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Utility of Current Risk Stratification Tests for Predicting Major Arrhythmic Events After Myocardial Infarction

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OBJECTIVES We surveyed the literature to estimate prediction values for five common tests for risk of major arrhythmic events (MAEs) after myocardial infarction. We then determined feasibility of a staged risk stratification using combinations of noninvasive tests, reserving an electrophysiologic study (EPS) as the final test.

BACKGROUND Improved approaches are needed for identifying those patients at highest risk for subsequent MAE and candidates for implantable cardioverter-defibrillators.

METHODS We located 44 reports for which values of MAE incidence and predictive accuracy could be inferred: signal-averaged electrocardiography; heart rate variability; severe ventricular arrhythmia on ambulatory electrocardiography; left ventricular ejection fraction; and EPS. A meta-analysis of reports used receiver-operating characteristic curves to estimate mean values for sensitivity and specificity for each test and 95% confidence limits. We then simulated a clinical situation in which risk was estimated by combining tests in three stages.

RESULTS Test sensitivities ranged from 42.8% to 62.4%; specificities from 77.4% to 85.8%. A three-stage stratification yielded a low-risk group (80.0% with a two-year MAE risk of 2.9%), a high-risk group (11.8% with a 41.4% risk) and an unstratified group (8.2% with an 8.9% risk equivalent to a two-year incidence of 7.9%).

CONCLUSIONS Sensitivities and specificities for the five tests were relatively similar. No one test was satisfactory alone for predicting risk. Combinations of tests in stages allowed us to stratify 91.8% of patients as either high-risk or low-risk. These data suggest that a large prospective study to develop a robust prediction model is feasible and desirable. (J Am Coll Cardiol 2001; 38:1902–11) © 2001 by the American College of Cardiology

Sudden cardiac death (SCD) is a major public health problem in both the U.S. and worldwide (1). In the U.S., coronary heart disease accounts for about 85% of episodes of SCD (2). Although some studies have suggested that certain drugs may reduce SCD (3–5), other trials with antiarrhythmic medications have shown a higher mortality on drug therapy (6,7). In contrast, several recent studies have demonstrated clearly that implantable cardioverter-defibrillators (ICDs) reduce SCD mortality significantly (8–12).

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Consensus guidelines (13) regarding indications for ICD implantation, however, cover only a minority of patients who die of SCD. Thus, there have been recent calls for better ways to identify those patients without an ICD who are at highest risk for SCD, because they are the ones most likely to benefit from prophylactic insertion of an ICD (14–16).

In this report we evaluate the utility of tests currently used for risk stratification of patients who have had a myocardial infarction (MI); most studies evaluating such tests have been done in post-MI patients. We used a reported technique for combining independent studies of a given diagnostic test into a summary receiver-operating characteristic (ROC) curve; this produced estimates for overall predictive accuracy (17). We then evaluated the effectiveness of combining noninvasive tests, and we also evaluated obtaining noninvasive tests in a staged manner, with an electrophysiologic study (EPS) as the final test. Our aim was to simulate a possible clinical approach. We also considered the monetary costs of this approach. The data for our study came from 44 reports in the literature (18–61).

METHODS

Report retrieval. Relevant reports were found by searching Medline using the following keywords: myocardial infarct, sudden cardiac death, risk stratification, ventricular fibrillation (VF), ventricular tachycardia (VT), signal-averaged electrocardiogram (SAECG), heart rate variability (HRV), left ventricular function, ejection fraction, ambulatory elec-

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Abbreviations and Acronyms

AECG = ambulatory electrocardiography
CI = confidence interval
EPS = electrophysiologic study
HRV = heart rate variability
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
MADIT = Multicenter Automatic Defibrillator Implantation Trial
MAE = major arrhythmic event
MI = myocardial infarction
NPA = negative predictive accuracy
PPA = positive predictive accuracy
ROC = receiver-operating characteristic
SAECG = signal-averaged electrocardiogram
SCD = sudden cardiac death
SVA = serious ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

trocardiography (AECG) and EPS. Additional reports were located with the aid of review articles. Only reports in English were used. About 80% of selected studies have been published since 1990. Reports were selected only if they contained adequate quantitative data to characterize patients and events as detailed in the following text. The follow-up period in most reports was at least one year. If several reports from the same institution appeared to describe the same prognostic tests on the same patients, then only one report from that institution was used.

Tests were selected for study of their prognostic value if at least 9 to 10 articles were found that each had 100 or more patients (one study selected had only 86 patients) and if the data could be analyzed using the approaches described below. Noninvasive tests selected were SAECG, left ventricular ejection fraction (LVEF) (as determined by echocardiography or nuclear scintigraphy) and AECG, which provides two tests, namely the presence of serious ventricular arrhythmia (SVA) and a measure of HRV. Invasive tests selected were programmed stimulation on EPS and LVEF from left ventriculography.

We use the term "major arrhythmic events" (MAEs) to describe the various episodes of fatal or life-threatening arrhythmic events reported in the surveyed papers. These events included episodes of SCD, resuscitated SCD, and defibrillation or cardioversion of VF or VT. Most reports used the criteria of the Cardiac Arrhythmia Suppression Trial (6) to define a MAE.

Data extraction. For each report, the numbers of true-positive, true-negative, false-positive and false-negative results were recorded as integer values. In most reports, these numbers were not explicitly given. When they were not given, we used the stated values for the number of patients studied, the sensitivity, specificity and predictive accuracy, and we estimated the integer values using standard formulas. If necessary, the estimated integer values were adjusted to produce, to three decimal places, those values for sensitivity, specificity and predictive accuracy that most closely approximated (usually within 0.5%) the values for the latter stated in the report.

Data analysis. For each risk stratification test, totals for all the reports were collected (Table 1). The one-year and two-year MAE rates for each report were modeled by using its value for MAE-free survival and its value for mean or median follow-up time, by assuming that MAE-free survival decreases exponentially with time. The aggregate one-year and two-year MAE rates for a collection of reports are average values weighted by the number of patients in each report.

We then constructed a summary ROC curve for each individual test, using the technique of Moses et al. (17). Weighted composite mean values for sensitivity and specificity and 95% confidence intervals (CI) for each were located on the summary ROC curve (Fig. 1, Table 2). The composite values of sensitivity and specificity were combined with the total MAE rate to derive estimates for predictive accuracy and risk (Table 2). The MAE risk after a positive test is equal to the positive predictive accuracy (PPA) of that test, and MAE risk after a negative test is equal to 100 minus the negative predictive accuracy (NPA).

To determine whether use of revascularization therapy for MI influenced event rates, we compared the data in reports published through 1993 with those published after 1993. The annualized incidence (weighted average) for the 22 reports published in 1993 and before was 3.8%, and for the 22 reports published after 1993 was 4.4%; hence, a trend in this survey for higher annualized incidences after 1993 was not significant ($p = 0.51$). The annualized incidence for 12 reports on SAECG published in 1993 and before was 4.6%, and for 10 SAECG reports published after 1993 was 4.1%; this trend for lower annualized incidences for SAECG reports after 1993 was not significant ($p = 0.81$).

Using the composite values for sensitivity and specificity in Table 2, the percentages of patients with various expected risks for several different test combinations were estimated and are shown in Table 3.

Cost estimates for the various tests were obtained from an American College of Cardiology Expert Consensus document (62).

RESULTS

Performances of individual tests. The results of combining studies are shown in Figure 1 and Tables 1 and 2.

The incidences of MAE in the patient populations reported (references 18–61; column 2 in Table 1) are the *prior probabilities* for MAE—that is, the probability of a MAE prior to a test. The individual values of prior probability varied widely (range 3.3% to 34.1%). As noted below, we obtained a weighted overall two-year prior probability of 7.9% for the 44 reports in this study.

The risk of MAE after a test is the *posterior probability*,

Table 1. Bayesian Statistics for Five Tests Used to Predict Risk of MAEs After Myocardial Infarction

References	Prior Probability (Incidence of MAE) (%)	No. of Patients	Average Follow-Up (months)	TP	FN	TN	FP	Sensitivity	Specificity	Positive Predictive Accuracy	Relative Risk	Odds Ratio
A. SAECG STUDIES												
Ahuja (18)	6.5	262	10.5	6	11	234	11	0.353	0.955	0.353	7.9	11.6
Breithardt (19)	11.8	628	39.0	40	34	345	209	0.541	0.623	0.161	1.8	1.9
De Chillou (20)	7.4	244	57.0	11	7	155	71	0.611	0.686	0.134	3.1	3.4
Denniss (21)	7.5	306	36.0	15	8	218	65	0.652	0.770	0.188	5.3	6.3
el-Sherif (22)	3.9	1,158	12.0	22	23	1,002	111	0.489	0.900	0.165	7.4	8.6
Farrell (23)	5.8	416	36.5	15	9	318	74	0.625	0.811	0.169	6.1	7.2
Gomes (24)	13.9	115	14.0	12	4	60	39	0.750	0.606	0.235	3.8	4.6
Hermosillo (25)	8.7	196	12.0	16	1	129	50	0.941	0.721	0.242	31.5	41.3
Kozer (26)	7.3	261	12.0	14	5	206	36	0.737	0.851	0.280	11.8	16.0
Kuchar (27)	9.0	233	31.0	17	4	137	75	0.810	0.646	0.185	6.5	7.8
Lander (28)	9.2	173	14.0	11	5	129	28	0.688	0.822	0.282	7.6	10.1
Mäkijärvi (29)	4.3	776	6.0	25	8	467	276	0.758	0.629	0.083	4.9	5.3
McClements (30)	3.7	297	12.4	7	4	232	54	0.636	0.811	0.115	6.8	7.5
Ohnishi (31)	8.0	100	18.0	6	2	67	25	0.750	0.728	0.194	6.7	8.0
Pedretti (32)	6.3	303	15.0	12	7	219	65	0.632	0.771	0.156	5.0	5.8
Richards (33)	6.2	225	12.0	8	6	173	38	0.571	0.820	0.174	5.2	6.1
Savard (34)	3.3	2,461	17.0	52	28	1,672	709	0.650	0.702	0.068	4.1	4.4
Sierra (35)	5.5	769	23.0	18	24	618	109	0.429	0.850	0.142	3.8	4.3
Steinberg (36)	8.8	182	14.0	11	5	103	63	0.688	0.620	0.149	3.2	3.6
Strasberg (37)	12.0	100	12.0	7	5	65	23	0.583	0.739	0.233	3.3	4.0
Verzoni (38)	2.7	220	12.0	5	1	157	57	0.833	0.734	0.081	12.7	13.8
Zimmermann (39)	7.0	458	70.0	15	17	351	75	0.469	0.824	0.167	3.6	4.1
SAECG Total		9,883										
B. STUDIES OF SVA ON AECG												
Bigger (40)	14.1	715	30.0	48	53	461	153	0.475	0.751	0.239	2.3	2.7
el-Sherif (22)	3.9	1,158	12.0	27	18	791	322	0.600	0.711	0.077	3.5	3.7
Farrell (23)	5.8	416	36.5	13	11	319	73	0.542	0.814	0.151	4.5	5.2
Gomes (24)	14.5	110	14.0	13	3	54	40	0.813	0.574	0.245	4.7	5.9
Hermosillo (25)	10.5	200	12.0	8	13	165	14	0.381	0.922	0.364	5.0	7.3
Hohnloser (41)	7.7	325	30.0	4	21	255	45	0.160	0.850	0.082	1.1	1.1
Kostis (42)	4.6	1,640	25.0	12	64	1,464	100	0.158	0.936	0.107	2.6	2.7
Kuchar (27)	7.3	206	31.0	11	4	129	62	0.733	0.675	0.151	5.0	5.7
La Rovere (43)	3.8	1,170	21.0	14	30	946	180	0.318	0.840	0.072	2.3	2.5
McClements (30)	4.3	301	12.4	5	8	214	74	0.385	0.743	0.063	1.8	1.8
Mukharji (44)	5.4	533	18.0	10	19	438	66	0.345	0.869	0.132	3.2	3.5
Pedretti (32)	6.3	303	15.0	13	6	190	94	0.684	0.669	0.121	4.0	4.4
Richards (33)	4.5	358	12.0	13	3	137	205	0.813	0.401	0.060	2.8	2.9
Ruberman (45)	7.3	1,739	60.0	69	58	1,225	387	0.543	0.760	0.151	3.3	3.8
Steinberg (36)	8.8	182	14.0	7	9	121	45	0.438	0.729	0.135	1.9	2.1
Verzoni (38)	2.9	208	12.0	4	2	144	58	0.667	0.713	0.065	4.7	5.0
SVA Total		9,564										
C. STUDIES OF HRV ON AECG												
Bigger (46)	14.1	715	30.0	42	59	579	35	0.416	0.943	0.545	5.9	11.8
Copie (47)	4.7	551	24.0	12	14	462	63	0.462	0.880	0.160	5.4	6.3
Farrell (23)	5.8	416	36.5	22	2	301	91	0.917	0.768	0.195	29.5	36.4
Hohnloser (41)	7.7	325	30.0	15	10	246	54	0.600	0.820	0.217	5.6	6.8
Katz (48)	34.1	185	16.0	30	33	87	35	0.476	0.713	0.462	1.7	2.3
Kleiger (49)	15.7	808	31.0	43	84	599	82	0.339	0.880	0.344	2.8	3.7
La Rovere (43)	3.8	1,170	21.0	17	27	969	157	0.386	0.861	0.098	3.6	3.9
Lanza (50)	7.9	239	28.0	6	13	202	18	0.316	0.918	0.250	4.1	5.2
Malik (51)	10.6	451	21.9	24	24	293	110	0.500	0.727	0.179	2.4	2.7
Pedretti (32)	6.1	292	15.0	16	2	187	87	0.889	0.682	0.155	14.7	17.2
Zuanetti (52)	9.2	567	32.9	22	30	446	69	0.423	0.866	0.242	3.8	4.7
HRV Total		5,719										

Table 1. (Continued)

References	Prior Probability (Incidence of MAE) (%)	No. of Patients	Average Follow-Up (months)	TP	FN	TN	FP	Sensitivity	Specificity	Positive Predictive Accuracy	Relative Risk	Odds Ratio
D. LVEF STUDIES												
Bigger (40)	14.1	715	30.0	59	42	446	168	0.584	0.726	0.260	3.0	3.7
De Chillou (20)	7.4	244	57.0	10	8	188	38	0.556	0.832	0.208	5.1	6.2
Copie (47)	8.1	520	24.0	17	25	373	105	0.405	0.780	0.139	2.2	2.4
el-Sherif (22)	3.9	1,158	12.0	32	13	768	345	0.711	0.690	0.085	5.1	5.5
Farrell (23)	5.8	416	36.5	11	13	294	98	0.458	0.750	0.101	2.4	2.5
Gomes (24)	14.5	110	14.0	11	5	69	25	0.688	0.734	0.306	4.5	6.1
Hermosillo (25)	11.9	201	12.0	17	7	142	35	0.708	0.802	0.327	7.0	9.9
Hohnloser (41)	7.7	325	30.0	12	13	261	39	0.480	0.870	0.235	5.0	6.2
Iesaka (53)	8.3	133	24.0	6	5	106	16	0.545	0.869	0.273	6.1	8.0
Kuchar (27)	7.1	210	31.0	13	2	144	51	0.867	0.738	0.203	14.8	18.4
Lander (28)	9.2	173	14.0	9	7	121	36	0.563	0.771	0.200	3.7	4.3
La Rovere (43)	3.8	1,276	21.0	22	27	1,045	182	0.449	0.852	0.108	4.3	4.7
McClements (30)	4.0	300	12.4	9	3	233	55	0.750	0.809	0.141	11.1	12.7
Pedretti (32)	6.3	303	15.0	15	4	242	42	0.789	0.852	0.263	16.2	21.6
Richards (33)	4.9	347	12.0	12	5	243	87	0.706	0.736	0.121	6.0	6.7
Rodriguez (54)	17.4	190	25.0	15	18	124	33	0.455	0.790	0.313	2.5	3.1
Steinberg (36)	8.8	182	14.0	9	7	101	65	0.563	0.608	0.122	1.9	2.0
Strasberg (37)	12.0	100	12.0	5	7	69	19	0.417	0.784	0.208	2.3	2.6
Verzoni (38)	5.4	111	12.0	4	2	65	40	0.667	0.619	0.091	3.0	3.3
Zabel (55)	6.8	280	32.0	11	8	185	76	0.579	0.709	0.126	3.1	3.3
LVEF Total		7,294										
E. EPS												
Bhandari (56)	12.8	86	18.0	6	5	62	13	0.545	0.827	0.316	4.2	5.7
Brembilla-Perrot (57)	8.5	492	44.4	29	13	262	188	0.690	0.582	0.134	2.8	3.1
Bourke (58)	4.0	1,000	28.0	12	28	912	48	0.300	0.950	0.200	6.7	8.1
Denniss (21)	6.7	403	36.0	14	13	309	67	0.519	0.822	0.173	4.3	5.0
Iesaka (53)	8.3	133	24.0	9	2	106	16	0.818	0.869	0.360	19.4	29.8
Middlekauff (59)	6.9	523	12.0	22	14	403	84	0.611	0.828	0.208	6.2	7.5
Richards (33)	3.8	313	12.0	7	5	286	15	0.583	0.950	0.318	18.5	26.7
Viskin (60)	14.9	786	25.5	105	12	241	428	0.897	0.360	0.197	4.2	4.9
Zoni-Berisso (61)	3.8	286	12.0	6	5	272	3	0.545	0.989	0.667	36.9	108.8
EPS Total		4,022										

AECG = ambulatory electrocardiography; EPS = electrophysiologic study; FN = false negative; FP = false positive; HRV = heart rate variability; LVEF = left ventricular ejection fraction; MAE = major arrhythmic event; SAECG = signal-averaged electrocardiography; SVA = serious ventricular arrhythmia; TN = true negative; TP = true positive.

that is, the risk of MAE given knowledge of the test result. In Table 2 we provide the sensitivities, specificities and posterior probabilities for the five individual tests of interest. Sensitivities ranged from 43% to 62%, but with considerable overlapping of 95% CI.

Specificities were higher, ranging from 77% to 86%, again with much overlapping of 95% CI. The two-year PPA, the risk of a MAE given a positive test result, was highest for HRV and EPS, and lowest for SVA (Table 2). The two-year risk of a MAE with a negative test (negative predictive accuracy, or NPA) was lowest for EPS and SAECG, and highest for HRV.

Performance of risk stratification tests can also be compared by estimating *relative risk* (i.e., the ratio of the PPA and [1 − NPA]). Relative risk was highest for EPS (6.6) and lowest for SVA (2.9). Another way to compare tests is the *odds ratio*, which was also highest for EPS (8.5) and lowest for SVA (3.2). Note that relative risk depends on the incidence of MAE in the population, but that the odds ratio does not.

Risk implications of combined tests. In all the reports of Table 1, there were 25,543 patients, with a weighted overall estimated two-year MAE incidence of 7.9%. Many reports contributed results for more than one test. In order to construct Table 3, an estimated two-year MAE incidence of 7.9% was used as a prior probability. Furthermore, to explore implications of combining tests the analysis was simplified by using only the composite weighted mean values for sensitivity and specificity.

Table 3 represents a staged application of noninvasive tests *followed by* the use of EPS. With this approach, the first step would be performance of both SAECG and LVEF at a cost of $275 per patient (62). If the two tests were both negative or both positive (as would be true for 64.2% of the patients, Table 3), further testing would not be done, as the two-year probability of a MAE would be very low in the former situation (2.2%), and high enough in the latter situation (38.7%) to warrant consideration of ICD implantation.

The second step would be performance of a 24-h

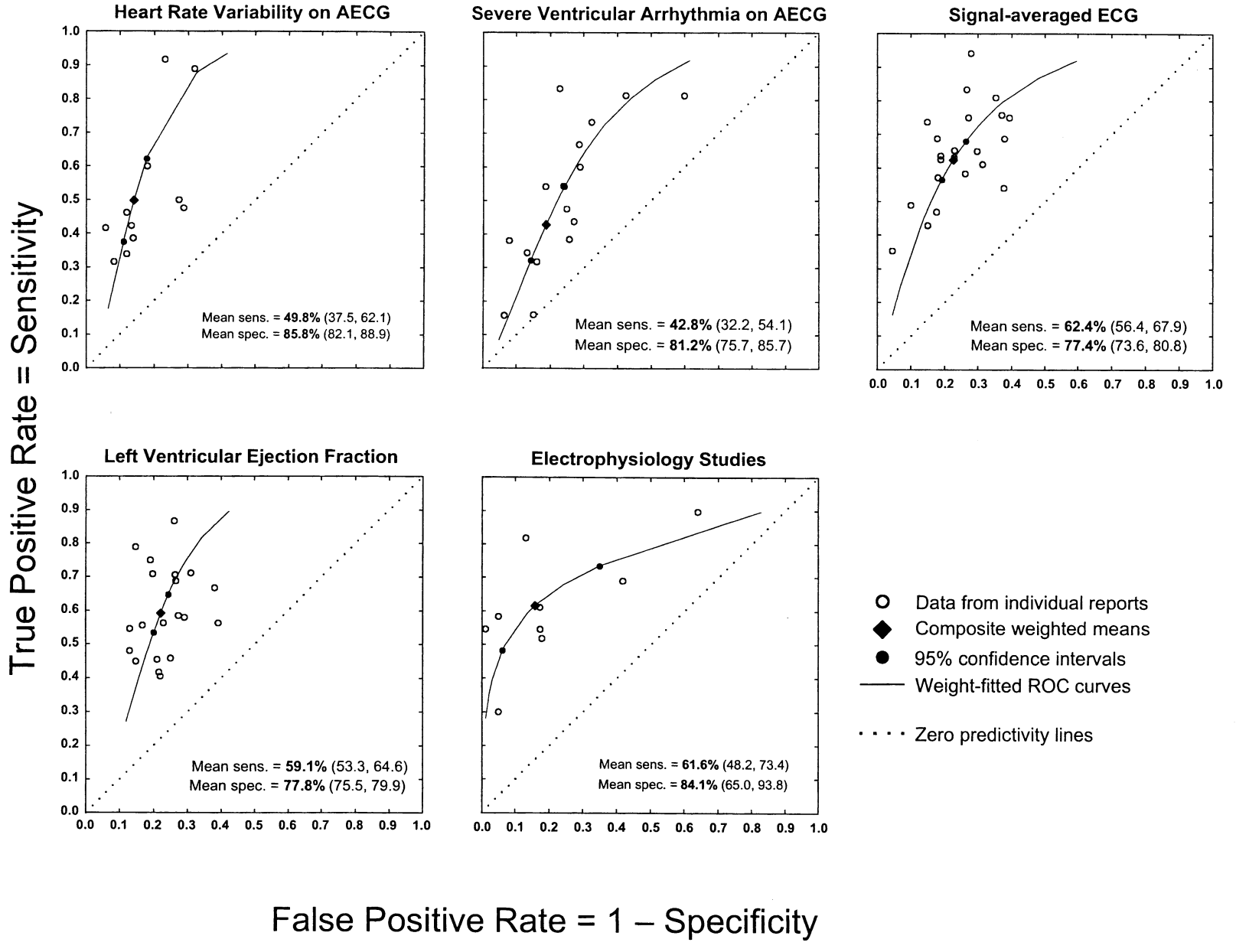

Figure 1. Receiver-operating characteristic (ROC) curves for the five tests evaluated in the study. The curves were generated using the approach of Moses et al. (17). AECG = ambulatory electrocardiography; ECG = electrocardiogram.

Table 2. Comparison of Tests for Predicting MAEs

Test (No. of Reports)	Number of Patient Studies	Prior Probability (i.e., Total MAE Incidence) (Annualized)	Composite Weighted Values for		Two-Year Probability of a MAE if		Relative Risk (Test+/ Test−)	Odds Ratio [(TP/FP)/ (FN/TN)]
			Sensitivity (95% CI)	Specificity (95% CI)	Test (+) (95% CI)	Test (−) (95% CI)		
ECG-Based Tests								
SAECG (22)	9,883	7.99% (4.1%)	62.4% (56.4%–67.9%)	77.4% (73.6%–80.8%)	19.3% (18.3%–20.3%)	4.05% (3.65%–4.48%)	4.8	5.7
SVA (16)	9,564	6.50% (3.33%)	42.8% (32.7%–53.7%)	80.9% (75.0%–85.7%)	13.4% (13.0%–13.7)	4.68% (4.12%–5.18%)	2.9	3.2
HRV (11)	5,719	9.02% (4.72%)	49.8% (37.5%–62.1%)	85.8% (82.1%–88.9%)	25.8% (25.0%–25.6%)	5.48% (4.37%–6.52%)	4.7	6.3
Left Ventricular Function								
LVEF (20)	7,294	8.57% (4.41%)	59.1% (53.3%–64.6%)	77.8% (75.5%–79.9%)	20.0% (19.8%–19.9%)	4.70% (4.21%–5.19%)	4.3	5.1
Electrophysiologic Studies								
EPS (9)	4,022	8.11% (4.17%)	61.6% (48.2%–73.4%)	84.1% (65.0%–93.8%)	25.5% (15.6%–40.7%)	3.88% (3.49%–4.65%)	6.6	8.5

CI = confidence interval; other abbreviations as in Table 1.

AECG (an additional $165 per patient) in the 35.8% of patients who had only a positive SAECG or only a low LVEF, resulting in an intermediate risk for a MAE (10.6% over two years). If SVA and HRV were both normal or both abnormal (25%), no further testing would be needed, because in the former situation, the posterior probability is still below the original prior probability, despite having either an abnormal SAECG or a low LVEF, and in the latter case, the posterior probability would again be high enough to warrant consideration of ICD implantation.

The third step would involve the remaining 10.8% of the original patients, who would have an intermediate risk of 17.5% (Table 3). They would undergo an EPS (at an additional $1,220 cost). Thus, 2.6% of the original group would have a positive EPS, again with a two-year risk high enough (45.1%) to justify consideration of ICD implantation.

The aggregate results show that at the end of applying all three stages, there is a small proportion (8.2%) of unstratified patients with essentially the same risk (8.9%) as the original prior probability (7.9%).

DISCUSSION

Sensitivity and specificity are inherent characteristics of a given test, and they do not depend on the incidence of the disease or condition in the population being studied, and they also do not depend on the probability of the disease or condition in the individual. However, the values obtained for sensitivity and specificity *do* depend on the spectrum of patients or subjects included in the evaluation. For example,

Table 3. Staged Application of Tests for Prediction of a MAE*

Test Combinations	Results of Tests	Proportion of Population (%)	Probability (Predictive Accuracy) of a MAE Over 2 Years (%)
Stage 1 = SAECG and LVEF	Both negative	56.6	2.2
	Only 1 positive	35.8	10.6
	Both positive	7.6	38.7
Stage 2 = AECG (SVA and HRV) performed on "only 1 positive" patient of stage 1	Both negative	23.3	4.7
	Only 1 positive	10.8	17.5
	Both positive	1.7	48.2
Stage 3 = EPS performed on "only 1 positive" patient in stage 2	Negative	8.2	8.9
	Positive	2.6	45.1
Aggregate results	Low-risk group	80.0	2.9
	High-risk group	11.8	41.4
	Unstratified group	8.2	8.9
Low LVEF, SVA and positive EPS (MADIT criteria)		1.9	66.5

*Probability of MAE based on composite means of sensitivities and specificities (prior probability) = 7.9%.
MADIT = Multicenter Automatic Defibrillator Implantation Trial; other abbreviations as in Table 1.

if LVEF is used to evaluate the risk of a MAE by comparing LVEFs in a group of healthy young subjects with a group of post-MI patients with very low LVEFs, sensitivity and specificity will appear to be much higher than when the risk is evaluated in only a group of post-MI patients with a wide range of LVEFs. This is likely one of the reasons that the separate sensitivities and specificities for a given test reported in Table 1 vary so widely. Other causes for the variances would include different cutoff points used in different studies, different measurement techniques, and experimental error.

Positive predictive accuracy of a test *does* depend on the incidence of the disease or condition in the population studied, and it also depends on the time since performance of the test. Thus, the differences in the prior probabilities in Table 1 also contribute to the differences in PPA, in addition to the factors causing variances in sensitivity and specificity mentioned in the previous text.

The significance of results in individual reports is compromised by a relatively low number of MAEs in each report surveyed. By estimating a global MAE rate (global MAE count/global patient count) over all the reports for each method, and by constructing summary ROC curves, we are better able to appreciate the different performances of risk stratification tests. By using thousands of patients, as opposed to hundreds in the individual reports, we achieve better accuracy and precision for the estimates of sensitivity and specificity for the different tests. Also, by using larger numbers of patients, plausible values for expected outcomes from combining tests could be reasonably simulated.

Using standard Bayesian formulas, it can be shown that risks increase with higher prior probabilities. Therefore, relative risk depends in part upon the global MAE incidence (or prior probability), whereas the odds ratio as well as sensitivity and specificity can be regarded as independent of MAE incidence.

Sources of variation in reports. Population variation from one risk stratification test to the next was evident in the different report values for prior probabilities (Table 1). There was also some diversity in the analytic approach used for the reported tests, especially in HRV. For example, some studies reported HRV as a standard deviation or an index (time domain), whereas others reported values for power derived from fast Fourier transforms (frequency domain). However, each report of a given test reflects the same aspect of the basic pathophysiology.

We assumed in the meta-analysis that the investigators in each report attempted to optimize criteria—that is, to choose cutoff points that gave the best separation of patients with MAE from those without MAE. Of course, the choice of a cutoff point affects the (always present) trade-off between sensitivity and specificity. If that trade-off were the only source of variation, the data for the individual reports would closely fit the summarizing ROC curve. That they do not probably also reflects study population variations between different reports more than differing analytic tests. For purposes of the survey collection and comparison in Table 1, report results were taken at face value, with no attempt to adjust them to make criteria uniform from report to report.

Choosing a threshold that arbitrarily segments the data is a fundamental problem with all reports surveyed. For example, a patient with an LVEF of 0.39 and another with an LVEF of 0.41 should clearly have similar risks, but by choosing a threshold of 0.40 they are arbitrarily separated into different risk categories.

Reinhardt et al. (63) proposed a solution to this problem. Their model accounted for the time of event occurrence after hospital discharge for each patient (25 MAE events in a population of 553 post-MI patients). Such a model could project a single risk versus time function for each patient, taking into account that risk decreases as time after MI increases. The transition of predicted probability of events between high and low groups would be continuous for test parameters and would not be stepwise with fixed cutoff thresholds.

Another source of variation resulted from the lack of a distinction between cardiac death and SCD in some reports, but where the focus was upon some measure of electrophysiologic or autonomic disturbance. In addition, VT/VF may not necessarily be the proximate cause of sudden death; bradyarrhythmias, acute reinfarction, pulmonary embolism, stroke and aneurismal rupture have also been implicated in SCD (64).

Effect of correlation on test combinations. The pathophysiology of infarct is related to the size and location of the lesion and should be directly manifested in the various parameters for electrical instability (SAECG, ventricular premature beats, EPS) and in mechanical integrity (LVEF); its effect upon the autonomic system (HRV) may be somewhat less direct. Hence, some degree of correlation between the parameters of electrical instability can be expected and possibly a lesser degree between those parameters and LVEF or HRV.

When two tests, A and B, are combined ($A \cup B$), there are true positives for A, but not B, $(A \cup B) - B$; true positives for B, but not A, $(A \cup B) - A$; and true positives for both A and B, $(A \cap B)$. The effect of correlation would be to increase the true positives for both, $(A \cap B)$, at the expense of the other positives, $(A \cup B) - (A \cap B)$. Also, because there would be a higher proportion of both tests positive relative to the false positives, the estimate for risk would be increased. Similarly, with both tests correlated and negative, a higher proportion of patients would have a lower risk. The effect upon results in Table 3 could be to improve greatly the risk stratification in the first two stages and to reduce the proportion of patients referred for EPS from 10.8% to 3.2%.

Unfortunately, quantitative estimates for degree of correlation between tests are not available from the literature, and this problem has not been well studied. Therefore, in constructing Table 3 the worst case was to assume no

correlation (i.e., independence) of tests. That assumption produces the most conservative estimate of what happens when two tests are combined.

Cost-effective combinations of tests. Some investigators have proposed a staged approach to determine risk for post-MI patients (32,65,66). With the staged approach shown in Table 3, the projected cost would be about $415 per patient averaged out over the post-MI population.

Implications for therapy. One must beware of cursorily applying group statistics to an individual patient. The clinical course of the individual patient must be carefully assessed in addition to the noninvasive tests. Nevertheless, based on a study of post-MI patients with inducible VT or VF that responded to drugs, Andresen et al. (67) found an almost 30% occurrence rate of SCD or sustained VT during a 14- to 24-month follow-up; as this incidence is as high as the recurrence rate for patients who had been resuscitated from VF—a group now routinely treated with ICD—they suggest that any asymptomatic post-MI patient with a risk near 30% should be considered for a prophylactic ICD.

Conclusions. Table 3 shows that it may be feasible to stratify as many as 90% of post-MI patients into "high risk" (>30%) and "low risk" (<3%) categories using combinations of four noninvasive risk stratification tests and reserving the invasive, expensive EPS for patients where the noninvasive tests are inconclusive.

Many would accept that the ≈2% of post-MI patients who meet the stringent criteria of the recent ICD trials (8–12) should receive an ICD, and two recent studies purport to demonstrate the cost-effectiveness of doing so (68,69). Indeed, using the positive criteria for acceptance into the Multicenter Automatic Defibrillator Implantation Trial (MADIT) (9,68), our simulation results project a two-year risk for MAE of over 66%, which is very similar to the 60% incidence of a first ICD discharge within two years in the MADIT study itself (9). Only 1.9% of the >25,000 post-MI patients in our study meet the MADIT criteria, however (see bottom line of Table 3). This projection of 1.9% is comparable to the findings of Every et al. (70), who estimated that no more than 1.1% of post-MI patients meet the MADIT criteria. However, our study suggests that there may be another 10% of post-MI patients who do not meet such stringent criteria but who do probably meet a criterion of a 30%+ risk. If, as Andresen et al. suggest (67), these patients should be treated prophylactically with ICDs, a very large expenditure in a sizable population is implied, in which perhaps 50% to 70% of the patients may not benefit from an ICD; the cost-effectiveness of ICDs in such patients may be difficult to demonstrate.

The further resolution of these issues may require another study such as that of Reinhardt et al. (63), in a much larger population, with the goal of constructing a robust risk model with continuous parameters that would allow better individualized risk predictions for each patient.

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