Journal of the American College of Cardiology Vol. 50, No. 12, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.04.095

Limitations of Ejection Fraction for Prediction of Sudden Death Risk in Patients With Coronary Artery Disease

Lessons From the MUSTT Study

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Objectives We determined the contribution of multiple variables to predict arrhythmic death and total mortality risk in patients with coronary disease and left ventricular dysfunction. We then constructed an algorithm to predict risk of mortality and sudden death.

Background Many factors in addition to ejection fraction (EF) influence the prognosis of patients with coronary disease. However, there are few tools to use this information to guide clinical decisions.

Methods We evaluated the relationship between 25 variables and total mortality and arrhythmic death in 674 patients enrolled in the MUSTT (Multicenter Unsustained Tachycardia Trial) study that did not receive antiarrhythmic therapy. We then constructed risk-stratification algorithms to weight the prognostic impact of each variable on arrhythmic death and total mortality risk.

Results The variables having the greatest prognostic impact in multivariable analysis were functional class, history of heart failure, nonsustained ventricular tachycardia not related to bypass surgery, EF, age, left ventricular conduction abnormalities, inducible sustained ventricular tachycardia, enrollment as an inpatient, and atrial fibrillation. The model demonstrates that patients whose only risk factor is EF ≤30% have a predicted 2-year arrhythmic death risk <5%.

Conclusions Multiple variables influence arrhythmic death and total mortality risk. Patients with EF ≤30% but no other risk factor have low predicted mortality risk. Patients with EF >30% and other risk factors may have higher mortality and a higher risk of sudden death than some patients with EF ≤30%. Thus, risk of sudden death in patients with coronary disease depends on multiple variables in addition to EF. (J Am Coll Cardiol 2007;50:1150–7) © 2007 by the American College of Cardiology Foundation

Sudden cardiac death accounts for 450,000 deaths yearly in the U.S. (1). Furthermore, the proportion of all cardiac deaths accounted for by sudden death is increasing (1). Multiple clinical trials completed over the past decade have documented the effectiveness of the implantable cardioverter-defibrillator (ICD) to reduce the risk of sudden death and overall mortality in patients at high risk for sudden death. However, no recent study to date has examined the most effective means of deploying this technology to make it available to the greatest number of people in a cost-effective manner.

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Manuscript received January 23, 2007; revised manuscript received April 17, 2007, accepted April 23, 2007.

A number of variables have been demonstrated to identify patients at increased risk for sudden death. Recent trials have focused on left ventricular ejection fraction (EF), because of its demonstrated association with mortality risk in patients with recent myocardial infarction. However, EF lacks sensitivity for prediction of sudden death; less than 50% of patients with prior infarction who die suddenly have EF ≤30% (2–4). Additionally, many factors besides EF affect the prognosis of patients with coronary artery disease, and several lines of evidence suggest that reduced EF is a risk factor only when it exists in combination with other risk factors (5,6). Given earlier studies pointing to factors other than EF that influence prognosis after MI, the purpose of the present study is to evaluate the relative importance of multiple factors and to compare their relative contribution to risk of arrhythmic death as well as total mortality using the MUSTT (Multicenter Unsustained Tachycardia Trial) database (7,8). We then constructed a risk stratification tool that could be used in clinical practice. We demonstrate that use of such a model may enable more precise risk stratification of patients with coronary disease considered for ICD implantation for primary prevention of sudden death.

Methods

The MUSTT study was a randomized, controlled study whose primary aim was to test the ability of electrophysiologically guided therapy to reduce the risk of arrhythmic death in patients with documented coronary artery disease, left ventricular EF ≤40%, and spontaneous nonsustained ventricular tachycardia (NSVT). All patients underwent a standardized electrophysiologic test (9). Patients with inducible sustained ventricular tachycardia (VT) (monomorphic VT induced by 1 to 3 ventricular extrastimuli or sustained polymorphic VT induced by 1 or 2 extrastimuli) at the baseline electrophysiologic study were randomized equally into 2 groups. One-half of the patients with inducible ventricular tachyarrhythmias were randomized to electrophysiologically guided therapy, which consisted of serial antiarrhythmic drug trials. Patients whose tachycardia remained inducible at electrophysiologic testing after treatment with at least 1 antiarrhythmic drug were advised to undergo defibrillator implantation. These patients who received pharmacologic antiarrhythmic therapy or implanted defibrillators are excluded from the present analysis. The remaining one-half of patients with inducible tachycardias were randomized to the control group and received no antiarrhythmic therapy. Patients without either inducible sustained monomorphic VT or sustained polymorphic VT or fibrillation induced by 1 or 2 ventricular extrastimuli were followed prospectively in a registry. The latter patients were not given antiarrhythmic therapy. The protocol encouraged administration of beta-adrenergic blocking agents and angiotensin-converting enzyme inhibitors to all patients. In the present study, we examined the effect of multiple parameters on the outcome of patients followed prospectively in the registry and the patients with inducible tachycardia randomized to the control group without antiarrhythmic treatment.

Abbreviations and Acronyms

EF = ejection fraction
ICD = implantable cardioverter-defibrillator
IVCD = intraventricular conduction delay
LBBB = left bundle branch block
NSVT = nonsustained ventricular tachycardia
VT = ventricular tachycardia

Study population. A total of 2,202 patients were enrolled in the study between 1990 and 1996. One thousand four-hundred thirty-five (65%) had no inducible sustained VT and were followed in the registry. At the time of hospital discharge after enrollment in the trial, 35% of the registry patients were receiving beta-blockers and 66% were receiving angiotensin-converting enzyme inhibitors. Seven hundred sixty-seven patients (35%) had inducible sustained VT. Of these, 704 (92%) agreed to be randomized. The 63 patients who refused randomization were followed on the same schedule with the registry patients. Of the 704 patients with inducible ventricular tachyarrhythmias who agreed to randomization, 353 were assigned to the control (nonantiarrhythmic therapy) arm. Although the importance of heart failure as a risk factor for both total mortality and sudden death is clear today, when the trial was initiated in 1990 this relation was not as well appreciated. We did not collect data regarding history of heart failure or New York Heart Association (NYHA) functional class for the first half of the trial. As a result, complete data for all prognostic variables, including descriptors of heart failure, were available for 674 patients that did not receive antiarrhythmic therapy (Fig. 1). These patients constitute the data set for analysis of total mortality. The cause of death could not be ascertained with certainty in 4 patients. Thus, 670 patients constituted the dataset for the evaluation of arrhythmic death/cardiac arrest. The characteristics of these patients did not differ significantly from those of the entire study population.

We evaluated 25 baseline variables for their relationship with the risk of total mortality or arrhythmic death/cardiac arrest (Table 1). The variables included demographics, clinical history, variables derived from the enrolling 12-lead electrocardiogram, characteristics of spontaneous NSVT, characteristics of a prior myocardial infarction, results of the baseline electrophysiologic test, EF, and the extent of coronary disease. It should be noted that the qualifying NSVT for entry into the trial had to occur within 6 months of enrollment and be documented 4 or more days after the most recent myocardial infarction or revascularization procedure (coronary artery bypass graft surgery [CABG] or percutaneous revascularization) (7,8). We have previously demonstrated that patients whose qualifying NSVT was discovered within 10 days of CABG had significantly

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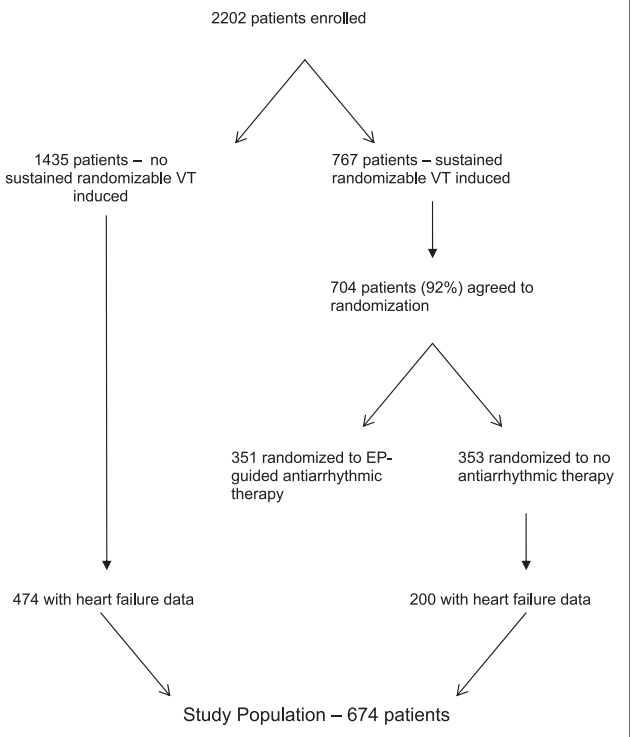

Figure 1 **Derivation of Study Population**

Flow diagram depicting patient enrollment in the MUSTT (Multicenter Unsustained Tachycardia Trial) study and derivation of patients for the present study. This figure depicts the evolution of patient enrollment in the MUSTT study, with randomization status. For the present study, only patients that did not receive antiarrhythmic treatment (including pharmacologic and device therapy) and in whom complete data on heart failure status was known were included. EP = electrophysiologic; VT = ventricular tachycardia.

lower mortality than patients who had never had CABG or whose NSVT was discovered more than 10 days after CABG (10). Another previous analysis demonstrated that patients who were enrolled while they were inpatients had significantly higher mortality than those enrolled as outpatients (11).

Definitions. ARRHYTHMIC DEATH. Witnessed instantaneous death, unwitnessed death in a patient who was stable in usual state of health when last seen (most often persons found dead in bed in the morning), deaths due to incessant tachycardia, or sequelae of cardiac arrest. Deaths of patients with end-stage heart failure or cardiogenic shock were not classified as arrhythmic.

CARDIAC ARREST. Sudden loss of consciousness requiring direct current countershock to restore consciousness or a stable blood pressure and rhythm.

LEFT BUNDLE BRANCH BLOCK (LBBB). A QRS duration of ≥0.12 s; delayed onset of intrinsicoid deflection in lead 1, V_5, and V_6 ≥0.05 s; broad monophasic usually notched R waves in lead 1, V_5, and V_6; and rS or QS complexes in right precordial leads.

INTRAVENTRICULAR CONDUCTION DELAY (IVCD). A QRS duration of ≥0.11 s but morphology different from LBBB or right bundle branch block.

Statistical methods. The Cox proportional hazards regression model was used to assess the relationship of each baseline clinical variable (both individually and jointly) with the time until the occurrence of: 1) total mortality; and 2) arrhythmic death or cardiac arrest (12). For continuous variables, we examined the shape and strength of their relationship with each of the 2 end points through use of a flexible model-fitting approach involving cubic spline functions (cubic polynomials) (13–17). These functions were graphically and statistically examined to assess the assumption of this regression model that patient characteristics are linearly related to the log of the hazard ratio. Where relationships were nonlinear, their shape was characterized either through a transformation to achieve linearity or using spline functions (17,18). Determining how variables should be modeled was an important step in characterizing the prognostic relationships and identifying which variables were most strongly related to the 2 end points. The ability of the prognostic models to discriminate among patients with respect to their length of survival was characterized using a generalized c-index, an extension to survival analysis of the c-index (area under the receiver-operating characteristic curve) frequently used with a dichotomous end point (19). After identifying the significant predictor variables from the multivariable modeling process, weights for each factor were derived from the Cox model regression coefficients to develop a prognostic score for each end point (20). The possible values of the scores were then translated into estimates of: 1) the probability of dying; or 2) the probability of having an arrhythmic event within 2 years of enrollment. The relationships between the prognostic scores and the respective outcome probabilities were then graphically presented. Confidence intervals for the prognostic estimates were generated using bootstrapping techniques. Our goal in these analyses was to develop predictive models for each end point that would be relatively simple to use in clinical practice yet provide adequate predictive accuracy in the assessment of risk.

Results

The median duration of follow-up was 39 months in the trial. Over the course of the trial, 241 of 674 patients in the study population died; 130 experienced arrhythmic death or cardiac arrest. Of 200 patients with inducible VT, 84 died and 53 patients experienced arrhythmic death or cardiac arrest. In contrast, of 474 patients without inducible VT, 157 died and 77 experienced arrhythmic death or cardiac arrest. The Kaplan-Meier 2-year total mortality rate was 22% for the entire study population. The Kaplan-Meier 2-year rate of arrhythmic death or cardiac arrest was 14%.

The factors having statistically significant associations in multivariable analysis with the end point of total mortality

Table 1 Univariate Prognostic Relationships

Variable	Patients With Characteristic–%	Total Mortality			Arrhythmic Death or Cardiac Arrest		
		Chi-Square	p Value	HR (95% CI)	Chi-Square	p Value	HR (95% CI)
NYHA functional class	I: 37; II: 39; III: 24	51.34	<0.0001		12.81	0.0017	
Class II vs. class I				2.43 (1.73–3.40)			1.84 (1.21–2.79)
Class III vs. class I				3.67 (2.57–5.24)			2.22 (1.40–3.52)
IVCD or LBBB	26	35.75	<0.0001	2.20 (1.70–2.85)	9.49	0.0021	1.75 (1.23–2.51)
History of heart failure	75	35.18	<0.0001	3.58 (2.35–5.47)	13.63	0.0002	2.55 (1.55–4.19)
Ejection fraction	29 (21, 35)	34.06	<0.0001	1.35 (1.22–1.41)*	16.30	<0.0001	1.32 (1.15–1.51)*
Age	66 (58, 72)	12.93	0.0003	1.28 (1.11–1.46)†	0.21	0.6460	1.04 (0.88–1.24)†
Atrial fibrillation (by ECG)	9	10.78	0.0010	1.84 (1.28–2.64)	0.07	0.7884	1.09 (0.60–1.96)
NSVT discovered as inpatient	75	8.06	0.0045	1.61 (1.16–2.23)	6.03	0.0141	1.76 (1.12–2.75)
Inducible VT	30	8.05	0.0046	1.47 (1.13–1.91)	12.73	0.0004	1.88 (1.33–2.65)
NSVT not discovered within 10 days after CABG	86	6.45	0.0111	1.73 (1.13–2.63)	4.94	0.0262	1.96 (1.08–3.55)
Prior thrombolytic therapy	21	4.69	0.0303	0.68 (0.48–0.96)	2.07	0.1502	0.72 (0.45–1.13)
Prior CABG	55	4.13	0.0422	0.77 (0.60–0.99)	0.59	0.4431	0.88 (0.62–1.23)
Prior Q-wave MI	47	3.83	0.0504	0.78 (0.60–1.00)	2.10	0.1470	0.78 (0.55–1.09)
History of angina	70	2.92	0.0877	0.79 (0.61–1.04)	0.14	0.7117	0.93 (0.65–1.35)
Number of diseased vessels (≥75% stenosed)	2 (1, 3)	1.82	0.1770	1.10 (0.96–1.26)	4.36	0.0368	1.22 (1.01–1.47)
Prior PTCA	25	1.75	0.1857	0.81 (0.60–1.10)	3.57	0.0589	0.66 (0.43–1.02)
Prior polymorphic NSVT	30	1.45	0.2280	1.18 (0.90–1.55)	0.54	0.4627	1.15 (0.80–1.65)
RBBB	5	0.94	0.3328	0.73 (0.39–1.38)	1.71	0.1913	0.52 (0.19–1.39)
LVH (by ECG)	47	0.92	0.3364	1.13 (0.88–1.46)	2.66	0.1028	1.33 (0.95–1.86)
Years from MI to enrollment	3 (0, 10)	0.56	0.4538	1.00 (0.99–1.01)	0.13	0.7232	1.00 (0.99–1.01)
Prior MI	88	0.49	0.4837	0.88 (0.61–1.27)	0.22	0.6367	0.89 (0.54–1.46)
Longest episode of NSVT ≥6 beats	5 (3, 8)	0.42	0.5186	1.02 (0.97–1.06)	1.59	0.2069	1.04 (0.98–1.11)
Gender (male)	85	0.38	0.5398	0.90 (0.64–1.27)	0.85	0.3571	1.28 (0.76–2.16)
History of palpitations	26	0.02	0.8889	1.02 (0.76–1.37)	0.02	0.8971	1.03 (0.70–1.51)
Race (European)	84	0.02	0.8839	1.03 (0.73–1.45)	0.01	0.9425	0.98 (0.62–1.55)
Prior inferior MI	48	<0.01	0.9847	1.00 (0.78–1.29)	0.02	0.8884	1.03 (0.73–1.44)

Continuous variables are expressed as median (25th, 75th percentiles). *Hazard ratio for a 5% decrease in ejection fraction. †Hazard ratio for a 10-year increase in age.

CABG = coronary artery bypass graft surgery; CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio; IVCD = nonspecific intraventricular conduction delay; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; RBBB = right bundle branch block; VT = ventricular tachycardia.

included EF, the presence of LBBB or nonspecific IVCD (these 2 variables were grouped together), NYHA functional class at the time of enrollment, inducible VT, age, prior CABG, atrial fibrillation at the time of enrollment, and history of heart failure (Table 2). The index of discrimination (c-index) for this model was 0.78.

The factors having statistically significant associations in multivariable analysis with the end point of arrhythmic death/cardiac arrest included inducible VT, history of heart failure, patients enrolled while inhospital, EF, NSVT not discovered within 10 days after CABG, LBBB, or IVCD (Table 3). Age and atrial fibrillation were not statistically significant predictors of arrhythmic death/cardiac arrest. As expected, the c-index for the end point of arrhythmic death/cardiac arrest was lower (0.70) than for total mortality, reflecting the fact that it is more difficult to predict 1 specific mode of death (arrhythmic) than to predict overall mortality.

A risk stratification algorithm was then constructed and weights assigned to each variable for the end points of total mortality and arrhythmic death/cardiac arrest (Tables 4 and 5). An individual patient's score for mortality or arrhythmic death risk was computed by ascertaining which variables characterize that individual and summing the corresponding points in Tables 4 and 5. This total score was then entered into the x-axis of Figure 2, which shows the curves depicting

Table 2 Multivariable Relationships With Total Mortality

Variable	Chi-Square	p Value	Hazard Ratio (95% CI)
Ejection fraction	19.15	<0.0001	1.26 (1.14–1.40)*
IVCD or LBBB	17.32	<0.0001	1.75 (1.35–2.28)
NYHA functional class	13.55	0.0011	
Class II vs. I			1.59 (1.06–2.38)
Class III vs. I			2.07 (1.35–3.17)
Inducible VT	8.52	0.0035	1.49 (1.14–1.94)
Age	8.28	0.0040	1.23 (1.07–1.41)†
Prior CABG	6.94	0.0052	0.71 (0.55–0.92)
Atrial fibrillation	6.80	0.0091	1.65 (1.13–2.40)
History of heart failure	4.02	0.0450	1.72 (1.01–2.91)

*Hazard ratio for a 5% decrease in ejection fraction. †Hazard ratio for a 10-year increase in age. Abbreviations as in Table 1.

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Table 3 Multivariable Relationships With Arrhythmic Death or Cardiac Arrest

Variable	Chi-Square	p Value	Hazard Ratio (95% CI)
Inducible VT	12.55	0.0004	1.89 (1.33–2.69)
History of heart failure	6.84	0.0089	1.99 (1.19–3.33)
Patient enrolled as inpatient	6.80	0.0091	1.88 (1.17–3.02)
Ejection fraction	6.35	0.0118	1.19 (1.07–1.37)*
NSVT not discovered within 10 days after CABG	4.04	0.0443	1.86 (1.02–3.40)
IVCD or LBBB	3.94	0.0473	1.46 (1.01–2.11)

*Hazard ratio for a 5% decrease in ejection fraction.
Abbreviations as in Table 1.

the 2-year event rates for total mortality and for arrhythmic death/cardiac arrest for the range of possible scores for patients in whom this model was developed. The score was then transposed onto the curve for the end point of interest (total mortality or arrhythmic death/cardiac arrest) and the corresponding predicted 2-year event rate read on the y-axis of the graph.

Examples of application of the risk-stratification algorithm appear in Figures 3 to 5. In example A (Fig. 3), a 60-year-old patient whose only risk factor is an EF of 25%, the predicted 2-year total mortality and arrhythmic death risks are quite low (5% and 2%, respectively) even though the EF is <30%.

In contrast, the patient depicted in example B (Fig. 4), who has multiple risk factors in addition to EF ≤30%, has much higher risks of both total mortality and arrhythmic death. Note that if this patient had inducible VT, the arrhythmic death risk is almost as high as the total mortality risk.

In general, the risks of both arrhythmic death and total mortality are lower for patients whose EF is >30%. However, example C (Fig. 5) demonstrates that some patients whose EF is >30% may be at similar or higher risk than certain patients whose EF is <30%. For example, in this case of a hypothetical patient with an EF of 35%, the total

Table 4 Calculation of Total Mortality Score

EF ≤20	20
For values of EF between 20 and 40, add 1 point for each EF point <40	
EF = 40	0
IVCD or LBBB	12
NYHA functional class	
Class III	14
Class II	7
Inducible VT	8
Age ≥80 yrs	15
For each year between 50 and 80, add 0.5 point	
Age ≤50 yrs	0
No prior CABG	7
History of atrial fibrillation	11
History of congestive heart failure	13

EF = ejection fraction; other abbreviations as in Table 1.

Table 5 Calculation of Arrhythmic Death/Cardiac Arrest Score

Inducible VT	17
History of CHF	19
Patient enrolled as inpatient	17
EF ≤20	20
For values of EF between 20 and 40, add one point for each EF point <40	
EF = 40	0
NSVT not discovered within 10 days after CABG	17
IVCD or LBBB	10

Abbreviations as in Tables 1 and 4.

mortality and arrhythmic death risks are virtually identical to those of the patient in the first part of example B (Fig. 4) whose EF was 25%.

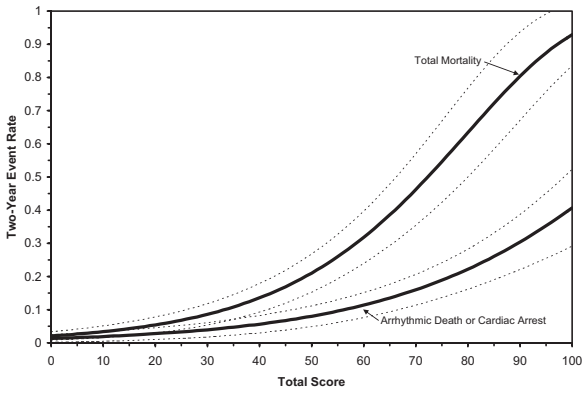
The execution and implications of this approach to risk stratification are influenced by the relative prevalence of various risk factors. Patients having an EF ≤30% had a higher prevalence of associated risk factors, such as electrocardiographic conduction abnormalities and symptomatic heart failure (Table 6). However, Table 6 demonstrates that a significant minority (25%) of patients whose EF was 30% or less did not have these additional risk factors.

Discussion

This analysis of patients enrolled in the MUSTT study who received neither pharmacologic antiarrhythmic therapy nor an implanted defibrillator demonstrates that multiple factors influence mortality of patients with chronic coronary artery disease. In addition, this study illustrates that much prognostic information can be gained from easily determined historical factors. We have shown that although EF is an important risk predictor, in this study population several other variables carry similar prognostic significance. Furthermore, the present study demonstrates the potential danger of focusing efforts to reduce risk of sudden death only on patients with EF ≤30%. We demonstrate that depending on the presence of other risk factors, patients with EF 30% to 40% may have total mortality and sudden death risks that exceed those of some patients with EF ≤30%.

The algorithm we developed does not represent the "ultimate" risk-stratification tool. Rather, it serves as an example of the potential utility of this approach to risk stratification. The algorithm developed in this study, or a similar one, could be applied easily to risk-stratify patients having the characteristics of those enrolled in the MUSTT study (and should only be applied to such patients). Of note, except for the electrophysiologic study, the variables in these prediction models are noninvasive and easily determined in the office setting without any special equipment.

The variables that were associated with highest risk for total mortality as well as arrhythmic death are not surprising. The association between inpatient (vs. outpatient) status and higher

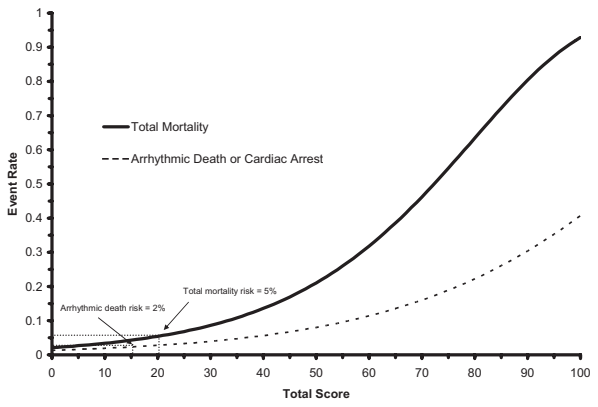


Score	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
TM	2	3	3	4	5	7	9	11	14	17	21	26	32	39	46	55	63	72	80	87	93
AD/CA	1	2	2	2	3	3	4	4	5	6	8	9	11	13	15	18	21	25	29	33	41

Figure 2 **Relationship of Multivariable Risk Scores to 2-Year Event Rates**

Graphical representation of risk stratification algorithm to predict 2-year event rate. **Dotted lines** surrounding each event curve depict 95% confidence intervals. The **table beneath the graph** relates numerical risk scores for total mortality (TM) and arrhythmic death or cardiac arrest (AD/CA) to 2-year mortality for each end point.

mortality risk was demonstrated for patients experiencing cardiac arrest in the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial (21). Older age would be expected to increase total mortality risk but not necessarily risk for arrhythmic death. Conversely, the independent prognostic significance of inducible sustained VT for prediction of arrhythmic death has been demonstrated and is expected (22).



Example A
A 60-year-old patient with prior CABG, NSVT only documented within 10 days after CABG, EF 25%, narrow QRS complex, no inducible sustained VT, no current or past heart failure

Parameter	Arrhythmic Death Score	Total Mortality Score
Age = 60 years		5
EF = 25%	15	15
Total score	**15**	**20**

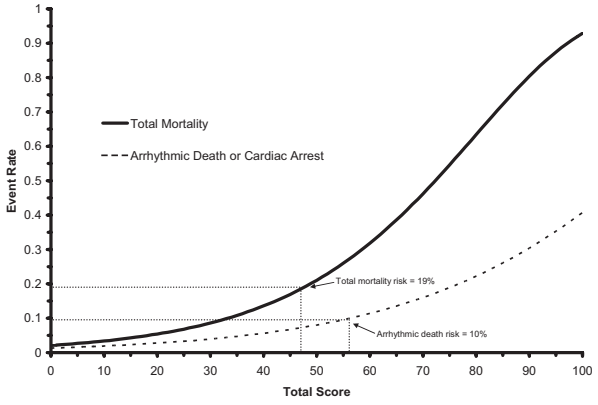
Figure 3 **Example of a Low-Risk Patient With EF <30%**

Graphical representation of the hypothetical patient described in the text as example A. This patient's only risk factors are reduced ejection fraction (EF) and age 60 years. CABG = coronary artery bypass graft; NSVT = nonsustained ventricular tachycardia; other abbreviations as in Figure 1.

Application of this model demonstrates that patients whose only risk factor is having an EF of 30% or less have a predicted 2-year total mortality risk of approximately 5%. This rate is considerably lower than the observed 2-year total mortality rate of 22% for control patients enrolled in the MADIT (Multicenter Automatic Defibrillator Implantation Trial)-II study (23). This difference in risk is especially striking when one considers 2 additional differences between these 2 studies. First, patients enrolled in the MUSTT study were required to have nonsustained VT, which is associated with higher mortality after myocardial infarction (9), whereas patients enrolled in the MADIT-II study were not required to have nonsustained VT documented. Second, only one-third of patients in the MUSTT study who did not have inducible sustained VT received beta-blocking agents versus 70% of patients enrolled in the MADIT-II study (because MADIT-II was conducted in the late 1990s, when beta-blockade was more widely accepted in this patient population). It seems likely that if the MUSTT population were treated with beta-blocking agents at rates consistent with current practice, the total mortality and arrhythmic death/cardiac arrest rates would have been even lower than those observed.

We believe the explanation for the much higher mortality observed in the control arm of the MADIT-II study compared with that of patients enrolled in the MUSTT study matching the entry requirements of the MADIT-II (chronic coronary artery disease and EF ≤30%, but having no other variables from the current model associated with increased mortality) lies in the characteristics of patients enrolled in the MADIT-II study. Sixty-one percent of patients enrolled in the MADIT-II study had symptomatic heart failure (NYHA functional class ≥2), and 44% had LBBB or nonspecific IVCD (23). The influence of these

Example B

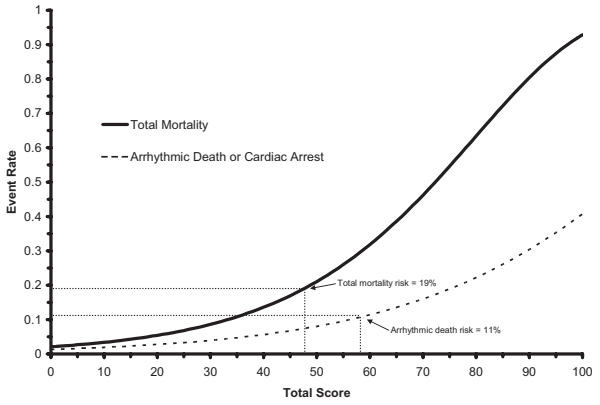


A 60-year-old patient with prior CABG, EF 30%, history of heart failure, currently NYHA class 2, with LBBB, no inducible sustained VT, NSVT documented and occurred remote (>10) days after CABG.

Parameter	Arrhythmic Death Score	Total Mortality Score
Age = 60 years		5
EF = 30%	10	10
History of heart failure	19	13
NYHA Class 2		7
LBBB	10	12
NSVT not within 10 d of CABG	17	
Total score	**56**	**47**
If this patient had inducible sustained VT at EP testing:		
Total score	**73**	**55**

Figure 4 **Example of a High-Risk Patient With EF <30%**

Graphical representation of the hypothetical patient described in the text as example B. Like the patient described in example A (Fig. 3), this patient is 60 years old with reduced EF. However, this patient has additional risk factors of symptomatic heart failure and left bundle branch block (LBBB). Predicted risk for both total mortality and arrhythmic death is much higher than that of the patient without heart failure symptoms or left bundle branch block. NYHA = New York Heart Association; other abbreviations as in Figures 1 and 3.



Example C.

A 65-year-old person has never undergone CABG, EF 35%, history of heart failure, currently NYHA class 2, with inducible VT, narrow QRS complex, documented NSVT.

Parameter	Arrhythmic Death Score	Total Mortality Score
Age = 65 years		8
No prior CABG		7
EF = 35%	5	5
History of heart failure	19	13
NYHA Class 2		7
Inducible VT	17	8
NSVT not within 10 d of CABG	17	
Total score	**58**	**48**

Figure 5 **Example of a High-Risk Patient With EF >30%**

Graphical representation of the hypothetical patient described in the text as example C. This patient's ejection fraction (EF) is greater than 30%, but because symptomatic heart failure and inducible VT are present, the risks for both total mortality and arrhythmic death are comparable to those of some patients with much lower EF. Abbreviations as in Figures 3 and 4.

patient characteristics on the observed 2-year mortality of 22% in the MADIT-II control patients is substantiated by comparison of this event rate with that observed in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (24). In that trial, which required patients to have symptomatic heart failure as well as EF ≤35%, patients with coronary disease as the cause of heart failure randomized to placebo had a 2-year mortality of 18%, similar to the mortality observed in MADIT-II patients. Note that 41% of SCD-HeFT patients with ischemic disease had the additional risk factor of QRS duration ≥120 ms, similar to the MADIT-II study population.

Study limitations. This model requires validation by a prospective trial. The use of this model must be restricted to patients having documented coronary artery disease, left ventricular EF of 40% or less, and asymptomatic spontaneous nonsustained VT. The application of this model is also dependent on performing an electrophysiologic study to determine if sustained VT is inducible. This algorithm should not be applied to patients with ventricular dysfunction due to noncoronary disease. It is also possible that use of other noninvasive tests, such as measurement of T-wave alternans or the signal-averaged electrocardiogram, might improve the performance of this model. This study should not be construed to be a test of defibrillator efficacy. However, the intelligent use of defibrillators demands an understanding of the risk of both sudden and nonsudden death risks tailored to individual patients. This model demonstrates both the complexity and the feasibility of such risk modeling.

Table 6 **Prevalence of Additional Risk Factors in Relation to Ejection Fraction**

	EF ≤30% (n = 433)	EF >30% (n = 241)
No other mortality risk factors (age excluded)	16 (4%)	27 (11%)
No IVCD or LBBB or NYHA functional class II or III	109 (25%)	99 (41%)
No IVCD or LBBB or NYHA functional class II or III, but randomizable VT	37 (9%)	28 (12%)

Abbreviations as in Table 1.

Conclusions

In summary, it is accepted that the ICD is the best therapy currently available to prevent sudden death in high-risk patients. However, recent clinical trials, which demonstrated the spectrum of efficacy of the ICD, were not designed to evaluate optimal methods for risk stratification of myocardial infarction survivors. Given the expense and risks of ICDs, it is logical to search for methods of using this technology in the most cost-effective manner. The present analysis presents one approach to solving this problem. Our model demonstrates that multiple variables in addition to left ventricular dysfunction (reflected by EF) influence mortality of patients with coronary artery disease. We have demonstrated that consideration of multiple risk factors has the potential to provide more accurate prediction for risk of sudden death as well as total mortality. As a result, the model identifies a population of patients that meets current guidelines for prophylactic ICD implantation in patients with coronary disease but is unlikely to derive a significant improvement in 2-year survival with the ICD.

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