Cost-Effectiveness of Alternative Test Strategies for the Diagnosis of Coronary Artery Disease

Alan M. Garber, MD, PhD, and Neil A. Solomon, MD

Background: The appropriate roles for several diagnostic tests for coronary disease are uncertain.

Objective: To evaluate the cost-effectiveness of alternative approaches to diagnosis of coronary disease.

Design: Meta-analysis of the accuracy of alternative diagnostic tests plus decision analysis to assess the health outcomes and costs of alternative diagnostic strategies for patients at intermediate pretest risk for coronary disease.

Data Sources: Studies of test accuracy that met inclusion criteria; published information on treatment effectiveness and disease prevalence.

Target Population: Men and women 45, 55, and 65 years of age with a 25% to 75% pretest risk for coronary disease.

Time Horizon: 30 years.

Perspective: Societal.

Interventions: Diagnostic strategies were initial angiography and initial testing with one of five noninvasive tests—exercise treadmill testing, planar thallium imaging, single-photon emission computed tomography (SPECT), stress echocardiography, and positron emission tomography (PET)—followed by coronary angiography if noninvasive test results were positive. Testing was followed by observation, medical treatment, or revascularization.

Outcome Measures: Life-years, quality-adjusted life-years (QALYs), costs, and costs per QALY.

Results of Base-Case Analysis: Life expectancy varied little with the initial diagnostic test; for a 55-year-old man, the best-performing test increased life expectancy by 7 more days than the worst-performing test. More sensitive tests increased QALYs more. Echocardiography improved health outcomes and reduced costs relative to stress testing and planar thallium imaging. The incremental cost-effectiveness ratio was $75 000/QALY for SPECT relative to echocardiography and was greater than $640 000 for PET relative to SPECT. Compared with SPECT, immediate angiography had an incremental cost-effectiveness ratio of $94 000/QALY.

Results of Sensitivity Analysis: Qualitative findings varied little with age, sex, pretest probability of disease, or the test indeterminacy rate. Results varied most with sensitivity to severe coronary disease.

Conclusions: Echocardiography, SPECT, and immediate angiography are cost-effective alternatives to PET and other diagnostic approaches. Test selection should reflect local variation in test accuracy.

This paper is also available at http://www.acponline.org.

Ann Intern Med. 1999;130:719-728.

Several current tests for the noninvasive diagnosis of coronary artery disease are more expensive and more accurate than traditional exercise electrocardiography (1–3). Little information exists to guide the clinician about which test to order or to inform policy makers about which tests represent the best value. One of the most expensive new methods, myocardial perfusion imaging with positron emission tomography (PET), seems more accurate than other noninvasive tests, but it is unclear whether the resulting improvements in health outcomes are large enough to justify the high cost (4–7). Insofar as the accuracy of noninvasive tests is similar, costs are likely to drive differences in cost-effectiveness.

To explore the relative merit of the tests in diagnosing coronary disease, we evaluated the cost-effectiveness of exercise testing and four imaging studies that use exercise or pharmacologic stress to provoke ischemic changes: 1) exercise electrocardiography (treadmill testing); 2) planar scanning using ^{201}thallium or ^{99m}technetium sestamibi; 3) single-photon emission computed tomography (SPECT) with thallium or technetium; 4) stress echocardiography with dobutamine, exercise, or dipyridamole as the stressors; and 5) PET. We compared these strategies to initial testing with coronary angiography. Our analysis applies to patients whose symptoms and risk factors place them at an intermediate (25% to 75%) pretest probability of having coronary disease.

Methods

Overview

We developed a decision analytic model to assess the health outcomes and costs that result from different test strategies for the diagnosis of coronary disease. The model represents options for therapy and diagnostic testing and demonstrates how probabilities of uncertain events (such as the development of subsequent myocardial infarction) influence life expectancy, quality-adjusted life-years (QALYs), and costs (8). All computations are based on a 30-year horizon, and all analyses are conducted from the societal perspective. Thus, all costs of health care, whether borne by the patient, the insurer, or any other entity, are relevant. We used

DATA 3.0 (TreeAge Software, Inc., Williamstown, Massachusetts) to calculate costs and outcomes.

Patient Population

The analysis applies to men and women with a history of chest pain whose age, sex, risk factors, and features of chest pain place them at a 25% to 75% pretest probability of coronary disease, such as middle-aged women with typical angina and middle-aged or older men with atypical angina (typical angina in men corresponds to a pretest risk > 75%) (9, 10).

Coronary disease is defined as stenosis of at least 50% in the left main coronary artery or stenosis of 70% or greater in any other coronary artery, as measured by angiography. The base case applies to men 55 years of age whose pretest risk for coronary disease is 50%.

Test Performance Characteristics

We estimated the sensitivity and specificity of each noninvasive test by reviewing the published literature. Articles considered for inclusion in the pooled analysis compared one or more of the five candidate diagnostic tests (exercise electrocardiography, planar thallium imaging, SPECT, echocardiography, and PET) with the findings of coronary angiography. We searched MEDLINE for English-language studies of each of the five diagnostic tests using the search strategy "(diagnostic test) AND *cardiac* AND *sensitivity*." We also examined the bibliographies of review articles about each of the diagnostic studies to identify additional candidate articles. Finally, test characteristics of planar thallium imaging and exercise testing were obtained from published meta-analyses. The Appendix, which can be accessed at http://smi-web.stanford.edu/CADtests.htm, gives details of study inclusion criteria.

We estimated sensitivities of the tests for both severe (left main or three-vessel) and all forms of coronary disease. No identified article reported the sensitivity of PET for severe disease alone; we estimated this value by assuming that the false-negative rate decreases by the same proportion for PET as for SPECT when the outcome in question is severe, rather than all, coronary disease.

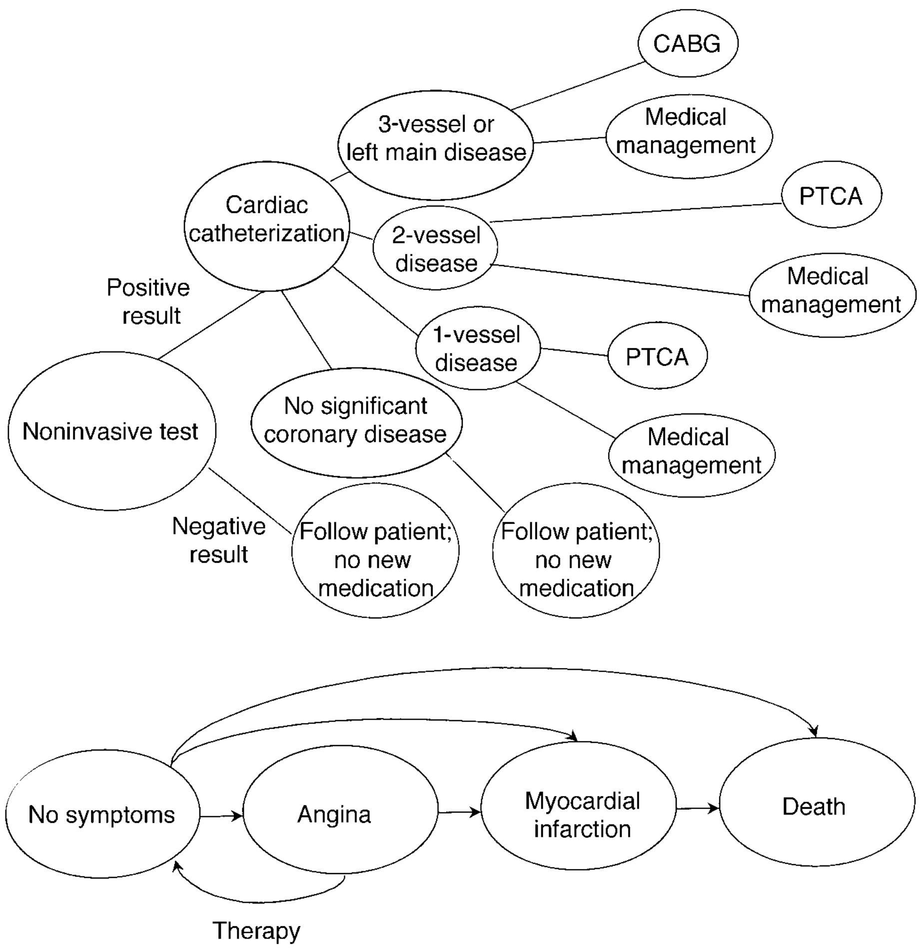

Figure 1. Algorithm for initial management (*top*) and possible progression of health states (*bottom*) for patient at intermediate pretest risk for coronary disease. Initial testing with cardiac catheterization bypasses the noninvasive test point in the top panel. Treatment options include medical management, coronary artery bypass grafting (*CABG*), and percutaneous transluminal coronary angioplasty (*PTCA*).

Table 1. Costs Used in Analysis, 1996 U.S. Dollars*

Variable	Cost, $	Source
Diagnostic test		
Positron emission tomography	1500	Insurer
	750–1500	Range of prices for sensitivity analysis
Single-photon emission computed tomography	475	Medicare
Stress echocardiography	265	Medicare
Planar thallium imaging	221	Medicare
Exercise electrocardiography	110	Medicare
Procedure, hospitalization, and other costs		
Coronary artery bypass surgery: 1- and 2-vessel	32 390	Medicare, average of 1- and 2-vessel procedures
Coronary artery bypass surgery: 3-vessel and left main	32 824	Medicare
Myocardial infarction: single admission	7415	Medicare
Cardiac catheterization with angiography	1810	Medicare
Percutaneous transluminal coronary angioplasty	11 685	Medicare, average of 1- and 2-vessel procedures

* Costs of coronary artery bypass surgery and percutaneous transluminal coronary angioplasty are calculated by adding Medicare's inpatient reimbursement and the professional fee components for initial evaluation, surgery, and inpatient follow-up. The cost of treating an acute myocardial infarction is derived by averaging payments for diagnosis-related groups 121 (uncomplicated myocardial infarction) and 122 (infarction with significant complication or comorbidity) plus professional fees for admission evaluation and daily inpatient follow-up. Outpatient medications are assumed to cost an average of $50 per month per medication for symptomatic patients not treated with revascularization. If new symptoms develop during a year and the patient does not undergo revascularization, a new drug is added.

Health Outcomes

We estimated the effects of each test on health outcomes by determining the test's sensitivity and specificity for the diagnosis of coronary artery disease (based on our review of the diagnostic test literature). We then used a Markov model to estimate the effects on health outcomes of correct and incorrect classification of disease, taking into account the greater benefits that result from detecting severe coronary disease.

The specific health outcome measures used here are life expectancy and QALYs (11–13). Quality-of-life improvements result from the successful treatment of angina pectoris and prevention of myocardial infarction. The specific quality weights attached to these events are derived from published utility assessments (14, 15). (Corrected values provided by Nease. Personal communication, 25 May 1995.)

The top panel of **Figure 1** displays the management algorithms used for the models. The bottom panel of **Figure 1** illustrates the possible progression of disease states, which are assumed to follow a Markov process with 1-year periods. Details of the algorithms appear in the Appendix.

We assume that patients with positive or indeterminate test results undergo angiography and that subsequent treatment (medications, angioplasty, or bypass surgery) depends on the anatomic distribution of obstruction. If patients have no coronary disease, they continue the previous management course. Angiography can cause severe complications (such as death and myocardial infarction) at rates reported in a large registry (16). Diseased patients are subject to the risks of angiography and the long-term consequences of their underlying disease and of treatment (such as subsequent angina, myocardial infarction, and death).

Survival and symptomatic outcomes vary with the anatomic pattern of obstruction. Estimated survival of patients with coronary disease treated surgically or medically is based on the corresponding arm of CASS (Coronary Artery Surgery Study) (17, 18). Data from that study are also the basis for estimates of the angina patterns experienced after surgical or medical intervention (17). The effects of treatment with angioplasty are based on a meta-analysis (19) showing that surgery was about 1.6 times as likely as angioplasty to relieve symptoms. Patients who have negative test results do not undergo angiography. If the result is false-negative, the patient continues to receive conservative management and delays or does not receive appropriate treatment with more aggressive medical therapy or revascularization. If the result is true-negative, the patient avoids the costs and health risks of unnecessary angiography.

Costs and Discounting

Because the analysis uses incremental costs, only components of costs that differ among the alternative diagnostic strategies need to be measured. The costs of the initial tests and of subsequent management contribute to differences in the total costs of each testing strategy. Test accuracy influences management: False-positive results lead to unnecessary angiography, and false-negative results reduce the immediate costs of surgery. Because the noninvasive tests rarely cause serious complications, complications of testing generate little cost and small differences in costs across alternative tests, except insofar as they lead to differences in the likelihood that angiography will be performed. Consequently, although all costs are considered potentially relevant, this analysis explicitly incorporates only costs arising from the testing strategies and treatment of coronary disease and its complications.

Medicare payments based on national average relative value units for 1996 are the principal source of outpatient and diagnostic costs; although private

Table 2. Studies Included in the Pooled Analysis of Test Performance*

Author, Year (Reference)	Patients	Patients with Myocardial Infarction	Extent of Stenosis for Coronary Disease	Fraction of Patients with Coronary Disease	Test Result				Sensitivity	Specificity
					True-Positive	False-Positive	False-Negative	True-Negative		
	n	%			←—— *n* ——→					
Planar thallium imaging										
Van Train et al., 1986 (21)	81	15	50	0.63	42	17	9	13	0.823	0.431
Mason et al., 1984 (22)	24	0	50	0.67	15	1	1	7	0.938	0.875
Weintraub et al., 1984 (23)	147	0	70	0.69	83	16	18	30	0.821	0.651
Bungo and Leland, 1983 (24)	81	0	70	0.67	38	8	16	19	0.704	0.704
Cinotti et al., 1983 (25)	96	0	70	0.72	52	3	17	24	0.753	0.890
Verani et al., 1978 (26)	82	0	50	0.59	38	1	10	33	0.792	0.971
Echocardiography										
Marangelli et al., 1994 (27)	80	0	75	0.41	42	3	5	30	0.894	0.909
Severi et al., 1994 (28)	429	0	75	0.57	185	18	61	165	0.752	0.902
Marwick et al., 1993 (29)	217	0	50	0.65	102	13	40	62	0.718	0.827
Previtali et al., 1993 (30)	80	19	50	0.71	45	4	12	19	0.789	0.826
Mazeika et al., 1992 (31)	50	26	70	0.72	23	1	13	13	0.639	0.929
Mazeika et al., 1992 (32)	55	0	70	0.73	16	1	24	14	0.400	0.933
Salustri et al., 1992 (33)	52	27	50	0.71	20	3	17	12	0.541	0.800
Segar et al., 1992 (34)	88	?	50	0.75	63	4	3	18	0.955	0.818
Cohen et al., 1991 (35)	70	27	70	0.73	44	1	7	18	0.863	0.947
Galanti et al., 1991 (36)	53	0	70	0.51	27	2	0	24	1.000	0.923
Single-photon emission computed tomography										
Maddahi et al., 1989 (37)	67	0	50	0.73	44	8	5	10	0.898	0.556
Tamaki et al., 1984 (38)	104	31	50	0.75	80	2	2	20	0.976	0.909
Mahmarian et al., 1990 (39)	296	40	70	0.45	56		6			
Marwick et al., 1993 (40)	97	0	70	0.57	49	13	6	29	0.891	0.690
Go et al., 1990 (41)	132	20+	50	0.74	77	8	21	26	0.786	0.765
Stewart et al., 1991 (42)	43	0	70	0.60	19	8	7	9	0.731	0.529
Nishimura et al., 1991 (43)	70	0	70	0.56	34	3	5	28	0.872	0.903
Galanti et al., 1991 (36)	53	0	70	0.51	25	1	2	25	0.926	0.962
Positron emission tomography										
Go et al., 1990 (41)	132	20+	50	0.74	93	6	5	28	0.949	0.824
Stewart et al., 1991 (42)	43	0	70	0.60	18	2	8	15	0.692	0.882
Grover-McKay et al., 1992 (44)	31	13	50	0.52	16	4	0	11	1.000	0.733

insurance payments, applicable to much of the population, are typically greater, Medicare payments serve as a rough proxy for the conceptually correct measure of marginal costs of each component of service (13).

Because Medicare does not reimburse for PET myocardial perfusion imaging, the assumed cost of this test is representative of private insurance payments. To account for uncertainty about the cost of PET scans, we calculated results for a range of costs, from 50% to 100% of the average insurer payment. Specific costs used in the analysis, with sources, are listed in **Table 1**.

Life-years, QALYs, and the present value of future health expenditures in 1996 U.S. dollars were calculated by using an inflation-adjusted interest rate of 3% (13).

Methods of Comparison

We ranked the testing strategies in ascending order of overall cost, eliminating from further consideration any strategy that was more expensive and less effective than (that is, strictly dominated by) another strategy (13, 20). We then calculated incremental cost-effectiveness ratios for all remaining alternatives. The cost-effectiveness ratio for SPECT compared with echocardiography, for example, is the difference between costs of the two testing strategies divided by the difference between the QALYs that each produces.

Results

Sensitivity and Specificity of Noninvasive Tests for Coronary Disease

A minority (27 of 68) of studies of the sensitivity and specificity of noninvasive tests identified in the literature review qualified for inclusion. **Table 2** shows the test characteristics reported in eligible studies; the Appendix Table lists excluded studies. **Table 3** reports the weighted average estimates of accuracy and results from meta-analyses of test performance characteristics of exercise testing and planar thallium imaging.

For the performance characteristics listed in the columns labeled "Sensitivity" and "Specificity" in **Table 3**, a positive test result is considered to be true-positive if angiographic disease in any vascular distribution is present. Values in the far right columns count as true-positives only the results in patients who have a 50% or greater obstruction of the left main coronary artery or significant stenosis in all three major coronary arteries.

Positron emission tomography is the most sensitive noninvasive test and exercise testing the least sensitive. Single-photon emission computed tomography is nearly as sensitive as and somewhat less specific than PET (specificity, 0.77 for SPECT and 0.82 for PET). Echocardiography is more specific than PET (0.88 compared with 0.82) but less sensitive (0.76 compared with 0.91). The ranges of reported accuracy for the noninvasive tests overlap because the sensitivity and specificity estimates for a given test vary across studies.

Published data on the sensitivity of PET for detecting severe (left main and three-vessel) coronary disease are unavailable, but as **Table 3** shows, planar thallium imaging, SPECT, and echocardiography are highly sensitive for detecting such disease. These figures are based on studies that included small numbers of patients. Exercise testing is not as sensitive, especially for one- or two-vessel disease.

Single-photon emission computed tomography has near-perfect sensitivity for severe disease. Specificity is not usually defined solely in terms of severe disease because few clinicians would consider a positive result in one- or two-vessel obstruction to be a false-positive result. Thus, on the basis of the included studies, PET seems to have sensitivity similar to that of SPECT, with slightly greater specificity; it is slightly less specific and more sensitive than stress echocardiography. Of the noninvasive tests, only exercise testing is likely to miss a significant fraction of patients with severe coronary disease.

Health Outcomes and Costs with Alternative Testing Strategies

Life Expectancy, Quality-Adjusted Life-Years, and Costs

Table 4 presents the effects of each testing strategy, for men and women 55 years of age, on life expectancy, QALYs, and costs of care. Figures for QALYs and life expectancy are presented to three decimal places to make apparent the small differences that result from using different test strategies, not because the estimates are as precise as this number of decimal places would imply. A false-positive test result causes little harm because coronary angiography imposes very little risk for death in a person without coronary disease. However, failure to detect disease can diminish life expectancy and the number of QALYs (the difference between the values in the true-positive and false-negative columns of **Table 4**). Thus, test sensitivity is the major cause of variation in health outcomes.

Life expectancy varies little by testing strategy at age 45 years, ranging from 23.832 years (exercise testing) to 23.841 years (PET and SPECT) among men and from 27.595 years (angiography) to 27.603 years (echocardiography) among women. The variation in life expectancy is similarly compressed at 65 years of age, when directly proceeding to angiography produces the most life-years. The testing strategies produce similar results when outcomes are measured in QALYs, but differences among tests in QALYs produced are greater because QALYs give "credit" for the detection and earlier treatment of less severe forms of disease. Initial testing with angiography produces the greatest increase in QALYs.

The total costs of care—including revascularization, medications, and treatment of myocardial infarction and other conditions—vary little among the alternative testing strategies. The lowest-cost strategy does not always start with the least expensive test, and it differs among demographic groups. For men and women 45 years of age and for women 55 years of age, initial testing with echocardiography is the least expensive option. For the other groups, initial exercise testing is the least expensive strategy.

Cost-Effectiveness of Alternative Strategies

The cost-effectiveness of each strategy is displayed in **Figures 2** (men) and **3** (women), which present costs in thousands of 1996 U.S. dollars and outcomes in QALYs at various ages associated with

Table 3. Sensitivity and Specificity of Noninvasive Tests for the Detection of Coronary Artery Disease

Diagnostic Test	Sensitivity (Range)*	Specificity (Range)*	Studies	Patients	Patients with Coronary Disease	Sensitivity for Left Main or Three-Vessel Disease	Studies	Patients
			n		%		*n*	
Planar thallium imaging	0.79 (0.70–0.94)	0.73 (0.43–0.97)	6	510	66	0.93	2	72
Single-photon emission computed tomography	0.88 (0.73–0.98)	0.77 (0.53–0.96)	8	628	70	0.98	3	92
Echocardiography†	0.76 (0.40–1.00)	0.88 (0.80–0.95)	10	1174	64	0.94	4	115
Positron emission tomography	0.91 (0.69–1.00)	0.82 (0.73–0.88)	3	206	68	Not available		
Exercise electrocardiography‡	0.68	0.77	132	24 074	66	0.86	48	

* Range of sensitivity and specificity reported in individual studies.
† Test characteristics for echocardiography are based on pooled studies of dobutamine, dipyridamole, and exercise as stressors. Pooling only studies that used dobutamine as a stressor gave similar results, with a sensitivity of 0.76 and a specificity of 0.87 for all coronary disease.
‡ Sensitivity of exercise electrocardiography for detection of all coronary artery disease is based on a meta-analysis that included 144 studies for estimates of sensitivity and 132 studies for specificity (45). Exercise electrocardiography results for sensitivity in left main and three-vessel disease were based on another meta-analysis (46). No studies of positron emission tomography reported sensitivity for left main and three-vessel disease.

Table 4. Costs, Life Expectancy in Years, and Quality-Adjusted Life-Years for Different Testing Strategies in 55-Year-Old Men and Women, with 3% Discount Rate and 50% Prevalence of Coronary Disease in Tested Population

Test Strategy	Men			Women		
	Cost	Life Expectancy	Quality-Adjusted Life-Years	Cost	Life Expectancy	Quality-Adjusted Life-Years
	$	*y*		*$*	*y*	
Angiography	34 661	16.601	12.259	41 101	19.735	14.137
Positron emission tomography	35 093	16.601	12.255	41 551	19.736	14.134
Single-photon emission computed tomography	34 047	16.600	12.253	40 510	19.736	14.132
Echocardiography	33 341	16.595	12.244	39 835	19.734	14.125
Planar thallium imaging	33 467	16.592	12.243	39 964	19.732	14.125
Exercise electrocardiography	33 281	16.581	12.234	39 815	19.724	14.119

each strategy. The incremental cost-effectiveness ratio for a comparison between any two strategies is the difference in their costs (the horizontal distance between the points), divided by the difference in outcomes (the vertical distance between the points); the ratio is thus the reciprocal of the slope of the line drawn between them. A dominated strategy refers to a strategy whose costs are greater than and outcomes inferior to those of another alternative (13); it appears in the figures as a point below (fewer QALYs) and to the right of (more expensive than) another test strategy (for example, PET compared with angiography).

Although the results are not identical for men and women, echocardiography, SPECT, and angiography are consistently favored under the baseline assumptions. The per-test cost of echocardiography exceeds that of exercise testing and planar thallium, yet the total cost of a strategy that uses echocardiography is about the same as or less than the cost of exercise testing and substantially less than the cost of a strategy that begins with planar thallium imaging. Because of its high sensitivity in severe disease, echocardiography produces better outcomes than exercise testing. Its outcomes are similar to or better than those of planar thallium imaging, at lower cost. Thus, it usually either dominates or is a highly cost-effective alternative to these tests.

Single-photon emission computed tomography produces more QALYs at higher cost than echocardiography; its cost-effectiveness ratio, compared with echocardiography, ranges from about $64 000 (in men 65 years of age) to nearly $150 000 (in women 45 years of age) per QALY gained. Positron emission tomography generally produces slightly better outcomes than SPECT, but at much greater cost, and immediate angiography dominates PET in every population group. As an initial testing strategy, immediate angiography is more expensive than SPECT. Its cost-effectiveness ranges from about $80 000 (in men 65 years of age) to nearly $200 000 (in women 45 years of age) per QALY gained relative to SPECT.

For every population group, the cost-effectiveness ratio for angiography compared with SPECT is somewhat higher than the cost-effectiveness ratio for SPECT compared with echocardiography. This implies that angiography would be preferred if a relatively high cost-effectiveness ratio is acceptable, that SPECT would be preferred if an intermediate cost-effectiveness ratio is acceptable, and that echocardiography would be preferred if the maximum acceptable cost-effectiveness ratio is lower. For example, for men 65 years of age, the cost-effectiveness ratio for SPECT compared with echocardiography is about $64 000; for angiography relative to SPECT, the ratio is about $80 000. Single-photon emission computed tomography will be chosen only if the acceptable cost per QALY is between these two numbers. When a cost-effectiveness ratio of greater than $80 000 is acceptable, angiography will be chosen.

A no-test strategy, in which patients are neither tested nor treated initially, is not a no-cost strategy. Persons who do not undergo testing for coronary disease avoid initial test costs but may experience myocardial infarction and undergo medical or surgical treatment in the future. In the populations considered here, a no-test strategy is unlikely to be considered attractive because echocardiography generates more QALYs at relatively low cost. The cost-effectiveness of echocardiography, compared with no testing, ranges from $31 000/QALY (in men 65 years of age) to $98 000/QALY (in women 45 years of age). Thus, testing is cost-effective with some but not all strategies. Depending on the acceptable cost-effectiveness ratio, echocardiography (for relatively low cost-effectiveness ratios), SPECT (for intermediate cost-effectiveness ratios), and immediate angiography (if a cost-effectiveness ratio of $80 000 per QALY is acceptable) are the choices that cost-effectiveness analysis tends to support.

Sensitivity to Prevalence of Disease in Tested Population and Costs of Positron Emission Tomography

At a different prevalence of disease, the ranking of tests changes little. In a population with a prevalence less than 50%, a screening test that has imperfect specificity will lead to more false-positive test results, adding unnecessary work-up costs. If the prevalence exceeds 50%, an insensitive test more frequently produces false-negative results, leading to failure to diagnose and treat the disease. For men 55 years of age with a 75% pretest risk for disease, initial angiography becomes more attractive (it will be chosen whenever a cost-effectiveness ratio of $45 000 is acceptable), and echocardiography remains preferable to exercise testing at conventionally acceptable levels of cost-effectiveness (with a cost-effectiveness ratio of $22 000/QALY).

At a 25% prevalence of disease, echocardiography seems to be the most attractive test under most circumstances; SPECT would be chosen over echocardiography only if a cost-effectiveness ratio of $110 000 is considered acceptable, and immediate angiography would be chosen over SPECT only at a cost-effectiveness ratio of $355 000. Thus, echocardiography remains a cost-effective strategy at a wide range of prevalence of disease, whereas immediate angiography is a cost-effective choice when the pretest probability of disease is high.

Myocardial perfusion imaging with PET would not appear cost-effective even if it cost half as much; at a per-test cost of $750, its cost-effectiveness ratio exceeds $180 000/QALY gained when compared with SPECT for men or women at any of the ages considered. At a per-test cost of $1000, the cost-effectiveness ratio is typically $335 000 or more.

Sensitivity to Indeterminacy Rate and Strategy after a Nondiagnostic Test Result

An increase in the indeterminacy rate generally increases the effective cost of a test but otherwise has no substantial effect on the results of the analysis. The indeterminacy rate is greatest for exercise testing (40% in the base case). The rate of nondiagnostic exercise tests varies widely (up to 60% in one large study [47]). Because it is often possible to predict which patients will have nondiagnostic exercise test results, we estimated the cost-effectiveness of exercise testing for a wide range of indeterminacy rates. In 55-year-old men, echocardiography dominates exercise testing by extended dominance unless the indeterminacy rate of exercise testing is well below 10%. Echocardiography has a cost-effectiveness ratio of less than $40 000 compared with exercise testing even when exercise testing never produces an indeterminate result.

Although we assume that an indeterminate test result leads directly to angiography, alternative strategies, such as following an indeterminate echocardiogram with SPECT, yield similar cost-effectiveness ratios.

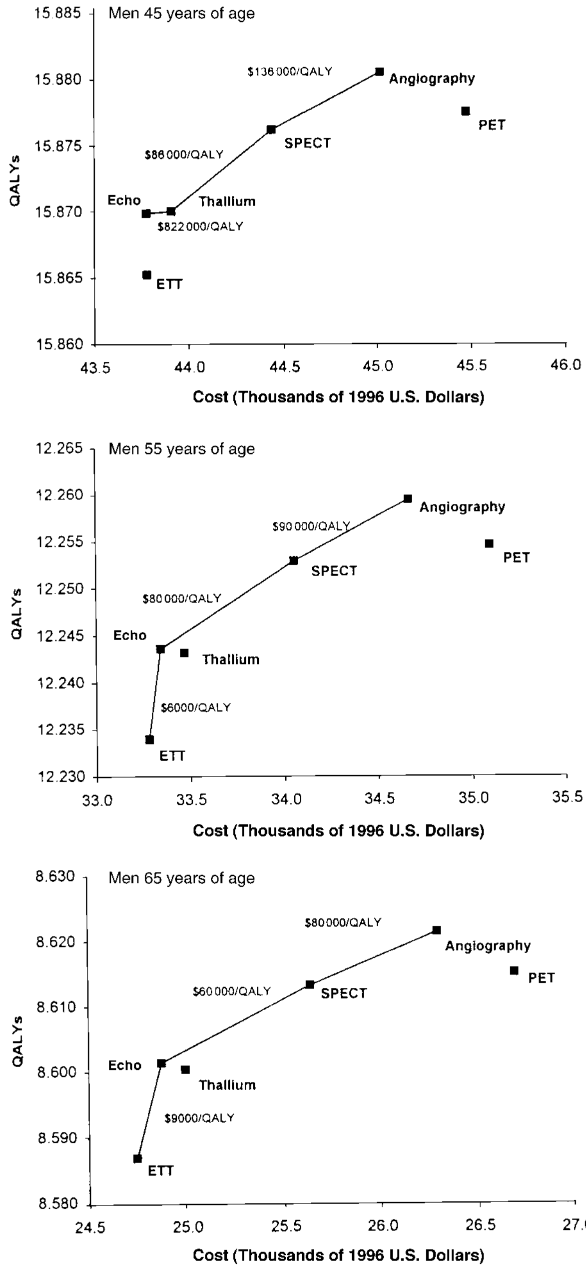

Figure 2. Cost-effectiveness of tests for coronary artery disease, in thousands of 1996 U.S. dollars per quality-adjusted life-year (*QALY*), for men at 50% pretest risk for disease. Echo = stress echocardiography; ETT = exercise electrocardiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

Complications of Angiography

Our results are not sensitive to assumptions about complications of angiography. In addition to the fatal complications (16) included in the base case, cardiac catheterization with angiography can cause stroke, myocardial infarction, and other nonfatal complications that might result in long-term disability or other health limitations (48). Because information about the duration of such complications is not available, we accounted for their effects by estimating life expectancy, QALYs, and costs by using an angiographic mortality rate three times as

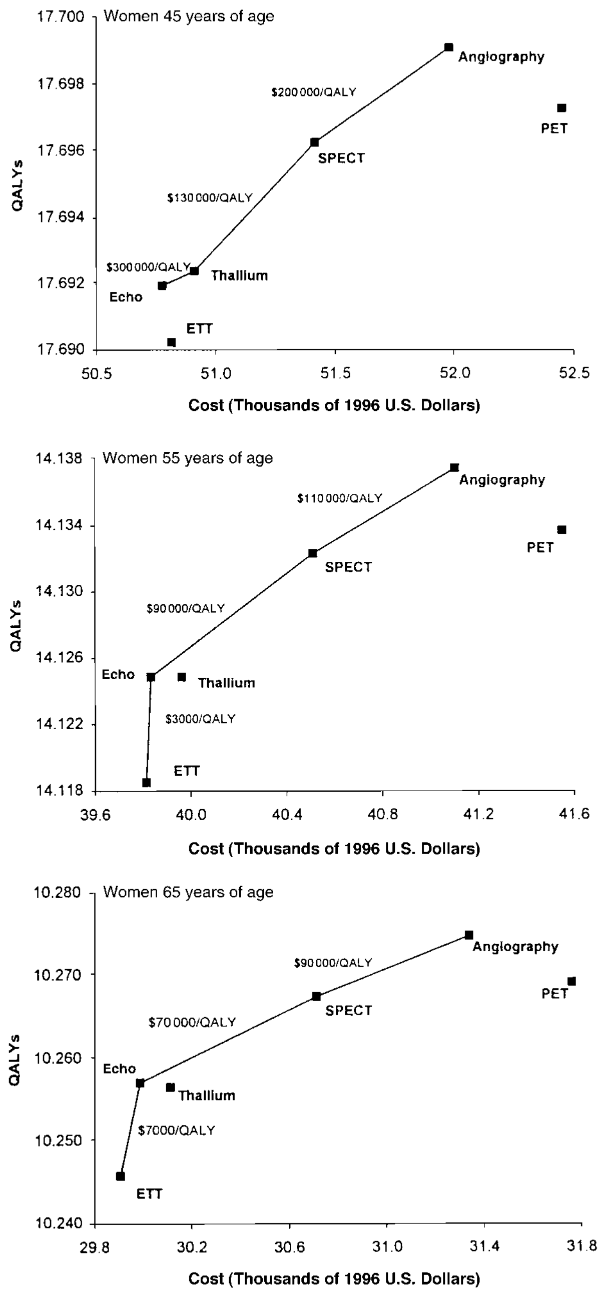

Figure 3. Cost-effectiveness of tests for coronary artery disease, in thousands of 1996 U.S. dollars per quality-adjusted life-year (*QALY*), for women at 50% pretest risk for disease. Echo = stress echocardiography; ETT = exercise electrocardiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

high as that assumed in the base case for 55-year-old men. Tripling the angiographic mortality rate has little effect on the rankings of the alternative tests. Echocardiography dominates planar thallium imaging and is highly cost-effective compared with exercise testing (the cost-effectiveness of echocardiography compared with exercise testing is about $5000/QALY). The cost-effectiveness ratio for SPECT compared with echocardiography is about $78 000/QALY. Angiography continues to dominate PET when outcomes are measured in QALYs, and the cost-effectiveness of angiography compared with SPECT is $166 000/QALY. Thus, echocardiography remains the dominant low-cost testing strategy; SPECT would be chosen over echocardiography if a cost-effectiveness ratio of $80 000 to $166 000/QALY is considered acceptable, and angiography would be selected only if a higher cost per QALY is acceptable.

Discussion

Cost-effectiveness considerations suggest that echocardiography, SPECT, and immediate angiography are the most appropriate diagnostic tests for patients at intermediate pretest risk for having coronary disease. Strategies based on exercise testing and planar thallium imaging lead to worse outcomes and, in some groups, higher overall costs than echocardiography. Positron emission tomography is dominated by angiography, which produces more favorable health outcomes and costs less. Furthermore, when PET is compared with SPECT, it results in cost-effectiveness ratios several-fold greater than those usually considered acceptable.

Although one article on PET for the detection of coronary disease concluded that PET is cost-effective relative to exercise testing, SPECT, and immediate angiography (49), it made several assumptions that tended to favor PET: an equal rate of angiographic complications for patients with and without coronary disease; equal test accuracy in the detection of severe coronary disease, for which treatment is highly beneficial, and more limited coronary disease; larger declines in quality of life from angina and myocardial infarction than methodologically rigorous utility estimates support (14, 15); and greater benefits from treatment of coronary disease than those found in randomized trials. Finally, the earlier study appeared to report "average" cost-effectiveness ratios, that is, costs of an intervention divided by the associated health outcomes. Average ratios cannot be applied directly for cost-effectiveness comparisons, whereas the current study uses standard incremental cost-effectiveness ratios (difference between the costs of two interventions divided by the difference in outcomes) (12, 13).

Our analysis relies on the published assessments of test performance that met a set of predefined quality criteria. Like every study relying on published information, ours may be subject to publication bias; studies of diagnostic test performance reporting lower figures for sensitivity or specificity may be less likely to be submitted or accepted for publication. Publication bias may be greater for tests whose apparent accuracy is more variable. The reported accuracy of a given test varies among published studies and may vary more in routine clinical settings, reflecting differences in patient populations and the expertise of the physician interpreting the image or test result. Such variation may be particularly important for echocardiography and could even alter the ranking of the outcomes achieved with each test strategy. Test accuracy may also be different in other patient populations; a recent meta-analysis of exercise echocardiography and SPECT, using inclusion criteria different from ours, reported that echocardiography had somewhat greater sensitivity and lower specificity than we found (50). Because costs also vary, the cost-effectiveness of a given test strategy can differ according to the setting. We suggest that local costs and provider-specific test characteristics be assessed wherever possible, and that physicians recognize this caveat when selecting a diagnostic test for a patient suspected of having coronary disease.

Noninvasive tests are often used to estimate prognosis, an indication not considered in this analysis. For example, exercise testing and imaging-based stress tests provide quantitative information that can be used to assess response to therapy and the functional significance of anatomic lesions. Thus, they can serve as adjuncts to coronary angiography. There is no consensus about how management should be modified by such information, but the value of such uses, which support an initial strategy of testing with echocardiography or SPECT rather than angiography, should be considered in choosing among testing strategies.

To prolong life, a noninvasive test must detect the most severe forms of coronary disease. Because current noninvasive tests are highly sensitive for three-vessel and left-main disease, improved test performance characteristics are unlikely to greatly affect mortality unless treatment of less severe forms of disease is also shown to prolong life substantially. That is why echocardiography and SPECT are relatively cost-effective testing options.

From Veterans Affairs Palo Alto Health Care System, and Stanford University, Stanford, California; and Kaiser Permanente, Oakland, California.

Grant Support: This research grew out of a project supported by the Blue Cross and Blue Shield Association. Dr. Garber was a Health Services Research and Development Senior Research Associate of the Department of Veterans Affairs and Dr. Solomon was a Veterans Affairs–Robert Wood Johnson Clinical Scholar when much of the work was performed. Opinions expressed here are not necessarily those of the Blue Cross and Blue Shield Association, the Department of Veterans Affairs, or Kaiser Permanente.

Acknowledgments: The authors thank Douglas K. Owens, MD, MSc; David M. Eddy, MD, PhD; Earl P. Steinberg, MD, MPP; and Mark A. Hlatky, MD, for their comments and suggestions and Ann Hwang, Jin Yang, and Nikhil Chanani for helpful research assistance.

Requests for Reprints: Alan M. Garber, MD, PhD, Center for Primary Care and Outcomes Research, Stanford University School of Medicine, 30 Alta Road, Stanford, CA 94305-8006.

Current Author Addresses: Dr. Garber: Veterans Affairs Palo Alto Health Care System and Stanford University School of Medicine, 30 Alta Road, Stanford, CA 94305-8006.
Dr. Solomon: Care Management Institute, Kaiser Permanente, 1 Kaiser Plaza, 16th Floor, Oakland, CA 94612.

References

1. **Brown KA.** Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age. Circulation. 1991;83:363-81.
2. **Hackshaw BT.** Excluding heart disease in the patient with chest pain. Am J Med. 1992;92:46S-51S.
3. **Chou TM, Amidon TM.** Evaluating coronary artery disease noninvasively—which test for whom? West J Med. 1994;161:173-80.
4. **Bonow RO, Berman DS, Gibbons RJ, Johnson LL, Rumberger JA, Schwaiger M, et al.** Cardiac positron emission tomography. A report for health professionals from the Committee on Advanced Cardiac Imaging and Technology of the Council on Clinical Cardiology, American Heart Association. Circulation. 1991;84:447-54.
5. **Schwaiger M.** Myocardial perfusion imaging with PET. J Nucl Med. 1994;35:693-8.
6. **Gewirtz H.** PET scanning in evaluation of ischemic heart disease. R I Med J. 1991;74:527-31.
7. **Gould KL.** Clinical cardiac positron emission tomography: state of the art. Circulation. 1991;84(3 Suppl):I22-36.
8. **Sox H, Blatt M, Higgins M, Marton K.** Medical Decision Making. Boston: Butterworths; 1988.
9. **Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R, et al.** Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation. 1981;64:360-7.
10. **Diamond GA, Forrester JS.** Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979;300:1350-8.
11. **Weinstein MC, Stason WB.** Hypertension: A Policy Perspective. Cambridge, MA: Harvard Univ Pr; 1976.
12. **Drummond MF, Stoddart GL, Torrance GW.** Methods for the Economic Evaluation of Health Care Programmes. New York: Oxford Univ Pr; 1987.
13. **Gold MR, Siegel JE, Russell LB, Weinstein MC.** Cost-Effectiveness in Health and Medicine. New York: Oxford Univ Pr; 1996.
14. **Nease RF Jr, Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Shaw L, et al.** Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic Heart Disease Patient Outcomes Research Team. JAMA. 1995;273:1185-90.
15. **Tsevat J, Goldman L, Soukup JR, Lamas GA, Connors KF, Chapin CC, et al.** Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making. 1993;13:161-5.
16. **Lozner EC, Johnson LW, Johnson S, Krone R, Pichard A, Vetrovec GW, et al.** Coronary arteriography 1984-1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. II. An analysis of 218 deaths related to coronary arteriography. Cathet Cardiovasc Diagn. 1989;17:11-4.
17. **Rogers WJ, Coggin CJ, Gersh BJ, Fisher LD, Myers WO, Oberman A, et al.** Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery. The Coronary Artery Surgery Study (CASS). Circulation. 1990;82:1647-58.
18. **Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR Jr, Chaitman BR, et al.** Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation. 1994;90:2645-57.
19. **Sim I, Gupta M, McDonald K, Bourassa M, Hlatky MA.** A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. Am J Cardiol. 1995;76:1025-9.
20. **Keeney RL, Raiffa H.** Decisions with Multiple Objectives. Cambridge, England: Cambridge Univ Pr; 1993.
21. **Van Train KF, Berman DS, Garcia EV, Berger HJ, Sands MJ, Friedman JD, et al.** Quantitative analysis of stress thallium-201 myocardial scintigrams: a multicenter trial. J Nucl Med. 1986;27:17-25.
22. **Mason JR, Palac RT, Freeman ML, Virupannavar S, Loeb HS, Kaplan E, et al.** Thallium scintigraphy during dobutamine infusion: nonexercise-dependent screening test for coronary disease. Am Heart J. 1984;107:481-5.
23. **Weintraub WS, Madeira SW Jr, Bodenheimer MM, Seelaus PA, Katz RI, Feldman MS, et al.** Critical analysis of the application of Bayes' theorem to sequential testing in the noninvasive diagnosis of coronary artery disease. Am J Cardiol. 1984;54:43-9.
24. **Bungo MW, Leland OS Jr.** Discordance of exercise thallium testing with coronary arteriography in patients with atypical presentations. Chest. 1983;83:112-6.
25. **Cinotti L, Meignan M, Usdin JP, Vasile N, Castaigne A.** Diagnostic value of image processing in myocardial scintigraphy. J Nucl Med. 1983;24:768-74.
26. **Verani MS, Marcus ML, Razzak MA, Ehrhardt JC.** Sensitivity and specificity of thallium-201 perfusion scintigrams under exercise in the diagnosis of coronary artery disease. J Nucl Med. 1978;19:773-82.

27. **Marangelli V, Iliceto S, Piccinni G, De Martino G, Sorgente L, Rizzon P.** Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography. J Am Coll Cardiol. 1994;24:117-24.
28. **Severi S, Picano E, Michelassi C, Lattanzi F, Landi P, Distante A, et al.** Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease. Comparison with exercise electrocardiography. Circulation. 1994;89:1160-73.
29. **Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM, et al.** Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both? J Am Coll Cardiol. 1993;22:159-67.
30. **Previtali M, Lanzarini L, Fetiveau R, Poli A, Ferrario M, Falcone C, et al.** Comparison of dobutamine stress echocardiography, dipyridamole stress echocardiography and exercise stress testing for diagnosis of coronary artery disease. Am J Cardiol. 1993;72:865-70.
31. **Mazeika PK, Nadazdin A, Oakley CM.** Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol. 1992;19:1203-11.
32. **Mazeika P, Nihoyannopoulos P, Joshi J, Oakley CM.** Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease. Br Heart J. 1992;67:144-9.
33. **Salustri A, Fioretti PM, Pozzoli MM, McNeill AJ, Roelandt JR.** Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease. Eur Heart J. 1992;13:70-7.
34. **Segar DS, Brown SE, Sawada SG, Ryan T, Feigenbaum H.** Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. J Am Coll Cardiol. 1992;19:1197-202.
35. **Cohen JL, Greene TO, Ottenweller J, Binenbaum SZ, Wilchfort SD, Kim CS.** Dobutamine digital echocardiography for detecting coronary artery disease. Am J Cardiol. 1991;67:1311-8.
36. **Galanti G, Sciagra R, Comeglio M, Taddei T, Bonechi F, Giusti F, et al.** Diagnostic accuracy of peak exercise echocardiography in coronary artery disease: comparison with thallium-201 myocardial scintigraphy. Am Heart J. 1991;122:1609-16.
37. **Maddahi J, Van Train K, Prigent F, Garcia EV, Friedman J, Ostrzega E, et al.** Quantitative single photon emission computed thallium-201 tomography for detection and localization of coronary artery disease: optimization and prospective validation of a new technique. J Am Coll Cardiol. 1989;14:1689-99.
38. **Tamaki N, Yonekura Y, Mukai T, Kodama S, Kadota K, Kambara H, et al.** Stress thallium-201 transaxial emission computed tomography: quantitative versus qualitative analysis for evaluation of coronary artery disease. J Am Coll Cardiol. 1984;4:1213-21.
39. **Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS.** Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. J Am Coll Cardiol. 1990;15:318-29.
40. **Marwick T, Willemart B, D'Hondt AM, Baudhuin T, Wijns W, Detry JM, et al.** Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and 99mTc-MIBI single photon emission computed tomography. Circulation. 1993;87:345-54.
41. **Go RT, Marwick TH, MacIntyre WJ, Saha GB, Neumann DR, Underwood DA, et al.** A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. J Nucl Med. 1990;31:1899-905.
42. **Stewart RE, Schwaiger M, Molina E, Popma J, Gacioch GM, Kalus M, et al.** Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. Am J Cardiol. 1991;67:1303-10.
43. **Nishimura S, Mahmarian JJ, Boyce TM, Verani MS.** Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacologic coronary vasodilation with adenosine for assessing coronary artery disease. J Am Coll Cardiol. 1991;18:736-45.
44. **Grover-McKay M, Ratib O, Schwaiger M, Wohlgelernter D, Araujo L, Nienaber C, et al.** Detection of coronary artery disease with positron emission tomography and rubidium 82. Am Heart J. 1992;123:646-52.
45. **Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, et al.** Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation. 1989;80:87-98.
46. **Detrano R, Gianrossi R, Froelicher V.** The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis. 1989;32:173-206.
47. **Christian TF, Miller TD, Bailey KR, Gibbons RJ.** Exercise tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiograms. Ann Intern Med. 1994;121:825-32.
48. **Johnson LW, Lozner EC, Johnson S, Krone R, Pichard AD, Vetrovec GW, et al.** Coronary arteriography 1984-1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. I. Results and complications. Cathet Cardiovasc Diagn. 1989;17:5-10.
49. **Patterson RE, Eisner RL, Horowitz SF.** Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. Circulation. 1995;91:54-65.
50. **Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS.** Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA. 1998;280:913-20.