CLINICAL PRACTICE

Selecting Asymptomatic Patients for Coronary Computed Tomography or Electrocardiographic Exercise Testing

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A healthy 40-year-old man exercises regularly, uses no tobacco, and has no cardiac symptoms. His blood pressure is 120/80 mm Hg, his total cholesterol concentration is 180 mg per deciliter (4.65 mmol per liter), his high-density lipoprotein (HDL) cholesterol concentration is 50 mg per deciliter (1.29 mmol per liter), his body-mass index (the weight in kilograms divided by the square of the height in meters) is 24, his fasting blood glucose concentration is 95 mg per deciliter (5.27 mmol per liter), and he has no family history of coronary disease. Should he be advised to undergo coronary computed tomography (CT) or electrocardiographic exercise testing so that the assessment of his coronary risk may be refined?

THE CLINICAL PROBLEM

The appropriate use of noninvasive cardiac testing in asymptomatic persons is different from that in patients with symptoms suggestive of heart disease. In symptomatic patients, testing is used to confirm a suspected diagnosis and to estimate the near-term prognosis. The goals of testing are to direct immediate treatments and longer-term interventions for secondary prevention. In contrast, in asymptomatic persons, the emphasis is on the assessment of long-term risk and primary prevention of future clinical disease.[1] Because of the different goals in these two populations, tests that may be useful in the case of a symptomatic patient might not be indicated for an asymptomatic person.

The prevention of clinical coronary events with the use of medical and behavioral therapies is effective in both symptomatic and asymptomatic persons.[1-3] However, interventions vary greatly in usefulness and cost effectiveness depending on the level of underlying coronary risk. The "number-needed-to-treat" computation illustrates this concept.[4] If a treatment reduces the relative risk of death from coronary causes by 25 percent, then for persons whose absolute risk is high (e.g., a 20 percent risk of death from coronary causes within 10 years), 20 patients must be treated for 10 years to prevent one death. However, if 10-year risk is very low (e.g., 1 percent over a 10-year period), then 400 patients must be treated for 10 years in order to save one life. Guidelines such as those from the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP) emphasize the importance of the estimation of risk and recommend the calculation of the absolute risk of coronary events in most asymptomatic persons (Fig. 1) as a guide to the intensity of treatment.[1]

Family history of coronary disease, use or nonuse of tobacco, presence or absence of diabetes, sex, age, blood lipid levels, weight, and blood pressure are well-recognized determinants of coronary risk in asymptomatic persons.[1,6] In spite of the widespread availability of office-based tools for the assessment of coronary risk factors, clinicians

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Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age (yr)	Points
20–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Total cholesterol (mg/dl)	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dl)	Points
≥60	–1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	Points	
	If untreated	If treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Point total	10-Year risk %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

10-Year risk_____%

Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age (yr)	Points
20–34	–7
35–39	–3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Total cholesterol (mg/dl)	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dl)	Points
≥60	–1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	Points	
	If untreated	If treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Point total	10-Year risk %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

10-Year risk_____%

Figure 1. Framingham Scoring System for Calculating the 10-Year Risk of Major Coronary Events in Adults without Diabetes.

HDL denotes high-density lipoprotein cholesterol, and BP blood pressure. All age ranges are given in years. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. Reprinted from the National Heart, Lung, and Blood Institute.[5]

have not widely adopted these tools in clinical practice; however, clinicians cannot accurately estimate the risk of coronary events by intuition.[7] In addition, although risk-factor models can improve the prediction of risk, their accuracy is considerably below 100 percent.[6] In this context, noninvasive tests typically used in the assessment of symptomatic patients have been proposed[8] as potential means for improving, and perhaps simplifying, the estimation of risk in asymptomatic persons. In this article, we consider the use of two noninvasive tests — coronary CT and electrocardiographic exercise testing — in the assessment of asymptomatic adults.

STRATEGIES AND EVIDENCE

CALCIUM SCORES DETERMINED BY CORONARY CT

Arterial calcium can be detected by various radiographic techniques, but coronary calcium poses a special problem because of cardiac motion. Detection and quantitation of coronary calcium is possible when CT imaging is coupled with electrocardiographic gating. Electron-beam CT, which requires specialized equipment, uses an electron sweep of stationary tungsten target rings that generates radiographic images very rapidly. Some 30 to 40 adjacent axial scans can be completed during one or two breath-holding sessions, usually requiring about 10 minutes of a patient's time.

Commercial software can quantify the area and density of calcium in the coronary arteries and generate a coronary calcium score.[9] Since coronary calcium occurs exclusively as a result of atherosclerosis, a calcium score of zero is normal, and abnormal scores range as high as several hundred or more.[10] Because the presence of coronary calcium has a high specificity for atherosclerosis, any detectable calcium is regarded as evidence of coronary disease. Higher calcium scores correlate with older age, higher levels of coronary risk factors, and a greater extent of coronary atherosclerosis.[10] For risk assessment in asymptomatic persons, studies have used various cutoff points for calcium scores to denote high risk — generally in the range of 80 to 160.[10-12] An abnormal scan with detectable coronary calcium is shown in Figure 2. Helical (or multislice) CT is more widely available than electron-beam CT and may be an acceptable alternative,[13] but the level of exposure to radiation is higher,[14] and data on the prediction of events are sparse for helical scanners. We therefore focus on electron-beam CT here.

When used to assess symptomatic patients, electron-beam CT has been criticized for being nonspecific as compared with coronary angiography, which represents the gold standard.[10] A meta-analysis of 16 studies that compared calcium scores with coronary stenoses detected on angiography reported a weighted average sensitivity of 80 percent for CT and a specificity of 40 percent.[10] Another meta-analysis reported a pooled sensitivity of 92 percent and a specificity of 51 percent.[11] Overall, the published literature suggests an unacceptably high false positive rate (i.e., low specificity) when the test is applied to mostly low-risk populations in order to rule out the presence of coronary stenoses that would be detectable on angiography. An additional concern about coronary CT is the high prevalence (as high as 50 percent) of unexpected noncardiac findings, most of which are ultimately determined to be of minimal or undefined clinical significance, in the adjacent lung segments.[15,16] These extremely common incidental findings can lead to extensive evaluations and can cause anxiety, providing a further reason not to use coronary CT unselectively for screening.

In the assessment of asymptomatic persons, coronary CT must be able to improve the prediction of the risk of coronary events in order to be useful. In individual studies, the relative risks of coronary

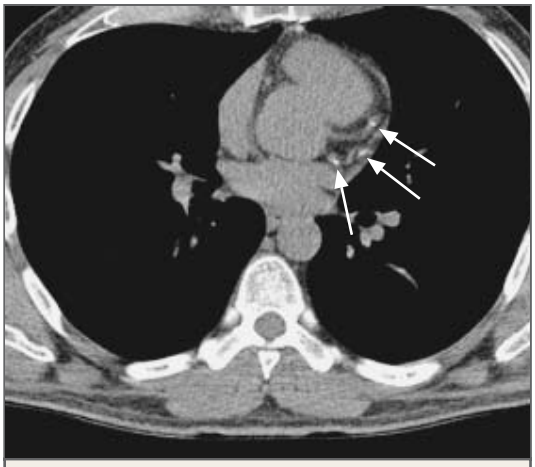

Figure 2. Electron-Beam Computed Tomographic Image Obtained in a 49-Year-Old Man.

The patient's total calcium score is 70. Three areas of calcification (arrows) are visible in the regions of the coronary arteries — one in the left anterior descending artery and two in the left circumflex artery. Courtesy of Dr. Stuart Rich, Chicago.

events (myocardial infarction or sudden death) associated with calcium scores above a cutoff value (usually greater than 160) have ranged from 2.3 to 22.0[10,12,17] in multivariate models with adjustment for available information on conventional risk factors. A meta-analysis[17] of five prospective studies involving asymptomatic persons derived a summary relative risk of coronary events of 4.2 (95 percent confidence interval, 1.6 to 11.3) among persons with calcium scores above the cutoff value, as compared with those with scores at the cutoff value or lower.

Studies of electron-beam CT for the prediction of risk are limited by the lack of data for younger populations or for women,[17] by losses to follow-up, and by low rates of events in unselected populations (about 1 percent per year).[17] Most studies also did not measure risk-factor–related variables in a systematic manner; consequently, it has been unclear whether calcium scores truly have incremental prognostic value. In the only published study that directly assessed the additive value of coronary calcium scores with respect to the predictive value of measurements of conventional risk factors, the CT results provided little incremental predictive information.[18] However, the population in that study was a selected, high-risk, older population, and the results may not be generalizable. There are no published studies involving populations of asymptomatic persons that have directly compared coronary CT with exercise testing for the prediction of risk; however, published sensitivity and specificity values for calcium scores are somewhat higher than those for electrocardiographic exercise testing in unselected populations of asymptomatic persons.[10,11,19]

ELECTROCARDIOGRAPHIC EXERCISE TESTING

The use of electrocardiographic exercise testing for the purpose of diagnosing coronary stenosis in patients without symptoms has been criticized as having low sensitivity and low specificity in persons with low risk.[19] The predictive value of a positive test for clinically significant angiographic stenosis in an unselected population has been reported to range from 25 percent to 72 percent.[19] Newer techniques, such as perfusion scintigraphy and stress echocardiography, may improve diagnostic capability, predictive capability, or both, as compared with the use of exercise electrocardiography alone.[10] However, these newer tests are more costly and less widely available and have not been as well studied for the prediction of risk in asymptomatic populations as the more common electrocardiographic exercise testing.

A number of studies of electrocardiographic exercise testing have shown that exercise-induced ischemia in healthy persons is associated with an increased risk of future myocardial infarction and sudden death.[19-24] In five large studies involving asymptomatic persons,[19-23] abnormal results on electrocardiographic exercise testing of middle-aged men with elevated levels of coronary risk factors at base line were associated with a rate of death from coronary causes that was at least 3.5 times that among similar patients with normal results on electrocardiographic exercise testing. Another report confirmed the prognostic value of electrocardiographic exercise testing among 25,927 men with a mean age of 43 years who were free of clinical disease and who underwent maximal exercise testing during a screening evaluation.[25] An abnormal result on electrocardiographic exercise testing was associated with a relative risk of death from coronary causes ranging from 8.0 to 10.0 among men with at least one coronary risk factor, as compared with ostensibly similar men with normal test results.

Published studies have often categorized exercise-test results primarily or exclusively on the basis of ST-segment changes, overlooking other potentially useful data such as exercise capacity, heart-rate recovery, presence or absence of arrhythmias, and hemodynamic responses. However, it is uncertain whether consideration of these additional variables in the interpretation of exercise-test results would improve the prediction of risk beyond that permitted by data on ST-segment changes alone. Data regarding the prognostic value of electrocardiographic exercise testing in asymptomatic women and the elderly (>75 years of age) are very sparse. Published data on electrocardiographic exercise testing in asymptomatic persons are summarized in Supplementary Appendix 1 (available with the full text of this article at http://www.nejm.org).

THE PREDICTIVE VALUE OF SCREENING TESTS

Because neither coronary CT nor electrocardiographic exercise testing is 100 percent sensitive and specific for the prediction of coronary events, the appropriate use of these tests requires careful consideration of the likelihood of disease in the particular person, as determined before testing.[26] In patients with a low probability of an event according to an assessment of multiple risk factors,[1,6] noninvasive tests will typically not be helpful, since a pos-

itive test will not yield a probability that is high enough to justify the reclassification of the risk as high. When the probability of coronary events is considered to be high before testing, a negative result on a noninvasive test is usually not considered sufficient evidence on which to base the withholding of long-term, intensive preventive interventions, which are considered to be warranted on the basis of high levels of risk factors alone.[1,27,28] In contrast, when findings regarding risk factors suggest that a person's level of risk is intermediate between low and high, the added information from a noninvasive test may be helpful in informing decisions regarding preventive measures.

What limits should define high, low, or intermediate risk of a future cardiovascular event depends on the cost and risks associated with a given preventive intervention. Guidelines from the NCEP,[1] in considering targets for the reduction of cholesterol levels, define high risk as a 20 percent or greater probability of a coronary event within 10 years. This level is similar to the level of risk of a major coronary event in patients with established atherosclerotic disease — a level at which secondary preventive interventions are routinely used.[1-3] In a patient in whom readily obtainable clinical information indicated a level of risk similar to that in a patient with coronary disease, noninvasive testing would not be required in order to establish the need for intensive preventive interventions. Approximately 25 percent of adults can be classified as having high risk on the basis of risk-factor assessment alone.[29,30]

Low risk can be defined both over the short term (a 10-year period) and over the long term (at least 20 years or a lifetime). The NCEP guidelines define low risk as a risk of a coronary event within 10 years of less than 10 percent.[1] The Framingham Heart Study found that asymptomatic persons with no major coronary risk factor had a risk of less than 5 percent over a 10-year period.[31] Data from four other large cohorts[32] similarly showed that the absence of major risk factors (i.e., no smoking, no diabetes, a systolic blood pressure below 120 mm Hg, a diastolic blood pressure below 80 mm Hg, and a total blood cholesterol concentration below 200 mg per deciliter [5.17 mmol per liter]) predicted low long-term risk. No more than 35 percent of adults older than 20 years of age have a low risk of coronary events.[29,30] Intermediate risk is defined as a 10-year risk of coronary events of 10 to 20 percent.[1] Forty percent of adults older than 20 years of age fall into the intermediate-risk category.

To illustrate how noninvasive testing can influence clinical decision making, we used data from a report on coronary CT and the risk of coronary events (death, myocardial infarction, or clinically indicated coronary revascularization).[12] A coronary calcium score of 80 or more had a sensitivity for any one of these events of 85 percent and a specificity of 75 percent.[12] Table 1 shows the effect of applying these reported test characteristics to patients with a range of levels of risk as defined above. Similar logic was applied in the evaluation of electrocardiographic exercise testing (Table 1). It is apparent that a negative result on either test in a patient with intermediate risk markedly lowers that patient's predicted risk. Conversely, a calcium score of 80 or higher results in a probability of a coronary event within 10 years of more than 20 percent

Table 1. Probability of a Coronary Event within 10 Years Calculated on the Basis of the Results of Electron-Beam CT or of Exercise Electrocardiography.*

Pretest Probability of a Coronary Event within 10 Yr	Probability within 10 Yr According to Results of Electron-Beam CT		Probability within 10 Yr According to Results of Exercise Electrocardiography	
	Calcium Score ≥80	Calcium Score <80	Abnormal	Normal
	percent			
1.0	3.0	0.2	4.0	0.4
2.0	6.5	0.4	8.0	0.9
3.0	9.5	0.6	12.0	1.3
4.0	12.5	0.9	15.0	1.9
5.0	15.0	1.0	19.0	2.3
6.0	18.0	1.2	22.0	2.8
7.0	20.0	1.4	25.0	3.3
10.0	27.0	2.2	33.0	4.8
15.0	38.0	3.4	44.0	7.4
20.0	46.0	4.8	52.0	10.0

* Pretest probability is estimated on the basis of data on risk factors. For electron-beam CT, test data are from Arad et al.[12] For a calcium score of 80 or higher, the sensitivity was 85 percent and the specificity was 75 percent for the prediction of clinical coronary events including death, nonfatal myocardial infarction, and clinically indicated revascularization. When the specificity is 75 percent, 25 percent of persons who will not have an event have a positive test. For electrocardiographic exercise testing, data are from Gibbons et al.[25] For an abnormal result on maximal exercise electrocardiography, the sensitivity for death from coronary causes was 61 percent, and the specificity was 86 percent.

among patients whose probability of such an event was thought to be 7 percent or higher before testing was performed; a positive result on electrocardiographic exercise testing results in a probability of more than 20 percent among patients whose probability was thought to be 6 percent or higher before testing was performed.

AREAS OF UNCERTAINTY

No clinical trials have specifically tested whether a strategy that includes coronary CT or electrocardiographic exercise testing in asymptomatic patients can improve patient outcomes. However, in a clinical trial involving a large number of asymptomatic men with hyperlipidemia,[21] the results on electrocardiographic exercise testing were useful in stratifying participants into several levels of risk (Supplementary Appendix 1, available with the full text of this article at http://www.nejm.org). In addition, as compared with placebo, the use of lipid-lowering therapy markedly reduced the risk in all subgroups defined according to exercise-test results but reduced it most strikingly among patients with abnormal results on electrocardiographic exercise testing. Similar findings were reported from the Multiple Risk Factor Intervention Trial, in which abnormal results on electrocardiographic exercise testing identified the asymptomatic participants who received the greatest benefit from interventions designed to reduce risk factors.[22] It is possible that better targeting of preventive strategies among patients with intermediate risk according to the assessment of standard risk factors could offset much of the cost of electrocardiographic exercise testing or coronary CT; however, data on cost–benefit ratios for these tests are not currently available. It also remains uncertain to what extent these tests will add to the information available from testing for other risk factors such as C-reactive protein.

Patients' concern about insurability and the stress of being labeled as having a disease need to be considered in the evaluation of screening strategies.[33] On the other hand, benefits of screening asymptomatic persons might include increased motivation for changes in behavior, improvement of the diet, engagement in exercise, and reduction of coronary risk in persons with unexpected positive results on tests. One study of electron-beam CT in asymptomatic persons[34] suggested that testing can have both desirable effects (changes in behavior) and undesirable effects (worry and increased stress). However, a clinical trial in which coronary CT was used during screening examinations of military personnel found that positive studies alone did not result in a potent motivation for changes in behavioral coronary risk factors.[35]

Table 2. Guidelines on the Use of Coronary CT or Electrocardiographic Exercise Testing in Asymptomatic Persons.

Organization (Document)	Coronary CT	Electrocardiographic Exercise Testing
U.S. Preventive Services Task Force[36]	Not discussed	Noninvasive testing of selected high-risk asymptomatic persons (e.g., those with multiple risk factors) may be indicated if results would influence the choice of preventive interventions
American Heart Association and American College of Cardiology (statement on exercise testing)[19]	Not discussed	May be appropriate — for example, when Framingham Risk Score indicates at least "moderate" risk within next 5 yr
American College of Cardiology and American Heart Association (consensus statement on coronary CT)[10]	May be used in "selected" patients with intermediate risk according to Framingham Risk Score	As in statement on exercise testing
American Heart Association (Prevention Conference V)[8]	Selected use, as in consensus statement on coronary CT	Selected use, as in statement on exercise testing
Blue Cross Blue Shield (medical policy on coronary CT)[37]	Not recommended for screening; considered "investigational"	Not discussed

GUIDELINES

Guidelines have been developed concerning the use of noninvasive testing to screen for asymptomatic coronary disease (Table 2). None of these guidelines recommend noninvasive testing in unselected asymptomatic people.[8,10,19,36,37] In addition, the authors of all these guidelines express concern that the results of noninvasive tests could lead to inappropriate or unnecessary diagnostic testing and interventions, including coronary angiography and revascularization, in asymptomatic people.

RECOMMENDATIONS AND CONCLUSIONS

The rational, selective use of these relatively expensive tests, whose use in assessing asymptomatic patients may not be covered by medical insurance, requires a pretesting estimate of the likelihood of a future coronary event based on a multivariate model for risk assessment such as that derived from the Framingham Heart Study (Fig. 1). Such an approach is advocated by the NCEP guidelines[1] for the initial estimation of risk in asymptomatic adults. A less desirable alternative is to count risk factors: patients with zero or one coronary risk factor are typically considered to be at low risk, whereas patients with diabetes or persons with three or more coronary risk factors are considered to be at high risk.[1]

For high-risk and low-risk patients, additional noninvasive testing will generally not modify decisions regarding preventive interventions. However, for intermediate-risk patients (those with an absolute 10-year risk of coronary events of approximately 10 to 20 percent), noninvasive testing with coronary CT, electrocardiographic exercise testing, or perhaps other tests that we have not reviewed here[38] could improve the assessment of risk and alter the categorization of these patients in such a way as to affect the probable cost effectiveness of intensive preventive strategies (Table 1). To avoid inappropriate or unnecessary follow-up procedures, even in properly selected patients, the clinician should determine a priori that the goal of such noninvasive testing is to refine the assessment of risk and then decide on the basis of the test results whether to use preventive interventions with proven efficacy. Generally, the use of invasive follow-up procedures should be limited to symptomatic patients, since there are few data to show benefit in terms of prolongation or quality of life in asymptomatic patients.[19,39] Table 3 summarizes a suggested approach to the use of these tests.

The patient described in the vignette is asymptomatic and has no unfavorable levels of cardiac risk factors. According to the model derived from the Framingham Study,[1] his 10-year risk of a coronary event is 1 percent. Given his very low estimated risk, noninvasive testing cannot generally be helpful and should be discouraged. A positive test result with electron-beam CT or exercise electrocardiography would not sufficiently increase the likelihood of a coronary event to affect clinical decision making.

Table 3. Suggested Approach to the Assessment of Coronary Risk and Selected Use of Noninvasive Tests in Asymptomatic Patients.

Level of Risk	Description of Risk*	Estimated Percentage of U.S. Population†	Recommendations
Low	Low multivariable risk score and no major risk factors for CHD	35	Provide reassurance; encourage patient to adhere to healthy habits; no further risk assessment for approximately 5 yr
Intermediate	One major risk factor outside desirable range or family history; global risk assessed at 0.6 to 2.0% per yr	40	Consider further risk stratification with use of noninvasive procedures to test for myocardial ischemia, atherosclerotic burden, or both
High	Established CHD; other forms of atherosclerotic disease (stroke, abdominal aneurysm, or peripheral artery disease); middle-aged or older persons with diabetes or multiple risk factors for CHD; risk of CHD within 10 yr >20%	25	Intensive intervention to reduce risk factors through a combination of behavioral improvement and medical therapy; noninvasive testing not required to determine treatment goals

* CHD denotes coronary heart disease.
† Percentages were estimated from the third National Health and Nutrition Examination Survey and adapted from Greenland et al.[30]

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