Effect of Implantable Defibrillators on Arrhythmic Events and Mortality in the Multicenter Unsustained Tachycardia Trial

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Background—The Multicenter Unsustained Tachycardia Trial (MUSTT) was designed to evaluate an antiarrhythmic treatment strategy, including drugs and implantable defibrillators (ICDs), guided by electrophysiological (EP) testing. We performed several statistical analyses to assess the contribution of defibrillators to the observed treatment benefit.

Methods and Results—First, the effects of defibrillators were indirectly examined by comparing the randomized treatment arms (EP-guided therapy versus no antiarrhythmic therapy) within subgroups that varied according to ICD usage. Use of ICDs increased during the trial; hence, the randomized treatments were compared according to date of enrollment. There were also site-specific differences in ICD use; hence, the randomized arms were compared within groups of sites defined by level of ICD use. There was a distinct “dose response” in relation to ICD use. Where ICD use was high, EP-guided therapy produced significant reductions in arrhythmic death or cardiac arrest ($P<0.004$). Where ICD use was low, there was no benefit of EP-guided therapy. Finally, outcomes of EP-guided therapy patients who received an ICD were directly compared with outcomes of other patients using the Cox proportional hazards model with receipt of an ICD as a time-dependent covariate. Adjusted for other prognostic factors, patients who received an ICD had risk reductions of $>70\%$ in arrhythmic death or cardiac arrest and $>50\%$ in total mortality ($P<0.001$ for both end points).

Conclusions—The benefit of EP-guided antiarrhythmic therapy observed in MUSTT was due to improved outcomes among patients who received an ICD but not among patients who received antiarrhythmic drugs. *(Circulation. 2002; 106:233-238.)*

Key Words: statistics ■ defibrillation ■ electrophysiology ■ antiarrhythmia agents ■ tachyarrhythmias

The Multicenter Unsustained Tachycardia Trial (MUSTT) was a prospective, randomized clinical trial designed to test the hypothesis that antiarrhythmic therapy, including drugs and implantable cardiac defibrillators (ICDs), guided by electrophysiological (EP) testing can reduce the risk of arrhythmic death or cardiac arrest in patients with coronary artery disease who are at increased risk for arrhythmic events.1–3 As previously reported, EP-guided therapy produced a significant 27% risk reduction in the primary end point of arrhythmic death or cardiac arrest and a 20% risk reduction in total mortality.2 However, the benefit was reported to be observed only in patients treated with an ICD.2 There are distinct challenges in arriving at this interpretation. The trial was not designed to test directly the efficacy of ICD therapy compared with other forms of antiarrhythmic therapy. The randomization was between EP-guided antiarrhythmic therapy and no antiarrhythmic therapy. Receiving an ICD was simply one component of the EP-guided treatment strategy. The assignment of patients to receive ICD therapy versus pharmacological antiarrhythmic therapy was not randomized. Patients had to fail at least one round of drug therapy before an ICD could be recommended. Thus, the decision to implant an ICD occurred after randomization, which adds complexity to assessing its effects.

The purpose of the present report is to provide an expanded set of analyses of the major outcomes of the MUSTT trial that examine, in detail, the impact of defibrillator therapy and thus elucidate the major conclusions of the study.

Methods

A description of the study protocol has been published previously.1 Patients at 85 sites in the United States and Canada who had documented coronary artery disease, left ventricular ejection fraction $\leq 40\%$, and asymptomatic nonsustained ventricular tachycardia (VT) were candidates for enrollment. The qualifying nonsustained VT had to occur within 6 months before enrollment and $\geq 4$ days after the most recent myocardial infarction or revascularization procedure.
Patients assigned to EP-guided therapy underwent serial drug testing with US Food and Drug Administration-approved antiarrhythmic drugs. Each round of drug therapy was accompanied by an EP study to assess the patient’s inducibility on that particular drug. Drugs were assigned randomly with the exception of amiodarone. Amiodarone could be tested at the discretion of the investigator if the patient had remained inducible in at least 2 previous drug tests. If no drug could be found that rendered the tachyarrhythmia noninducible, the investigator could discharge the patient on a drug that was associated with hemodynamic stability during induced tachycardia. No empirical antiarrhythmic drug therapy was used.

Implantation of a defibrillator could be recommended after at least one unsuccessful drug test. This feature of the protocol was changed during the trial to reflect changes in practice. The protocol initially required that ≥3 drug tests had to fail before a defibrillator could be implanted. After 358 patients had been randomized, the protocol was changed to allow implantation of a defibrillator after one or more unsuccessful drug trials. Patients who declined the implant were discharged receiving no antiarrhythmic drugs. Patients underwent outpatient clinic follow-up 1 month after discharge and every 3 months thereafter.

The primary end point of the trial was death due to arrhythmia or resuscitated cardiac arrest. Secondary end points included death from all causes, death from cardiac causes, and spontaneous sustained VT. Deaths and cardiac arrests were classified by an events committee that was blinded to inducibility and treatment status, as previously reported.

Statistical Analysis

To assess the effect of ICD therapy on major study end points and the relative contribution of ICD versus pharmacological antiarrhythmic therapy to the overall benefit observed with EP-guided antiarrhythmic therapy, several analyses were performed. First, we noted that use of ICDs in the EP-guided therapy arm of MUSTT increased considerably after January 1994 (roughly midway through the enrollment phase) because nonthoracotomy ICD systems became available and also because of the protocol change allowing implantation of a defibrillator after only one unsuccessful drug trial. To gain insight regarding the influence of defibrillators in comparisons of the 2 randomized arms, outcomes of the treatment groups as randomized were compared among patients enrolled during the early phase of the trial (before January 1, 1994) when use of ICDs was lower, and among patients enrolled during the latter part of the study (after January 1, 1994) when there was greater use of ICDs. This date was chosen on the basis of when nonthoracotomy defibrillator systems became available, independent of clinical outcomes.

Second, we noted considerable variability across participating clinical sites in the extent to which ICDs were used as part of the EP-guided treatment strategy. Sites were grouped, therefore, according to level of ICD use. For simplicity, 3 groups of sites were defined: low-use, which consisted of all centers where less than one-third of patients randomized to EP-guided therapy received an ICD; medium-use, which consisted of centers where between one-third and two-thirds of patients randomized to EP-guided therapy received an ICD; and high-use, which consisted of centers where more than two-thirds of EP-guided therapy patients received an ICD. Within each of these subgroups, the outcomes of the randomized treatments were compared. By comparing the randomized treatment arms within subgroups of sites that varied in the amount of ICD usage, the benefits of randomization were preserved and the effect of EP-guided antiarrhythmic therapy could be examined in the setting of low, moderate, and high levels of ICD use.

Finally, we assessed the effects of the ICD by directly comparing the outcomes of EP-guided therapy patients who received an ICD versus patients in the EP-guided therapy arm who did not receive an ICD and also versus the no antiarrhythmic therapy control arm. These comparisons were performed using the Cox proportional hazards model with receipt of an ICD analyzed as a time-dependent covariate; adjusting for multiple baseline prognostic factors including age, sex, race, ejection fraction, coronary anatomy, enrollment date, prior myocardial infarction, prior coronary artery bypass grafting, prior percutaneous revascularization, history of palpitations, history of angina, baseline induction of uniform versus polymorphic sustained VT, use of β-blockers, and use of ACE inhibitors. Assessing the effect of defibrillators using time-dependent covariate analysis means that the survival time of EP-guided therapy patients who received an ICD was credited to the EP therapy non-ICD group until the patient actually received the defibrillator.

Results

A total of 704 patients with inducible sustained ventricular tachyarrhythmia were randomized in the trial. Among the 351 patients randomized to EP-guided therapy, 161 (46%) received an ICD before discharge. A total of 196 patients received a defibrillator either before discharge or during follow-up after discharge but before experiencing any cardiac arrest. The median time from randomization to implant in these 196 patients was 11 days (25th and 75th percentiles of 6 and 33 days, respectively). A total of 167 patients (85%) received the implant within 90 days. Thus, patients randomized to EP-guided therapy who received a defibrillator generally had the device implanted early after randomization.

Treatment Comparisons According to Date of Enrollment

The groups formed by subdividing patients according to enrollment date (before versus after January 1, 1994) consisted respectively of 41% and 59% of the randomized patients (Table 1). Among patients randomized to EP-guided therapy before January 1, 1994, 41% received an ICD (31% within 90 days after enrollment), in contrast to 66% (59% within 90 days) of the patients enrolled after January 1, 1994 (Table 1). There was no observable benefit of EP-guided therapy in reducing the incidence of arrhythmic death or cardiac arrest (hazard ratio, 1.03; 95% CI: 0.68, 1.57) among the pre-1994 cohort (the group with lower use of ICDs; Figure 1A). In the cohort enrolled after January 1, 1994, in which use of ICDs increased markedly, there was a statisti-
cally significant reduction of arrhythmic death or cardiac arrest in the EP-guided therapy arm (hazard ratio, 0.46; 95% CI: 0.28, 0.76; Figure 1B). There was a significant interaction between treatment and enrollment period \((P=0.015)\), indicating that among patients enrolled before January 1, 1994, the effect of EP-guided therapy was statistically different than its effect among patients enrolled in the latter half of the trial. Kaplan-Meier curves for the end point of total mortality reflect comparable results (Figure 2).

**Treatment Comparisons According to Site ICD Use**

The percentage of patients at each site who received an ICD as part of the EP-guided therapeutic strategy varied from 0% to 100%. With clinical sites grouped according to ICD usage as defined previously, there was an approximately even number of centers in the low-, medium-, and high-use subgroups. Within the low-use group, 24% of patients randomized to EP-guided therapy received an ICD (12% within 90 days after enrollment). For the medium- and high-use groups, 52% and 84% of patients, respectively, received an ICD (Table 2).

Kaplan-Meier curves comparing the 2 randomized treatment arms with respect to the primary end point of arrhythmic death or cardiac arrest are presented in Figure 3 for the low-, medium-, and high-use subgroups. In the low-use group, no benefit of EP-guided therapy was observed (Figure 3A). In fact, there was a trend for higher long-term event rates among the EP-guided therapy patients compared with control arm patients (hazard ratio, 1.30; 95% CI: 0.68, 2.48). For the group of sites with medium-level use of ICDs, there was a favorable trend for EP-guided therapy compared with the control arm (hazard ratio, 0.75; 95% CI: 0.49, 1.15; Figure 3B). For the group of sites with a high level of ICD use, there was a clear and highly significant benefit of EP-guided therapy (hazard ratio, 0.36; 95% CI: 0.17, 0.75; Figure 3C). There was also a significant interaction between treatment (as randomized) and the subgroups defined by ICD use \((P=0.047\) based on 2 degrees of freedom), indicating that the effect of EP-guided therapy differed statistically according to level of ICD use. Kaplan-Meier curves for total mortality reflect comparable results, including a significantly lower mortality of EP-guided therapy relative to control among patients enrolled at sites with a high level of ICD use (Figure 4).

**Direct Observational Comparisons**

Baseline characteristics of the patients randomized to EP-guided therapy who received an ICD versus EP-guided therapy patients who did not receive an ICD and also versus the no-antiarrhythmic therapy control patients were similar with respect to ejection fraction, extent of coronary disease, and other known prognostic factors (Table 3). There was a
significantly higher proportion of whites in the group receiving an ICD. EP-guided therapy patients had lower use of β-blockers at discharge compared with the control arm. However, among EP-guided therapy patients who received an ICD, there was a higher percentage receiving β-blockers compared with the EP-guided non-ICD group.

Results of assessing the effects of ICDs using the Cox proportional hazards model, in which receiving an ICD was treated as a time-dependent covariate and after adjusting for all available prognostic factors, are presented in Table 4. The hazard ratios reflect that among EP-guided therapy patients who received an ICD, the risk of arrhythmic death or cardiac arrest was reduced by >70% compared with EP-guided therapy patients who did not receive an ICD or compared with control-arm patients. Furthermore, the risk of all-cause mortality was reduced by >50% among patients who received ICD therapy. These risk reductions were consistent among patients who did versus those who did not receive β-blockers. In contrast, the adjusted hazard ratio for patients randomized to EP-guided therapy who did not receive an ICD compared with the control arm patients was 1.12 (95% CI: 0.79, 1.59) for arrhythmic death or cardiac arrest and 1.08 (95% CI: 0.82, 1.42) for total mortality, reflecting a slight trend for worse outcomes.

Discussion

Results of the several analyses in this report strengthen the major conclusions of MUSTT, namely that the reduction in arrhythmic events and in total mortality associated with EP-guided therapy was due to the use of defibrillators, not to antiarrhythmic drugs. We emphasize that MUSTT was designed to evaluate the strategy of EP-guided antiarrhythmic therapy, including drugs and ICDs, in treating patients with coronary artery disease, reduced ejection fraction, nonsustained VT, and inducible sustained VT. With EP-guided therapy demonstrating a significant 27% reduction in the primary end point of arrhythmic death or cardiac arrest and a 20% reduction in total mortality, it is important to determine whether the benefit is due to EP-guided delivery of drug therapy, whether it is due to the use of defibrillators, or whether the benefits are attributable to both drugs and defibrillators as implemented in this trial. A more complete interpretation is needed to help clinicians appropriately apply these results to patients. It is also important to understand these results in the context of published reports of the effects of ICD therapy in other trials and other patient populations.7–10

To address the questions raised by the treatment benefit observed in MUSTT, we performed several complementary analyses. The first 2 analyses compared the treatments as randomized, and indirectly assessed the effects of ICDs by examining treatment differences within subgroups that varied according to the amount of ICD usage. The benefits of EP-guided therapy in reducing arrhythmic events and total mortality were observed only in patient subgroups where there was a moderate to high degree of ICD use. Where ICD use was high, the reduction in clinical events was substantial and highly significant. Where ICD use was low, there was no evidence of improved outcomes with EP-guided therapy. In both of these analyses, the benefits of randomization were preserved, and the results strongly support the conclusion that the benefits of the EP-guided strategy were attributable to the use of ICDs. A possible criticism of the second analysis presented is that subdivision of sites according to ICD usage was based on information that only became known after the randomization of patients was completed. This fact is of little or no consequence in this case, however. The analysis was based on a simple grouping of clinical sites, the randomization of patients in the study was stratified by clinical site, and the comparisons presented were based strictly on the outcomes in the 2 treatment arms as randomized.

The direct comparison of outcomes of patients who received an ICD versus patients in the EP-guided therapy arm who did not receive an ICD and patients randomized to the control arm also reflected significantly improved outcomes in patients who received an ICD. As previously emphasized,

### Table 2. Subgroups of Sites According to ICD Use

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Sites*</th>
<th>EP-Guided Therapy Patients Who Received an ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Within 90 Days</td>
</tr>
<tr>
<td>Low (0%–33%)</td>
<td>25</td>
<td>12%</td>
</tr>
<tr>
<td>Medium (33%–67%)</td>
<td>26</td>
<td>43%</td>
</tr>
<tr>
<td>High (67%–100%)</td>
<td>24</td>
<td>80%</td>
</tr>
</tbody>
</table>

*Ten of the 85 sites enrolled only registry patients or had no patients randomized to EP-guided therapy.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Kaplan-Meier curves for arrhythmic death or cardiac arrest comparing EP-guided therapy versus no antiarrhythmic therapy among patients randomized at sites with low ICD use (A), medium ICD use (B), and high ICD use (C).
these comparisons were observational because receiving an ICD was simply one component of the overall EP-guided strategy. The choice of whether patients received an ICD was not determined by randomization. However, assessing the effect of defibrillators using Cox model time-dependent covariate analysis and adjusting for all known baseline prognostic factors represents a state-of-the-art approach for deriving inferences in the context of these observational comparisons.

Although these analyses consistently reflect a substantial beneficial effect of ICD therapy in reducing arrhythmic events and total mortality in this patient population, they also lead to the equally compelling conclusion that EP-guided antiarrhythmic drug therapy does not decrease arrhythmic events or total mortality in these patients. This is also critical information for the clinical management of patients like those enrolled in MUSTT.

It is conceivable that there are alternative explanations for the benefit of defibrillators observed in this trial. For example, it is possible that patients who failed at least one round of drug therapy had an improved risk profile or somehow experienced a protective effect compared with patients who did not fail at least one round of drug therapy. Several lines of evidence suggest this is very unlikely. The baseline clinical characteristics of patients who received an ICD reflected a group that was at least as sick as the patients who did not receive a defibrillator. The Cox model assessment of the effects of ICD therapy included adjustment for all known major prognostic factors. Data from the Cardiac Arrhythmia Suppression Trial (CAST) showed that patients with ventricular arrhythmias that were harder to suppress with encainide, flecainide, and moricizine had a significantly higher risk of arrhythmic death than did patients whose ventricular arrhythmias were more easily suppressed by the antiarrhythmic drugs.11 Other studies have also reported better outcomes in patients with more easily suppressed ventricular tachyarrhythmias.12,13 Data from the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial and other patient series support the conclusion that continued inducibility of ventricular arrhythmias with programmed stimulation while receiving antiarrhythmic drug therapy is associated with an elevated risk of arrhythmic death or cardiac arrest.

Table 3. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>EP-Guided With ICD (n=196)</th>
<th>EP-Guided Without ICD (n=155)</th>
<th>No Antiarrhythmic Therapy (n=353)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66 (60,72)</td>
<td>68 (61,72)</td>
<td>66 (58,72)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>91</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>White race, %</td>
<td>94†</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>30 (20,35)</td>
<td>30 (20,35)</td>
<td>29 (22,35)</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>95</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>History of palpitation, %</td>
<td>29</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Angina symptoms within 6 weeks before enrollment, %</td>
<td>40</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Prior coronary-bypass grafting, %</td>
<td>59</td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td>Prior percutaneous coronary revascularization, %</td>
<td>21</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Multivessel coronary artery disease, %</td>
<td>72</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Uniform sustained VT induced, %</td>
<td>91‡</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>NYHA class, %*</td>
<td>I</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medications at hospital discharge, %</td>
<td>β-Blockers</td>
<td>33†¶</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Digitalis</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Diuretic agent</td>
<td>60</td>
<td>56</td>
</tr>
</tbody>
</table>

Values are median (25th, 75th percentiles) or percentage of patients. NYHA indicates New York Heart Association.

*Data for this variable were available in only 59% of patients.
†P<0.01, ‡P<0.05 for EP-guided therapy patients who received an ICD versus those who did not. §P<0.01, ¶P<0.001 for EP-guided therapy patients who received an ICD versus the no antiarrhythmic therapy control arm.

Table 4. Relative Risks of Defibrillator Therapy (95% CL) Adjusted for Baseline Prognostic Factors

<table>
<thead>
<tr>
<th></th>
<th>Compared With Other EP-Guided Therapy Patients</th>
<th>Compared With Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmic death or cardiac arrest</td>
<td>0.27 (0.14,0.50)</td>
<td>0.26 (0.15,0.46)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.42 (0.28,0.62)</td>
<td>0.43 (0.31,0.60)</td>
</tr>
</tbody>
</table>

Figure 4. Kaplan-Meier curves for total mortality comparing EP-guided therapy versus no antiarrhythmic therapy among patients randomized at sites with low ICD use (A), medium ICD use (B), and high ICD use (C).
therapy is a predictor of increased risk for recurrent arrhythmias and/or sudden death.\textsuperscript{14–16} Thus, a stronger argument could be made that patients in MUSTT who remained inducible after at least one round of drug therapy were actually at increased risk for an arrhythmic event or mortality than patients whose inducibility was suppressed by drug therapy.

We conclude that the results of the various analyses in this article are consistent with the message that the benefit of the EP-guided treatment strategy in MUSTT was due to a reduced incidence of arrhythmic events and total mortality among the patients who received an ICD and not because of any beneficial effects of EP-guided antiarrhythmic drug therapy.

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References


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