DIAGNOSTIC NUCLEAR MEDICINE

What Promise the Preliminary Tests of Coronary Artery Disease?

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For some patients with coronary artery disease (CAD), bypass operations prolong life. Angiograms, incurring some risk and considerable expense, are prerequisites to surgical therapy; they delineate the region and extent of disease. However, many people who complain of chest pain do not have disease that can be benefited by operation. Therefore, tests that will safely and economically select the appropriate individuals for angiography are most welcome. Yet, if the preliminary tests falsely declare affected people to be free of CAD, they will deny these patients angiography, and, consequently, surgical treatment that would prolong their lives. Decision analysis determines that a false-negative rate of less than 2% is necessary for tests preliminary to angiography if the average survival of patients is not to be shortened. No currently used procedure has attained this sensitivity. Radionuclide ventriculography approaches this precision, but its sensitivity must be sustained in more broadly based studies.

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Promises, even when earnest, sometimes cannot be kept. By minimally altering patients' homeostasis, preliminary tests of coronary artery disease (CAD) promise safety in their estimates of the narrowing of coronary arteries. And their sensitivities ensure that few affected people will escape detection. But the few patients with CAD who do elude discovery (i.e., the false negatives) may undo these diagnostic techniques. In fact, by disregarding only a small proportion of patients, preliminary tests of CAD may cost more lives than they save.

Much evidence indicates that bypass operations prolong the lives of patients in certain categories of CAD, particularly the groups with three-vessel disease and left main artery lesions (*1*,*2*). For those who would receive surgical therapy, a prerequisite is a characterization of the extent and severity of lesions by angiography, a procedure costing considerable time, money, and occasionally life. An efficient preliminary sorting process is then welcome. By disclosing the presence of CAD, radionuclide methods—measuring ventricular function through red blood cells labeled with Tc-99m and ventricular perfusion through Tl-201—might, with economy and safety, select patients for angiography from a population whose common complaint is recurrent chest pain.

Safety, however, is relative, and no test, short of fulfilling absolute criteria of diagnosis, gives perfect results. By falsely declaring a few CAD victims to be free of CAD, radionuclide studies deny individuals angiography and, consequently, the surgical treatment that would prolong their lives. It is these patients with CAD that the tests disregard. Such deleterious events must be weighed against the benefits that accrue to these techniques when, by revealing patients to be truly without CAD, they abrogate unnecessary angiography. But whatever balance is achieved, the demands on these tests for sensitivity—the minimizing of numbers of patients excluded from life-preserving treatment—are likely to be stringent.

Having established that a therapy is beneficial for a disease, we seek the best pathway to the diagnosis. Many factors contribute to the diagnostic process, but the outcome of patients, their health or illness, ultimately determines the best pathway. We must then choose the

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diagnostic route that will, with economy, bring about the greatest health, or, put conversely, the least illness.

In the study of a well-defined disorder, such as CAD, decision analysis, a formalized method of reasoning, can determine the relative efficacies of the diagnostic choices (*3–5*). Decision analysis not only takes into account the probabilities of events that shape a diagnostic test, it also weighs the benefit or harm of outcomes that are at the end of each diagnostic pathway.

For symptomatic CAD, bypass grafts have become an accepted therapy after narrowed coronary arteries have been delineated. But an important question is: Will tests of CAD preliminary to coronary arteriography offer a better route to diagnosis than a direct move from clinical findings to angiography? In this report, decision analysis addresses the question.

METHODS

The premises of this study are:

1. By determining what grafting can be done, an angiogram is a prerequisite to bypass operations, and, as such, it establishes the criteria for the diagnosis of CAD.

2. Coronary artery bypass grafts prolong the lives of patients exhibiting left main artery lesions that reduce the lumen by 50% or more (*2*) and/or three-vessel disease of similar severity (*1*).

The analysis was confined to men, since they are more affected by CAD and since survival rates have not been determined for women. The method of decision analysis has been described in detail before (*3–5*). More briefly, four steps are followed.

(a) The decisions available to the physician are defined, then all possible events consequent to each choice are plotted in the form of a decision tree.

(b) Probabilities are assigned to each of the possible events that follow a decision.

(c) Utility values or losses are determined for each final event or outcome (e.g., in terms of life or death).

(d) The overall value or loss of each decision is computed.

a) The decision tree for CAD is portrayed in Fig. 1. The decisions are denoted after the square or decision node: to perform an angiogram directly or first to use a Preliminary Test of CAD. As an example of defining possible events consequent to a decision, let us follow a

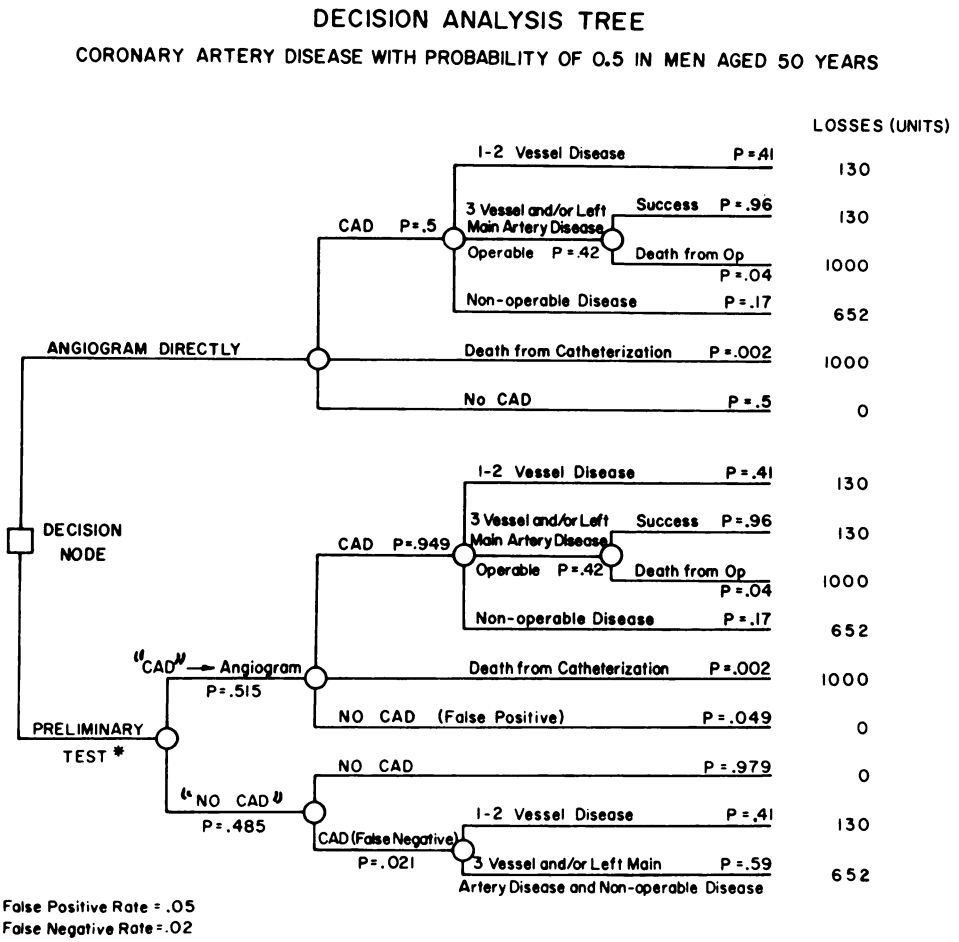

FIG. 1. Example of a decision analysis tree applied to two decisions: to use or not to use a preliminary test with specified errors in the search for CAD when the *a priori* probability is 0.5.

pathway in the use of a Preliminary Test. This Preliminary Test provides imperfect data on CAD; thus its results are designated "CAD" or "NO CAD." The finding of "CAD" leads to the performance of an angiogram, which is followed by three possible designations: CAD, NO CAD (thus making the diagnosis of the Preliminary Test a false positive), or death from the catheterization procedure. In the discovery of CAD, angiography delineates three types: one- or two-vessel disease; more severe, but inoperable disease; and operable three-vessel and/or left main coronary disease. Patients exhibiting the last type of CAD are those whose lives are likely to be prolonged by bypass operations. In turn, operations are followed by the possibilities of either varying degrees of therapeutic success, all of which are viewed as a single event and analyzed on the basis of mean survival; or by immediate death. The aborization for events following "NO CAD," and for events consequent to the decision to perform the angiogram directly, are developed in analogous ways.

b) Probabilities for events were derived from the literature.

(1) Death rates are:

(a) from angiography, 0.002 (an estimate assuming that no more than 10% of patients exhibited left main coronary artery lesions (*2*)); and

(b) from bypass operation; 0.04 (*6*).

(2) Left main coronary artery lesions and/or three-vessel disease comprise 42% of the CAD detected by angiography, one- and two-vessel disease 41%, and patients with nonoperable disease (aneurysms and poor contraction of the left ventricle) 17%. (*5*). At lower *a priori* probabilities, severe disease appears less common (*6*); thus, at a probability of CAD of 0.2, estimates were: one- and two-vessel disease 80%, operable disease 14%, and nonoperable disease 6%.

(3) Rates of false-negative and false-positive results from a Preliminary Test of CAD are varied to correspond to values that might be attained by currently available procedures. The probabilities in Fig. 1 depict a patient for whom the clinical information gives an *a priori* probability of 0.5 for CAD. Also in this example, the Preliminary Test for CAD exhibits rates of 5% for false-positive and 2% for false-negative results.

c) Utilities of outcomes are calculated in terms of loss (*3*) and for death only. Normal survival is viewed as the ideal, an end not improved upon by medical care. Death before the average life span causes loss. This method has the advantage of dealing with only one form of numbers in a ledger; difficulties arising from trying to reconcile benefits (positive values) with injury or death (negative values) are avoided.

Survivals after bypass operations have been determined for men whose mean age was 50–52 yr (*1*,*2*,*7*). Therefore, 51 years was used in this analysis. Utility values have been inserted into Fig. 1; they were calculated as follows.

(1) Normal survival for men aged 51 is 23 yr (*8*); this length of life is assigned 1000 units, the maximum. Lesser years of survival lose units proportional to the loss of years from the ideal.

(2) Deaths from angiography or from bypass operations of course permit no survival; in these circumstances losses are 1000 units.

(3) For patients with left main artery and/or three-vessel disease not treated by bypass operation, the mean survival is projected to about 8 yr (*12*); the loss, 15 out of 23 yr, equals 652 units. Individuals with severe but nonoperable CAD were assumed to live the same number of years.

(4) When left main artery and/or three-vessel disease was surgically repaired, the mean survival time of the recipients (estimated from incomplete data on longitudinal studies (*1*)) was 20 yr, and their loss was 3 yr or 130 units.

(5) Since bypass operations do not clearly prolong the lives of patients with one- or two-vessel disease, their survival was assumed to be the same as those with more severe arterial lesions who had received grafts: 20 years. Thus their loss is also 130 units.

d) The overall value—in this analysis, the overall loss—for each decision was computed by an "averaging" process (*9*) wherein the magnitude of a loss is multiplied by the probability of its occurrence. For example, in the bottom branches of the tree in Fig. 1, disease of only one or two vessels has a probability of 0.41 and a loss of 130 units, giving a product or predicted loss of 53.3 units. Three-vessel and/or left main artery disease and nonoperable disease carry the probability of 0.59 and the loss of 652 units; the product or predicted loss is 384.7 units. The sum of these two products, the "averaged" loss for these branches, is 438 units, and this now becomes the loss at the preceding node in the tree to which the probability of 0.021 pertains. This method of calculation is applied sequentially for the entire tree until the losses on the initial limbs of the tree are determined. These ultimate losses are those incurred by the respective decisions: angiogram directly or Preliminary Test.

RESULTS

In the defined circumstance of Fig. 1 (wherein the *a priori* probability of coronary artery disease is 0.5 and the rates of false-negative and false-positive results of the hypothetical Preliminary Test were 2 and 5%, respectively) a direct move to the Angiogram lost 118.7 units while the use of the Preliminary Test yielded 119.8 units. The difference is small, especially when compared with a loss of 214 units when neither Angiogram nor Preliminary Test was applied. But, in terms of life alone,

the best decision is to proceed directly to the Angiogram.

Figure 2 relates losses to a spectrum of *a priori* probabilities of CAD for each of three choices of diagnostic pathways. In addition to the move directly to Angiography (line A), the losses from two hypothetical Preliminary Tests of CAD, lines B and C, are displayed. These tests are characterized by rates of false-negative and false-positive results of, respectively, 2 and 5% for Test B and 10 and 20% for Test C. The higher the line on the graph, the less the loss, and, with respect to life, the better the decision for a diagnostic pathway. Thresholds, where decisions for pathways accrue equal merit, are located where the lines cross. Thus, a decision for test B becomes equal to that of a direct move to Angiography when the probability of CAD is about 0.3; and a decision for Test C reaches a threshold with Angiography at a probability of 0.2.

Each diagnostic pathway leads to much better results than no test at all (shown in Fig. 2 only for CAD at a probability of 0.5). However, even when embued with false-negative rates of 10 and 2% (and thus with levels of sensitivity of 90 and 98%), Preliminary Tests suffer compared with a direct move to Angiography. Over a broad range of probabilities of CAD, inserting these Preliminary Tests into a diagnostic program shortens the mean survivals of patients.

DISCUSSION

The method of appraising diagnostic pathways, decision analysis. Erroneous premises—particularly of utilities and probabilities—may misguide reasoning and flaw conclusions from decision analysis (*10*). In this study, the assignment of utilities, often controversial when the opinions of patients must be sought, requires no subjective preferences for outcomes, since only deaths are considered; and the purpose in approaching CAD by any diagnostic route was to prolong life. The effects of morbidity were omitted for two reasons: first, information about disability and discomfort attendant to the natural history of CAD has not been quantified, and

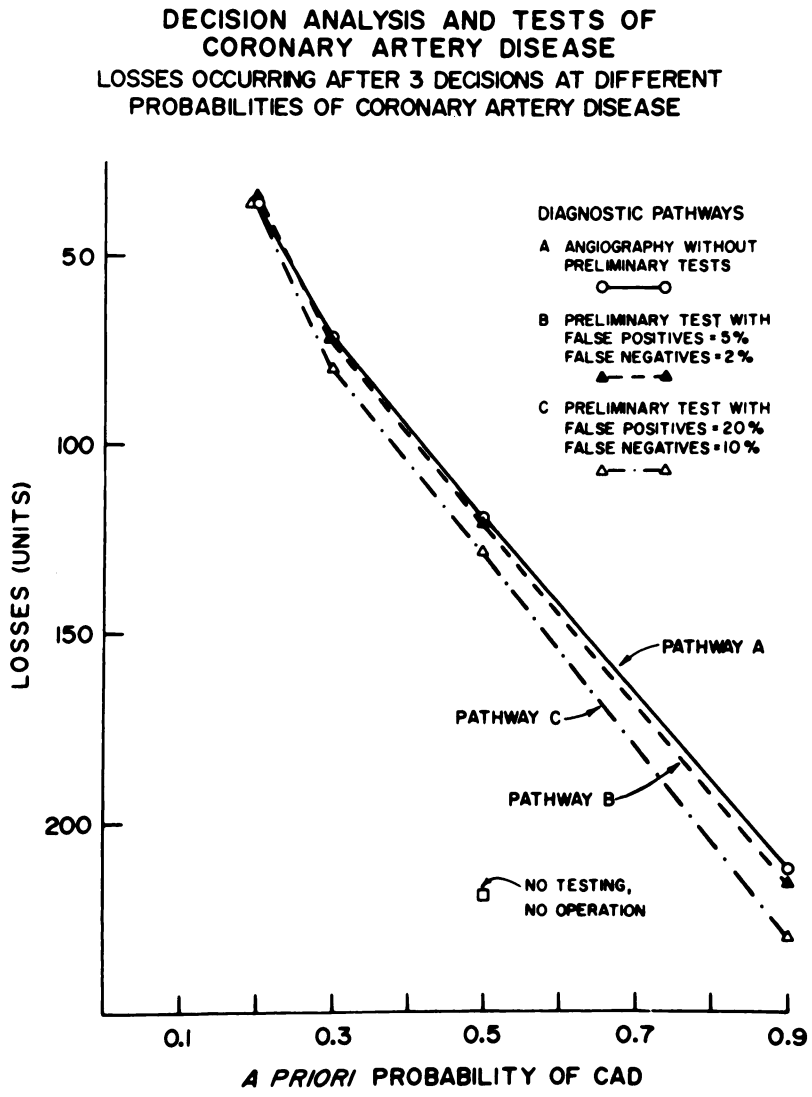

FIG. 2. Losses related to different *a priori* probabilities of CAD determined by decision analysis for three different diagnostic pathways.

second, it was assumed that morbid events would precede death in a regular pattern, so that mortality rates would also serve as indices of illness.

Probabilities for events may not be uniform over different probabilities of disease. The reports from *The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease* (*1*,*2*,*6*), on which this analysis was largely based, dealt with patients whose probability of CAD was about 0.85. We assumed that the extent of disease in 50-year-olds would be similar at lower probabilities of CAD until 0.2 is reached. For men with clinically designated, definite, or typical angina, the probability of CAD is about 0.9, and for men with probable or atypical angina, 0.6 (*11*,*12*). The frequencies of multiple-vessel disease in the two categories of patients were only modestly different: 73% against 63% (*11*).

When examined for their particular importance, the different rates of false-positive results for the Preliminary Tests had a negligible effect on the relative losses produced by the pathways.

In this analysis two factors have special power to separate the outcomes of the diagnostic pathways. Increasing the false-negative rate adversely affects the consequences of using a Preliminary Test. On the other hand, a higher death rate from catheterization especially prejudices the outcomes when Angiogram pathway is followed. Although deaths from catheterization impinge on both diagnostic choices, the Preliminary Test delivers most patients without CAD from this risk. Yet, doubling the mortality rate from catheterization only modestly alters the conclusions of the decision analysis. If coronary arteriography causes death of four rather than two in 1000, the losses from Preliminary Test B in Fig. 2 still will not reach a threshold with the angiogram until the *a priori* probability of CAD is 0.5.

Since accurate life-span data beyond 6 yr of observation are lacking for patients with CAD (*1*), survival times different from those selected could be estimated. For example, patients treated by bypass operations and those with one- to two-vessel coronary disease might survive on the average only 15 yr instead of 20. The effect of this new estimate is to diminish the advantage of a direct move to the Angiogram: The losses from the Angiogram are then equal to those from Preliminary Test B in Fig. 2 when the *a priori* probability of CAD is 0.5. This change in results is modest, and the losses from Preliminary Test C still exceed those from the Angiogram at most *a priori* probabilities of CAD.

Another revised estimate of survival, 10 yr instead of 8 for patients who received bypass grafts, alters the relative positions of the pathways in Fig. 2 even less. Finally, a doubling or halving of the mortality rate for the bypass operations, from 0.04 to 0.08, or to 0.02, produces inconsequential effects on the results of the decision analysis.

The significance of the analysis to available techniques. If deaths from a disease can be prevented or delayed by treatment, a diagnostic test for the disease incurs risk when, through error, it excludes affected people. This is inevitable for preliminary tests of CAD that must inherently beget some rate of false-negative results. If the acceptable rate for false negatives is almost unattainably small, say less than 2%, the concept of testing must be questioned.

When the Preliminary Test exhibited a false-negative rate of 2%, and thus a sensitivity of 98%, the difference in mean life expectancies between using the Test and moving directly to Angiography was trivial for most *a priori* probabilities for CAD, e.g., 1.1 out of 119 units or 10 days out of a mean survival of 20.3 yr when P = 0.5. The economic virtues of the Preliminary Test may then predominate. Nonetheless, the requirements for sensitivity in such preliminary procedures remain rigorous, and few tests can meet the demands.

Exercise-generated depression of ST segments in electrocardiograms has generally fallen short of 90% sensitivity in the diagnosis of CAD (*11*,*13*). But a recent report claims that, by computations taking into account the electrical axis of premature contractions, sensitivity could reach 94% (*14*).

In searches for CAD, measurements of ventricular perfusion with Tl-201 during exercise achieved a sensitivity of 93% (*15*). However, the *a priori* probability of CAD in the patients studied was high: half had previously endured myocardial infarction, and all complained of chest pain unrelieved by anti-anginal therapy. For those without myocardial infarcts, the sensitivity of the Tl-201 study was only 86%.

Using Tl-201 perfusion as an index, most diagnostic pursuits of CAD have failed to exceed a sensitivity of 90% (*16*,*17*). Although a sensitivity of 90% and specificity of 80% were suggested as guides to an efficacious technique (*16*), the computations for Preliminary Test C in Fig. 2 demonstrate that, in these circumstances, the use of Tl-201 would cost almost 3 mo more of life than would the more immediate selection of Angiography for men aged 50 whose probability of CAD is 0.5.

Exercise ventriculography—ejection fractions and wall motions of the heart determined from emissions by Tc-99m adherent to red blood cells—attained a sensitivity of 98% in the diagnosis of CAD (*15*,*18*). In these studies the prior probability of CAD was also high, and if the calculations excluded patients known to have infarcts, the sensitivity declined to 95% (*15*). Still, if sustained when viewing patients with lower probabilities of CAD, this high level of precision may, at small risk to life, save money in the many evaluations of patients with chest pain.

But the key to efficacy is performance when the presence of CAD is less certain, for even with lofty sensitivities, preliminary tests will probably aid only those patients in the clinical category of probable or in-

definite angina where the probability of CAD is 0.45–0.85. When the clinical assessment designates chest pain to be definite or typical angina, and the probability of CAD before testing is therefore already 0.85 or more (*11,12*), it is unlikely, as Fig. 2 depicts, that any procedure preliminary to angiography will improve expected survival. At the other end of the spectrum, probabilities of CAD less than 0.2 are associated with nonischemic or nonanginal chest pain (*11,12*), and the people so classified merge with the asymptomatic population. Because this group evinces a paucity of data on survival and response to therapies, the values of various diagnostic approaches cannot be accurately determined. Probing this idea, decision analysis predicted that asymptomatic patients with CAD would not benefit from bypass operations (*19*).

Because health cannot be equated with monetary costs, these two factors, each momentous in medical practice, cannot be weighed in the same balance. However, when outcomes of two diagnostic pathways become equal, the monetary costs of each can be meaningfully compared. If a procedure with acceptable sensitivity and a reasonably high specificity, such as radionuclide ventriculography, is priced at one-tenth that of coronary angiography, then the use of the preliminary test incurs about half the fiscal expense of moving directly to angiography at a probability of CAD of 0.5. Moreover, if the preliminary test were appropriately able to remove patients with ventricular aneurysms and poor ventricular contraction from further consideration, savings would appreciate. At lower probabilities of CAD, the use of preliminary diagnostic measures costs progressively less money, and, conversely, the monetary expenses of their use approach those of directly performing angiography when the probability of CAD is 0.9. These financial relationships should further disuade prescriptions of preliminary tests for patients with definite or typical angina.

Tests of CAD that do not immediately threaten life are compelling, especially when they seem reasonably precise and relatively economical. But promise alone is not enough. The full effects of these tests upon life, now and in the future, must be accounted if they are to be fairly judged.

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