ANALYSIS OF PROBABILITY AS AN AID IN THE CLINICAL DIAGNOSIS OF CORONARY-ARTERY DISEASE

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Abstract The diagnosis of coronary-artery disease has become increasingly complex. Many different results, obtained from tests with substantial imperfections, must be integrated into a diagnostic conclusion about the probability of disease in a given patient.

To approach this problem in a practical manner, we reviewed the literature to estimate the pretest likelihood of disease (defined by age, sex and symptoms) and the sensitivity and specificity of four diagnostic tests: stress electrocardiography, cardiokymography, thallium scintigraphy and cardiac fluoroscopy. With this information, test results can be analyzed by use of Bayes' theorem of conditional probability.

This approach has several advantages. It pools the diagnostic experience of many physicians and integrates fundamental pretest clinical descriptors with many varying test results to summarize reproducibly and meaningfully the probability of angiographic coronary-artery disease. This approach also aids, but does not replace, the physician's judgment and may assist in decisions on cost effectiveness of tests. (N Engl J Med 300:1350-1358, 1979)

THE diagnosis of coronary-artery disease on the basis of history and physical examination alone is often difficult. Many sophisticated tests have thus been developed to allow an early and more accurate diagnosis. Although many tests are now firmly established in clinical practice, none is particularly suited to wide-scale, cost-effective application,[1] because each has limitations concerning sensitivity and specificity. Thus, when a positive test result occurs in a patient with a low likelihood of disease, it is of limited diagnostic importance.[2-4] A "positive" electrocardiographic stress test in an asymptomatic patient, for example, has a predictive accuracy of only 30 per cent for the presence of angiographic coronary-artery disease.[3,5,6]

Because many tests can be used to diagnose coronary-artery disease,[7,8] the physician must decide on their optimum use. This article, therefore, has two purposes. First of all, it describes how the probability of coronary-artery disease can be determined in a given patient before testing from information readily obtainable by clinical evaluation. Secondly, it describes a method by which the results of different noninvasive diagnostic tests can be integrated into a quantitative statement of the post-test probability of coronary-artery disease.

The methods are based on concepts included in Bayes' theorem of conditional probability, the subject of a continuing dialogue in the *Journal*.[9-12] Thus, although it is now well recognized that sensitivity and specificity define the quality of the test, the result cannot be satisfactorily interpreted without additional knowledge of the prevalence of disease in a given population.[12] For example, if a test with a 70 per cent sensitivity and 90 per cent specificity is "positive" in a patient with a 5 per cent pretest likelihood of disease, the likelihood of disease after testing is only 27 per cent. The steps in this simple calculation are given in the Appendix. An essential concept of noninvasive diagnostic tests, therefore, is that in a person with a low pretest probability of disease, a positive result has a low predictive accuracy. In contrast, the identical positive result in a person with a 50 per cent pretest likelihood yields a 88 per cent post-test likelihood of disease. In a patient with an intermediate pretest likelihood, therefore, a positive result indicates a substantial likelihood of disease.

Just as a positive result determines a new probability of disease, so does a negative result.[9] In the two examples described above, negative results reduce the likelihood of disease from 5 to 2 per cent and from 50 to 25 per cent, respectively. If the pretest likelihood of disease and the sensitivity and specificity of the test are known, it is possible to quantify the likelihood of disease in any patient. In the next section, we will review studies on the prevalence of coronary-artery disease (defined as narrowing of the diameter of at least one major artery by more than 50 per cent) in readily identifiable subgroups of patients and the sensitivity and specificity of diagnostic tests used to detect such disease. After providing specific estimates of sensitivity, specificity and prevalence, we describe how diagnostic tests modify the clinical estimate of disease likelihood. Review of the literature is unavoidably biased in several respects. All data on sensitivity and specificity were derived from selected groups of patients studied by means of coronary angiography. Some authors did not report distributions of their patients according to age and sex, whereas others showed a biased selection of male patients. Moreover, there has been a lack of uniformity in the way symptoms were classified and how coronary-artery disease was documented. The use of autopsy data, in particular, to estimate the average prevalence of coronary-artery disease has several well recognized limitations.[13] Because of possible methodologic bias, the review of the literature was intentionally unselective, and the data were pooled, rather than averaged, to account for differences in methodology and to provide a closer approximation of true population means.[14] Nevertheless, the data presented

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in the tables should not be considered as absolute standards but, rather, as preliminary estimates that will require modification as more precise data become available.

Characterization of the Pretest Likelihood of Coronary-Artery Disease

Symptoms

The prevalence of coronary-artery disease varies widely in specifically defined subgroups of adults. Table 1 summarizes the prevalence of angiographically confirmed coronary-artery disease in 4952 patients described as having "typical angina," "atypical angina" and "nonanginal chest pain."[15-32] The prevalence of disease in persons with typical angina is about 90 per cent, whereas atypical angina shows a 50 per cent prevalence ($P<0.001$) and nonanginal chest pain a 16 per cent prevalence ($P<0.001$).

Estimation of prevalence in asymptomatic persons is less reliable. Far fewer angiographic studies have been performed in such patients, and those studied by use of angiography may not truly represent the total group of patients. However, some authors have provided insight into the prevalence of such disease in asymptomatic persons. Gensini and Kelly reported that the prevalence of coronary-artery disease was 4.5 per cent in patients receiving cardiac catheterization for reasons other than chest pain,[33] whereas Erikssen et al. observed a prevalence of 3.4 per cent in asymptomatic men screened by means of a historical questionnaire and exercise testing.[34] These data suggest that the prevalence of coronary-artery disease in asymptomatic adults is about 4 per cent.

Age and Sex

Several pathological studies have defined the prevalence of atherosclerotic disease in the adult United States' population.[35-41] A few studies were performed only in persons not known to have coronary-artery disease before death, such as those dying of trauma or other unrelated conditions. These studies thus provide information on the prevalence of disease in asymptomatic persons. Table 2 summarizes pathological data obtained from 23,996 persons at autopsy. The mean prevalence of coronary-artery disease in these studies was 4.5 per cent. The prevalence of disease observed at autopsy is therefore similar to that seen in asymptomatic patients by use of coronary angiography. Table 2 shows that significant differences ($P<0.001$) in disease prevalence occur when patients are classified according to age and sex; the differences range from 0.3 per cent for women 30 to 39 years of age to greater than 12 per cent for men 60 to 69 years of age.

Table 1. Prevalence of Angiographic Coronary-Artery Disease in Symptomatic Patients.

Symptom	Proportion of Patients Affected	Pooled Mean ± SEP* (%)
Nonanginal chest pain	146/913	16.0±1.2
Atypical angina	963/1931	49.9±1.1
Typical angina	1874/2108	88.9±0.7

*Standard error of the per cent (see the Appendix). These values establish statistical levels of error but do not include errors due to sampling bias & other factors, which are probably of greater magnitude.

Table 2. Prevalence of Coronary-Artery Stenosis at Autopsy.

Age	Men		Women	
yr	Proportion Affected	Pooled Mean ± SEP* (%)	Proportion Affected	Pooled Mean ± SEP (%)
30–39	57/2,954	1.9±0.3	5/1,545	0.3±0.1
40–49	234/4,407	5.5±0.3	18/1,778	1.0±0.2
50–59	488/5,011	9.7±0.4	62/1,934	3.2±0.4
60–69	569/4,641	12.3±0.5	130/1,726	7.5±0.6
Totals	1,348/17,013		215/6,983	
Population-weighted mean†		6.4±0.2		2.6±0.2

*Standard error of the per cent (see the Appendix).

†Population weighting was performed by use of the 1970 U.S. Census figures.

These data yield one estimate of disease likelihood when the patient's age and sex are known (Table 2) and a second estimate when the presence or absence of symptoms is known (Table 1). The pretest likelihood of disease for any patient (according to any combination of age, sex and symptoms) may be determined by conditional-probability analysis[42,43] (see the Appendix for an example). Table 3 summarizes the results of this analysis for all combinations of age, sex and symptoms. The results show a wide range of pretest likelihood. For example, the pretest likelihood in a 55-year-old man with typical angina is 92 per cent, but the likelihood in a 35-year-old woman with atypical angina is only 4 per cent.

Risk Factors

The estimate of pretest likelihood in the asymptomatic patient may be further refined by consideration of so-called risk factors other than age and sex. The *Coronary Risk Handbook*,[44] which is based on results of the Framingham Study,[45] provides estimates of the risk of coronary-artery disease in asymptomatic patients; these estimates were determined from blood pressures, serum cholesterol values, smoking histories, glucose intolerances and resting electrocardiograms. Rifkin and Hood[10] believe that the tables in that handbook can be used to estimate disease prevalence in asymptomatic patients. Their contention is not necessarily valid, however, because those tables represent incidence estimates (the rate of development of disease) and not prevalence (the number of persons with disease at a given time). Although incidence and prevalence are intimately related,[2,46] they are thus not interchangeable. By use of appropriate conversion procedures, however, the incidence data from the *Coronary Risk Handbook* can be used to estimate the pretest likelihood of disease in asymptomatic patients.[12] Figure 1 shows that a precisely linear correlation ex-

Table 3. Pretest Likelihood of Coronary-Artery Disease in Symptomatic Patients According to Age and Sex.*

AGE	NONANGINAL CHEST PAIN		ATYPICAL ANGINA		TYPICAL ANGINA	
YR	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
30–39	5.2±0.8	0.8±0.3	21.8±2.4	4.2±1.3	69.7±3.2	25.8±6.6
40–49	14.1±1.3	2.8±0.7	46.1±1.8	13.3±2.9	87.3±1.0	55.2±6.5
50–59	21.5±1.7	8.4±1.2	58.9±1.5	32.4±3.0	92.0±0.6	79.4±2.4
60–69	28.1±1.9	18.6±1.9	67.1±1.3	54.4±2.4	94.3±0.4	90.6±1.0

*Each value represents the per cent ±1 standard error of the per cent, calculated from the data in Tables 1 & 2 as described in the Appendix.

ists between the age-related prevalence estimated from the pooled autopsy data discussed earlier and the six-year incidence reported in the Framingham Study. Since six-year incidence correlates well with estimated prevalence, the risk-factor data allow further refinement of the range of pretest likelihood in an asymptomatic patient from less than 1 per cent to more than 50 per cent.

The approach described above is a mathematical formalization of the intuition used by physicians when they review the literature or when they use past experience to assess patients' pretest likelihoods. Both approaches rely on the use of data from specific groups of patients, but they do allow reasonable estimates of the probability of coronary-artery disease on the basis of a given patient's age, sex, symptoms and (in those without symptoms) risk-factor profile.

Characterization of Diagnostic Tests for Coronary-Artery Disease

If an estimate of the pretest likelihood of coronary-artery disease is available, a diagnostic test can establish a new estimate of disease likelihood. This post-test likelihood depends on the sensitivity and specificity of the test.[2] Table 4 summarizes the pooled mean sensitivity and specificity of four different tests used to diagnose coronary-artery disease in 6599 patients. We selected each test on the assumption that it detects a different, potentially independent marker of the disease: electrophysiologic (depression of S–T segment), anatomic (coronary-artery calcification), mechanical (segmental dysfunction) and perfusive (thallium maldistribution). This assumption of independence is critical to serial analysis of likelihood according to Bayes' theorem.[42] Preliminary data from our laboratory support the validity of this assumption as it relates to the use of these tests in patients with coronary-artery disease. As yet, however, the number of patients studied is inadequate to determine the independence of these tests in the absence of disease.

The sensitivity and specificity of each test vary widely, depending on how the results are interpreted. Since post-test likelihood is highly influenced by the sensitivity and specificity of the test, the results are far more meaningful when such terms as "normal" and "ischemic" are replaced by a nonjudgmental quantitative estimate. In this connection, some semiquantitative criteria are listed in Table 4 for comparison. Although many other criteria are also used for interpreting the results (e.g., slow, upsloping electrocardiographic depression of the S–T segment), data on sensitivity and specificity are either limited, highly controversial or referenced to a less rigorous standard than coronary angiography,[14] for example, long-term follow-up evaluation or clinical judgment.

Clinical Relevance of Likelihood Analysis

Exercise Electrocardiography

The physician can interpret the diagnostic exercise test quantitatively if he knows the patient's pretest likelihood of disease and the sensitivity and specificity of electrocardiographic stress tests.[10] For example, a 45-year-old man with atypical angina has a pretest likelihood of coronary-artery disease of 46 per cent (Table 3). If the patient shows a 1.0-mm depression of the S–T segment after a stress test, the post-test likelihood of disease may be calculated in a manner identical to that described in the Appendix. The post-test likelihood is 64 per cent according to this calcula-

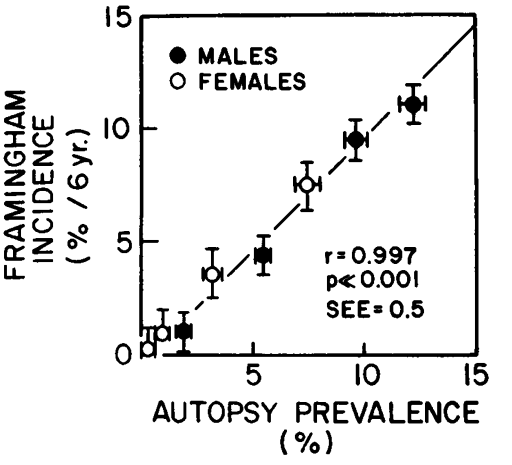

Figure 1. Relation of the Prevalence of Coronary-Artery Disease (Derived from the Autopsy Data in Table 1) and the Incidence of Ischemic Heart Disease (from the Framingham Study).

Open circles represent the four deciles of age in Table 2 for women and closed circles for men. There is a precise linear correlation (r=0.997) between the variables. The slope of the regression line through the origin is 1.05. Disease prevalence may therefore be estimated from the *Coronary Risk Handbook* incidence data by multiplying the listed value by this constant.

tion. A woman with otherwise identical data would, on the other hand, have a likelihood of only 25 per cent. Conversely, if 2.5-mm depression of the S–T segment is observed, the corresponding post-test likelihoods would be 97 per cent for the man and 87 per cent for the woman.

A positive result, therefore, may have a different meaning, depending both on the person tested and on the severity of disease (Fig. 2). Table 5 lists post-test likelihood of disease for a range of depressions of the S–T segment according to age, sex and symptoms.

Serial Interpretation of Additional Test Results

The examples given above illustrate a common problem in diagnostic stress testing: the test often establishes only an intermediate level of post-test likelihood of disease and leaves the physician uncertain concerning diagnosis and management. This uncertainty in the post-test likelihood may be reduced by use of other tests.

When a second independent test is used, the post-test likelihood determined from the first test becomes the pretest likelihood for the second test. For example, several pathological studies have documented the relation between coronary-artery stenosis and postmortem coronary calcification.[85-87] This observation has long been considered of little diagnostic importance because calcification was thought to be an insensitive indicator of coronary-artery disease in young patients and nonspecific in old patients. Recently, however, newer-generation, image-intensification fluoroscopy systems have permitted a reappraisal of this point of view; the results obtained by fluoroscopy were confirmed by use of coronary angiography. In this way, Bartel et al.[68] found that calcification, as detected fluoroscopically, showed an overall sensitivity of 56 per cent and a specificity of 97 per cent for substantial coronary-artery disease in 360 patients studied with coronary angiography. The effects of age and sex were not noteworthy.

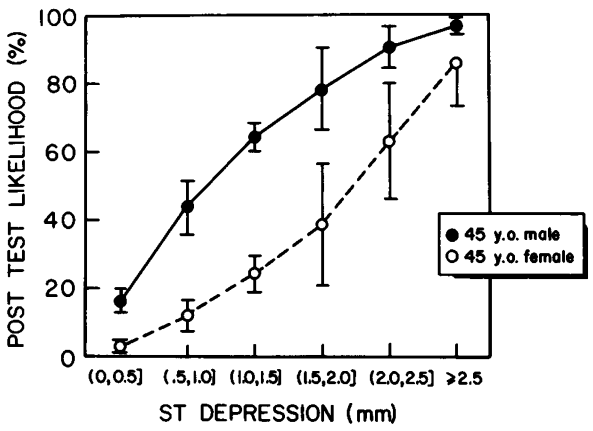

Figure 2. Relation between Post-test Likelihood and Magnitude of Depression of the S–T Segment Expressed as Half-open Intervals in a 45-Year-Old Man (●) and a 45-Year-Old-Woman (○) with Atypical Angina.

Each symbol represents the mean (calculated from Bayes' theorem) ± SEP. Post-test likelihood increases substantially as the magnitude of depression of the S–T segment increases, but the likelihood for the woman is less than for the man at equivalent levels of test abnormality. Our current custom of reporting a result simply as an "ischemic response" is, therefore, indiscriminate and would seem to be misleading and less meaningful than a probability statement.

Table 4. Sensitivity and Specificity of Diagnostic Tests for Angiographic Coronary-Artery Disease.

PROCEDURE	NO. OF PATIENTS	CRITERION	SENSITIVITY % ±1 SEP*	SPECIFICITY % ±1 SEP
Electrocardiographic stress[6,15-23,47-67]	4838	*Nonupsloping depression of S–T segment (mm)*		
		(0,0.5]*	14.3±3.3	37.5±5.7
		(0.5,1.0]	20.8±3.4	77.3±5.8
		(1.0,1.5]	23.3±2.5	89.0±1.4
		(1.5,2.0]	8.8±2.9	97.9±1.3
		(2.0,2.5]	13.3±2.3	98.8±0.8
		≥2.5	19.5±1.6	99.5±0.5
Cardiac fluoroscopy[68]	507†	*Coronary calcification (vessels)*		
		0	42.0±2.5	3.9±1.7
		1	23.5±2.2	97.7±1.3
		2	20.1±2.1	98.4±1.1
		3	14.5±1.8	100.0±0.0
Cardiokymographic stress	122†	*Systolic motion*		
		Inward	25.7±5.2	5.8±3.4
		Partially outward	44.3±5.9	96.2±2.7
		Totally outward	30.0±5.5	98.1±1.9
Stress thallium scintigraphy[64-67,71-84]	1132	*Perfusion defect*		
		None	14.7±1.7	16.4±3.1
		Fixed	14.6±2.6	89.7±3.4
		Reversible	70.7±1.9	93.9±1.3

*The standard notation (x,y] represents the half-open interval, x≤ mm < y.
†Includes the authors' unpublished data.

The use of more than one test can help tremendously in the noninvasive diagnosis of coronary-artery disease. If, for example, an exercise-induced 1.0-mm depression of the S–T segment were observed in a patient in whom the pretest likelihood was 15 per cent, the post-test likelihood would increase to only 27 per cent. If cardiac fluoroscopy then showed that one coronary artery had calcification, the post-test likelihood would increase again, from the new (post-electrocardiogram) pretest likelihood of 27 per cent, to 79 per cent. The use of cardiac fluoroscopy is of substantial diagnostic value in this case: instead of a 25 per cent chance of disease, as would be observed with stress testing alone, the probability increases to 80 per cent (Fig. 3). This hypothetic example is consistent with the observations of Kelley et al.[88] These workers combined fluoroscopy with electrocardiographic stress testing and observed a ninefold increase in the frequency of a positive stress test when coronary-artery calcification was present in asymptomatic, middle-aged men. Our example is consistent also with the results of Aldrich (whose unpublished data are cited in Epstein[4]), who observed that the probability of disease in asymptomatic patients with both an abnormal stress test and coronary calcification was 82 per cent.

Table 5. Post-test Likelihood after an Electrocardiographic Stress Test According to Age, Sex, Symptom and Depression of S–T Segment.*

Age	Asymptomatic		Nonanginal Chest Pain		Atypical Angina		Typical Angina	
yr	men	women	men	women	men	women	men	women
				≥2.5				
30–39	43.0±24.9	10.5±9.9	68.1±22.1	23.9±19.5	91.8±7.7	63.1±24.5	98.9±1.1	93.1±6.8
40–49	69.4±21.3	28.3±20.8	86.5±11.8	52.9±25.8	97.1±2.8	85.7±12.7	99.6±0.4	98.0±2.1
50–59	80.7±15.6	56.3±24.9	91.4±7.9	78.1±17.3	98.2±1.7	94.9±4.9	99.8±0.2	99.3±0.7
60–69	84.5±13.1	76.0±18.4	93.8±5.8	89.9±9.2	98.8±1.2	97.9±2.1	99.8±0.2	99.7±0.3
				(2.0,2.5]				
30–39	17.7±10.3	3.2±2.4	37.8±16.6	8.2±5.9	76.0±12.8	32.7±16.7	96.2±2.6	79.4±12.6
40–49	39.2±16.5	10.1±6.5	64.5±16.0	24.2±13.5	90.5±6.0	63.0±17.1	98.7±0.9	93.2±4.7
50–59	54.3±17.1	26.8±13.8	75.2±13.0	50.4±17.7	94.1±3.9	84.2±9.4	99.2±0.5	97.7±1.6
60–69	60.9±16.4	47.3±17.3	81.2±10.6	71.7±14.2	95.8±2.8	93.0±4.5	99.5±0.4	99.1±0.6
				(1.5,2.0]				
30–39	7.5±5.0	1.2±1.0	18.7±10.9	3.3±2.5	54.5±17.8	15.5±10.1	90.6±6.1	59.3±18.9
40–49	19.6±11.1	4.1±2.8	40.8±17.1	10.8±7.2	78.2±12.0	39.1±17.7	96.6±2.3	83.8±10.2
50–59	31.0±15.0	12.2±7.6	53.4±17.6	27.8±14.4	85.7±8.6	66.8±15.9	98.0±1.4	94.2±3.9
60–69	37.0±16.4	25.4±13.4	62.1±16.7	48.9±17.8	89.5±6.6	83.3±9.8	98.6±1.0	97.6±1.7
				(1.0,1.5]				
30–39	3.9±0.9	0.6±0.2	10.4±2.2	1.7±0.7	37.7±5.2	8.5±2.8	83.0±3.2	42.4±9.4
40–49	11.0±1.7	2.1±0.5	25.8±3.8	5.8±1.7	64.4±4.2	24.5±5.6	93.6±1.1	72.3±6.2
50–59	18.5±2.6	6.5±1.3	36.7±4.5	16.3±3.1	75.2±3.3	50.4±5.4	96.1±0.7	89.1±2.2
60–69	22.9±3.1	14.7±2.3	45.3±4.7	32.6±4.6	81.2±2.7	71.6±3.9	97.2±0.5	95.3±0.9
				(0.5,1.0]				
30–39	1.7±0.6	0.3±0.1	4.8±1.6	0.7±0.4	20.7±5.5	3.9±1.6	67.8±7.4	24.2±8.4
40–49	5.1±1.5	0.9±0.3	13.1±3.7	2.6±1.0	43.9±7.7	12.3±4.3	86.3±3.7	53.0±10.0
50–59	9.0±2.5	2.9±0.9	20.1±5.1	7.8±2.4	56.8±7.6	30.5±7.1	91.3±2.5	77.9±5.8
60–69	11.4±3.1	6.9±2.0	26.4±6.2	17.3±4.7	65.1±7.0	52.2±7.9	93.8±1.8	89.8±2.9
				(0,0.5]				
30–39	0.4±0.1	0.1±0.0	1.2±0.4	0.2±0.1	6.1±1.7	1.0±0.4	24.5±6.6	7.4±2.9
40–49	1.3±0.3	0.2±0.1	3.6±0.9	0.7±0.2	16.4±3.5	3.4±1.2	61.1±6.3	22.0±6.2
50–59	2.4±0.6	0.8±0.2	5.9±1.5	2.1±0.6	24.7±4.8	9.9±2.5	72.5±5.2	46.9±7.2
60–69	3.1±0.8	1.8±0.6	8.2±2.0	5.0±1.3	31.8±5.5	21.4±4.5	79.1±4.3	68.8±5.9

*These data are calculated from the pretest likelihoods in Table 3 & the sensitivity & specificity data in Table 4 according to methods described in the Appendix. Each symbol (x,y] represents depression of the S-T segment in millimeters.

Clinical Application of Serial-Likelihood Analysis

The above examples illustrate the potential value of likelihood analysis in the noninvasive diagnosis of coronary-artery disease. The practical application of many tests is shown in Table 6, which is a modification of the test report now used in our cardiac diagnostic laboratory. This report lists each factor used in analysis of pretest likelihood after each test is done. For example, an asymptomatic 50-year-old man had a pretest likelihood of 9.7 per cent according to Table 2. After an electrocardiographic stress test, the post-test likelihood was 54.3±17.1 per cent (Table 5), an intermediate value for which the use of further diagnostic tests would be particularly helpful. A cardiokymographic stress test and cardiac fluoroscopy were therefore performed. The observed abnormalities increased the overall likelihood for coronary disease to 99.3±0.8 per cent. At this point, a thallium stress test would not appreciably alter this high diagnostic likelihood. A positive perfusion result would increase the likelihood from 99.3 to 99.9 per cent, whereas a negative result would decrease the likelihood to only 96.1 per cent. Therefore, the physician cannot only analyze the cumulative effect of many possibly discordant test results but can also evaluate the cost effectiveness of other tests before using them. In the patient described above, thallium scintigraphy would appear to add little information concerning the likelihood of disease, but this procedure would substantially increase the cost of estimation. This asymptomatic man had coronary-artery disease of three vessels, as determined by coronary angiography.

Validity of Likelihood Analysis

The usefulness of likelihood analysis depends on how accurately the results correlate with the prevalence of coronary-artery disease as demonstrated by coronary angiography or long-term follow-up studies. Although limited direct validation is available, the accuracy of this approach is suggested by the recent observations of Charuzi et al.[89] Forty-one patients with chest-pain syndromes underwent stress testing with electrocardiography, thallium scintigraphy and cardiokymography. Serial determination of the post-test likelihood predicted well the angiographic findings. Thus, in 22 patients who had two or three positive results, the average post-test likelihood was 98.4 per cent; the presence of disease was later proved in all of them by use of coronary angiography. Thirteen patients had only one positive result, for an

average likelihood of 45.2 per cent. Angiography confirmed the presence of disease in eight of the 13 patients. Six patients had three negative results, producing an average post-test likelihood of 4.5 per cent; all were angiographically normal. The average post-test likelihood in the 30 diseased patients was 85.1±4.3 per cent and in the 11 nondiseased patients was 20.5±6.1 per cent.

The accuracy of likelihood analysis is further supported by retrospective calculations of post-test likelihood from data in the literature.[8,22,31,32,34,48,54,70,75,89] Figure 4 illustrates the relation between observed frequency of coronary-artery disease and calculated post-test likelihood for some studies shown in Tables 1 and 4. In those studies, the

Table 6. Cumulative Analysis of Likelihood in a 50-Year-Old Asymptomatic Man in Whom the Pretest Likelihood was 9.7±0.4 Per Cent.

Test	Result	Post-test Likelihood (%)
Electrocardiographic stress	2.0-mm depression of S–T segment	99.3±0.8
Cardiokymographic stress	Midsystolic outward motion	
Fluoroscopy	Right-coronary-artery calcification	
Thallium stress scintigraphy	If normal	96.1±4.3
	If abnormal	99.9±0.1
Coronary angiography	Coronary-artery disease of three vessels	

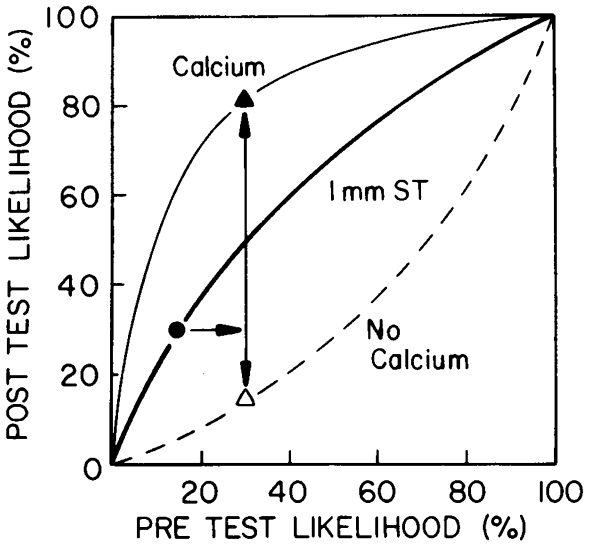

Figure 3. Influence of Serial Tests on Post-test Likelihood.
The closed circle represents a patient with a pretest likelihood of 15 per cent (x axis) and a 1.0-mm depression of the S–T segment after a stress test (heavy solid line). The resultant post-test likelihood is 27 per cent (y axis). If cardiac fluoroscopy showed calcification of one coronary vessel (light solid line), the resultant post-test likelihood would rise (↑) to 79 per cent (▲). If no calcification was observed (dashed line), the likelihood would fall (↓) to 14 per cent (△). Note that the post-test likelihood from the first test becomes the pretest likelihood of the second test (horizontal arrow).

results of electrocardiographic or thallium stress tests (or both) were reported for 45 groups of patients categorized according to age, sex and symptom. The observed prevalence of disease in these groups ranged from 0 to 100 per cent. The correlation between calculated post-test likelihood and observed prevalence of coronary-artery disease is highly linear around the line of identity, regardless of the type or amount of data involved. This observation indicates that the retrospectively calculated post-test likelihoods from these studies correspond closely to the actual presence of coronary-artery disease observed in these patients. Thus, although additional data may modify the absolute value of calculated likelihood for a given patient, the accuracy of the estimate as a representation of group prevalence is apparently independent of the absolute value.

Other statistical methods, such as multivariate discriminant regression, may also be useful in quantitative diagnostic analysis[90] but are more difficult to apply. The data summarized in this section suggest that, despite the many assumptions inherent in the estimation of pretest and post-test likelihoods, the application of likelihood analysis in clinical diagnosis is of value.[4]

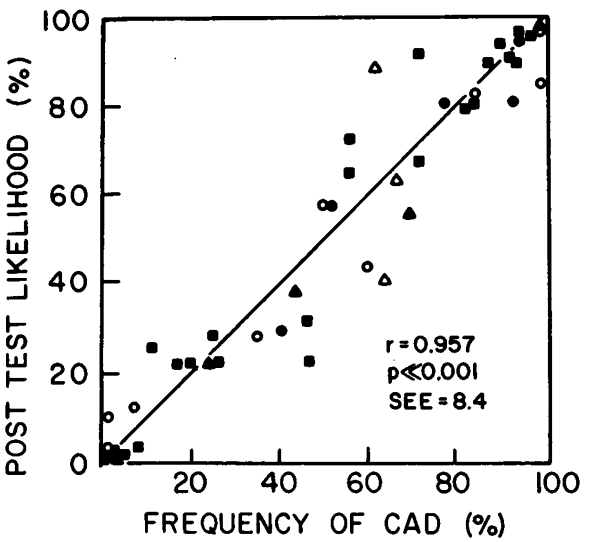

Figure 4. Relation between Post-test Likelihood and Observed Frequency of Documented Coronary-Artery Disease Calculated from Results in the Literature.
The circles represent patients who were defined on the basis of symptoms only; the triangles, on the basis of sex and symptoms; and the squares, on the basis of age, sex and symptoms. The closed symbols represent patients who received electrocardiographic stress tests only, and the open symbols represent stress tests and thallium scintigraphy. For the 45 groups of patients, there is a close correlation between "predicted" prevalence and the prevalence observed by the authors. SEE is the standard error of the estimate.

Conditional-probability analysis thus aids in the "complex and uncertain problems of medical decision making" and is "presented in a format that allows the experience of many physicians to be pooled...."[1] Also, since the effect of other test results on post-test likelihood can be analyzed before testing, this method "encourages...cost-effective analysis."[1] This ability to define the likelihood of disease in any patient may help both the practicing physician and risk-factor intervention programs to achieve better patient compliance to therapy. Finally, it may someday be possible to reduce the morbidity and mortality of coronary-artery disease by use of prevention programs directed at high-likelihood, asymptomatic persons before they suffer myocardial infarction or sudden death.

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Appendix

Definitions

Pretest likelihood is the probability of disease in a patient to be tested:

$$P(D+) = \frac{\text{number of patients with disease in the test population}}{\text{total number of patients in the test population}}.$$

Sensitivity is the probability of a given test result in a patient with disease:

$$P(T+|D+) = \frac{\text{number of patients with disease showing a given test result}}{\text{total number of tested patients with disease}}.$$

Specificity is the probability of not having the given test result in a patient without disease:

$$P(T-|D-) = \frac{\text{number of disease-free patients not showing the test result}}{\text{total number of disease-free patients tested}}.$$

Post-test likelihood is the probability of disease in a patient showing a given test result:

$$P(D+|T+) = \frac{\text{number of patients with disease showing a given test result}}{\text{total number of patients showing the test result}}.$$

Bayes' Theorem

Post-test likelihood may be expressed in common notation[10,42,91] as a function of pretest likelihood, sensitivity and specificity according to Bayes' theorem of conditional probability[2,42,92]:

$$P(D+|T+) = \frac{P(D+) \times P(T+|D+)}{P(D+) \times P(T+|D+) + (1-P(D+)) \times (1-P(T-|D-))} \quad (1)$$

Sample Calculations of Post-test Likelihood

In a patient who shows the test result:

$$P(D+) = 5 \text{ per cent};$$
$$P(T+|D+) = 70 \text{ per cent};$$
$$P(T-|D-) = 90 \text{ per cent};$$
$$P(D+|T+) = \frac{0.05 \times 0.70}{(0.05 \times 0.70) + (1-0.05)(1-0.90)} = 27 \text{ per cent}.$$

In a patient who does not show the given test result:

$$P(D+) = 5 \text{ per cent};$$
$$P(T-|D+) = 1-P(T+|D+) = 30 \text{ per cent};$$
$$P(T+|D-) = 1-P(T-|D-) = 10 \text{ per cent};$$
$$P(D+|T-) = \frac{0.05 \times 0.30}{(0.05 \times 0.30) + (1-0.05)(1-0.10)} = 2 \text{ per cent}.$$

Determination of P(T+|D+) According to Age, Sex and Symptom

Any observable characteristic has a definable sensitivity and specificity in relation to the diagnosis in question and may therefore be considered a test (T).

For example, let T be the characteristic of being a man 30 to 39 years of age. From Table 2, we derive the following probabilities:

	T+	T−	Total
Patients with coronary-artery disease (D+)	57	1,506	1,563
Patients without disease (D−)	2,897	19,536	22,433
Total	2,954	21,042	23,996

$$P(T+|D+) = 57/1,563 = 0.036;$$
$$P(T-|D-) = 19,536/22,433 = 0.871.$$

For any P(D+), we may now use these values to determine the associated P(T+|D+) by Bayes' theorem. For example, to determine the likelihood of coronary-artery disease in a 35-year-old man with atypical angina, we obtain P(D+), the likelihood of coronary-artery disease in all patients with the symptom (from Table 1), as 49.9 per cent. According to Bayes' theorem:

$$P(D+|T+) = \frac{0.499 \times 0.036}{(0.499 \times 0.036) + (1-0.499)(1-0.871)} = 21.8 \text{ per cent}.$$

All the values in Table 3 were obtained in a similar fashion. These values depend only minimally on the actual composition of the patients at autopsy according to age and sex. A hypothetic 440 per cent increase in the number of 35-year-old men, for example, would have produced only a 5 per cent increase in P(D+|T+).

Analysis of Error

When one knows the number of patients from whom a percentage has been determined, the standard error of the per cent (the square root of the variance, analogous to the standard deviation) is defined as:

$$\sigma = \sqrt{\frac{pq}{n}} \quad (2)$$

where p = the per cent expressed as a decimal, $q = 1-p$, and n = number of patients.

In the example above, P(D+) was estimated from 1931 patients with atypical angina, 963 of whom had coronary-artery disease (Table 1):

$$P(D+) = \frac{963}{1931} = 0.499 \pm \sqrt{\frac{0.499(1-0.499)}{1931}} = 49.9 \pm 1.1 \text{ per cent}.$$

The standard error of the per cent P(T+|D+) [sensitivity] and P(T−|D−) [specificity] is determined in a similar manner.

When these independent and uncorrelated errors are introduced into Bayes' equation for calculation of P(D+|T+), the resultant associated variance is given by the partial differential equation[92]:

$$\sigma_x^2 = \left(\frac{\partial x}{\partial a}\right)^2 \times \sigma_a^2 + \left(\frac{\partial x}{\partial b}\right)^2 \times \sigma_b^2 + \left(\frac{\partial x}{\partial c}\right)^2 \times \sigma_c^2 \quad (3)$$

where $x = P(D+|T+)$, $a = P(D+)$, $b = P(T+|D+)$, and $c = P(T-|D-)$.

To determine the standard error of the per cent for post-test likelihood (σ_x), we solve for:

$$\frac{\partial x}{\partial a} = \frac{b(1-c)}{[ab+(1-a)(1-c)]^2}; \quad (4)$$

$$\frac{\partial x}{\partial b} = \frac{a(1-c)(1-a)}{[ab+(1-a)(1-c)]^2}; \quad (5)$$

$$\frac{\partial x}{\partial c} = \frac{ab(1-a)}{[ab+(1-a)(1-c)]^2}. \quad (6)$$

By substitution of Equations 4 to 6 into Equation 3:

$$\sigma_x = \sqrt{\frac{b^2(1-c)^2\sigma_a^2 + a^2(1-c)^2(1-a)^2\sigma_b^2 + a^2b^2(1-a)^2\sigma_c^2}{[ab+(1-a)(1-c)]^4}}. \quad (7)$$

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