Relation of Ejection Fraction and Inducible Ventricular Tachycardia to Mode of Death in Patients With Coronary Artery Disease

An Analysis of Patients Enrolled in the Multicenter Unsustained Tachycardia Trial

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Background—Fifty percent of deaths in patients with coronary disease occur suddenly. Although many factors correlate with increased mortality, there is little information regarding the influence of these factors on mode of death. As such, optimum methods to determine patients most likely to benefit from implantable defibrillator therapy are unclear.

Methods and Results—We analyzed the relation of ejection fraction and inducible ventricular tachyarrhythmias to mode of death in all 1791 patients enrolled in the Multicenter Unsustained Tachycardia Trial who did not receive antiarrhythmic therapy. Total mortality and arrhythmic deaths/cardiac arrests occurred more frequently in patients with ejection fraction <30% than in those with ejection fraction of 30% to 40%. The percentage of deaths classified as arrhythmic was similar in patients with ejection fraction <30% or ≥30%. The relative contribution of arrhythmic events to total mortality was significantly higher in patients with inducible tachyarrhythmia (58% of deaths in inducible patients versus 46% in noninducible patients, P=0.004). The higher percentage of events that were arrhythmic among patients with inducible tachyarrhythmia appeared more distinct among patients with an ejection fraction ≥30% (61% of events were arrhythmic among inducible patients with ejection fraction ≥30% and only 42% among noninducible patients, P=0.002).

Conclusions—Both low ejection fraction and inducible tachyarrhythmias identify patients with coronary disease at increased mortality risk. Ejection fraction does not discriminate between modes of death, whereas inducible tachyarrhythmia identifies patients for whom death, if it occurs, is significantly more likely to be arrhythmic, especially if ejection fraction is ≥30%. (Circulation. 2002;106:2466-2472.)

Key Words: death, sudden ■ risk factors ■ electrophysiology

A number of factors are known to correlate with increased mortality of patients with coronary artery disease. Notably, as ejection fraction decreases, mortality risk increases continuously.1–3 Sustained ventricular tachycardia induced by programmed electrical stimulation is also associated with increased mortality risk in patients with left ventricular ejection fraction ≤40%.4 Previous studies of patients with chronic coronary disease have documented that approximately half of reported deaths occur suddenly.5,6 Although sudden death may result from a variety of underlying causes, a majority of sudden deaths in patients with chronic coronary disease result from ventricular tachyarrhythmias.7,8 Even though it is difficult to be certain in individual cases whether a sudden death results from tachyarrhythmia, such information is important if therapy such as the implantable cardioverter/defibrillator (ICD) is to be used in a cost-effective manner. The effect of left ventricular ejection fraction and inducible sustained ventricular tachycardia on the mode of death (arrhythmic versus nonsudden) in patients with chronic coronary disease is unknown. A

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recent study, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) has demonstrated that implantable defibrillators reduce total mortality in patients with myocardial infarction at least 1 month earlier and left ventricular ejection fractions ≤30%.

Results of a prior study evaluating ICDs for primary prevention of mortality in patients with coronary disease (the MADIT-I trial) suggested that these devices have no significant benefit in patients with ejection fractions >26%.

Another analysis from the Multicenter Unsustained Tachycardia Trial (MUSTT) Investigators demonstrated that ICDs do reduce mortality in patients with ejection fractions of 30% to 40% (M.R.G., unpublished data, 2000). In addition, a recent secondary-prevention trial of patients who had survived life-threatening tachyarrhythmias suggested that empiric amiodarone was as effective as ICDs onstrated that ICDs do reduce mortality in patients with chronic coronary disease and moderate reductions of ejection fraction.

The purpose of the present analysis was to evaluate the relation between ejection fraction, inducible ventricular tachyarrhythmia, and the modes of death for patients enrolled in MUSTT. We sought to provide further information regarding how best to stratify sudden death risk in patients with chronic coronary disease and moderate reductions of ejection fraction (30% to 40%) compared with those with severely reduced left ventricular function (ejection fraction <30%).

Methods

Patient Population

MUSTT was a randomized clinical trial designed to determine whether antiarrhythmic therapy guided by electrophysiological testing would reduce the risk of sudden death and total mortality in patients with documented coronary artery disease, left ventricular ejection fraction ≤40%, and asymptomatic nonsustained ventricular tachycardia. A detailed description of the study protocol has been published. Patients who met the entry criteria were enrolled at 85 sites in the United States and Canada after undergoing evaluation and appropriate treatment of myocardial ischemia. A standardized protocol of programmed stimulation was then performed in the absence of antiarrhythmic drugs. Patients with sustained monomorphic ventricular tachycardia induced by 1, 2, or 3 extrastimuli or sustained polymorphic ventricular tachycardia or ventricular fibrillation induced by 1 or 2 extrastimuli were randomly assigned to receive either antiarrhythmic therapy guided by serial electrophysiological studies or no antiarrhythmic therapy. Patients in whom no randomizable tachyarrhythmia was induced at the baseline electrophysiological study were followed up without antiarrhythmic therapy in a registry. The use of β-blocking agents and ACE inhibitors was strongly encouraged in all patients.

Patients assigned to electrophysiologically guided therapy underwent serial drug testing with antiarrhythmic drugs. If no drug regimen could be found that rendered the tachyarrhythmia noninducible or hemodynamically stable, implantation of an ICD was recommended. ICDs could be recommended after ≥1 unsuccessful drug trial. Patients who declined implantation of a defibrillator were discharged receiving no antiarrhythmic drugs.

A total of 2202 patients were enrolled in the study. Randomizable sustained ventricular tachyarrhythmias were induced in 767 patients (35%) at the baseline electrophysiological study, and 704 (92%) agreed to randomization (351 were randomized to no antiarrhythmic therapy, whereas 351 were randomized to electrophysiologically guided therapy). Antiarrhythmic therapy was not used in 1791 of the 2202 patients. It is the latter group of patients that forms the basis for the present analysis. Four hundred twenty-nine patients with inducible sustained ventricular tachyarrhythmia and 1362 patients without inducible randomizable tachyarrhythmias received no antiarrhythmic therapy. Of the 429 patients with inducible tachyarrhythmia included in the present analysis, 332 were randomized to no antiarrhythmic therapy, 33 were randomized to electrophysiologically guided therapy, and 64 refused randomization and were followed up in the Trial Registry. The breakdown of these patients based on inducibility and ejection fraction is outlined in Table 1.

End Points

We used a modified Hinkle-Thaler system to classify deaths. The classification of events was performed by an Events Committee of 8 experienced electrophysiologists. Narrative descriptions of events were prepared by investigators and edited by the Data Coordinating Center to ensure that the narrative did not contain information pertaining to the presence of inducible arrhythmias or antiarrhythmic therapy. Two members of the Events Committee reviewed events independently. If they did not agree on the event classification, the entire committee reviewed the details of the event and arrived at a classification by consensus. Arrhythmic deaths included unwitnessed deaths (if stable when last observed before death), witnessed instantaneous deaths, nonsudden deaths due to incessant tachycardia, sequelae of cardiac arrest, antiarrhythmic drug toxicity, and complications of implanted defibrillators. Deaths of patients with end-stage heart failure or cardiogenic shock were not classified as arrhythmic.

Cardiac arrest was defined as sudden loss of consciousness that required DC countershock to restore consciousness or stable blood pressure and rhythm. For the purpose of the present analysis, we grouped arrhythmic deaths and cardiac arrests together.

Statistical Analysis

The distributions of baseline characteristics are summarized with medians and 25th and 75th percentiles for continuous variables and percentages for categorical variables. Group differences in baseline

### Table 1. Relation Between Inducible Tachyarrhythmia, Ejection Fraction, and Kaplan-Meier Event Rates Among Untreated Patients in MUSTT

<table>
<thead>
<tr>
<th></th>
<th>Inducible</th>
<th>Noninducible</th>
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<tbody>
<tr>
<td></td>
<td>EF &lt;30% (n=217)</td>
<td>EF ≥30% (n=212)</td>
</tr>
<tr>
<td>2-Year mortality</td>
<td>0.33</td>
<td>0.22</td>
</tr>
<tr>
<td>5-Year mortality</td>
<td>0.57</td>
<td>0.43</td>
</tr>
<tr>
<td>2-Year AD/CA</td>
<td>0.21</td>
<td>0.16</td>
</tr>
<tr>
<td>5-Year AD/CA</td>
<td>0.40</td>
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Inducible/noninducible indicates presence/absence of inducible sustained randomizable ventricular tachyarrhythmia at baseline electrophysiological study; EF, ejection fraction; mortality, total mortality rates; and AD/CA, rate of arrhythmic death and cardiac arrest.

P values refer to Cox model comparison of overall mortality and of AD/CA in patients with EF <30% vs ≥30%, respectively.
characteristics, baseline medication use, and ECG characteristics were assessed with the Wilcoxon rank-sum test (for continuous variables) and the χ² test (for categorical variables). All tests of significance were 2-tailed. Cumulative event rates and survival curves were calculated by the Kaplan-Meier method, and outcome differences were assessed with the Cox proportional hazards model. We evaluated the effect of ejection fraction on clinical outcomes in 2 ways, namely, treating it as a continuous variable and dichotomizing it at <30% versus ≥30%. The value of 30% was chosen because the median ejection fraction of patients enrolled in the trial was 29%. As a continuous variable, we examined the shape and strength of the relation of ejection fraction with mortality and with arrhythmic events using a flexible model-fitting approach that involved cubic spline functions (cubic polynomials). In addition, covariate-adjusted analyses of the effects of inducible tachyarrhythmia and ejection fraction on outcomes were performed with the Cox model. Covariates included in these analyses were age, sex, race, duration (in beats) of the longest episode of nonsustained ventricular tachycardia, number of vessels with ≥75% stenosis, left bundle-branch block, intraventricular conduction delay, use of digitalis at baseline, and whether the patient had had a previous myocardial infarction, undergone bypass surgery, had angioplasty, or had symptoms of angina within 6 weeks before enrollment. To descriptively summarize key relationships, hazard ratios and 95% CIs were calculated with the Cox model.

Although ejection fraction and inducibility status were recorded in all patients, there were occasionally patients with missing values for 1 or more of the other covariates. Analyses were performed in patients with complete data for all variables (73% of the study population); we also performed analyses with the full study population using multiple imputation to estimate missing values for the adjustment variables. The software used for these calculations (NORM) was developed by Schafer and is available electronically in the public domain (http://www.stat.psu.edu/~jls/misoftwa.html).

Analysis based on the subset of patients with complete data compared with analysis based on the full study population using imputed values for missing covariates produced very similar results. We report here the results based on the analysis that included all patients.

To assess the effects of inducible tachyarrhythmia and ejection fraction on mode of death (ie, on whether or not an event was arrhythmic), 2 approaches were used. With ejection fraction dichotomized, the percentages of deaths/cardiac arrests that were arrhythmic in each of the 4 inducibility/ejection fraction groups were tabulated and compared. Additionally, logistic regression analysis was used to jointly assess the relationship of these factors to whether an outcome event was arrhythmic, also taking into account other patient characteristics. All patients with any clinical event (death or cardiac arrest) that could be classified by the Events Committee were included in this assessment. The outcome variable was whether the event was arrhythmic (as assessed by the Events Committee).

Results

The median ejection fraction of patients enrolled in the trial was 29%. The ejection fraction of patients with inducible sustained ventricular tachycardia did not differ significantly from that for those patients without inducible sustained tachycardia.

Total Mortality

The 5-year mortality rate of all patients with ejection fraction <30% (54%) was significantly higher than that of patients having an ejection fraction ≥30% (36%, P=0.0001). This difference occurred in patients with and without inducible tachyarrhythmia (Table 1; Figure 1). Over the course of 5 years, the mortality curves of patients based on inducibility and ejection fraction remained distinct (Figure 1); that is, both ejection fraction and inducibility contributed to mortality risk.

Incidence of Arrhythmic Death/Cardiac Arrest

The 5-year risk of arrhythmic death or cardiac arrest of all patients with ejection fraction <30% (33%) was significantly higher than that of patients having an ejection fraction ≥30% (20%, P=0.0001). The increased risk of arrhythmic death or cardiac arrest with a low ejection fraction was present in patients without inducible tachyarrhythmia (P=0.0001; Table 1), and a similar trend was observed for patients with inducible tachyarrhythmia (Table 1; Figure 2). As noted for total mortality, over the course of 5 years, the arrhythmic death/cardiac arrest event curves, based on inducibility and ejection fraction, remained distinct (Figure 2). Multivariable analysis confirmed that both ejection fraction and inducible ventricular tachycardia were independent predictors of total mortality and arrhythmic death/cardiac arrest (Table 2). Although inducibility is a modest predictor of total mortality (hazard ratio 1.22, P=0.0202), it has a stronger relationship with arrhythmic death/cardiac arrest (hazard ratio 1.62, P=0.0001).

Contribution of Arrhythmic Death to Total Mortality

There were a total of 782 events (754 deaths and 28 cardiac arrests) among the 1791 patients included in the present analysis. There was sufficient information available for the
Events Committee to classify 760 (97%) of the events. A similar proportion of events were arrhythmic regardless of ejection fraction. Fifty percent of events in patients with ejection fraction $<30\%$ were classified as arrhythmic, whereas 47% of events in patients whose ejection fraction was $\geq 30\%$ were classified as arrhythmic ($P=0.47$). When patients were grouped by tachyarrhythmia inducibility, ejection fraction did not significantly influence the mode of death within individual groups. That is, the percentage of total mortality accounted for by arrhythmic events was similar regardless of whether the ejection fraction was $<30\%$ or $\geq 30\%$ within the group of patients without inducible tachyarrhythmia, and also among patients with inducible tachyarrhythmia (Figure 3).

The presence of inducible tachyarrhythmia identified a group of patients whose events were significantly more likely to be arrhythmic death or cardiac arrest rather than nonarrhythmic death. Among patients with inducible sustained tachyarrhythmia, 58% of deaths were arrhythmic, whereas only 46% of deaths were arrhythmic in patients without inducible sustained tachyarrhythmia ($P=0.004$). Ejection fraction appeared to influence the relation between tachyarrhythmia inducibility and the mode of death. For patients whose ejection fraction was $<30\%$, although the percentage of deaths that were arrhythmic was higher among patients with inducible tachyarrhythmia than among those without (55% versus 48%), this difference was not statistically significant ($P=0.20$; Figure 4). In contrast, among patients whose ejection fraction was $\geq 30\%$, 61% of deaths in patients with inducible tachyarrhythmia were attributed to arrhythmia, whereas only 42% of deaths were arrhythmic in patients without inducible tachyarrhythmia ($P=0.002$; Figure 4).

Logistic multivariable regression analysis of these 2 factors confirmed that inducibility but not ejection fraction was significantly associated with whether events were arrhythmic. This analysis did not reveal a significant interaction between inducibility and ejection fraction with respect to mode of death ($P=0.132$). When inducibility and ejection fraction were considered jointly with the various demographic, historical, and clinical covariates considered in these analyses, the only significant predictors of whether an event was arrhythmic were inducibility ($P=0.005$) and age ($P<0.0001$). Events in patients with inducible tachyarrhythmia were significantly more likely to be arrhythmic, and events in older patients were significantly less likely to be arrhythmic than events that occurred in younger patients.

### Relation Between Ejection Fraction and Events

The relation between ejection fraction and event rates was highly significant whether ejection fraction was treated as a continuous or dichotomized variable (Table 2). When ejection fraction was treated as a continuous variable, the rates of both total mortality and arrhythmic death or cardiac arrest decreased monotonically as ejection fraction increased from 25% to 40% (Figure 5). In addition, the hazard ratios for both mortality and arrhythmic death/cardiac arrest as related to

<table>
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<th>TABLE 2. Adjusted Cox Models*</th>
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<tr>
<td><strong>Total Mortality</strong></td>
</tr>
<tr>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>EF (5% decrease from EF 40% to 20%)</td>
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<tr>
<td>EF &lt;30%</td>
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<tr>
<td>Inducibility</td>
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*Adjusted for age, sex, race, duration (in beats) of longest episode of nonsustained ventricular tachycardia, number of vessels with 75% or greater stenosis, left bundle-branch block, intraventricular conduction delay, use of digitalis at baseline, previous myocardial infarction, prior bypass surgery, prior angioplasty, and symptoms of angina within 6 weeks before enrollment.

EF indicates ejection fraction.

Hazard ratios for each end point are depicted, with ejection fraction treated as a continuous variable (EF, 5% decrease from EF 40% to 20%) and dichotomized around the median value (<30%).
ejection fraction were nearly identical (Table 2). This supports the conclusion that ejection fraction is not effective in discriminating mode of death. In contrast, the hazard ratio for arrhythmic death/cardiac arrest was greater than that for total mortality when related to the presence of inducible ventricular tachycardia (Table 2). Thus, inducible ventricular tachycardia is a relatively specific predictor of arrhythmic deaths.

**Discussion**

We have demonstrated that within a population of patients with chronic coronary artery disease who have significant left ventricular dysfunction and spontaneous asymptomatic nonsustained ventricular tachycardia, mortality is significantly greater in those whose ejection fraction is <30%, regardless of the presence or absence of inducible sustained ventricular tachycardia. However, the degree of left ventricular dysfunction does not appear to influence the mode of death, because approximately half of the deaths were accounted for by arrhythmia in patients with ejection fraction <30% and ≥30%. The lack of association of ejection fraction with mode of death was confirmed in multivariable analysis of ejection fraction and inducibility, along with various other possible predictors. Although patients with sustained tachyarrhythmia inducible by programmed stimulation overall were significantly more likely than those without inducible tachyarrhythmias to experience an arrhythmic event as the mode of death, this distinction appeared more striking in patients with ejection fractions ≥30% than in those with an ejection fraction <30%. Although there was not a significant interaction between ejection fraction and inducibility in predicting mode of death, there is limited power for detecting such interactions even with the large number of events in the present study. Younger age was also a significant predictor that an event, if it occurred, would be arrhythmic.

Although arrhythmic events accounted for a similar percentage of deaths in patients with ejection fractions above and below 30%, it is likely that the mechanisms underlying these events are influenced by ejection fraction. Patients with ejection fractions <30% are more likely to have clinical evidence of congestive heart failure and to have severely distorted ventricular anatomy. Hormonal and electrolyte alterations, myocardial stretch, and repolarization abnormalities, among other factors, may generate arrhythmias in such patients. These conditions may come and go unpredictably and are not detected by current methods of electrophysiological testing. The stronger association of electrophysiological testing with mode of death in patients with ejection fraction ≥30% is likely due to the fact that patients with higher ejection fractions are less likely to have severe heart failure.

Several recent trials have suggested that ICDs do not confer significant survival benefit in patients with moderate degrees of left ventricular dysfunction, in comparison with
antiarrhythmic drugs. The MADIT-I trial found that patients with coronary disease, spontaneous nonsustained ventricular tachycardia, and inducible sustained tachycardia whose ejection fractions were >26% did not achieve improved survival with ICD therapy compared with “conventional” therapy. However, that study was small (196 patients) and used an ejection fraction cutoff of 35% for entry into the study. Thus, the power of that study to detect a beneficial effect in patients with ejection fraction >30% was limited. The Antiarrhythmics Versus Implantable Defibrillator (AVID) Trial found no advantage of ICD therapy over empiric antiarrhythmic drug therapy in survivors of cardiac arrest or sustained ventricular tachycardia whose ejection fraction was >35%. Although it was a large study (>1000 patients), the trial was stopped prematurely. The abbreviated follow-up may have limited its power to detect significant benefit of defibrillator therapy, because patients with higher ejection fractions tend to have less frequent arrhythmic events. It is also conceivable that the observed difference in ICD benefit for patients with ejection fraction >35% between the results of the AVID trial and MUSTT is explained by the fact that patients in AVID who did not receive ICDs were treated with amiodarone or sotalol.

There is no doubt that patients with coronary artery disease whose ejection fraction is <30% have higher mortality than those with ejection fraction ≥30%. The importance of evaluating patients with ejection fractions between 30% and 40% derives from the fact that although this group has a lower overall mortality than patients whose ejection fraction is <30%, the number of patients surviving myocardial infarction with an ejection fraction ≥30% is much greater than those having ejection fraction <30% and is likely to increase with more widespread use of reperfusion therapy in acute infarction. For example, in the Cardiac Arrhythmia Suppression Trial (CAST), 1.7 times as many patients had an ejection fraction of 30% to 39% (n=1318 patients) as had ejection fractions of 20% to 29% (n=797 patients). In that analysis, ~60% of deaths were due to arrhythmias in patients whose ejection fraction was 20% to 29%, as well as in those with ejection fraction 30% to 39%. In fact, although the rate of death or cardiac arrest was lower for patients with an ejection fraction of 30% to 39% (17%) than for those with an ejection fraction of 20% to 29% (30%), the greater number of patients in the group with an ejection fraction between 30% and 39% resulted in virtually equal numbers of deaths or cardiac arrests in the 2 groups.

Further evidence of the contribution of patients with ejection fraction >30% to sudden death events in survivors of acute infarction is provided by an analysis by Copie et al. These authors divided 579 survivors of acute infarction by quartiles of ejection fraction: ≥58%, 49% to 58%, 36% to 49%, and ≤36%. Although 2-year all-cause mortality was higher in the quartile whose ejection fraction was ≥36% than in the quartile with ejection fraction of 36% to 49% (19.4% versus 9.0%), the incidence of sudden death was the same for both quartiles (6.3% and 6.2%, respectively).

The angiographic substudy of the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial provides a powerful demonstration of the relative numbers of patients surviving acute infarction with ejection fraction of 30% to 40% versus <30%. This substudy included 2400 patients who had cardiac catheterization at various times after the onset of acute infarction, under protocol. An ejection fraction ≤30% was present in 5.1% of patients at 5 to 7 days, whereas 11.6% had an ejection fraction of 31% to 40% (oral communication, Kerry Lee, PhD, 2002). Thus, more than twice as many patients survive acute infarction after thrombolytic therapy with an ejection fraction of 30% to 40% versus <30%.

Both left ventricular systolic dysfunction, reflected by the ejection fraction, and potential for reentrant ventricular arrhythmias, reflected by inducibility of sustained tachyarrhythmias with programmed stimulation, were associated with mortality risk in the present study population. However, they influence mortality in different ways. The presence of inducible tachyarrhythmia is a relatively specific predictor of arrhythmic events, whereas ejection fraction does not significantly predict mode of death. These observations suggest that programmed stimulation may have greater prognostic utility for risk stratification in coronary disease patients whose ejection fraction is 30% to 40% than in those whose ejection fraction is <30%.

Conclusions

The present analysis suggests potential strategies for more cost-effective utilization of programmed stimulation for risk stratification in patients with coronary disease. In light of the results of recent trials, such as MADIT-II, our analysis suggests that the major utility of electrophysiological testing may be restricted to patients having an ejection fraction between 30% and 40%. The results of the present study and MADIT-II demonstrate the need for better methods of risk stratification. On the other hand, mortality was significant even in patients with ejection fraction ≥30% without inducible tachyarrhythmia. If one assumes that implantable defibrillators reduce mortality primarily by preventing arrhythmic events, our observations suggest that such devices have the potential to reduce mortality significantly not only in patients with coronary disease and left ventricular ejection fraction <30% but also in those whose ejection fraction is ≥30%. The latter hypothesis suggests the basis for future trials.

Acknowledgments

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