Racial Differences in Outcome in the Multicenter UnSustained Tachycardia Trial (MUSTT) A Comparison of Whites Versus Blacks

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Background—The Multicenter UnSustained Tachycardia Trial (MUSTT) demonstrated the benefit of implantable cardioverter-defibrillators (ICDs) in patients with coronary disease, asymptomatic nonsustained ventricular tachycardia, and reduced left ventricular function. Previous studies have shown racial differences in risk of sudden death in patients with ischemic heart disease.

Methods and Results—We analyzed the influence of race on results of MUSTT. Whites were more likely to have prior revascularization and inducible, randomizable sustained ventricular arrhythmias and less likely to have left ventricular hypertrophy than were blacks. Compared with blacks, whites randomly assigned to electrophysiologically (EP)-guided therapy had a lower risk of arrhythmic death/cardiac arrest (adjusted \( P=0.003 \)) and lower total mortality rates (adjusted \( P=0.051 \)). In contrast, there was no racial difference in the risk of arrhythmic death/cardiac arrest among patients randomly assigned to no EP-guided therapy (adjusted \( P=0.477 \)). Among whites, EP-guided therapy resulted in a survival benefit compared with no EP-guided therapy. However, survival of blacks randomly assigned to no EP-guided therapy was better than blacks receiving EP-guided therapy. This difference is partially explained by a higher ICD implantation rate in whites versus blacks (50% versus 28%, \( P=0.034 \)). Whites were more likely to remain inducible after serial EP-guided drug testing (67% versus 42%, \( P=0.011 \)), making them more likely to become eligible for ICDs.

Conclusions—The outcome in this trial and the benefit of EP-guided therapy appeared to be influenced by race. In addition to differences in ICD implantation rates, differences in arrhythmic substrates and proarrhythmic responses to antiarrhythmic drugs may have influenced outcome. (Circulation. 2003;108:67-72.)

Key Words: arrhythmia ■ coronary disease ■ death, sudden ■ tachycardia
Methods

The MUSTT protocol has been described previously. This was a National Institutes of Health–sponsored, multicenter, randomized trial that evaluated the role of EP-guided therapy in patients with inducible sustained ventricular arrhythmias. Patients were eligible for enrollment if they had coronary artery disease, left ventricular ejection fraction ≤40%, asymptomatic NSVT, and no history of spontaneous sustained VT, syncope, or cardiac arrest, except in the setting of acute myocardial infarction. Patients who had inducible sustained VT were randomly assigned to a standard medical regimen, which included treatment with β-blockers and ACE inhibitors, versus the same regimen with the addition of EP-guided therapy. EP-guided therapy included antiarrhythmic drug treatment guided by the results of EP testing and ICD therapy for patients who did not respond to antiarrhythmic drugs. Inducible tachycardias eligible for randomization included sustained monomorphic VT induced by 1, 2, or 3 ventricular extrastimuli, as well as sustained polymorphic VT or ventricular fibrillation (VF) induced by 1 or 2 extrastimuli. Patients without inducible sustained VT were followed in a registry without antiarrhythmic therapy.

Patients

A total of 2202 patients were enrolled in the trial at 85 sites, including 704 patients with inducible, sustained VT who were randomly assigned to EP-guided therapy versus medical therapy without specific antiarrhythmic treatment (“no EP-guided therapy”). The remaining 1498 patients were followed in a registry without EP-guided therapy. Although multiple nonwhite racial groups were represented in the trial, in addition to whites, only blacks were represented in sufficient numbers to permit meaningful analysis (Table 1). Therefore, we restricted this analysis to racial differences within the randomized arm of the trial was similar for the EP-guided therapy and no EP-guided therapy groups.

Statistical Analysis

Values for continuous variables are presented as medians with 25th and 75th percentiles. Values for categorical variables are presented as percentages. Differences in clinical characteristics and discharge medications between racial groups were assessed by means of 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 log-rank test. In addition, covariate-adjusted analyses of outcomes were performed with the Cox proportional hazards model. Covariates included in these analyses were the induction of randomizable VT, age, ejection fraction, gender, prior bypass surgery, prior angioplasty, prior myocardial infarction, number of vessels with >75% stenosis, duration (in beats) of the longest episode of NSVT, symptoms of angina within 6 weeks of enrollment, left bundle-branch block, intraventricular conduction delays, and use of digitalis at baseline. Hazard ratios and 95% confidence intervals were also calculated by means of the Cox proportional hazards model.

Results

A total of 1884 whites were enrolled, representing 86% of the total study population (Table 1). The nonwhite population (n=314) included 231 (74%) blacks. Eighty-eight percent of patients enrolled in the randomized arm were white. The race distribution within the randomized arm of the trial was similar for the EP-guided therapy and no EP-guided therapy groups.

Baseline Characteristics

Within the randomly assigned patients, there was no significant difference in age, ejection fraction, gender, presence of 3-vessel coronary artery disease, time from myocardial infarction to enrollment, or angina within 6 weeks in whites versus blacks (Table 2). Whites were more likely to have undergone prior CABG (P=0.001) or other forms of revascularization (P=0.001) than blacks before enrollment in the trial. Blacks were more likely to have left ventricular hypertrophy (LVH) by ECG than whites (P=0.019).

Electrophysiological Testing

There was a trend toward increased inducibility of ventricular tachycardia in whites versus blacks (37% versus 31%, P=0.054). With respect to the type of randomized VT induced, 15% of blacks versus only 9% of whites had inducible sustained polymorphic VT induced with single or double extrastimuli at baseline (P=0.068). Sustained monomorphic VT was induced with single, double, or triple extrastimuli in all remaining patients in the randomly assigned group.

Nonantiarrhythmic Medical Therapy

Among randomly assigned patients, there were no differences between whites and blacks with respect to nonantiarrhythmic cardiac therapy in the EP-guided therapy or no EP-guided therapy groups at the time of hospital discharge (Table 3).
There were no significant differences in β-blocker or ACE inhibitor usage between whites and blacks.

**Outcome: Survival Free From Arrhythmic Death or Cardiac Arrest**

The arrhythmic event-free survival of whites and blacks randomly assigned to no EP-guided therapy was similar (adjusted \(P=0.477\), Figure 1). Among patients randomly assigned to EP-guided therapy, the 5-year arrhythmic event-free survival of whites was significantly better than that of blacks (78% versus 46%, adjusted \(P=0.003\), Figure 2). Within the EP-guided therapy group, blacks were more than 3 times as likely as whites to have an arrhythmic event (adjusted hazard ratio, 3.08; 95% CI, 1.47, 6.44) (Table 4).

There was a 38% reduction in arrhythmic death or cardiac arrest in whites who received EP-guided therapy compared with whites who were randomly assigned to no EP-guided therapy (adjusted hazard ratio, 0.62; 95% CI, 0.44, 0.86). In contrast, blacks randomly assigned to EP-guided therapy had a nearly 3-fold increase in arrhythmic death or cardiac arrest compared with blacks assigned to no EP-guided therapy (adjusted hazard ratio, 2.82; 95% CI, 0.87, 9.14). The difference in the effect of treatment between blacks and whites was significant (adjusted \(P=0.004\)) and the reason for the difference in treatment effect is multifactorial.

In the EP-guided therapy group, 7 of 25 (28%) blacks received an ICD within 90 days of random assignment as part of the initial treatment strategy, compared with 158 of 316 (50%) of whites (\(P=0.034\)). Of the 7 blacks who received ICDs within 90 days of enrollment, 1 (14%) had an arrhythmic death after ICD implantation. Of the 158 whites who received an ICD within 90 days of enrollment, 34 died and 11 (7%) had an arrhythmic death or cardiac arrest after ICD implantation.

Blacks in the EP-guided therapy group who did not receive an ICD had poorer survival than whites without an ICD. The 5-year survival free of arrhythmic death or cardiac arrest for blacks who did not receive an ICD in the EP-guided therapy group was only 27%, compared with 66% for whites who did not receive an ICD (\(P=0.012\)).

**Outcome: Overall Survival**

There was no significant difference in overall survival of whites versus blacks who were randomly assigned to no EP-guided therapy (52% versus 55%, adjusted \(P=0.384\), Table 4). In contrast, whites who were randomly assigned to EP-guided therapy had improved overall 5-year survival.

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**TABLE 3. Discharge Medications**

<table>
<thead>
<tr>
<th></th>
<th>No EP-Guided Therapy</th>
<th>EP-Guided Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White, % (n=301)</td>
<td>Black, % (n=36)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>ACE inhibitors</td>
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<td>Diuretics</td>
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<td>67</td>
</tr>
<tr>
<td>Nitrates</td>
<td>42</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>White, % (n=316)</td>
<td>Black, % (n=25)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^*\)P value for test of white vs black.

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**Figure 1.** Kaplan-Meier estimates of survival free from arrhythmic death or cardiac arrest for patients randomly assigned to "no EP-guided therapy." There was no difference in survival free from arrhythmic death or cardiac arrest in whites compared with blacks in the "no EP-guided therapy" group (\(P=0.477\), adjusted).

**Figure 2.** Kaplan-Meier estimates of survival free from arrhythmic death or cardiac arrest for patients randomly assigned to EP-guided therapy. There was an improved survival free from arrhythmic death or cardiac arrest in whites compared with blacks in the EP-guided therapy group (\(P=0.003\), adjusted).
compared with blacks randomly assigned to EP-guided therapy (60% versus 37%, adjusted \( P=0.051 \)) (Figure 3 and Table 4).

The total mortality rate of whites randomly assigned to EP-guided therapy was 26% lower than those randomly assigned to no EP-guided therapy (adjusted hazard ratio, 0.75; 95% CI, 0.34, 1.67) (Figure 3 and Table 4). This benefit of EP-guided therapy was not seen in blacks. Within the black group, those randomly assigned to EP-guided therapy had a nonsignificant 17% higher mortality rate than blacks randomly assigned to no EP-guided therapy (adjusted hazard ratio, 1.17; 95% CI, 0.47, 2.91). The difference in the effect of EP-guided therapy between whites and blacks was significant (adjusted \( P<0.016 \)). Blacks also had a higher death rate than whites before hospital discharge (8% versus 1%, \( P=0.014 \)).

The survival rate for patients discharged on antiarrhythmic drugs was 65 of 126 (52%) in whites versus 4 of 14 (29%) in blacks in the EP-guided therapy group (\( P=0.10 \)). This contrasts with the survival rates among ICD recipients, which were 124 of 158 (78%) in whites versus 6 of 7 (86%) in blacks (\( P=0.65 \)). Although numbers in this subanalysis are very small, and any conclusions are only speculative, data are presented for completeness.

**Type of EP-Guided Treatment: Antiarrhythmic Drug Therapy**

Among patients randomly assigned to EP-guided therapy, 56% of blacks were discharged with pharmacological antiarrhythmic therapy, in contrast to 43% of whites (\( P=0.220 \)). Blacks had a higher rate of drug response at EP testing. There was no significant difference between whites and blacks with regard to the type of antiarrhythmic agents used. Amiodarone, sotalol, propafenone, group IA drugs, or the combination of a group IA drug plus mexiletine was used in 9%, 9%, 4%, 18%, and 3% of whites versus 16%, 8%, 0%, 28%, and 4% of blacks, respectively.

**Type of EP-Guided Treatment: ICD Implantation**

At the time of hospital discharge, there was no significant difference between whites and blacks with respect to percentage of patients who had ICDs recommended in the EP-guided therapy group (54% versus 40%, \( P=0.173 \)). Within the first 90 days of randomization, ICDs were implanted in 50% of whites and 28% of blacks before reaching an end point (\( P=0.034 \)). Possible reasons why ICDs were implanted more often in whites were examined. Whites underwent a mean of 1.8 antiarrhythmic drug trials compared with blacks, who underwent a mean of 2.0 trials (\( P=0.44 \)). After the last antiarrhythmic drug trial, VT remained inducible in 67% of whites compared with 42% of blacks (\( P=0.011 \)). For patients in whom ICDs were recommended, 12 of 171 (7%) of whites and 2 of 10 (20%) of blacks refused (\( P=0.001 \)).

**Discussion**

This analysis demonstrates that a treatment strategy with the use of EP-guided therapy had a beneficial effect on survival in whites but not in blacks. In fact, blacks who received no EP-guided therapy had better survival than those who received EP-guided therapy. However, it should be noted that blacks were less likely to receive ICDs than whites, and the main trial results of MUSTT demonstrated that the benefit of treatment in the EP-guided therapy group was related to ICDs.\(^{10}\) Previous trials, such as the Cardiac Arrhythmia Suppression Trial (CAST), have shown that patients who receive treatment with antiarrhythmic drugs after myocardial infarction have a higher mortality rate than those who receive
no antiarrhythmic drug therapy. Other randomized, multicenter trials have demonstrated the benefit of ICDs over antiarrhythmic therapy for secondary and primary prevention.

As noted above, one reason for the better survival of whites randomly assigned to EP-guided therapy was the higher ICD implantation rate in whites. Blacks received ICDs less often than whites in part because they were more likely to respond to antiarrhythmic drugs at EP testing. Blacks were also more likely than whites to refuse ICD implantation when it was recommended.

The difference in treatment effect of EP-guided therapy may not be completely explained by the lower ICD implantation rate in blacks. In the EP-guided therapy group, there was a 2-fold greater 5-year survival free of arrhythmic death/cardiac arrest for whites who did not receive an ICD compared with their black counterparts who did not receive an ICD (66% versus 27%, P=0.012). In addition, there was nearly a 3-fold greater arrhythmic death/cardiac arrest event rate among blacks treated with EP-guided therapy versus no EP-guided therapy. It is also noteworthy that the arrhythmic death/cardiac arrest rate among blacks randomly assigned to no EP-guided therapy was not different from the event rate among whites randomly assigned to no EP-guided therapy (Table 4). Thus, both blacks and whites had similar arrhythmic death or cardiac arrest event rates when not exposed to EP-guided therapy, whereas the two racial groups diverged in the way they responded to EP-guided therapy. This suggests the possibility of increased susceptibility to proarrhythmic effects of antiarrhythmic agents (primarily classes IA and III) in blacks.

If confirmed in subsequent studies, such differential proarrhythmic susceptibility might reflect ethnic variations in frequencies of genetic polymorphisms capable of influencing electrophysiological responses to certain (eg, repolarization-prolonging) antiarrhythmic drugs. On the other hand, blacks in the randomly assigned group were more likely to have LVH by ECG and less likely to have undergone prior revascularization than whites. There was a trend toward a greater prevalence of inducible polymorphic VT in blacks, which may influence the predictive value of EP-guided antiarrhythmic drug therapy. Previous studies have shown that LVH may have an adverse effect on outcome. Blacks enrolled in the Beta Blocker Heart Attack Trial (BHAT) had a higher prevalence of hypertension and ECGs with LVH as well as a higher mortality than whites. LVH may predispose to potentially lethal arrhythmias, including proarrhythmic responses. Conceivably, therefore, a different anatomic substrate may have affected outcome in the current study and could also be responsible for more proarrhythmic effects of antiarrhythmic drugs in blacks.

It is possible that blacks may have received care inferior to that given to whites. The fact that β-blocker and ACE inhibitor usage were similar in blacks and whites argues against this. Although β-blocker usage was relatively low in both racial groups, the fact that blacks had lower rates of prior surgical or percutaneous revascularization does raise the possibility of a potentially greater ischemic burden. In the current study, the higher in-hospital mortality rate in blacks suggests that some may have been “sicker” than whites at the time of enrollment.

This report is unique in that it appears to be the first to show racial differences in outcome in a multicenter trial that evaluates primary prevention in patients with asymptomatic arrhythmias and ischemic heart disease. Patients were enrolled in this trial across the United States and Canada, including patients from private practitioners as well as those associated with University and Veterans’ Administration Hospitals. This study provides a representative sample of patients with NSVT, abnormal left ventricular function, and ischemic heart disease.

Limitations
This is a post hoc analysis of MUSTT, a trial not prospectively designed to assess the impact of race on outcome. The number of patients who underwent defibrillator implantation is small, particularly in the black group. The percentage of nonwhites in this trial is relatively small, with blacks making up 74% of the nonwhite population. The results of the current study cannot necessarily be generalized to other nonwhite groups.

Conclusions
This study suggests important racial differences in outcome associated with different therapies in MUSTT. The apparent “response” to antiarrhythmic drugs at EP testing, combined with a lower acceptance rate of ICD therapy by blacks, contributed to a lower ICD implantation rate and resulted in poorer outcome in blacks. Further studies are needed to confirm possible ethnic differences in proarrhythmic susceptibility and the potential contributory effects of genetic polymorphisms and confounding factors, such as LVH. Until these issues are clarified, the present observations suggest that extra caution may be warranted when contemplating pharmacological antiarrhythmic therapy in high-risk patients, especially in blacks having characteristics of the MUSTT population. Our data emphasize the importance of considering racial composition when planning multicenter trials. Effective strategies should be designed to reduce mortality rates in all segments of the population. Finally, extra effort must be made to gain acceptance of ICD therapy in blacks at increased risk for arrhythmic death or cardiac arrest.

References


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