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Diagnosis of Acute Myocardial Infarction from Two Measurements of Creatine Kinase Isoenzyme MB with Use of Nonparametric Probability Estimation

Larry H. Bernstein,[1] I. J. Good,[2] Golde I. Holtzman,[2] Michael L. Deaton,[3] and Joseph Babb[1]

By using bivariate probability estimation for the diagnosis of acute myocardial infarction (AMI) we show how to overcome the difficulties encountered for patients whose clinical presentation is atypical and those encountered when multiple isoenzyme determinations are treated by univariate methods. We use the values for creatine kinase isoenzyme MB measured at the time of admission and 12 h later to estimate the Bayes factors in favor of AMI. The Bayes factors are compiled into a table that the clinician can use to estimate the posterior probability that a patient has AMI. The table of Bayes factors is based on data for a sample of 802 non-AMI patients and 180 AMI patients. Further to validate the method, we randomly chose 200 of the non-AMI and 50 of the AMI patients as an evaluation sample, then used the remaining 602 non-AMI and 130 AMI patients to recompute the Bayes factors. These Bayes factors were used to find the probability of AMI for each of the 250 patients in the evaluation sample. The method resulted in only one false positive and no false negatives. For the misclassified patient the measurements at admission and 12 h later were 1 and 11 U/L; the posterior odds were 15 to 1 in favor of AMI, but in fact the patient was non-AMI.

Our purpose here is twofold: (*a*) to describe a quantitative procedure for aiding the diagnosis of acute myocardial infarction (AMI), and (*b*) to illustrate the use of bivariate probability estimation in place of the use of two tests, each interpreted in a univariate manner.[4] This statistical method has wide applicability. Most of the details are omitted because they are covered by literature citations, but some of the elementary statistical ideas and terminology are described in the appendices.

AMI is often difficult to diagnose when a patient is known to have "pre-existing" coronary occlusive disease. The classic criteria (*1*) for diagnosis include (*a*) the presence of chest pain; (*b*) specific characteristics of the pain, and its relief by nitroglycerin; (*c*) the occurrence of changes in the electrocardiogram (EKG) indicative of AMI; and (*d*) the detection in the serum of increased concentration of enzymes derived from damaged heart muscle: creatine kinase (CK; EC 2.7.3.2), lactate dehydrogenase (EC 1.1.1.27), and aspartate aminotransferase (EC 2.6.1.1).

The principal problem with using the classic criteria for diagnosis of AMI is that patients may present with atypical histories, such as nonpressing substernal pain, lack of appropriate EKG findings, and increased enzyme activities in serum that are not specific for AMI. Consequently, it has become common practice, in assessing the occurrence of AMI in widely differing institutional settings, to measure the MB isoenzyme of CK (CK-MB), which usually is increased in serum within 6 h after the onset of chest pain and is usually found to be above normal at the time of admission. Its activity in serum usually increases to its maximum 12 h later, unless the patient has been admitted unusually early or late in relation to the time of onset of infarction or there has been early coronary reperfusion (*2*). Although the diagnostic efficiency of the MB isoenzyme thus is high at the time of admission, some of our patients have no such increased value for CK-MB at the time of admission but an increase during the next 6 h, and in some others it decreases during the 18 h after admission. It has now become common to evaluate CK-MB serially because, as we have observed (*3*), physicians are accustomed to making comparisons of CK-MB measurements, and they consider the value obtained at the peak of the increase in CK-MB to be an indicator of the *extent* of damage (*4*). If the serially measured values decline sufficiently, then this may also reflect occurrence of AMI.

We here report on the diagnostic value of a predictor derived from the combined measurement of CK-MB at the time of admission and 12 h later—measurements denoted here by "CK0" and "CK12." This procedure can be used to reduce errors of classification.

Materials and Methods

We measured CK-MB isoenzyme activities at 30 °C with an immunoinhibition assay as previously described (*5*), making serial measurements at 6-h intervals during the first 24 h after admission. In particular, we made the measurements of CK0 and CK12. Upon reviewing the medical records, and after discharge of the patients, we classified them as AMI or non-AMI before the statistical analysis was performed. We thus created a sample (that is, a database) of CK0 and CK12 readings for 215 AMI patients and 811 non-AMI patients.

For these 1026 patients, the CK0 values ranged from 0 to 232 U/L with a 97.5 percentile of only 34 U/L; and CK12 values ranged from 0 to 266 U/L with a 97.5 percentile of only 66 U/L. We decided to eliminate from the study the 44 patients (4.4%) for whom one or both of the CK values were above the 97.5 percentile. There were two reasons for "trimming" the sample by eliminating these statistical outliers: (*a*) the extremes of the data are less reliable and their inclusion would have affected the results for the body of the data (95% of the patients), and (*b*) the use of all the data to illustrate the technical details of our statistical methods would resemble the use of a map of the Pacific when the main interest is Hawaii.

Our statistical methods were then applied to the remaining "trimmed" database of 982 patients: 180 AMI and 802 non-AMI. First we applied the method known as "maximum penalized likelihood" (*6–9*) to estimate (*a*) the probability distribution of CK0 and CK12 values for AMI patients, and

[1] Departments of Pathology and Medicine, Bridgeport Hospital, 267 Grant St., Bridgeport, CT 06610.
[2] Department of Statistics, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061.
[3] E. I. DuPont de Nemours & Co., Inc., Louviers Bldg., Milford Crossroads, Wilmington, DE 19898.
[4] Nonstandard abbreviations: AMI, acute myocardial infarct; CK, creatine kinase; and EKG, electrocardiogram.
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(*b*) the same for non-AMI patients. The ratio of the two probabilities corresponding to a given pair of readings (CK0, CK12) is a *measure*, but not the *definition*, of the Bayes factor (see *Appendix A*). The method of use of the Bayes factors is exemplified in the next section.

Results

To describe the results, we shall use the terminology of prior and posterior odds, which are discussed or defined in *Appendix A*.

Table 1 gives the Bayes factor in favor of AMI corresponding to specified values of CK0 and CK12. In using the table, one would obtain the posterior odds of AMI by multiplying the Bayes factor by the prior odds of AMI. In general, prior odds are based on other evidence for or against AMI, such as an EKG or other test results. These prior odds are a roughly quantified judgement that is based on the experience of the clinician other than the measurements of CK0 and CK12. However, we might imagine a situation in which the *only* evidence consists of measurements of CK0 and CK12 (taking into account that the reason these are requested is for evaluating chest pain). Then we would take as the prior probability the relative frequency of AMI patients among those who presented with chest pain; using our trimmed database, we get 180/982 = 0.1833. Likewise, the prior odds in such a case are 180/802 = 0.2244. For example, in this situation, if a new patient had CK0 = 19 and CK12 = 5, then, by Table 1, the Bayes factor is 51; the initial odds are 0.2244, and therefore the posterior odds of AMI are 51 × 0.2244 = 11.4 or a probability of 11.4/(11.4 + 1) = 0.92.

The reciprocal of the Bayes factor in favor of AMI is the Bayes factor against AMI (in favor of non-AMI).

Table 1. Estimated Bayes Factors in Favor of AMI Based on the Entire Trimmed Sample (n = 982, CK0 = 0 to 35, CK12 = 0 to 44 U/L)

CK0	CK12 0	1	2	3	4	5	6	7	8	9	10	11	12
0	1:16000	1:43000	1:34000	1:15000	1:6700	1/360	1/9	4/1	360:1	630:1	810:1	1500:1	1600:1
1	1:42000	1:160000	1:130000	1:66000	1:25000	1/390	1/23	1/4	6/5	5/2	4/1	11/1	13/1
2	1:26000	1:130000	1:140000	1:92000	1:47000	1/8200	1/330	1/56	1/9	1/3	2/3	3/1	4/1
3	1:10000	1:64000	1:92000	1:73000	1:45000	1:22000	1/870	1/100	1/10	1/3	2/3	3/1	4/1
4	1:3700	1:25000	1:44000	1:43000	1:30000	1:18000	1/1300	1/160	1/12	1/4	1/2	2/1	2/1
5	1:1900	1:9500	1:19000	1:24000	1:22000	1:16000	1/2800	1/360	1/27	1/8	1/5	1/1	6/5
6	1:570	1:3000	1:7300	1:11000	1:14000	1:13000	1/7700	1/1000	1/53	1/15	1/9	1/2	2/3
7	1:95	1:1000	1:3200	1:6000	1:8600	1:9000	1:7700	1/2800	1/91	1/23	1/13	2/5	1/2
8	1:7	1:480	1:1600	1:3600	1:5200	1:6500	1:6400	1/2200	1/110	1/28	1/16	1/3	2/5
9	0:0	1:230	1:1000	1:2300	1:3400	1:4500	1/1900	1/470	1/61	1/27	1/16	1/4	1/3
10	0:0	1:100	1:760	1:1600	1:2300	1/680	1/240	1/120	1/44	1/19	1/13	1/4	1/3
11	0:0	1:54	1:670	1:1200	1/580	1/130	1/62	1/43	1/23	1/13	1/9	1/4	1/3
12	0:0	1:34	1:670	1:850	1/100	1/30	1/18	1/14	1/10	1/7	1/6	1/3	1/3
13	0:0	1:24	1:470	1:490	1/23	1/8	1/5	1/4	1/3	1/3	2/5	1/2	1/2
14	0:0	1:19	1:370	1/250	1/12	1/4	1/3	2/5	1/2	1/2	1/2	2/3	3/4
15	0:0	1:10	1:130	1/59	1/4	2/3	4/3	5/3	2/1	3/2	3/2	3/2	3/2
16	0:0	1:7	1:82	1/36	2/5	6/5	5/2	3/1	3/1	5/2	2/1	2/1	2/1
17	0:0	1:3	1:20	1/10	4/3	4/1	8/1	11/1	9/1	7/1	6/1	5/1	4/1
18	0:0	1:2	1:12	1/6	2/1	7/1	14/1	19/1	15/1	11/1	10/1	6/1	6/1
19	0:0	0:0	1:1	6/5	13/1	51/1	110/1	150/1	90/1	48/1	37/1	14/1	12/1
20	0:0	0:0	0:0	4/3	15/1	60/1	130/1	170/1	110/1	56/1	44/1	16/1	13/1
21	0:0	0:0	0:0	2:1	45:1	200:1	440:1	720:1	1100:1	550/1	340/1	47/1	34/1
22-23	0:0	0:0	0:0	4:1	81:1	350:1	790:1	1300:1	1900:1	750/1	460/1	60/1	43/1
24-25	0:0	0:0	0:0	3:1	63:1	270:1	600:1	980:1	1500:1	1600:1	1700:1	190/1	120/1
26-27	0:0	0:0	0:0	2:1	38:1	160:1	350:1	570:1	900:1	1100:1	1200:1	990/1	550/1
28-29	0:0	0:0	0:0	3:2	29:1	120:1	270:1	440:1	700:1	850:1	950:1	1100:1	1100/1
30-31	0:0	0:0	0:0	0:0	17:1	73:1	160:1	270:1	440:1	560:1	640:1	810:1	820:1
32-33	0:0	0:0	0:0	0:0	10:1	44:1	99:1	170:1	280:1	370:1	430:1	570:1	580:1
34-35	0:0	0:0	0:0	0:0	6:1	28:1	65:1	110:1	200:1	270:1	310:1	440:1	450:1

CK0	CK12 13	14-15	16-17	18-19	20-21	22-23	24-25	26-27	28-29	30-32	33-35	36-38	39-41	42-44
0	2200:1	4900:1	5300:1	4900:1	4000:1	3700:1	2400:1	2400:1	1500:1	2200:1	1500:1	1300:1	1000:1	930:1
1	49/1	89/1	410/1	5200/1	16000:1	16000:1	15000:1	15000:1	14000:1	20000:1	18000:1	17000:1	15000:1	13000:1
2	20/1	41/1	230/1	3500/1	14000/1	24000:1	22000:1	21000:1	18000:1	26000:1	20000:1	18000:1	14000:1	13000:1
3	12/1	23/1	83/1	550/1	2100/1	18000:1	16000:1	16000:1	13000:1	19000:1	15000:1	13000:1	10000:1	9500:1
4	7/1	12/1	41/1	250/1	930/1	11000:1	10000:1	9900:1	8500:1	12000:1	10000:1	9300:1	7600:1	7000:1
5	4/1	8/1	31/1	210/1	780/1	8000:1	7600:1	7500:1	6400:1	9700:1	8300:1	7700:1	6500:1	5900:1
6	5/2	5/1	19/1	120/1	440/1	3100/1	6400:1	6400:1	5600:1	8200:1	7100:1	6500:1	5500:1	5100:1
7	2/1	4/1	11/1	60/1	210/1	970/1	5600:1	5500:1	4900:1	7100:1	5900:1	5500:1	4600:1	4200:1
8	4/3	5/2	8/1	36/1	120/1	370/1	4700:1	4700:1	4100:1	5900:1	4900:1	4400:1	3600:1	3300:1
9	1/1	2/1	5/1	21/1	59/1	150/1	2400/1	2500/1	3500:1	5000:1	4000:1	3600:1	2800:1	2500:1
10	3/4	4/3	4/1	12/1	30/1	60/1	470/1	480/1	3000:1	4300:1	3400:1	3000:1	2200:1	2000:1
11	2/3	6/5	5/2	7/1	17/1	30/1	170/1	180/1	2500:1	3000/1	2800:1	2500:1	1800:1	1600:1
12	3/4	1/1	2/1	5/1	9/1	15/1	70/1	72/1	690/1	790/1	2200:1	2000:1	1500:1	1300:1
13	5/6	6/5	2/1	3/1	6/1	8/1	33/1	34/1	230/1	260/1	1800:1	1600:1	1200:1	1000:1
14	1/1	6/5	2/1	3/1	5/1	7/1	26/1	27/1	160/1	180/1	1600:1	1400:1	1100:1	970:1
15	3/2	5/3	2/1	3/1	4/1	5/1	18/1	18/1	85/1	96/1	890/1	1200/1	1000:1	900:1
16	2/1	2/1	2/1	3/1	4/1	5/1	16/1	17/1	67/1	75/1	500/1	690/1	1000:1	910:1
17	3/1	5/2	5/2	3/1	4/1	5/1	14/1	14/1	50/1	56/1	300/1	420/1	1000:1	940:1
18	4/1	3/1	5/2	3/1	4/1	5/1	12/1	12/1	40/1	45/1	220/1	310/1	1100:1	970:1
19	5/1	4/1	5/2	3/1	4/1	5/1	10/1	10/1	30/1	34/1	160/1	230/1	1100:1	1000:1
20	6/1	4/1	3/1	3/1	4/1	5/1	9/1	9/1	28/1	32/1	150/1	210/1	1100:1	1000:1
21	11/1	7/1	4/1	4/1	4/1	4/1	6/1	7/1	21/1	24/1	110/1	160/1	1000:1	930:1
22-23	14/1	9/1	5/1	5/1	5/1	5/1	7/1	7/1	21/1	24/1	110/1	150/1	1400/1	1700:1
24-25	35/1	20/1	12/1	9/1	7/1	7/1	8/1	8/1	22/1	24/1	100/1	150/1	1100/1	1400/1
26-27	140/1	75/1	41/1	25/1	19/1	17/1	18/1	19/1	38/1	42/1	140/1	180/1	870/1	940:1
28-29	260/1	130/1	68/1	38/1	28/1	25/1	26/1	26/1	50/1	55/1	160/1	210/1	840:1	740:1
30-31	910:1	920/1	360/1	150/1	96/1	83/1	77/1	78/1	120/1	120/1	260/1	310/1	550:1	490:1
32-33	660:1	1200:1	730/1	310/1	190/1	160/1	140/1	140/1	190/1	200/1	360/1	430/1	350:1	310:1
34-35	520:1	970:1	850:1	690:1	570:1	530:1	440:1	430:1	360:1	510:1	390:1	340:1	240:1	210:1

The entries containing colons represent only inequalities; for example, 200:1 means that the estimated Bayes factor is at least 200, whereas 1:95 means that the estimated factor *against* AMI is at least 95. These inequalities arise when the denominator or numerator of the estimate is less than 10^{-23}.

Evaluation of the Statistical Method

To evaluate the efficacy of our method for discriminating between AMI and non-AMI based on readings of CK0 and CK12, we repeated the whole calculation on a random subsample of the data so that the remainder of the sample could be regarded as a collection of new patients to be diagnosed. The subsample from which the new Bayes factors are calculated is called the *learning sample*, and the remainder the *evaluation sample*. The learning sample consisted of 602 non-AMI and 130 AMI patients; the evaluation sample comprised 200 non-AMI and 50 AMI patients. The new Bayes factors computed from the learning sample gave rise to a table strongly resembling Table 1, Table 1*A* (this table is omitted to save space; a copy is available from the authors).

Table 2 gives the result of applying Table 1*A* to the evaluation sample. To save space, we present here only a small part of these results but, again, the whole table (Table 2*A*) is available from the authors. Table 3, deduced by hand calculation from Table 2*A*, gives a comparison between the theoretical "expected" numbers of AMI and non-AMI patients and the observed numbers. The comparison is made for 15 intervals of values of the posterior odds o such as $1/8 \leq o < 1/4$. The agreement between observed and expected values is excellent. For 10 patients the odds were between 2 to 1 in favor of AMI and 2 to 1 against, and five of them had AMI, which is as "expected." When the odds are so close to 1, a patient cannot be said to be "diagnosed," and it is then especially important to allow for other evidence before making a medical decision. (Again, refer to *Appendix A*.) Some of the additional evidence might involve subjective judgment such as that previously mentioned, whereas other evidence might arise from inclusion of another test, such as the use of the lactate dehydrogenase isoenzyme 1 (*10, 11*). The addition of another isoenzyme, owing to statistical dependencies, would strictly require that trivariate probabilities be estimated for quantitative treatment. We do not have enough data to attempt this at present.

Table 2. Three Rows of Table 2*A* Corresponding to the Four Observations at Which the Posterior Odds Were between 1/16 and1/8

x	y	AMI	Non-AMI	Bayes factor	Posterior odds	Posterior prob
2	8	0	2	0.31	0.0775	0.0719
13	8	0	1	0.32	0.0800	0.0741
13	9	0	1	0.34	0.0850	0.0783

Table 2*A*, available from the authors, gives the results for 250 observations.

Table 3. Observed vs Expected Numbers of Patients Having AMI or Non-AMI in the Evaluation Sample, for 15 Intervals of Values of the Posterior Odds

	No. of patients			Expected no.	
Posterior odds	Total	With AMI	Without AMI	AMI	Non-AMI
<1/1024	172	0	172	0.002	172.00
[1/1024, 1/64)	5	0	5	0.03	4.97
[1/64, 1/32)	5	0	5	0.10	4.90
[1/32, 1/16)	1	0	1	0.05	0.95
[1/16, 1/8)	4	0	4	0.30	3.70
[1/8, 1/4)	4	0	4	0.54	3.46
[1/4, 1/2)	4	1	3	0.99	3.01
[1/2, 1)	4	3	1	1.62	2.38
[1, 2)	6	2	4	3.50	2.50
[2, 4)	3	3	0	2.15	0.85
[4, 8)	2	2	0	1.64	0.36
[8, 16)	4	3	1	3.68	0.32
[16, 32)	2	2	0	1.92	0.08
[32, 64)	3	3	0	2.93	0.07
>64	31	31	0	30.96	0.04
Total	250	50	200		

The "expected" numbers of patients with AMI, for each of the intervals of the posterior odds, were obtained from Table 2*A* by multiplying each relevant posterior probability by the corresponding number of patients and summing. For example, for the interval [1/16, 1/8), the "expected number" of AMI patients is (2 × 0.0719) + 0.0741 + 0.0783 = 0.30 (after rounding off). [This example can be checked from Table 2*A*.]

Discussion

Just one patient among the 250 in the evaluation sample was "misdiagnosed" by the CK0 and CK12 readings alone, namely, one for whom the posterior odds were 15 to 1 in favor of classifying as AMI but who was in fact non-AMI, a "false positive." This patient had a CK0 value of 1 U/L and a CK12 value of 11 U/L. We conclude therefore that the CK0 and CK12 values alone come close to discriminating between non-AMI and AMI, but we are by no means claiming that other information should be ignored!

We have not carried out an analysis of the 44 statistical outliers that were trimmed from the original database, but we can make the following observation. If *all* that is taken into account is the fact that a value for CK0 and CK12 constitutes an outlier, then the probability of AMI is (215 − 180)/(1026 − 982), or 0.80; i.e., the odds are 4 to 1. Because the initial odds were 215/811, or 0.265, the Bayes factor in favor of AMI, provided by the information that the measurements constitute an outlier, is 0.80/0.265, or 3.0. Of course, the actual pair of measurements would be more informative. It should also be remembered that outliers are, by definition, unlikely values, and sometimes can be a consequence of an error in recording or measurement.

Appendix A. Odds and Bayes Factors

Odds. If p denotes a probability, then the corresponding odds (o) are defined by:

$$o = \frac{p}{1-p}, \text{ while } p = \frac{o}{1+o}$$

For examples see Table 4. Another way of expressing odds of 4.0 is "4 to 1 in favor of", while odds of 0.25 can be expressed as "4 to 1 against."

If p denotes the prior probability of a hypothesis H (the probability before some specified evidence is taken into account), then of course $p/(1-p)$ is called the "prior odds." Similar definitions apply to posterior probability and posterior odds.

The Bayes factor. When some evidence E is obtained, it can affect the probability of H and we say that the probability of H is changed from its prior probability P(H) to its posterior probability P($H \mid E$) (read, *the probability of* H *given* E) and the prior odds O(H) are changed to the posterior odds O($H \mid E$). The ratio of the posterior to the

Table 4. Probabilities and the Corresponding Odds

		Probability, p						
		0	0.1	0.2	0.5	0.8	0.9	1.0
Odds in favor of:	o	0	0.111	0.25	1.0	4.0	9.0	∞
Odds against:	o^{-1}	∞	9	4	1	0.25	0.111	0

prior *odds* of H, that is, $O(H \mid E)/O(H)$, is called the *Bayes factor in favor of* H *provided by* E. The Bayes factor is the factor by which the prior odds are multiplied to get the posterior odds. It may be denoted by $B(H{:}E)$ where the colon is read *provided by*. There is always background information G and it can be brought into the notation, if desired, by writing $B(H{:}E \mid G)$, where the vertical stroke is read *given (all along)*. The notation brings out the fact that E is the evidence that is additional to what was previously taken into account. Note the distinction between the colon and the vertical stroke. The symbol E that refers to the *new* information is preceded by a colon. Of course

$$B\,(H{:}E \mid G) = \frac{O(H \mid E\&G)}{O(H \mid G)}$$

expresses the Bayes factor by which the odds are multiplied as a consequence of the new information E, where G had already been taken into account.

The estimation or calculation of a Bayes factor usually depends on the easily proved Wrinch–Jeffreys (*12*) equation:

$$B(H{:}E) = \frac{P(E \mid H)}{P(E \mid \overline{H})}$$

The probabilities can also be interpreted as probability densities. In the present application H denotes AMI, and $\overline{H}$ ($\equiv$ not H) denotes non-AMI; the two probability densities were separately estimated by means of our program for probability density estimation.

When the posterior odds are close to 1, for example, between ½ and 2 (posterior probability between ⅓ and ⅔) it is especially important to take other evidence, say F, into account. This can be done, in principle, by making use of the multiplicative property of Bayes factors, namely:

$$B(H{:}E\&F) = B\,(H{:}E)B(H{:}F \mid E).$$

That is, the Bayes factor in favor of H provided by E & F is equal to that provided by E alone times that provided by F when E has already been taken into account. This fact may be expressed by saying that the posterior odds after E is taken into account become the prior odds before taking F into account (these odds could be called the "intermediate odds"). As a special case,

$$B(H{:}E\&F) = B(H{:}E)B(H{:}F)$$

if E and F are independent. Here the concept of independence might be understood either in an intuitive sense or defined formally thus: E and F are independent given H and also independent given $\overline{H}$: that is,

$$P(E\&F \mid H) = P(E \mid H)P(F \mid H)$$

and

$$P(E\&F \mid \overline{H}) = P(E \mid \overline{H})P(F \mid \overline{H}).$$

It may be that physicians could be trained to judge approximate Bayes factors from pieces of evidence for some hypothesis (disease state), even when careful statistics are not available. Informally, this is implicit in their daily practice (*13, 14*). Presumably, physicians would not all be of equal ability in this respect.

Suppose, for example, that a physician had judged a patient as AMI with odds of 2 to 1 in favor of, based on information independent of the CK0 and CK12 information. That would imply that the Bayes factor was 2/0.2244 = 8.9. Now suppose the factor from the CK0 and CK12 reading was 3.2. Then the odds allowing for both lots of information would be $2 \times 3.2 = 6.4$. If the physician's judgment were in much conflict with the CK0 and CK12 evidence, this would indicate that an error might have been made somewhere, for example, in the recording of the CK0 and CK12 readings.

Sometimes the logarithm—to base 10, say—of the Bayes factor is used, called the "weight of evidence," in units of *bans* when the base is 10. In this report we do not use weights of evidence but mention it here for interested readers. Weights of evidence, being logarithms, have an additive instead of a multiplicative property.

Some physicians might eventually find it easier to develop an intuitive judgment of weights of evidence instead of Bayes factors, or might be comfortable in judging both as a check. In this report we have adhered to Bayes factors. Further information about weight of evidence is presented in references *15* and *16*.

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