results in symptomatic patients in whom proper management of CHD is the goal of testing—as opposed to enhanced risk assessment and selective use of preventive interventions as described here. Noninvasive testing for improved risk assessment has been greeted cautiously by critics in part because of the inappropriate response to test results inherited from the cardiologic workup of symptomatic patients. It is crucial that the use of such tests used to improve assessment

of prognosis not be confused with the use of such tests for coronary disease diagnosis.

In conclusion, primary prevention measures are available, effective, and relatively safe. Emphasis has shifted substantially in the past few years from a question of whether to treat patients in the primary prevention setting to the matter of selection of the highest-risk patients to maximize the benefit/cost ratio of treatments.³² The AHA Prevention V Conference suggested the potential for more routine use of office-based risk assessment for initial patient stratification.³³ Several noninvasive tests are already available, in our judgment, that should be considered as a means of further stratifying risk in a large group of apparently intermediate-risk patients. We encourage adoption of the approaches discussed here to improve and refine the risk assessment and risk reduction processes.^{12,34}

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KEY WORDS: coronary disease ■ prevention ■ prognosis ■ risk factors