ABSTRACT

Background  The mortality rate among patients with coronary artery disease, abnormal ventricular function, and unsustained ventricular tachycardia is high. The usefulness of electrophysiologic testing for risk stratification in these patients is unclear.

Methods  We performed electrophysiologic testing in patients who had coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and asymptomatic, unsustained ventricular tachycardia. Patients in whom sustained ventricular tachyarrhythmias could be induced were randomly assigned to receive either antiarrhythmic therapy guided by electrophysiologic testing or no antiarrhythmic therapy. The primary end point was cardiac arrest or death from arrhythmia. Patients without inducible tachyarrhythmias were followed in a registry. We compared the outcomes of 1,397 patients in the registry with those of 353 patients with inducible tachyarrhythmias who were randomly assigned to receive no antiarrhythmic therapy in order to assess the prognostic value of electrophysiologic testing.

Results  Patients were followed for a median of 39 months. In a Kaplan–Meier analysis, two-year and five-year rates of cardiac arrest or death due to arrhythmia were 12 and 24 percent, respectively, among the patients in the registry, as compared with 18 and 32 percent among the patients with inducible tachyarrhythmias who were assigned to no antiarrhythmic therapy (adjusted P<0.001). Overall mortality after five years was 48 percent among the patients with inducible tachyarrhythmias, as compared with 44 percent among the patients in the registry (adjusted P=0.005). Deaths among patients without inducible tachyarrhythmias were less likely to be classified as due to arrhythmia than those among patients with inducible tachyarrhythmias (45 and 54 percent, respectively; P=0.06).

Conclusions  Patients with coronary artery disease, left ventricular dysfunction, and asymptomatic, unsustained ventricular tachycardia in whom sustained ventricular tachyarrhythmias cannot be induced have a significantly lower risk of sudden death or cardiac arrest and lower overall mortality than similar patients with inducible sustained tachyarrhythmias. (N Engl J Med 2000;342:1937-45.)

©2000, Massachusetts Medical Society.

Mortality from cardiovascular disease continues to decline, but patients with coronary artery disease, left ventricular dysfunction, and asymptomatic ventricular arrhythmias remain at high risk for sudden or nonsudden death.1-5 Although myocardial ischemia is responsible for many events, most sudden deaths and cardiac arrests among patients who have had a myocardial infarction result from reentrant ventricular tachycardia or fibrillation.6 Electrophysiologic testing has been used to stratify patients according to the risk of sudden death, but previous analyses of this approach have involved relatively small numbers of patients and relatively short follow-up periods (≤2 years).7-16

The primary objective of the Multicenter Unsustained Tachycardia Trial was to evaluate the efficacy of antiarrhythmic therapy guided by electrophysiologic testing in reducing the risk of sudden death and cardiac arrest among patients with coronary artery disease, left ventricular dysfunction, and asymptomatic, unsustained ventricular tachycardia.17 A secondary goal was to evaluate the usefulness of electrophysiologic testing for risk stratification in this group of patients. In this report, we describe the outcomes of patients in whom sustained ventricular tachyarrhythmias were not induced on electrophysiologic testing, and we compare the rates of death due to arrhythmia and of death from any cause among these patients with the rates among patients with inducible ventricular tachyarrhythmias who were randomly assigned to receive no antiarrhythmic therapy.

METHODS

Patients

The complete study protocol has been described previously.17,18 Patients at 85 study sites in the United States and Canada were
identified as having coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and asymptomatic, unsustained ventricular tachycardia (lasting for three or more beats or a maximum of 30 seconds). Patients who met these criteria were enrolled four or more days after the most recent myocardial infarction or revascularization procedure and at least 72 hours after the most recent documented instance of hemodynamic instability or myocardial ischemia. Written informed consent was obtained from all the patients before enrollment. The institutional review board at each study site approved the protocol.

Patients were excluded if they had a history of syncpe or had sustained ventricular tachycardia or ventricular fibrillation more than 48 hours after the onset of acute myocardial infarction. Patients were also excluded if they had unsustained ventricular tachycardia that occurred only in the setting of drug-induced long-QT syndrome or acute myocardial ischemia or that was attributable to acute metabolic disorders or drug toxicity, or if they had symptomatic, unsustained ventricular tachycardia.

**Protocol**

An electrophysiologic study was performed without the use of antiarrhythmic drugs.18 The study included one to three extrastimuli at two right ventricular sites during two drive-cycle lengths. Stimulation was stopped if uniform, sustained ventricular tachycardia was reproducibly induced or if more than 15 complexes of polymorphic ventricular tachycardia or flutter with three extrastimuli were reproducibly induced. If cardioversion was required to terminate an induced arrhythmia, reproducibility was not required before the stimulation was stopped. Patients with sustained monomorphic ventricular tachycardia induced by any method of stimulation and those with sustained polymorphic ventricular tachycardia (including ventricular flutter and fibrillation) induced by one or two extrastimuli were randomly assigned in equal proportions to receive either antiarrhythmic therapy guided by the results of electrophysiologic testing or no antiarrhythmic therapy: Ventricular flutter (tachycardias with a cycle length of <220 msec and no isoelectric interval between consecutive QRS complexes) and fibrillation were considered to be polymorphic ventricular tachycardia.

Patients without inducible ventricular tachyarrhythmias were not treated with antiarrhythmic therapy and were followed in a registry. This registry also included patients in whom only unsustained ventricular tachycardia (lasting <30 seconds) was induced, patients with sustained polymorphic ventricular tachycardia that was induced only by three extrastimuli or burst pacing, and patients with sustained monomorphic ventricular tachycardia that could not be reproduced.

Treatment of all the patients with beta-adrenergic-blocking agents and angiotensin-converting-enzyme inhibitors was strongly recommended. Patients were examined at the outpatient facility of one of the participating centers one month after discharge and every three months thereafter. The follow-up regimen was the same for the patients who underwent randomization and the patients in the registry.

**Study End Points**

The primary end point was cardiac arrest from which the patient was resuscitated or death due to arrhythmia. Secondary end points included death from all causes, death from cardiac causes, and spontaneous, sustained ventricular tachycardia. Deaths were classified according to a modification of the Hinkle–Thaler system.19 Deaths classified as due to arrhythmia included unwitnessed deaths, witnessed deaths that were instantaneous, nonsudden deaths due to incessant ventricular tachycardia, deaths considered to be sequelae of cardiac arrest, deaths caused by toxic effects of antiarrhythmic drugs, and deaths caused by complications of implanted defibrillators. Deaths in patients with end-stage heart failure or cardiogenic shock were not classified as sudden. Cardiac arrest was defined as a sudden loss of consciousness requiring direct-current countershock to restore consciousness or a stable blood pressure and rhythm.

**Analysis of Events**

Investigators at each study site provided a narrative description of the clinical circumstances surrounding all deaths and cardiac arrests, with accompanying electrocardiographic recordings, relevant hospital records, and laboratory data (when available). The data-coordinating center then edited the descriptions and documents to ensure that members of the events committee would be able to classify outcomes without knowing the results of the baseline electrophysiologic studies, the patients’ randomization status, or whether a defibrillator had been implanted. The edited descriptions of each event, including the supporting source documents and case-report forms, was then reviewed independently by two members of the events committee, each of whom classified the event according to the definitions of the study end points. If these two members disagreed on the classification, the event was reviewed by the entire events committee, which arrived at a classification by consensus.

**Statistical Analysis**

Values for continuous variables are presented as medians with 25th and 75th percentiles, and values for categorical variables are presented as percentages. Differences in clinical characteristics and medication use at base line between the patients in the registry and the patients with inducible ventricular tachyarrhythmias who were randomly assigned to no antiarrhythmic therapy were assessed with use of the Wilcoxon rank-sum test (for continuous variables) or the chi-square test or Fisher’s exact test (for categorical variables). All tests of significance were two-tailed. Cumulative event rates were calculated by the Kaplan–Meier method, with the time to a first event as the outcome variable.20 The statistical significance of differences in outcome between the two groups was assessed with the log-rank test.21

In addition, covariate-adjusted analyses of outcomes among the registry patients and the patients with inducible ventricular tachyarrhythmias who were assigned to no antiarrhythmic therapy were performed with the Cox proportional-hazards model.22 Covariates included in these analyses were age; sex; race; the time of enrollment relative to the start of the trial; the ejection fraction; whether the patient had had a previous myocardial infarction, had undergone bypass surgery, had undergone angioplasty, or had a history of angina; and whether the patient used beta-blockers. Covariate-adjusted comparisons were also performed of the outcomes among three subgroups of the patients in the registry (patients without inducible tachyarrhythmias, patients in whom only unsustained ventricular tachycardia was induced, and patients in whom sustained polymorphic ventricular tachycardia was induced only by three extrastimuli). Relative risks, expressed as hazard ratios (with 95 percent confidence intervals), were calculated with use of the Cox proportional-hazards model.

To compare the patients randomly assigned to no therapy and the patients in the registry with respect to types of events, the proportions of total events in each group that were classified as arrhythmia were compared with use of a conventional chi-square test.

**RESULTS**

We enrolled 2202 patients in the study, including 767 patients with inducible sustained ventricular tachyarrhythmias. Of these 767 patients, 704 agreed to undergo random group assignment, and 353 were subsequently assigned to receive no antiarrhythmic therapy. There were 1435 patients in the registry: 661 in whom no ventricular tachyarrhythmia was induced, 531 in whom only unsustained ventricular tachycardia was induced, and 205 with sustained polymorphic ventricular tachycardia induced only by three extrastimuli or burst pacing, as well as 38 additional patients whom we excluded from the present analy-
sis. Of the 38 excluded patients, 24 had inducible sustained monomorphic ventricular tachycardia that was not reproducible; 10 had inducible sustained monomorphic ventricular tachycardia, but no attempt was made to reproduce the findings; and 4 had sustained polymorphic ventricular tachycardia that was induced with two extrastimuli but that was not reproducible. Complications of the base-line electrophysiologic study occurred in 7 of the 2202 enrolled patients (0.3 percent). Thus, in this analysis we compared the outcomes of the 353 patients with inducible sustained tachyarrhythmias who were randomly assigned to no antiarrhythmic therapy with the outcomes of the 1397 patients in the registry.

Characteristics of the Patients

The clinical characteristics of the patients in the registry were similar in most respects to those of the patients with inducible ventricular tachyarrhythmias who were assigned to no antiarrhythmic therapy (Table 1). However, the registry included greater proportions of women and of patients who had previously undergone bypass surgery. The group assigned to no antiarrhythmic therapy included significantly more patients who had a history of myocardial infarction.

Medical Therapy

At the time of discharge from the hospital, 35 percent of the registry patients were taking beta-blockers, as compared with 51 percent of the patients assigned to no antiarrhythmic therapy (P=0.001) (Table 2). At the last follow-up, use of beta-blockers had increased to 45 percent and 53 percent, respectively, among the surviving patients. Most patients in both groups were taking angiotensin-converting–enzyme inhibitors and aspirin at the time of discharge (Table 2).

Antiarrhythmic Therapy

At the time of discharge from the hospital, 97 percent of the registry patients were not receiving anti-
The New England Journal of Medicine

arrhythmic therapy, 2 percent (33 patients) were taking an antiarrhythmic drug, and less than 1 percent (3 patients) had received an implantable defibrillator. At the last follow-up, 84 percent of the registry patients were receiving no antiarrhythmic therapy, 12 percent (163 patients) were receiving an antiarrhythmic drug, and 4 percent (61 patients) had received a defibrillator. Of the patients with a defibrillator, 75 percent (46 patients) had received the device after a cardiac arrest, an episode of sustained ventricular tachycardia, or syncope.

At the time of discharge from the hospital, 96 percent of the patients with inducible ventricular tachyarrhythmias who were randomly assigned to no therapy were receiving no antiarrhythmic therapy, 2 percent (6 patients) had been given a defibrillator, and 2 percent (8 patients) were receiving antiarrhythmic drugs. At the last follow-up, 72 percent of these patients were not receiving antiarrhythmic therapy, 11 percent (38 patients) were receiving an antiarrhythmic drug, and 18 percent (62 patients) had received a defibrillator. Of the patients with a defibrillator, 79 percent (49 patients) had received the device after a cardiac arrest, spontaneous sustained ventricular tachycardia, or syncope.

**Follow-up**

The median duration of follow-up was 41 months for the patients in the registry and 37 months for the patients randomly assigned to no antiarrhythmic therapy. All but 16 of the registry patients and all but 5 of the randomly assigned patients (99 percent in each case) were followed for two or more years. Thirty-two percent of the patients in each of these groups were followed for five or more years. Information adequate to classify events was available for all but 19 (1 percent) of the registry patients and all but 1 (<1 percent) of the patients who underwent randomization.

Two-year and five-year rates for the primary end point of cardiac arrest or death due to arrhythmia, calculated by Kaplan–Meier methods, were 12 percent and 24 percent, respectively, among the registry patients. The corresponding rates for patients with in-

---

**TABLE 2. Medications at Discharge from the Hospital.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients in the Registry (N=1397)</th>
<th>Patients with Inducible Ventricular Tachyarrhythmias and No Antiarrhythmic Therapy (N=353)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>35</td>
<td>51</td>
<td>0.001</td>
</tr>
<tr>
<td>Angiotensin-converting–enzyme inhibitor</td>
<td>72</td>
<td>77</td>
<td>0.06</td>
</tr>
<tr>
<td>Aspirin</td>
<td>60</td>
<td>63</td>
<td>0.29</td>
</tr>
<tr>
<td>Digitalis</td>
<td>57</td>
<td>53</td>
<td>0.21</td>
</tr>
<tr>
<td>Diuretic agent</td>
<td>59</td>
<td>58</td>
<td>0.75</td>
</tr>
<tr>
<td>Calcium-channel–blocking agent</td>
<td>20</td>
<td>25</td>
<td>0.05</td>
</tr>
<tr>
<td>Nitrate</td>
<td>42</td>
<td>44</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*There were no substantial changes in the percentages of patients receiving these medications at the time of their last follow-up, with the exception of beta-blockers.

---

**Figure 1.** Kaplan–Meier Estimates of the Rates of Cardiac Arrest or Death from Arrhythmia in the Registry Patients and the Patients with Inducible Ventricular Tachyarrhythmias Who Were Not Assigned to Antiarrhythmic Therapy.
ducible ventricular tachyarrhythmias who were assigned to no antiarrhythmic therapy were 18 percent and 32 percent (unadjusted P=0.005 by the log-rank test and covariate-adjusted P<0.001 for the five-year period) (Fig. 1 and Table 3). Overall mortality rates after two and five years were 21 percent and 44 percent, respectively, among the registry patients, as compared with 28 percent and 48 percent among the patients assigned to no antiarrhythmic therapy (unadjusted P=0.09 and covariate-adjusted P=0.005 for the five-year period) (Fig. 2 and Table 3). The increased significance of the difference in mortality between the randomly assigned patients and the patients in the registry after adjustment for covariates was largely due to the imbalance in the use of beta-blockers between these two groups.

The proportion of deaths classified as resulting from arrhythmia was higher among the patients randomly assigned to no antiarrhythmic therapy (54 percent) than among the registry patients (45 percent) (P=0.06). Spontaneous sustained ventricular tachycardia not associated with cardiac arrest also occurred more often among patients with inducible ventricular tachyarrhythmias (21 percent) than among the patients in the registry (6 percent) over the five-year follow-up.

The rates of cardiac arrest or death due to arrhythmia and of death from all causes were very similar among the three subgroups of patients in the registry (Table 4). The differences among these subgroups with respect to the rate of cardiac arrest or death due to arrhythmia and the rate of death from all causes were not statistically significant after adjustment for base-line imbalances among the groups in key prognostic factors such as the ejection fraction, age, and the use of beta-blockers (Table 4).

**DISCUSSION**

The results of this study indicate that among patients with coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and spontaneous, unsustained ventricular tachycardia, the induction of sustained ventricular tachyarrhythmias by programmed stimulation identifies patients who are at significantly greater risk for sudden death due to cardiac causes or death from any cause than patients without inducible tachyarrhythmias. However, even patients without inducible tachyarrhythmias have a relatively high risk of death. The presence of inducible sustained ventricular tachycardia proved to be a relatively specific predictor of death from arrhythmia in this group of patients. The proportion of deaths classified as due to arrhythmia was greater among the patients with inducible tachyarrhythmias who were randomly assigned to no antiarrhythmic therapy than among the patients in the registry, in whom sustained tachyarrhythmias could not be induced.

Subgroup analysis of event rates among the patients in the registry, according to the type of induced arrhythmia (no inducible ventricular tachyarrhythmia, only unsustained ventricular tachycardia induced, or sustained polymorphic tachyarrhythmias induced only by three extrastimuli), suggests that there is no significant difference in risk among these three subgroups.

Previous analyses of the prognostic usefulness of electrophysiologic testing in patients with coronary disease and unsustained ventricular tachyarrhythmias have suggested that the negative predictive value of these tests with respect to sudden death is approximately 90 percent over follow-up periods of one to two years. We found that electrophysiologic testing had a negative predictive value of 88 percent for

---

**Table 3.** Rates of Events Among the Patients in the Registry and the Patients with Inducible Ventricular Tachyarrhythmias Who Were Randomly Assigned to No Antiarrhythmic Therapy.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RATE OF CARDIAC ARREST OR DEATH FROM ARRHYTHMIA</th>
<th>OVERALL MORTALITY RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REGISTRY (N=1397) NO ANTIARRHYTHMIC THERAPY (N=52)</td>
<td>REGISTRY (N=1397) NO ANTIARRHYTHMIC THERAPY (N=52)</td>
</tr>
<tr>
<td>No. of events</td>
<td>260</td>
<td>90</td>
</tr>
<tr>
<td>Two-year rate (%)</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Five-year rate (%)</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Hazard ratio*</td>
<td>Unadjusted</td>
<td>0.71 (0.56–0.90)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>0.66 (0.51–0.84)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Values in parentheses are 95 percent confidence intervals. Covariates included in the adjusted model were age, sex, race, time of enrollment, history of myocardial infarction, history of bypass surgery, history of angioptasty, history of angina, ejection fraction, and use or nonuse of beta-blockers at hospital discharge. Hazard ratios refer to the entire five-year follow-up period.
cardiac arrest or death due to arrhythmia within two years in the registry patients. The current results indicate that the risk of cardiac arrest or death due to arrhythmia in the study population persists over a median follow-up of nearly 3.5 years.

The prognostic usefulness of electrophysiologic testing has also been studied in a group of patients slightly different from ours — one made up of survivors of recent myocardial infarction (less than one month before enrollment), without regard to left ventricular function or the presence of spontaneous arrhythmias. These studies reported rates of arrhythmic events ranging from less than 1 percent to 3 percent among patients without inducible ventricular tachyarrhythmias over follow-up periods of one to two years. The higher rates of events in the present study are probably due to several characteristics of our patient population, including the reduced ejection fraction and the presence of unsustained ventricular tachycardia, which were criteria for enrollment. A documented myocardial infarction was not required for entry into the trial, but we did require patients without infarction to have left ventricular dysfunction that was presumed to be due to coronary disease on the basis of coronary anatomy. Only 87 percent of the registry patients had a history of infarction, as opposed to 94 percent of the patients with inducible ventricular tachyarrhythmias who were
assigned to no therapy. Mechanisms of sudden death among patients with left ventricular dysfunction but no history of infarction probably differ from those among patients with a previous infarction, and programmed stimulation may not provoke tachycardia in the former patients.23–27

A previous analysis of data on our patients identified several factors in addition to myocardial infarction that differentiate patients in whom ventricular tachyarrhythmias can be induced from those without inducible ventricular tachyarrhythmias.28 Sustained tachyarrhythmias were significantly more likely to be induced in patients who were male, patients who were white, and patients who had recent angina (within six weeks before enrollment), left ventricular dysfunction, or greater numbers of fixed defects on thallium imaging. The rate of inducible ventricular tachyarrhythmias increased progressively with increasing numbers of diseased coronary arteries. In addition, inducibility of ventricular tachyarrhythmias was more likely in patients who had had an infarction complicated by congestive heart failure 48 hours or more after the onset of symptoms or complicated by ventricular tachycardia or fibrillation 48 hours or less after the onset of symptoms. Thus, several potentially important prognostic factors differentiated registry patients from those with inducible tachyarrhythmias. These factors could influence the efficacy of therapy; for instance, patients without inducible tachyarrhythmias might not respond as favorably to implantable defibrillators as patients with inducible tachyarrhythmias.17

The negative predictive value of electrophysiologic testing that we calculated may be viewed as lower than expected. However, the 12 percent rate of death due to arrhythmia among our registry patients at two years is similar to the rates of 8 to 13 percent reported previously.12–15 It is to be expected, in a population of patients with coronary disease as severe as that in our patients, that the risk of death from all causes and the risk of sudden death will persist over a five-year period. There are other possible explanations for arrhythmic events in patients without inducible sustained ventricular tachycardia. The results of electrophysiologic testing vary from day to day and over the long term by 10 to 50 percent.29–33 It is also likely that progression of coronary disease, resulting in the formation of new circuits that can cause reentrant tachycardia or sudden death due to recurrent ischemia, will occur. The former problem might be detected by periodic repetition of electrophysiologic testing in patients who are identified as potentially at risk. Finally, cardiac disease progressed in many of our patients during follow-up, causing the development of heart failure, with its attendant risk of sudden death.

In conclusion, the results of electrophysiologic testing can be used to assess the prognosis of patients with coronary disease, left ventricular dysfunction, and sustained ventricular tachycardia, but the value of this information may diminish with time.

Supported by grants from the National Heart, Lung, and Blood Institute (UO1 HL45700 and UO1 HL45726), C.R. Bard, Berlex Laboratories, Boehringer–Ingelheim Pharmaceuticals, Guidant, Knoll Pharmaceuticals, Medtronic, Merck, Searle, Ventritex, and Wyeth– Ayerst Laboratories.

Dr. DiCarlo is currently an employee of Guidant.

APPENDIX

The following persons and institutions participated in the Multicenter Unsustained Tachycardia Trial:


The results of electrophysiologic testing vary from day to day and over the long term by 10 to 50 percent.29–33 It is also likely that progression of coronary disease, resulting in the formation of new circuits that can cause reentrant tachycardia or sudden death due to recurrent ischemia, will occur. The former problem might be detected by periodic repetition of electrophysiologic testing in patients who are identified as potentially at risk. Finally, cardiac disease progressed in many of our patients during follow-up, causing the development of heart failure, with its attendant risk of sudden death.

In conclusion, the results of electrophysiologic testing can be used to assess the prognosis of patients with coronary disease, left ventricular dysfunction, and sustained ventricular tachycardia, but the value of this information may diminish with time.
REFERENCES


