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Bayesian Comparison of Cost-Effectiveness of Different Clinical Approaches to Diagnose Coronary Artery Disease

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The objective of this study was to compare the cost-effectiveness of four clinical policies (policies I to IV) in the diagnosis of the presence or absence of coronary artery disease. A model based on Bayes' theorem and published clinical data was constructed to make these comparisons. Effectiveness was defined as either the number of patients with coronary disease diagnosed or as the number of quality-adjusted life years extended by therapy after the diagnosis of coronary disease.

The following conclusions arise strictly from analysis of the model and may not necessarily be applicable to all situations. 1) As prevalence of coronary disease in the population increased, it caused a linear increase in cost per patient tested, but a hyperbolic decrease in cost per effect, that is, increased cost-effectiveness. Thus, cost-effectiveness of all policies (I to IV) was poor in populations with a prevalence of disease below 10%, for example, asymptomatic people with no risk factors. 2) Analysis of the model also indicates that at prevalences less than 80%, exercise thallium scintigraphy alone as a first test (policy II) is a more cost-effective initial test than is exercise electrocardiography alone as a first test (policy I) or exercise electrocardiography first combined with thallium imaging as a second test (policy IV). 3) Exercise electrocardiography before thallium imaging (policy IV) is more cost-effective than exercise electrocardiography alone (policy I) at prevalences less than 80%. 4) Noninvasive exercise testing before angiography (policies I, II and IV) is more cost-effective than using coronary angiography as the first and only test (policy III) at prevalences less than 80%. 5) Above a threshold value of prevalence of 80% (for example patients with typical angina), proceeding to angiography as the first test (policy III) was more cost-effective than initial noninvasive exercise tests (policies I, II and IV).

One advantage of this quantitative model is that it estimates a threshold value of prevalence (80%) at which the rank order of policies changes. The model also allows substitution of different values for any variable as a way of accounting for the uncertainty inherent in the data. In conclusion, it is essential to consider the prevalence of disease when selecting the most cost-effective clinical approach to making a diagnosis.

Both exercise thallium-201 myocardial perfusion imaging (1,2) and cardiac blood pool imaging (1,3) have been reported to offer improved sensitivity and specificity over exercise electrocardiography to diagnose coronary artery disease. Other studies have demonstrated less improvement in diagnostic accuracy by radionuclide imaging, and the optimistic reports from large medical centers may not be reproducible everywhere. These radionuclide tests certainly remain imperfect and more expensive than exercise electrocardiography. The cost and false results of noninvasive studies, plus the relative safety of coronary angiography, have led some physicians to recommend angiography rather than noninvasive testing early in evaluation of patients with suspected coronary disease (4–6).

Assessment of the cost-effectiveness of health care is exceedingly complex (7), particularly because of multiple factors needed to define effectiveness (7–9). Estimating cost-effectiveness of management of coronary disease is particularly difficult because of the uncertainty concerning the role of coronary artery bypass surgery (10–13). The magnitude of the problem of coronary disease and rising health

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care costs (1,14–16), however, require consideration of cost-effectiveness of various clinical approaches to the diagnosis of coronary disease despite problems inherent in the analysis.

The purpose of the present study was to devise a model to test the following hypotheses: 1) the prevalence of disease in the population influences cost-effectiveness of any clinical policy; 2) thallium-201 imaging is more cost-effective than exercise electrocardiography as an initial screening test; 3) coronary angiography as an initial screening test is more cost-effective than the less accurate noninvasive tests; and 4) sequential use of exercise electrocardiography followed by thallium-201 imaging is more cost-effective than either test alone as an initial screening test.

We used actual data from patients at Mount Sinai Medical Center (17), the Framingham Study (18) and other epidemiologic data (19,20) as well as the fees for tests allowed by New York City Medicaid-Medicare. Furthermore, we used previously published data for complication rates of procedures (5,21–22) and coronary disease (5,11,12,23–35). These real data were employed to develop a model to compare the cost-effectiveness of four different specific clinical policies to diagnose coronary disease. This limited objective appears attainable and allows several important and realistic comparisons of different clinical policies which are uniquely determined by physicians.

Methods

A conceptual model was developed based on available real data to estimate comparative cost-effectiveness of different clinical policies (policies I to IV) (Table 1) for utilization of noninvasive exercise tests. This model permits varying the values of data that are very difficult to obtain, such as the rates and costs of complications due to diagnostic procedures or due to coronary disease in particular patient groups.

Definitions of effectiveness of tests. The most difficult problem in any assessment of cost-effectiveness is to define effectiveness of health care (7–9). For our purposes, we defined effectiveness of the noninvasive tests in two ways, the first being the ability to identify accurately a patient who has coronary artery disease (8). This straightforward definition assumes that the goal of a test is to make a diagnosis; it does not attempt to account for more controversial variables such as the risk, cost and benefit of medical or surgical therapies.

Second, in an attempt to account for several of the complex clinical variables that influence the effectiveness of management of coronary disease, we also defined effectiveness of tests for coronary disease in terms of the clinical outcome for patients undergoing the tests, that is, an increase in the number of quality-adjusted life years for a patient over a 10 year follow-up period (Appendix I) (36). We multiplied the number of years of life extended by therapy (over a 10 year follow-up period) by the adjusted quality of life, expressed as a fraction of full health without symptoms. Although this value of quality-adjusted life years adjusted as a fraction of full quality of life per 10 years is controversial, it does account for many important clinical variables (36). It seems justifiable for our purpose because it is used here only as a common denominator to facilitate the comparison of effectiveness of different clinical policies. Briefly, we assumed that the accurate diagnosis of coronary disease increased the number of quality-adjusted life years by 2 years over a 10 year follow-up period, based on a synthesis of available data (12,21–35). We restricted this variable to a 10 year follow-up period because the natural history of patients treated with modern medical or surgical therapies is not known beyond 10 years. If therapies have a sustained long-term effect on the natural history of coronary disease, then the outcome of therapy (number of quality-adjusted life years) would be more favorable than our analysis indicates.

Calculation of cost-effectiveness (Appendix II). Cost-effectiveness was illustrated as its inverse: cost per effect. Specifically, we calculated total costs as direct costs (fees for tests) times the number of patients tested (as decided by physician's policy) plus the induced costs (the number of patients tested times the costs of complications resulting from test procedures or of coronary disease missed by false negative test results) (8). Mortality from coronary disease,

Table 1. Clinical Policies (I to IV)* to Diagnose Coronary Disease

Clinical Policy	Exercise Electrocardiography	Exercise Thallium (Tl-201) Imaging	Coronary Angiography
I	1st	None	2nd if ECG = positive or nondiagnostic
II	None	1st	2nd if Tl-201 = positive or nondiagnostic
III	None	None	1st
IV	1st	2nd if ECG = positive or nondiagnostic	3rd if Tl-201 = positive or nondiagnostic

*These policies represent proposals for testing, not our recommendations. ECG = electrocardiography; Tl-201 = thallium-201 imaging.

or from test procedures was not assigned any arbitrary dollar value, but was considered separately or incorporated into the calculation of quality-adjusted life years. We calculated $(\text{cost-effectiveness})^{-1}$ as cost (in dollars) per effect:

$$\frac{\text{Direct costs} + \text{Induced costs}}{\text{Effectiveness}},$$

where effectiveness is either a patient with coronary disease diagnosed or an extension of the number of quality-adjusted life years over a 10 year follow-up period. Calculation of direct and induced costs is described briefly and with detailed equations (Appendix II, using variables in Table 2). The total direct costs, therefore, were calculated as the fee for each test multiplied by the number of patients having the test and summed for all tests. The fees for each test were obtained from Medicare Part B Prevailing Charges for All Covered Services, New York City, 1981, rather than trying to estimate incremental costs. The fees for tests are relatively fixed, but the number of patients who have a particular test depends on the policy used by the physician to decide which patients should have each test (Table 1).

Estimation of costs. The induced costs of exercise tests are derived from the complications and mortality resulting from each test, as well as from the complications and mortality resulting from coronary disease that is inadequately treated because of false negative test results. Costs of complications are difficult to estimate, but we synthesized actual data for this purpose. We assumed that the typical complication of each test or of coronary artery disease would be nonfatal myocardial (or cerebral for angiography) infarction, requiring 2 weeks in the hospital and 3 months away from employment (5,22) at an average cost of $20,000 per complication. We adjusted the annual rate of nonfatal myocardial infarction in patients with coronary disease (23) to estimate the rate of infarction in the subgroup of patients with symptoms not severe enough to require surgery and with false negative exercise test results. Because we required that the patient achieve 85% of age-predicted maximal heart rate to interpret the test as negative, most patients with false negative tests would have good exercise capacity and, therefore, a low risk of nonfatal myocardial infarction or death (34,35). Furthermore, only patients with mild to moderate symptoms are likely to avoid coronary angiography despite negative exercise test results because patients with severe symptoms are likely to be referred for angiography pending surgery to relieve symptoms. There is evidence that patients with mild to moderate symptoms have a relatively good prognosis (35). Thus, we assumed a 15% rate of nonfatal myocardial infarction over 10 years in patients with false negative exercise test results.

We analyzed the sensitivity of the model to changes in this variable by testing the effect of higher rates of complications (50%) over 10 years in patients with coronary disease missed because of false negative test results (Table 3). We assumed mortality rates for coronary artery disease missed by false negative test results of 15% over 10 years, after adjusting for the good exercise tolerance, mild to moderate symptoms (34,35) and relative frequency of left main or three vessel coronary artery disease in patients with false negative exercise test results (17).

We used a modification of Bayes' theorem (37,38) to calculate the number of patients having each test or experiencing the complications (Appendix II). These calculations were based on the sensitivities and specificities of each test

Table 2. Parameters Used in Calculation

F_E = fee for exercise electrocardiography = $175
F_T = fee for exercise thallium-201 imaging = $385
F_A = fee for coronary angiography = $2,825
C = cost of a complication = $20,000 (assumed to be myocardial infarction)
R_E = rate of complications with exercise electrocardiography = 0.0005
R_T = rate of complications with exercise thallium-201 imaging = 0.0005
R_A = rate of complications with coronary angiography = 0.0075
R_F = rate of complications per 10 years for patients with coronary disease but false negative exercise tests = 0.15
M_E = mortality due to exercise electrocardiography = 0.00005
M_T = mortality due to exercise thallium-201 imaging = 0.00005
M_A = mortality due to coronary angiography = 0.0003
M_F = mortality per 10 years for patients with coronary disease but false negative exercise tests = 0.15
Sn_E = sensitivity for exercise electrocardiography = 0.84 = true positive tests/all patients with coronary disease who have a diagnostic test
Sp_E = specificity for exercise electrocardiography = 0.62 = true negative tests/all patients with diagnostic tests who do not have coronary disease
Ndx_E = rate of nondiagnostic exercise electrocardiography = 0.36 = patients with test result which is equivocal or not diagnostic/all patients who had test
Sn_T = sensitivity of exercise thallium-201 imaging = 0.88
Sp_T = specificity of exercise thallium-201 imaging = 0.74
Ndx_T = rate of nondiagnostic exercise thallium-201 imaging = 0.09
ΔQALY = quality-adjusted life years extended by therapy after making diagnosis of coronary disease (per 10 years of follow-up) = 2.0 years

Numbers represent fraction of patients unless indicated otherwise.

Table 3. Sensitivity Analysis

A. Since each parameter is subject to error, we tested the effect on calculations of varying parameters as follows from the standard values in Table 2.
B. Low risk coronary angiography
C = \$20,000 → \$10,000
R_A = 0.0075 → 0.0020
M_A = 0.0003 → 0.0001
C. High risk if false negative, F(−), exercise tests
C = \$20,000 → \$200,000
R_F = 0.15 → 50
M_F = 0.15 → 50
D. High impact of therapy to improve $^{\Delta}$QALY
Q = 2.0 → 5.0 (yr/10 yr)
E. Low cost coronary angiography
F_A = \$2,825 → \$1,500
F. Low cost Tl-201
F_T = \$385 → \$175

Abbreviations as in Table 2.

in our institution (17) (Table 2) and the assumed rates (0.0 to 1.0) of complications over the full range of prevalence of coronary disease.

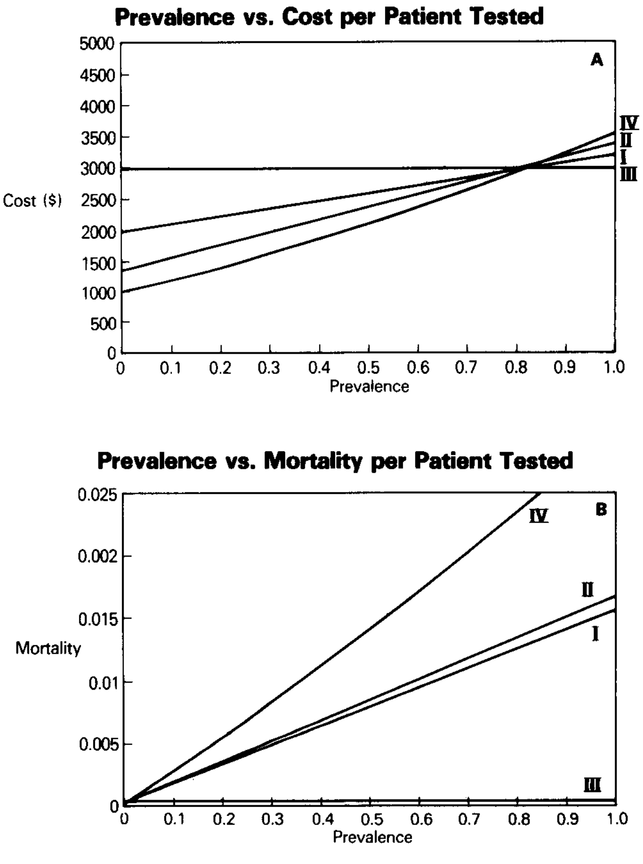
Clinical policies for employing diagnostic tests. Using this model, we tested four different clinical policies for employing diagnostic tests for coronary disease. The policies express several different and, necessarily, simplified diagnostic approaches to coronary disease (Table 1). These policies represent proposals to be tested, not our recommendations. Patients are screened by exercise electrocardiography (policy I) or exercise thallium-201 imaging (policy II) and are referred for coronary angiography only if the noninvasive test is positive or nondiagnostic. Although the electrocardiogram would be monitored for arrhythmias during exercise in policy II, the ST segment changes would not be used to predict the presence or absence of coronary artery disease by policy II. Policy III assumes that coronary angiography is performed as the initial screening test. Policy IV assumes that all patients have exercise electrocardiography and that patients with positive or nondiagnostic results are referred for exercise thallium imaging. Only those patients who also have positive or nondiagnostic thallium imaging are referred for coronary angiography.

Analysis of data. Since many assumptions are necessary in any model of cost-effectiveness, we performed sensitivity analysis of the model to these variables by repeating calculations after making changes in the values of sensitivity, specificity, fees, rates and costs of complications and mortality (Table 3). In this way we attempted to deal with the inherent inaccuracies of the available data, particularly to determine whether these variables would influence merely the quantitative cost-effectiveness or, more importantly, the rank order comparison of different clinical policies. All variables used in the model could be varied to reflect the situation at a particular institution and substituted in the general equations (Appendix I and II).

Results

Effect of prevalence on costs. As the prevalence of coronary artery disease increases in the population tested, the cost and mortality rate over a 10 year follow-up period also increase as linear functions (Fig. 1). As prevalence increases, there are hyperbolic decreases in cost per patient with coronary disease diagnosed and in cost per increased number of quality-adjusted life years (Fig. 2), both indicating increased cost-effectiveness. Thus, despite the increase in absolute cost and mortality rate with increasing

Figure 1. Effects of disease prevalence on cost (**A**) and mortality rate (**B**) per patient tested for clinical policies I to IV. Prevalence of coronary disease increases along the horizontal axis. Dollar cost (**A**) or mortality per patient tested over a 10 year follow-up period (**B**) increases up the vertical axis. Note that cost and mortality rate per patient tested increase with prevalence of disease for all policies except policy III (angiography only). Cost is lowest at low prevalences for policy IV (electrocardiography before thallium), but mortality rate is also highest for policy IV because of the high false negative rate of sequential noninvasive test results. False negative test results cause the cost of policy IV to become highest at high disease prevalences, and false positive test results increase the cost of policy I at the lowest disease prevalence.



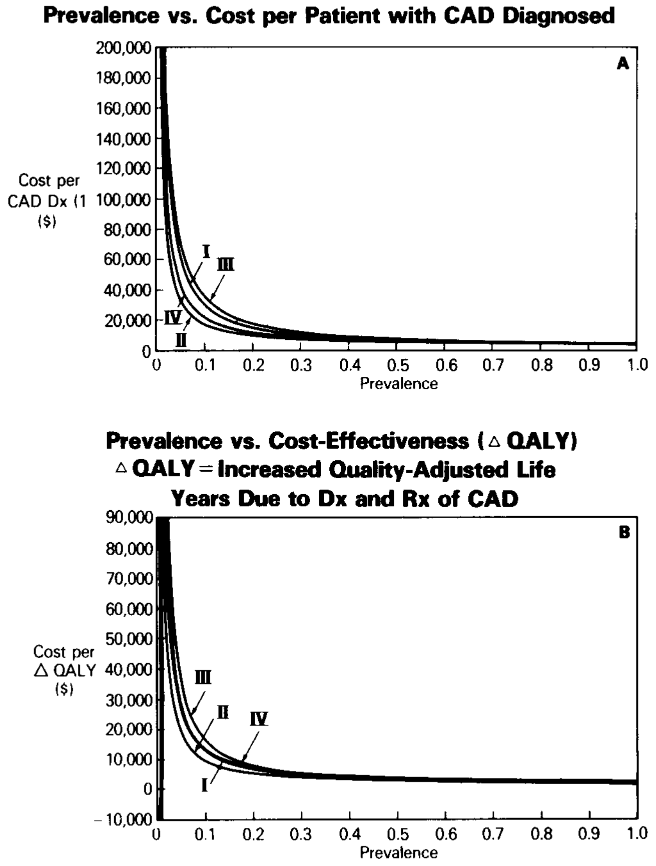


Figure 2. Effects of disease prevalence on cost-effectiveness. As the prevalence of coronary disease increases along the horizontal axis, there are dramatic decreases in the dollar cost per patient with coronary artery disease diagnosed (CAD Dx) (**A**), and the cost per quality-adjusted life years ($^{\Delta}$QALY) extended (**B**). The vertical axis is expressed as cost per effect, or (cost-effectiveness)$^{-1}$. The number of quality-adjusted life years is defined in the text and Appendix I. Note that policy II (thallium imaging only) is most cost-effective (lowest cost per CAD Dx or cost per $^{\Delta}$QALY), and policy III (angiography only) is least cost-effective at low prevalences. CAD = coronary artery disease.

prevalence of disease, cost-effectiveness improves at higher prevalence. The most dramatic features of the hyperbolic relation between prevalence and cost-effectiveness are the very high cost (low cost-effectiveness) at low prevalences and the dramatic differences among policies I to IV at lower prevalences.

Comparison of clinical policies. Comparison of cost-effectiveness of different clinical policies is clearest in particular patient examples selected to illustrate varied prevalences of disease (Fig. 3). In a population of 45 year old men with no symptoms or risk factors to indicate a 3% prevalence, policy II (thallium imaging only) is most cost-effective, that is, lowest cost per effect, followed by policy IV (electrocardiography before thallium) and policy I (electrocardiography alone). Policy III (angiography only) is the least cost-effective at the 3% prevalence. The rank order of cost-effectiveness is the same at a 17% prevalence. At 50% prevalence (atypical chest pain), policy II remains the most cost-effective, but policy IV is least cost-effective and differences among policies are less dramatic. At 90% prevalence (typical angina) policy III (angiography only) becomes most cost effective and policy IV is the least cost-effective. Thus, the rank order of cost-effectiveness of policies I to IV changes as prevalence increases (Fig. 3).

Sensitivity analysis of variables influencing cost-effectiveness. Because accurate data are hard to obtain and many assumptions are involved in these calculations, we systematically changed several variables in the equations to test their influence on cost-effectiveness (Table 2, Fig. 4 and 5). We analyzed the effects of changes in clinically related variables; for example, low risk coronary angiography involved a lower cost of complications as well as lower rates of complications and death. When each policy is examined over the range of prevalences (Fig. 4), cost-effectiveness is improved most (lowest cost per quality-adjusted life-years extended) if therapeutic results are better, that is, if this value is extended from 2 to 5 years at full health over a 10 year follow-up period (Fig. 5D) or if angiography is provided at a low cost (Fig. 5E). Reducing the risk of angiography (Fig. 5B) or the cost of thallium imaging (Fig. 5F) also improves cost-effectiveness. Cost-effectiveness is reduced dramatically if the risk of complications and death is high in patients whose coronary disease is missed by false negative tests. Increasing the risk of a false negative result has its greatest impact on policy IV (electrocardiography before thallium imaging) because the probability of a false negative result is highest.

Policy III (angiography only) became most cost-effective under these conditions of increased risk (Fig. 5C) because it had the fewest false negative results. Reducing the risk of coronary angiography (Fig. 5B) caused a greater improvement in the cost-effectiveness of policy III (angiography only) than did reducing the fee for angiography (Fig. 5E). In fact, low risk angiography made policy III even more cost-effective than policy II (thallium) at all prevalences.

Discussion

Assessment of cost-effectiveness. Accurate assessment of the cost-effectiveness of medical care is difficult, but in view of the current spiraling cost of care, further analyses are essential (7–9,14–17). Our study set out to achieve a specifically limited objective, that is, to compare the relative cost-effectiveness of four diagnostic approaches to the patient suspected of having coronary disease. We focused on the aspect of cost-effectiveness—test selection, which is uniquely decided by the physician and not currently by the health care administrator or public policy maker. To compare various clinical policies, a conceptual model was constructed based on available real data and Bayes' theorem

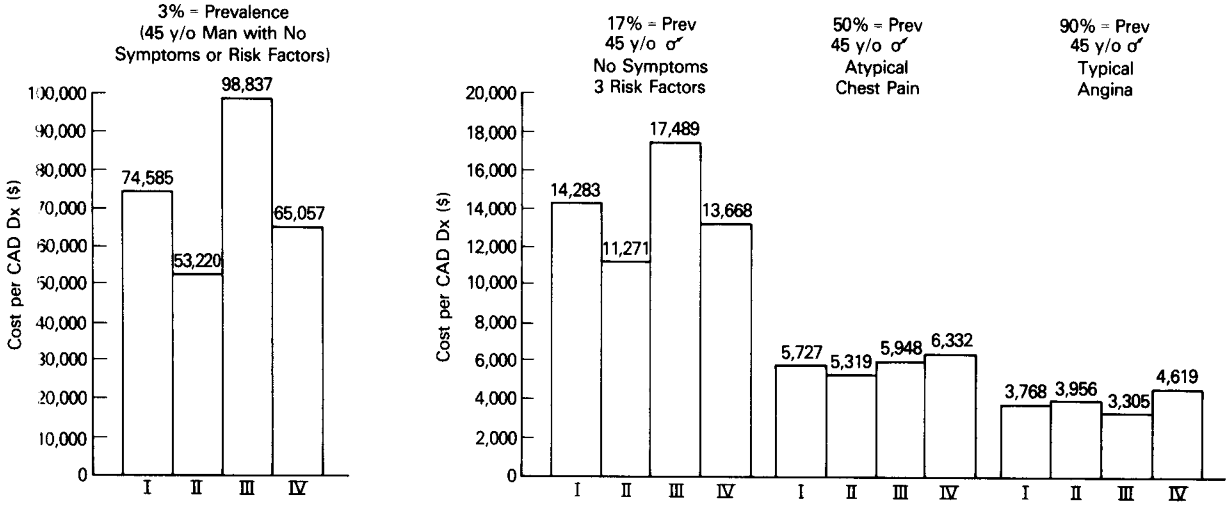


Figure 3. Comparison of clinical policies I to IV in four specific patient examples. The vertical axes show dollar cost per patient with coronary artery disease diagnosed, and the horizontal axes show policies I to IV for four different groups of 45 year old men with a prevalence of coronary disease increasing from **left to right**: 3, 17, 50 and 90% because of the clinical features cited (18,19). Note that policy II (thallium imaging only) is most cost-effective (lowest cost per CAD Dx) at disease prevalences of 3, 17 and 50%. Policy III (angiography only) is least cost-effective at disease prevalences of 3 and 17%, but becomes most cost-effective when disease prevalence increases to 90%. Abbreviations as in Figure 2.

(17,37,38). Our conclusions arise strictly from analysis of this model and should not necessarily be construed as general policy statements.

The most elusive aspect of assessing cost-effectiveness has been an adequate definition of effectiveness so we used two definitions of effectiveness. These two definitions of effectiveness yielded concordant results when comparing the rank order of different clinical policies, and did not require placing a dollar value on human life. The agreement of results using two definitions of effectiveness supports the validity of the model. Our analysis addressed the use of these tests for the specific purpose of determining whether coronary disease was present or absent. There are other indications for these tests that are not addressed by the present study, for example, predicting prognosis or functional significance of a particular coronary lesion. Although these indications are important, data evaluating the reliability of the tests for these indications are quite limited. Thus, we chose not to try to evaluate cost-effectiveness of the tests when used for these indications.

Our calculations of the number of quality-adjusted life-years did not assess costs of medical versus surgical or no therapy over 10 years. There is considerable controversy concerning the cost-effectiveness of medical versus surgical therapy for coronary disease (39–41). Most important for our purposes, these therapeutic variables would not influence the rank order of different clinical diagnostic policies, but rather would cause similar changes in the absolute cost of all policies. Finally, we used a simplified approach to calculating costs by using the test fees as the cost of the test, rather than a more precise cost-accounting analysis of all the factors that influence incremental costs (36). Because our analysis of the model depends on the relative rather than the absolute cost of different tests, our use of Medicaid fees seems justifiable.

Effects of prevalence. Although both absolute dollar costs and mortality rates increase linearly with the prevalence of coronary artery disease, cost-effectiveness also increases. The cost per effect decreased dramatically as the prevalence of coronary disease in the population increased above 10 to 15% because there are few patients with coronary disease to benefit from therapy in populations with a low prevalence of coronary disease. This analysis illustrates the fact that diagnostic testing for coronary disease in asymptomatic low-risk populations is not generally cost-effective. An important exception is illustrated by the 45 year old man with no symptoms, but with three risk factors for coronary disease (Fig. 3).

Increasing prevalence was associated with increased cost-effectiveness for all clinical policies involving noninvasive tests, because negative results of the noninvasive tests led to decreased need for coronary angiography. At low prevalences, where most negative tests will be correct to exclude coronary artery disease (lower predictive error at lower prevalence), the clinical noninvasive test policies I, II and IV are more cost-effective than policy III (angiography only).

In contrast, at higher prevalences of coronary disease (above a threshold value of 80%), avoiding angiography leads to missing many patients with coronary artery disease and decreasing cost-effectiveness. Decreased cost-effectiveness at high prevalences results from the increasing percent of patients with negative noninvasive tests results who actually have coronary disease (higher predictive error at

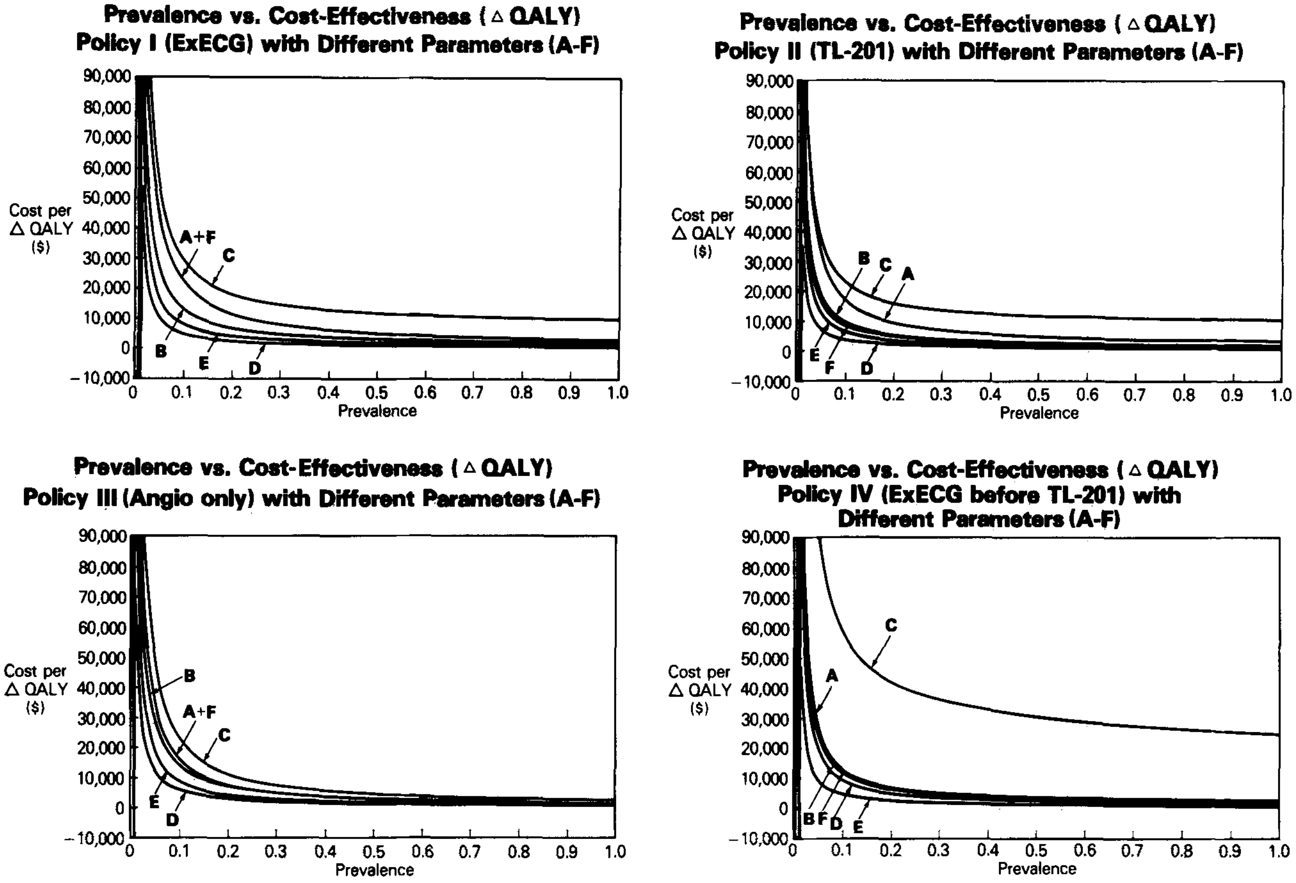


Figure 4. Sensitivity analysis of variables influencing cost-effectiveness, comparing variations for each clinical policy plotted individually. Horizontal axes show prevalence of disease. Vertical axes show dollar cost per increased ΔQALY. Policies I to IV are plotted individually in panels I to IV, respectively. **Curve A** uses the standard values of all variables and the variations (**B to F**) are defined in Table 3. Abbreviations as in Figure 2.

higher prevalence). Thus, at high prevalences (above 80%), performing coronary angiography as the only test to diagnose coronary disease is the most cost-effective clinical policy (policy III) according to this model.

Exercise electrocardiography versus thallium-201 imaging. Thallium-201 imaging is more cost-effective than electrocardiography during exercise to diagnose coronary artery disease in populations with low to high prevalences of coronary disease (Fig. 2 and 3). It should be noted that our values of sensitivity and specificity (17) were not significantly higher for thallium-201 imaging than for exercise electrocardiography. Thus, the advantage of thallium-201 imaging in the present study seems to result from its lower rate of nondiagnostic tests ($p < 0.05$), despite its two-fold greater cost. Above a threshold value of 80% prevalence, exercise electrocardiography becomes slightly more cost-effective than thallium-201 because a higher percent of positive or nondiagnostic tests are correct (higher predictive value) at a higher prevalence.

Sequential use of exercise electrocardiography before thallium-201 imaging (Policy IV) is more cost-effective than exercise electrocardiography alone in populations with a low prevalence, because this combined test approach offers the greatest chance of avoiding angiography. As prevalence increases, cost-effectiveness of policy IV (sequential tests) decreases because there is a greater chance of false negative results and subsequent deaths using two noninvasive tests in this way (Fig. 1). Surprisingly, thallium-201 imaging alone was more cost-effective than sequential tests over all prevalences, probably because of the added costs of exercise electrocardiography at low prevalences and the added chance of false negative test results at high prevalences.

Sensitivity analysis of factors influencing cost-effectiveness. A major advantage of our approach to evaluate cost-effectiveness by a model is the ease with which one can substitute any variable into any equation to test its impact. This approach is one way to deal with the inherent uncertainties of available data for costs, risks and clinical outcomes. For example, the differences in cost-effectiveness of policies I and II arise primarily from the differences in sensitivity, specificity and the frequency of nondiagnostic test results between exercise electrocardiography and thal-

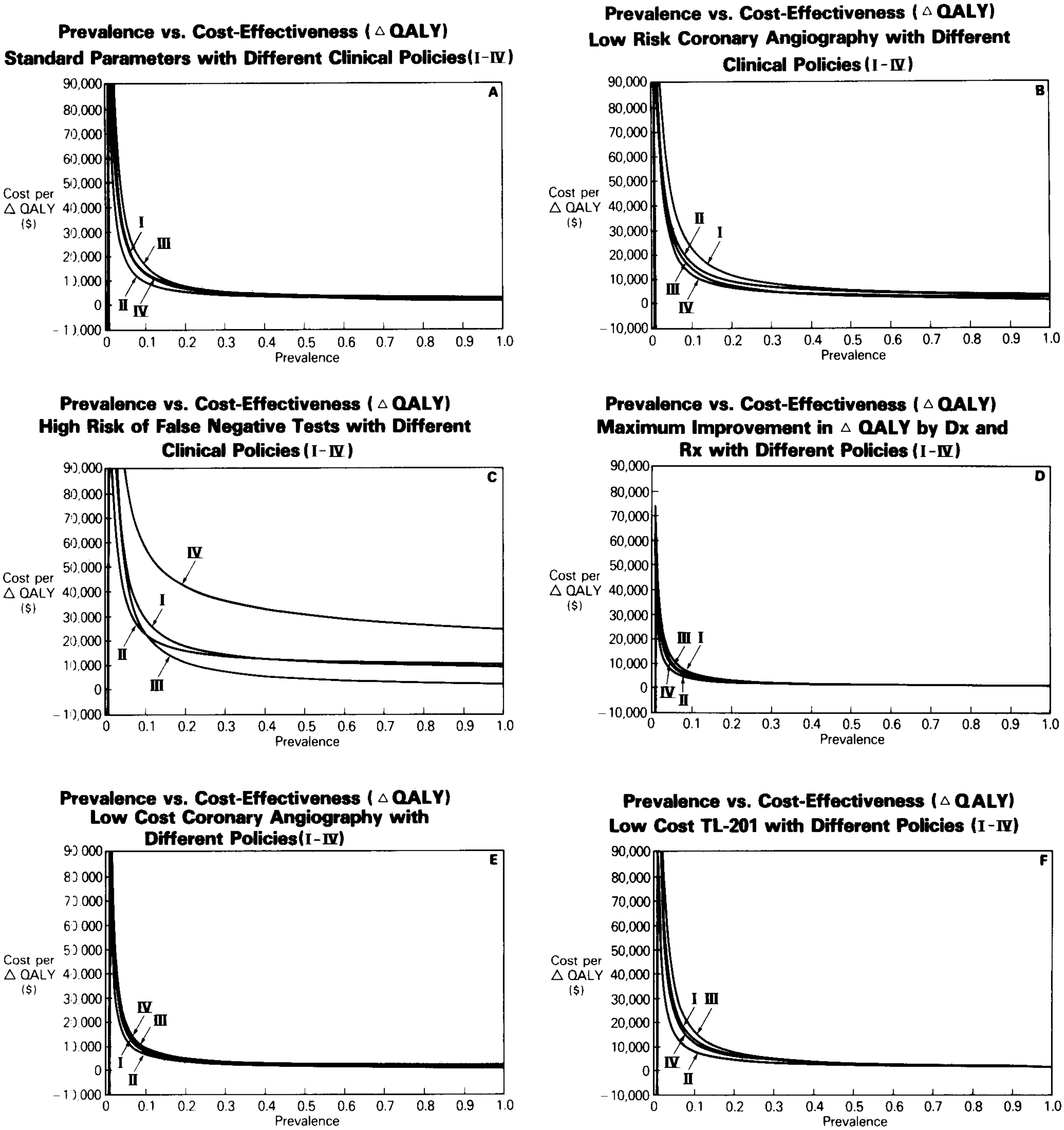


Figure 5. Sensitivity analysis of variables influencing cost-effectiveness, comparing clinical policies I to IV in each plot for their sensitivity to each variation in values of variables. Axes are same as Figure 4. All policies are plotted in each **panel (A to F). Labels (A to F) for panels** correspond to the variation in variables shown in Table 3. Abbreviations as in Figure 2.

lium imaging. Furthermore, we found that decreasing the risk or cost of thallium-201 or angiography improved the cost-effectiveness of policy II or III, respectively (Table 3, Fig. 4 and 5). The most dramatic changes in cost-effectiveness, however, arose from changes in patient outcome rather than from changes in costs. If the risk of death over 10 years after a false negative test increases from 15 to 50%, there is a dramatic decrease in cost-effectiveness (Fig. 4C and Fig. 5C). This decrease in cost-effectiveness is most marked for policy IV (sequential tests), which permits the most false negative results.

Thus, the physician who is concerned primarily with the risk of missing coronary disease in a particular patient would believe it is most cost-effective to recommend coronary angiography (policy III) and not to recommend sequential noninvasive tests (policy IV). Similarly, if the physician takes an optimistic view of the impact of surgical therapy on the natural history of coronary disease, he or she might assume an increase in the number of quality-adjusted life-years from 2 to 5 years, and an increase in this value would improve the cost-effectiveness of all tests. Thus, physicians who have the most aggressive optimistic view of therapy would be expected to consider all testing for coronary artery disease, particularly angiography, to be more cost-effective than would a physician with a more conservative therapeutic view.

Clinical implications. Analysis of this model suggests cost-effective approaches to the clinical use of noninvasive and invasive tests to make the diagnosis of coronary artery disease. Most important, the physician should select a diagnostic approach based on the probability of coronary disease in the patient, estimated by symptoms and risk factors. It is possible to estimate the probability of coronary disease clinically before and after noninvasive testing (20,42,43). Specifically, in patients with no symptoms or risk factors, the probability of coronary disease is so low (18–21) that it is difficult for even noninvasive testing to be cost-effective. This analysis may be important to physicians who include exercise stress testing as part of an annual examination, regardless of the patient's history or risk factors.

Asymptomatic patients with risk factors. In contrast, persons with no symptoms but with some risk factors will have a higher likelihood of coronary artery disease (19), which makes testing much more cost-effective (Fig. 2). Exercise thallium-201 imaging appears to be more cost-effective than exercise electrocardiography because the greater cost is offset by the lower incidence of false positive and nondiagnostic tests. In the event that exercise electrocardiography is used in asymptomatic persons, it is more cost-effective to perform exercise thallium imaging in patients with positive or nondiagnostic exercise electrocardiography (policy IV), rather than proceeding directly to coronary angiography (policy I). Use of coronary angiography as an initial screening test (policy III) is not justifiable in terms of cost-effectiveness in asymptomatic persons, even those with multiple risk factors.

Atypical chest pain. In patients with chest pain symptoms not typical of angina pectoris, there is an intermediate probability of coronary artery disease. This higher pretest likelihood of disease makes all testing approaches more cost-effective and reduces the dramatic cost differences among different clinical approaches to the use of diagnostic tests. Thallium-201 imaging remains the most cost-effective initial screening test, but the initial use of coronary angiography becomes quite competitive in terms of cost-effectiveness.

Coronary spasm. Our analysis did not consider the additional benefits of testing for coronary spasm in patients with atypical chest pain. Since these provocative tests are performed with greatest safety and accuracy during cardiac catheterization, coronary angiography might be most useful in patients who are suspected of having coronary spasm. In addition, the model did not account for the cost savings in a small percent of patients with disabling symptoms of chest pain who are found to have normal coronary angiograms. This small but important group may avoid repeated hospitalizations after a normal coronary angiogram (44). The demonstration of coronary spasm in many of these patients in recent years, however, indicates that their best management may require hospitalization to avoid acute myocardial infarction in some patients (45).

Because of these multiple uncertainties about management, we did not attempt any calculation of cost savings related to excluding coronary disease. Sequential use of exercise electrocardiography and thallium-201 imaging is slightly less cost-effective than angiography in patients with atypical chest pain because of the increased incidence of false negative results using two noninvasive tests. Note that patients with false negative results who avoid angiography by this policy would include patients with positive or nondiagnostic exercise electrocardiography but negative thallium-201 imaging. In contrast, we previously indicated that it would be more cost-effective to avoid angiography in patients with atypical chest pain if both exercise electrocardiography and thallium-201 imaging are negative at a heart rate greater than 85% of the age-predicted maximum (17).

Typical angina pectoris. In patients with typical angina pectoris, the most cost-effective approach to confirm the diagnosis of coronary artery disease is to perform coronary angiography as the initial test. In addition, angiography provides the most reliable prognostic information for coronary disease and is the essential test before considering surgery (4). Since functional aerobic capacity for exercise may add useful prognostic information, noninvasive exercise tests might be indicated after angiography in some patients to help clarify which patients need surgery (21,34,35). To incorporate these indications for tests into the model would require many additional assumptions and use of data that have not been widely tested. For example, available studies (34,35) using stress tests to predict prognosis are based on a very small number of deaths. Furthermore, the use of stress tests to evaluate the hemodynamic significance of an anatomic lesion observed angiographically remains intuitively attractive but not validated. Thus, we sacrificed testing some potentially important and clinically relevant hypotheses in the interest of making the conclusions more reliable. This approach to modeling cost-effectiveness of various health care policies may have useful applications in clinical problems outside cardiology.

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Appendix I

Calculation of Improvement in $^{\Delta}$QALY for Patients With and Without an Accurate Diagnosis of Coronary Artery Disease (Fig. 6)

The particular value of the increase in quality-adjusted life years ($^{\Delta}$QALY) is obviously controversial and based on conflicting data. The calculation is used in the present study only as a common denominator to modify the benefit of diagnosing coronary artery disease by each of the four clinical policies. Rather than to compute the absolute cost of each individual policy, the goal of the present study was to compare cost-effectiveness of four different clinical policies to diagnose coronary artery disease.

Figure 6. Calculation of the improvement in $^{\Delta}$QALY for patients with an accurate diagnosis of coronary artery disease (**upper diagram**) or without an accurate diagnosis of coronary artery disease (**lower diagram**). Decimals refer to fraction of all patients (1.0) entering each subgroup, that is, medical versus surgical therapy and alive versus dead after 10 years. The fraction of patients is recomputed for each subgroup and multiplied by average life span (over 10 year follow-up period) and the average subjective quality of life shown by the decimal fraction of life at full health with no symptoms (1.0). The $^{\Delta}$QALY values for each group are then added to show that a positive diagnosis leads to surgery in 0.4 of the patients and a better $^{\Delta}$QALY (6.07 − 4.05). Abbreviations as in Figure 2.

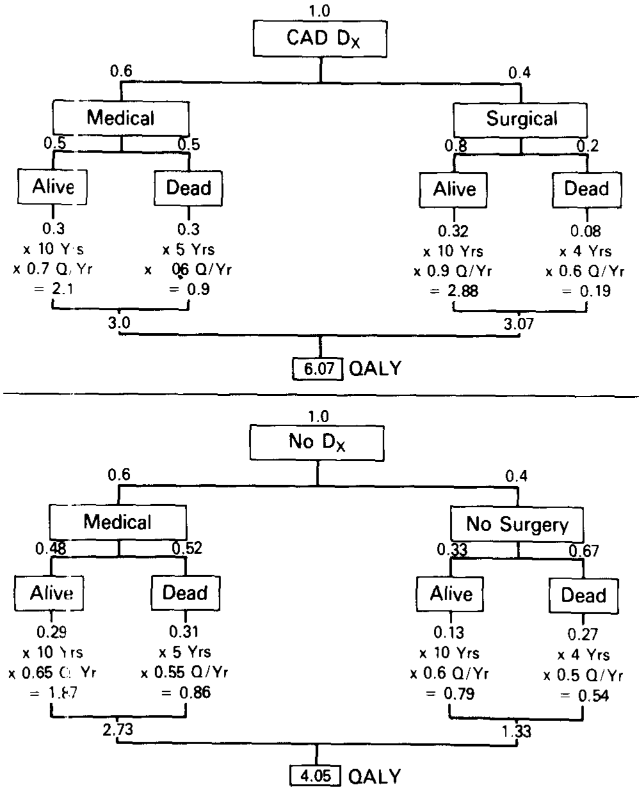

Figure 6 represents the difference in $^{\Delta}$QALY over a 10 year follow-up period between patients in whom coronary artery disease was diagnosed accurately ("CAD Dx," upper panel) versus the same patients if they had not had angiography to confirm coronary artery disease ("No Dx," lower panel). The average length of life over a 10 year follow-up period is shown, as is the subjective quality of life, expressed as a fraction of life at full health (Q/yr). Making the diagnosis of coronary artery disease leads to a higher $^{\Delta}$QALY: 6.07 − 4.05 = 2.02 years (Fig. 6, upper panel minus lower panel). This calculation is based on a synthesis of available data. First, 40% of patients with coronary artery disease diagnosed would have coronary bypass surgery for left main or three vessel coronary artery disease or intractable symptoms (upper panel) (11). These surgical patients would have an 80% 10 year survival (upper panel) compared with a 33% 10 year survival of the same patients treated without surgery ("No Surgery," lower panel) (11,25–29). Patients who died after surgery had a 4 year average lifespan after surgery and a lower quality of life (Q/yr = 0.6) than did surgical survivors (Q/yr = 0.9). The number of quality-adjusted life years for surgical patients is calculated by multiplying the fraction of patients having surgery (0.4) by the fraction of patients surviving 10 years (0.8) = 0.32 (upper panel). This figure is multiplied by the number of years survived (10) and the Q/yr (0.9) to yield 2.88 years. Similar computations for patients who died after surgery yield 0.19 years, which is added to yield $^{\Delta}$QALY of 3.07 years for surgical patients.

Sixty percent of patients were treated medically, and half of these patients lived at 10 years after angiography (upper panel). Multiplying the fraction of patients alive at 10 years (0.3) times the average length of life after angiography (10 years for survivors versus 5 years for those who died) times Q/yr (0.7 in survivors versus 0.6 in those who died) yielded $^{\Delta}$QALY values of 2.1 years for survivors versus 0.9 years for those who died. The overall $^{\Delta}$QALY for patients treated medically after angiography (3.0 years, upper panel) is 10% higher than that for the same group of patients if they had not had angiography to prove the diagnosis of coronary artery disease (2.73 years, lower panel). This slight improvement in $^{\Delta}$QALY by angiography is assumed to result from a small improvement in Q/yr due to more vigorous therapy of patients known to have coronary artery disease.

Sensitivity analysis of the model indicated no change in the rank order of cost-effectiveness for different policies when the improvement in $^{\Delta}$QALY was varied from 0.5 to 5.0 years. Thus, the particular value of improved $^{\Delta}$QALY due to coronary artery disease diagnosis changed the absolute dollar cost, but not the relative ranking of different clinical policies. This value of improved $^{\Delta}$QALY due to diagnosis of coronary artery disease estimated in Figure 6 was then applied to each individual clinical policy (I to IV) using the equations in Appendix II. We calculated net quality-adjusted life-years for each policy and this reflects not only the effect of diagnosis (${}^{\Delta}$QALY) but also the effects of complications and mortality rates due to tests and coronary artery disease missed by false negative tests.

Appendix II

Equations to Estimate Cost-Effectiveness for Each Clinical Policy

Table 2 shows variables used in calculations.

Policy I: exercise electrocardiography (EX ECG) only in all patients; coronary angiography (angio) performed only if Ex ECG = positive (+) or nondiagnostic (Non-Dx).

Costs = $N_E \cdot (F_E \cdot R_E \cdot C) + N_A \cdot (F_A + R_A \cdot C) + N_F \cdot (R_F \cdot [R_F \cdot C]$ and
mortalities = $N_E \cdot M_E + N_A \cdot M_A + N_F \cdot M_F$,

where P = prevalence of coronary artery disease (CAD) in population;
N_E = number of patients having initial test; Ex ECG, = 1.0;
N_A = number of patients having angiography because of (+) or Non-Dx Ex ECG = $N_E \cdot (1 - Ndx_E) \cdot P \cdot Sn_E + (1 - P) \cdot (1 - Sp_E) + N_E \cdot Ndx_E$;
N_F = number of patients with false negative (−) Ex ECG who do not have angio for CAD Dx = $N_E \cdot (1 - Ndx_E) \cdot P \cdot (1 - Sn_E)$;
CAD Dx = patients with CAD diagnosed correctly by the policy (first definition of "effectiveness" of policy)
= $N_E \cdot (1 - Ndx_E) \cdot P \cdot Sn_E + N_E \cdot P \cdot Ndx_E$;
ΔQALY = quality-adjusted life years extended by therapy due to the diagnosis of CAD by the policy = 2 years (Appendix I) (second definition of "effectiveness" of policy).

Net QALY = net quality-adjusted life years extended by therapy for a particular policy, taking into account not only the favorable effect of CAD diagnosis (ΔQALY), but also the deaths and complications of tests and CAD missed that result from application of the particular policy.

$$\text{Net QALY} = (\text{CAD Dx}) \cdot ({}^{\Delta}\text{QALY}) - 10 \cdot (N_E \cdot M_E \cdot + N_A \cdot M_A) + 5 \cdot (N_F \cdot M_F) + 10(0.1)\,(N_E \cdot R_E + N_A \cdot R_A + N_F \cdot R_F),$$

where deaths due to diagnostic tests subtract 10 years and deaths due to coronary artery disease missed by false negative tests subtract an average of 5 years. Complications due to tests or coronary artery disease missed reduce the quality of life per year (Q/yr) by 1/10 per year.

Policy II: exercise thallium-201 imaging (Ex T1-201) only; angio performed only if T1-201 = positive or Non-Dx (equations are identical to policy I, substituting values for fees, test sensitivity, specificity and rates of nondiagnostic tests of T1-201 for Ex ECG).

Policy III: coronary angiography is the first and only test to diagnose coronary artery disease.

Costs = $N_A \cdot (F_A + R_A \cdot C)$,
mortality = $N_A \cdot M_A$,

where N_A = N_E from policy I = 1.0;
N_F = O;
CAD Dx = $N_A \cdot P$;
Net QALY = $(N_A \cdot {}^{\Delta}\text{QALY} \cdot P - [10 \cdot N_A \cdot M_A + N_A \cdot R_A]$.

Policy IV: exercise ECG in all patients; T1-201 performed only if Ex ECG = positive or Non-Dx; angio performed only if T1-201 = positive or Non-Dx.

Costs = $N_E \cdot (F_E + R_E \cdot C) + N_T \cdot (F_T + R_T \cdot C) + N_A \cdot (F_A \cdot + R_A \cdot C) + N_F \cdot R_F \cdot C$,
Mortality = $N_E \cdot M_E + N_T \cdot M_T + N_A \cdot M_A + N_F \cdot M_F$,

where N_E = 1.0 = all patients having Ex ECG;
N_T = patients having T1-201 because of (+) or Non-Dx Ex ECG = $N_E \cdot (1 - Ndx_E) \cdot P \cdot Sn_E + N_E \cdot (1 - Ndx_E) \cdot (1 - P) \cdot (1 - Sp_E) + N_E \cdot Ndx_E$;
N_A = patients having angiography because of (+) or Non-Dx Tl-201 = $N_T \cdot (1 - Ndx_T) \cdot P \cdot Sn_T + N_T \cdot (1 - Ndx_T) \cdot (1 - P) \cdot (1 - Sp_T) + N_T \cdot Ndx_T$;
N_F = number of patients with false negative Ex ECG or Tl-201, or both, who do not have angiography for CAD Dx
= $N_E \cdot (1 - Ndx_E) \cdot P \cdot (1 - Sn_E) + N_T \cdot (1 - Ndx_T) \cdot P \cdot (1 - Sn_T)$;
CAD Dx = patients with coronary artery disease diagnosed correctly by the policy
= $N_T \cdot (1 - Ndx_T) \cdot Sn_T \cdot P + N_T \cdot Ndx_T \cdot P$;

${}^{\Delta}$QALY = quality-adjusted life years extended by therapy due to diagnosis of CAD by the policy = 2 years.

Net QALY for this particular policy

$$= (\text{CAD Dx}) \cdot (\Delta\text{QALY}) - 10 \cdot (N_E \cdot M_E + N_T \cdot M_T + N_A \cdot M_A) + 5 \cdot (N_F \cdot M_F) + 10(0.1)\,(N_E \cdot R_E + N_T \cdot R_T + N_A \cdot R_A) + N_F \cdot R_F.$$

We did not attempt to compute the 10 year cost of medical versus surgical therapies for coronary artery disease with versus without a positive diagnosis. These highly controversial values (39–41) would influence each patient diagnosed with coronary artery disease similarly and, thus, would have little effect on the comparison of different clinical policies.

References

1. Strauss WM, Pitt B. Evaluation of cardiac function and structure with radioactive tracer techniques. Circulation 1978;57:645–52.
2. Ritchie J, Troubaugh G, Hamilton G, et al. Myocardial imaging with thallium-201 at rest and during exercise: comparison with coronary arteriography and resting and stress electrocardiography. Circulation 1977;56:66–71.
3. Borer JS, Kent KM, Bacharach SL. Sensitivity, specificity and pre-

dictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease: comparison with exercise electrocardiography. Circulation 1979;60:572–80.

4. Pichard AD. Coronary arteriography: for everyone? Am J Cardiol 1976;38:533–5.
5. Hurst JW, King SB, Walter PF, Friesinger GC, Edwards JE. Atherosclerotic coronary heart disease: angina pectoris, myocardial infarction, and other manifestations of myocardial ischemia. In: Hurst JW, Logue RB, Rackley CE, et al., eds. The Heart, Arteries and Veins. 5th Ed. New York: McGraw-Hill, 1982:1009–149.
6. Friesinger GC. The reasonable workup before recommending medical or surgical therapy: an overall strategy. Circulation 1982;65(suppl II):II-21–6.
7. Enthoven AC. Shattuck lecture: cutting costs without cutting the quality of care. N Engl J Med 1978;298:1229–38.
8. McNeil BJ, Varady PD, Burrows BA, Adelstein SJ. Measures of clinical efficacy: cost-effectiveness calculations in the diagnosis and treatment of hypertensive renovascular disease. N Engl J Med 1975;293:216–21.
9. Bell RS. Efficacy . . . what's that? Semin Nucl Med 1978;8:316–23.
10. Braunwald E. Coronary artery surgery at the crossroads. N Engl J Med 1977;297:661–2.
11. McIntosh HD, Garcia JA. The first decade of aortocoronary bypass grafting, 1967–1977. A review. Circulation 1978;57:405–19.
12. Hurst JW, King SB III. The prolongation of life by coronary bypass surgery—the Emory University Hospital experience. In: Hurst JW, ed. Update II, The Heart:Bypass Surgery for Obstructive Coronary Disease. New York: McGraw-Hill, 1980:141–50.
13. Frye RL, Frommer PL, McCallum DB. Consensus development conference on coronary artery bypass surgery: introduction. Circulation 1982 65(suppl II):II-1–2.
14. Hiatt HH. Protecting the medical commons: who is responsible? N Engl J Med 1975;293:235–41.
15. The ailing health care system—Medical Staff Conference, University of California, San Francisco. West J Med 1978;128:512–28.
16. America's Ω39 billion heart business. U.S. News and World Report. March 15, 1982.
17. Patterson RE, Horowitz SF, Eng C, et al. Can exercise electrocardiography and thallium-201 myocardial imaging exclude the diagnosis of coronary artery disease? Am J Cardiol 1982;49:1127–35.
18. WB Kannel, T Gordon ed. The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. vol XII. Bethesda: National Heart, Lung, and Blood Institute, 1968.
19. Coronary Risk Handbook. New York: American Heart Association, 1973:1–23.
20. 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.
21. Bruce RA, Irving JB. Exercise electrocardiography. In: Hurst JW, Logue RB, Schlant RC, Wenger NK, eds. The Heart, Arteries and Veins. 4th ed. New York: McGraw-Hill, 1978:336–48.
22. Adams DF, Abrams HL. Complications of coronary arteriography: a follow-up report. Cardiovasc Radiol 1979;2:89–97.
23. Proudfit WL, Bruschke AVG, Sones FM Jr. Natural history of obstructive coronary artery disease: ten-year study of 601 nonsurgical cases. Prog Cardiovasc Dis 1978;21:53–68.
24. King SB III, Hurst JW. The relief of angina pectoris by coronary bypass surgery. In Ref 12:71–84.
25. Rackley CE. Prolongation of life after coronary artery bypass surgery at the University of Alabama. In Ref 12:151–8.
26. Greene DG, Bunnell IL, Arani DT, et al. Preservation of the myocardium by coronary bypass surgery: The effect on survival. In Ref 12:159–74.
27. Hall RJ, Mathur VS, Garcia E, deCastro CM. The prolongation of life by coronary bypass surgery. In Ref 12:175–204.
28. Cosgrove DM, Loop FD, Sheldon WC. Results of myocardial revascularization: a 12-year experience. Circulation 1982;65(suppl II):II-37–43.
29. Lawrie GM, Morris GC Jr. Survival after coronary artery bypass surgery in specific patient groups. Circulation 1982;(suppl II):II-43–8.
30. Whalen RE, Harrell FE Jr, Lee KL, Rosati RA. Survival of coronary artery disease patients with stable pain and normal left ventricular function treated medically or surgically at Duke University. Circulation 1982;65(suppl II):II-49–52.
31. Hammermeister KE, De Rouen TA, Dodge HT. Comparison of survival of medically and surgically treated coronary disease patients in Seattle Heart Watch: a nonrandomized study. Circulation 1982;65(suppl II):II-53–9.
32. Takaro T, Hultgren HN, Detre KM, Peduzzi P. The Veterans Administration Cooperative Study of Stable Angina: current status. Circulation 1982;(suppl II):II-60–7.
33. European Coronary Surgery Study Group: prospective randomized study of coronary artery bypass surgery in stable angina pectoris: a progress report on survival. Circulation 1982;66(suppl II):II-67–71.
34. McNeer JF, Margolis JR, Lee KL, et al. The role of the exercise test in the evaluation of patients for ischemic heart disease. Circulation 1978;57:64–72.
35. Kent KM, Rosing DR, Ewels CJ, Lipson L, Bonow R, Epstein SE. Prognosis of asymptomatic or mildly symptomatic patients with coronary artery disease. Am J Cardiol 1982;49:1823–31.
36. Weinstein MC, Fineberg HV, Elstein AS, et al. Clinical Decision Analysis. Philadelphia: WB Saunders, 1980:228–65.
37. Lusted LB. Introduction to Medical Decision-Making. Springfield: Charles C Thomas, 1968:1–46.
38. Rifkin RD, Hood WB Jr. Bayesian analysis of electrocardiographic exercise stress testing. N Engl J Med 1977;297:681–6.
39. Pauker SG. Coronary artery surgery: the use of decision analysis. Ann Intern Med 1976;85:8–18.
40. Collins JJ Jr. The cost of coronary bypass surgery. In Ref 12:271–80.
41. Oberman A, Wayne JB, Kouchoukos NT, Charles ED, Russell RO Jr, Rogers WJ. Employment status after coronary artery bypass surgery. Circulation 1982;65(suppl II):II-115–9.
42. Diamond GA, Staniloff HM, Forrester JS, Pollock BH, Swan HJC. Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. J Am Coll Cardiol 1983;1:444–55.
43. Patterson RE, Eng C, Horowitz SF. Bayesian analysis of a nomogram of sequential tests for coronary disease:indications for exercise ECG and Tl-201 imaging (abstr). Clin Res 1982;30:212A.
44. Kemp HG, Vokonas PS, Cohn PF, Gorlin E. The angina syndrome with normal coronary arteriograms. Report of a six year experience. Am J Med 1973:54:735–45.
45. Maseri A, L'Abbate A, Baroldi G, Chierchia S, et al. Coronary vasospasm as a possible cause of myocardial infarction: a conclusion derived from the study of "preinfarction" angina. N Engl J Med 1978;299:1271–7.