EDITORIAL COMMENT

Mindfully Mining MUSTT*

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In this issue of the *Journal* the MUSTT (Multicenter Unsustained Tachycardia Trial) investigators (1), extend their post hoc analyses of the original trial. By comparing outcomes of those patients in the EP group (patients discharged on drugs predicted effective by electrophysiologic testing) who received implanted cardioverter defibrillators (ICDs) to those randomized to no antiarrhythmic therapy, the investigators conclude that electrophysiologic-pharmacologic study (EPS) provides no benefit in patients with spontaneous-unsustained, and inducible-sustained ventricular tachycardia associated with coronary artery disease (CAD) and impaired left ventricular (LV) function.

The primary analysis in the original report of MUSTT (2) showed that the EP patients did obtain a survival benefit. In that report the investigators performed a post hoc analysis by separately examining outcomes in patients in the EP group that did and did not receive ICDs. The analysis showed that the survival advantage in the EP group was apparently exclusively due to ICDs, as those who did not

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receive them, and thus were treated only with antiarrhythmic drugs, had a poorer outcome than did those who received ICDs. They concluded that electrophysiologically selected antiarrhythmic therapy per se did not account for improved outcome in the EP group, but, rather, that ICDs did.

In the current study (1), the MUSTT investigators further explore the influence on outcome of drugs selected by EPS. They employ actuarial analyses similar to those used in the original study (2) to compare treatment groups, with one major difference: in the current study they censor patients when they receive an ICD. The intent is to remove the influence of ICDs so that the survival effect of drugs selected by EPS could be isolated. The analysis shows no difference in survival in patients without ICDs who were treated with drugs selected by EPS compared to those who received no antiarrhythmic therapy. A subanalysis of specific drugs does not appear to demonstrate a statistically significant difference in outcome among the drugs, although there was a large spread in actuarial survival at two years (as estimated from the actuarial plots): sotalol, 76% (n = 30);

class IA + others, 71% (n = 88); propafenone, 50% (n = 13); amiodarone, 45% (n = 21). Interestingly, sotalol was also found to be superior to class IA and IC drugs in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) study (3).

A post hoc analysis is one that was not planned prior to initiation of a trial. Clinical trials are designed to answer one or a few questions. The number of subjects recruited to the trial, their clinical characteristics and the conduct of the trial from start to finish are constructed to address one or a few primary hypotheses specifically. Analyses that were not incorporated into the original trial design may lead to important findings and should be undertaken. However, these post hoc analyses should be interpreted cautiously and should not, except in unusual cases, be relied upon to establish new guidelines for clinical care. You might argue that statistics take care of this problem, that any statistically significant finding is valid and reliable. Isn't that what statistics are for? No.

Statistical methods are mathematically complex and sophisticated, but they are incapable of shielding against biases that may influence results. Trial design must do that. In clinical trials, investigator bias is assiduously avoided by randomization and blinding procedures. There are three types of bias to consider. The first bias is in trial design, favoring one outcome over another. The second is bias of investigators, resulting in differential management of treatment groups. The third bias is in reporting. All three types of bias are evident in the conduct and analyses of MUSST. This does not constitute a criticism. Bias affects many clinical trials, usually without investigator intent; however, it is important to recognize its presence to understand fully a trial's results.

Trial design bias is well illustrated by the midcourse change in the MUSTT protocol. After enrollment of approximately one-half of the final patient sample, the protocol was changed to allow ICDs in the EP group after a single drug failure. Prior to that change, patients had been required to fail to respond to three drugs at EPS before receiving an ICD. Trials often must adapt to changes in medical knowledge and practice. The change made in the MUSTT protocol was necessary because of a growing preference that developed among physicians while the trial was in progress to use ICDs rather than antiarrhythmic drugs. This preference initially evolved as a result of spectacular technical improvements in ICDs, which allowed minimally invasive implantation and marked reduction in inappropriate shock delivery.

At about the same time, three trials were published that reduced confidence in use of EPS for selection of drug therapy in patients with ventricular tachyarrhythmias (4–6). Also, the shortcomings of antiarrhythmic therapy were highlighted in several trials that demonstrated their inability to prevent sudden death (7–10). The investigators were

forced to revise the protocol so as to make it more consistent with current clinical practice and to encourage enrollment into the trial. As a result of the midcourse change, MUSTT, in essence, became a device efficacy trial rather than a study of the efficacy of electrophysiologically selected drugs in primary prevention of sudden death. The trial had not been designed for that purpose, and, in fact, its original hypothesis could no longer be tested because the protocol change resulted in the implanting of ICDs in the majority of patients in the EP group (161 of 319 discharged patients). The EP group was no longer an antiarrhythmic drug-treated group as originally intended (11). Instead, the main finding of the study had to be provided by a post hoc analysis. This, then, is a clear example in which design bias changed the outcome of a clinical trial. We cannot easily use statistics to remove that bias, although the investigators attempt to do so in the current analysis (1), which addresses the original hypothesis.

The second type of bias, differential management of patients in separate treatment limbs, is also evident in MUSTT. Why did 41 patients in the EP group, but only, at most, 11 in the control group, receive ICDs during follow-up after hospital discharge? At least 339 control patients, compared with only 158 in the EP group, began follow-up without an implanted device. Because more than twice as many control patients could have received an ICD if an arrhythmia event mandated therapy, there was, in effect, an eightfold greater rate of ICD implantation during follow-up in the EP group. I assume that indications for adding a new antiarrhythmic therapy during follow-up were absolute, applying equally to patients in both limbs. Clinical characteristics of the patients in the EP group and the control group were the same, as provided by the randomization process. Arrhythmia recurrence rates in follow-up would be expected to be similar in the two groups, unless the therapies had differing efficacy. Because the original report (2) showed only a modestly higher incidence of arrhythmia recurrence in the drug-treated patients without ICDs, that certainly cannot account for an eightfold greater rate of device implantation. Could antiarrhythmic drug intolerance account for the eightfold difference? Only if both of two unlikely conditions pertained: intolerance occurred at a rate inexplicably greater than usual for the drugs used in MUSTT, and all alternate antiarrhythmic drugs were also not tolerated. The original null hypothesis of the trial was that electrophysiologically guided therapy and no therapy were equivalent. Well before the conclusion of the trial it appears that some investigators had not only made up their minds that therapy was better than no therapy, but they had also decided which specific therapy (ICDs) was better. That bias strongly influenced the subsequent conduct of the trial.

A feature of trial design may have introduced another instance of differential treatment bias. Because of the change in protocol permitting increased ICD use, the nature of follow-up care became, necessarily, more intense in the EP group, because most of those patients required periodic defibrillator checks. They had to be seen by cardiac arrhythmia specialists, and those specialists were provided, through device interrogation, with arrhythmia data unavailable to physicians managing patients without ICDs. Could this higher intensity of care and clinical information have improved outcome in the EP group independently of the therapeutic effect of ICDs?

Potential reporting bias is implicit in the post hoc analysis presented in the current study (1). The preplanned analysis was an intention-to-treat comparison of the entire EP and control groups. This implies a primary interest in evaluating efficacy of a clinical practice pathway in which the initial therapy to which a patient is assigned is viewed as the first step in a treatment strategy that may include additional or alternative therapies as needed during follow-up. Here the question is: "How does this initial therapy influence long-term results, regardless of whether or not the therapy is continued?" This is the usual and most appropriate question asked in clinical trials. An analysis only of patients who continue taking the original therapy is less reliable, especially when a large proportion of subjects drop out.

You may say, "So what? The trial has shown us the truth—ICDs are effective and better than drugs in preventing death in patients with asymptomatic, unsustained ventricular tachycardia associated with coronary disease and impaired LV function." Are you sure? Surprisingly, the new analysis in this issue (1) provides a suggestion that this may not be uniformly true. At two years the actuarial survival of patients randomized to sotalol, with follow-up censored in those who received ICDs, was 76%. Using data from the original and current studies it is possible to roughly estimate an additional survival benefit provided by ICDs in patients receiving antiarrhythmic drugs selected by EPS in MUSTT. Figure 1A in the current study (1) shows actuarial survival of 68% at two years in patients receiving EPS-selected antiarrhythmic drugs with censoring on receipt of an ICD. In Figure 2 of the original report (2) the corresponding estimate is 78% without censoring of follow-up after ICD placement. Comparison of these two rates suggests that the ICD adds 10% to the two-year actuarial survival of patients assigned to antiarrhythmic therapy by EPS. (Parenthetically, survival at two years in the no-therapy group was 72%, both with and without censoring at the time of device implantation. Few patients in that group had received ICDs.) If we now add this 10% increment to the two-year survival of patients receiving sotalol alone, we estimate a survival of 86% at two years for patients assigned to sotalol and with access to ICD therapy if needed. This survival rate is little different from the 89% survival of the original EP-ICD group (2).

My analysis is an overly aggressive mining of data. As merely another post hoc analysis, it, like all such analyses, should only be used to generate ideas for future evaluation and should not be used to establish treatment guidelines. The analysis suggests that a treatment strategy that calls for

initial use of sotalol, if predicted effective by EPS, with addition of an ICD if indicated during follow-up, might be as effective as that recommended by the investigators, who state in their conclusions that antiarrhythmic drug therapy is a secondary alternative for most patients, and ICD therapy should be considered early.

The study of Wyse et al. (1) in this issue of the *Journal* is an interesting exploratory analysis. I do not believe it should prompt a change in clinical practice. Rather, it suggests a need for a future trial to examine alternatives to immediate device implantation. Prevailing interpretations of MUSTT and the Multicenter Automatic Defibrillator Implantation Trial (MADIT) (12) hold that patients with postinfarction LV dysfunction and unsustained ventricular tachycardia should receive ICDs if they have sustained ventricular arrhythmia inducible by programmed ventricular stimulation. Based upon data from MUSTT, as well as the recently reported Amiodarone vs. Implantable Defibrillator in Patients with non-Ischemic Cardiomyopathy and Asymptomatic nonsustained Ventricular Tachycadia (AMIOVIRT) trial, which failed to show superiority of ICDs over amiodarone in patients with unsustained ventricular tachycardia related to dilated cardiomyopathy (13,14), a study that directly compared initial therapy with an ICD to initial therapy with sotalol or amiodarone in patients fitting MUSTT enrollment criteria would be helpful. The intensity of follow-up care and data collection in these two groups should be made as equal as possible. Many practicing physicians, and patients, hesitate to embark upon relatively aggressive, expensive, lifelong therapy based upon projected risk rather than symptoms. Furthermore, ICDs are not readily available in many countries. If a simpler initial preventive therapy were demonstrated to be effective, more patients would have access to it throughout the world and a larger number would benefit.

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REFERENCES

1. Wyse DG, Talajic M, Hafley GE, et al. Antiarrhythmic drug therapy in the Multicenter UnSustained Tachycardia Trial (MUSTT): drug testing and as-treated analysis. J Am Coll Cardiol 2001;38:344–51.
2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial investigators. N Engl J Med 1999;341:1882–90.
3. Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring investigators. N Engl J Med 1993;329:452–8.
4. Mason JW. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic-drug efficacy for ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring investigators. N Engl J Med 1993;329:445–51.
5. Steinbeck G, Andresen D, Bach P, et al. A comparison of electrophysiologically guided antiarrhythmic drug therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. N Engl J Med 1992;327:987–92.
6. Greene HL. The CASCADE Study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. CASCADE investigators. Am J Cardiol 1993;72:70F–4F.
7. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial investigators. Lancet 1997;349:675–82.
8. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781–8.
9. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial investigators. Lancet 1997;349:667–74.
10. Waldo AL, Camm AJ, deRuyter H, et al. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD investigators. Survival With Oral *d*-Sotalol. Lancet 1996;348:7–12.
11. Buxton AE, Fisher JD, Josephson ME, et al. Prevention of sudden death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT). Prog Cardiovasc Dis 1993;36:215–26.
12. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial investigators. N Engl J Med 1996;335:1933–40.
13. SoRelle R. Cardiovascular news. AMIOVIRT. Circulation 2000;102:E9050–1.
14. Strickberger SA. AMIOVIRT (Amiodarone vs. Implantable Defibrillator in Patients with non-Ischemic Cardiomyopathy and Asymptomatic non-Sustained Ventricular Tachycardia). Clin Cardiol 2001;24:87.