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THE MUSTT TRIAL

Preventing sudden death in coronary cardiomyopathy: Implantable defibrillators lead the way

ABSTRACT

The Multicenter Unsustained Tachycardia Trial (MUSTT) demonstrated that electrophysiologic testing (EP)-guided therapy significantly reduces arrhythmic death and cardiac arrest in patients with coronary artery disease, a left ventricular ejection fraction of 40% or less, nonsustained ventricular tachycardia, and inducible ventricular arrhythmia on EP testing—but only if the therapy includes an implantable defibrillator. All patients who meet the MUSTT inclusion criteria should undergo an EP test and if positive, should undergo defibrillator implantation.

IN PATIENTS AT HIGH RISK of sudden death, implantable defibrillators can significantly reduce the risk of cardiac arrest or death from arrhythmia. Antiarrhythmic drugs, however, appear to confer no survival benefit.

These were the major findings of the recently completed Multicenter Unsustained Tachycardia Trial (MUSTT).¹ The MUSTT was not designed to compare the benefit of antiarrhythmic drugs vs the benefit of implantable defibrillators. Rather, the aim was to determine if antiarrhythmic treatment per se, guided by electrophysiologic testing, is better than no treatment.

Still, the trial found a significant reduc-

tion in mortality *only* if implantable defibrillators were used.

This paper summarizes the rationale, design, findings, and implications of this trial.

PRIOR STUDIES EXAMINE THOSE AT GREATEST RISK OF SUDDEN DEATH

Sudden death due to arrhythmias accounts for a sizeable number of deaths in survivors of a myocardial infarction (MI). However, although antiarrhythmic drugs have been available for decades, attempts to find a strategy for using them effectively to prevent sudden death have frustrated investigators for years.

With any preventive strategy it is best to determine who is at highest risk, as high-risk patients should derive the most benefit. Two risk factors for sudden death in MI survivors are left ventricular systolic dysfunction (responsible for most cases of heart failure) and unsustained ventricular arrhythmias (ventricular tachycardia or premature ventricular contractions).² Of people who have an MI and develop heart failure, at least 20% die within 5 years,³ and about a third of the deaths are sudden and presumably due to arrhythmias.⁴ Accordingly, investigators have used these factors as entry criteria in several trials of antiarrhythmic drug therapy, with varying success.

The Cardiac Arrhythmia Suppression Trial (CAST)⁵ recruited 2,309 MI survivors who had asymptomatic or mildly symptomatic ventricular arrhythmias and left ventricular dysfunction. Patients underwent an open-

In several large trials, defibrillators reduced mortality, but antiarrhythmic drugs did not

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label phase taking the antiarrhythmic drugs encainide, flecainide, and moricizine, titrated to suppress the arrhythmia. If the regimen succeeded in suppressing the arrhythmia, the patient was randomized to continue taking it or to take a placebo.

Results, published in 1989, were sobering: the trial had to be stopped early because of an excess of deaths in the patients taking encainide and flecainide.

The **European Myocardial Infarct Amiodarone Trial (EMIAT)**⁶ enrolled 1,486 MI survivors with a left ventricular ejection fraction of 40% or less, with or without arrhythmias, who were randomized to receive amiodarone or placebo. Results, published in 1997, were better than with the CAST study: at 21 months there was a 35% reduction in arrhythmic deaths in the amiodarone group. However, the total mortality rate did not differ at all between the two groups.

The **Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)**⁷ recruited 1,202 MI survivors with frequent or repetitive ventricular premature depolarizations with or without left ventricular dysfunction and randomized them to receive amiodarone or placebo. Findings were published in 1997. At 1.79 years, the rate of resuscitated ventricular fibrillation or arrhythmic death was 49% lower in the amiodarone group. Total mortality was 21% lower, but the trend did not reach statistical significance.

■ CAN ELECTROPHYSIOLOGIC TESTING IDENTIFY THOSE AT GREATEST RISK?

With the early trials unsuccessful, researchers wondered if selection of patients and drugs could be refined, so that only patients at highest risk would receive treatment, and the most effective drugs for the individual patient would be used. Electrophysiologic (EP) testing seemed to hold the answer.

In this invasive test, a programmed sequence of electrical stimuli is applied to the inside of the ventricle to determine if an arrhythmia can be induced. EP testing yields a positive result in 20% to 45% of MI survivors with nonsustained ventricular tachycardia, depending on the aggressiveness of the stimulation protocol and the degree of left ventric-

ular dysfunction.

The positive predictive value of EP testing, ie, the percent of patients with a positive EP test who subsequently suffered an arrhythmic event, ranged widely in published studies from 11% to 88% over 14 to 30 months of follow-up. In contrast, the negative predictive value—the percent of patients with negative EP tests who suffered no event—is impressive at 88% to 96%.⁸

Antiarrhythmic drug therapy guided by EP testing

In the past decade, many patients with non-sustained ventricular tachycardia and positive EP tests were treated with an antiarrhythmic drug. Furthermore, cardiologists often used serial EP tests to guide therapy. With this approach, the patient began taking an antiarrhythmic drug and then underwent another EP test. If an arrhythmia could not be induced on this EP test, the current therapy was continued; if an arrhythmia could be induced, the therapy was changed and the process repeated until a regimen that could suppress the inducible arrhythmia was found. Due to lack of reproducibility and variable results, this approach has been essentially abandoned.

Implantable defibrillators

Implantable defibrillators are effective in terminating malignant ventricular arrhythmias, and clinical trials have established that they are superior to antiarrhythmic drugs in decreasing mortality in survivors of out-of-hospital cardiac arrests.^{9,10} However, since fewer than 25% of people survive who have a cardiac arrest,¹¹ it is paramount to prevent cardiac arrests in the first place. The MUSTT investigators included defibrillators in the mix of therapies, but did not intend the trial to be a comparison of defibrillators vs antiarrhythmic drugs.

■ WHICH THERAPY IS SUPERIOR?

The MUSTT (Multicenter Unsustained Tachycardia Trial) began enrollment in 1990 to address whether EP-guided antiarrhythmic therapy is better than no antiarrhythmic therapy.¹ "Therapy" included antiarrhythmic drugs and implantable defibrillators.

Sudden death due to arrhythmia accounts for many deaths in MI survivors

The landmark Multicenter Automatic Defibrillator Implantation Trial (MADIT),¹² launched at the same time as MUSTT, was specifically designed to examine whether defibrillators might be superior to antiarrhythmic drugs in a similar population.

■ STUDY DESIGN

MUSTT was a multicenter, randomized, controlled trial.

Inclusion criteria

Patients in the study were at high risk of sudden death: to enter, they had to have all of the following:

- Coronary artery disease, as determined by exercise stress testing or coronary angiography or both
- A revascularization procedure, if appropriate, to limit deaths from repeat acute myocardial infarctions
- A left ventricular ejection fraction of 40% or less
- Asymptomatic, spontaneous nonsustained ventricular tachycardia lasting from 3 beats to 30 seconds, occurring more than 4 days after revascularization or MI, and within 6 months of randomization.

Exclusion criteria

Patients could not enter the study if they had any of the following:

- Symptomatic ventricular arrhythmia
- Nonsustained ventricular tachycardia with a presumed reversible cause
- Age older than 80 years
- Comorbidity limiting projected survival to less than 2 years
- Syncope.

Four rounds of therapy

The patients underwent a baseline EP test while taking no antiarrhythmic drugs. Those who tested positive (who were presumed to be at high risk) were randomized to receive either EP-guided antiarrhythmic therapy or no antiarrhythmic therapy. EP-guided therapy proceeded in up to four rounds:

Round 1. In the first round, patients received either a class IA drug (ie, quinidine,

procainamide, or disopyramide), propafenone, or sotalol, and then underwent another EP test. If the first-round drug failed to suppress or render the inducible ventricular arrhythmia hemodynamically stable, the patient proceeded to round 2.

Round 2. The treatment was changed to either another first-round drug, a combination of class IA drug plus mexiletine, or an implantable defibrillator, and the patient underwent another EP test. If the second-round therapy was a drug rather than a defibrillator and did not suppress the arrhythmia, the patient proceeded to round 3.

Round 3 consisted of either any of the above drugs or combinations, amiodarone, or a defibrillator.

Round 4 consisted of any drug not chosen in the first three rounds or a defibrillator.

Patients with negative EP tests at baseline (who were presumed to be at low risk) were not given antiarrhythmic therapy but were followed in a registry. The use of beta-blockers and ACE inhibitors was strongly encouraged for all patients. No empiric antiarrhythmic drug therapy was prescribed.

End points

The primary end point of the study was the combination of arrhythmic death or cardiac arrest. These events were defined in advance and adjudicated by a blinded events committee. Total mortality was a secondary end point.

Results

In all, 2,202 patients entered the study, 767 had positive EP tests at baseline, and 704 agreed to be randomized, 351 to the EP-guided antiarrhythmic therapy group and 353 to the no-therapy group.

Baseline characteristics were similar in the therapy and no-therapy groups. The mean left ventricular ejection fraction was 30% in both groups. Beta-blocker use was initially higher in the no-therapy group (51% vs 29%). However, another 23% in the therapy group were receiving an antiarrhythmic drug with beta-blocking properties, and as the study continued beta-blockers were added in another 11% in the therapy group and 2% in the no-therapy group. ACE inhibitor use was sim-

The MUSTT investigators did not set out to compare defibrillators vs drugs

ilar for both groups: 72% in the therapy group and 77% in the no-therapy group. Given that these conventional therapies have proven efficacy, it is important that they were used equally in the two groups.

Treatment given. At discharge, in the EP-guided therapy group, the percent of patients receiving the various therapies was as follows:

- Defibrillators 46%
- Class IA drugs 19%
- Amiodarone 10%
- No therapy 7%
- Sotalol 9%
- Propafenone 4%
- A class IA drug plus mexiletine 3%.

Follow-up. The median follow-up was 39 months, and all but 4 patients were followed for at least 2 years. At the last visit, 87% of the group receiving EP-guided therapy was still on treatment (29% receiving antiarrhythmic drugs and 58% with implantable defibrillators). Three percent of the no-therapy group had received an implantable defibrillator.

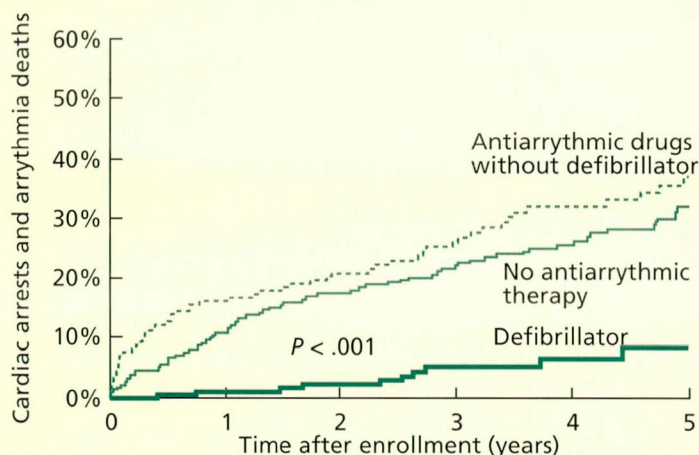
Benefit of therapy. EP-guided therapy proved superior to no therapy: at 2 years, 12% of the therapy group had died of an arrhythmia or had a cardiac arrest (the primary end points of the trial), compared with 18% of the no-therapy group. At 5 years, the rates were 25% vs 32%—a 22% relative risk reduction and a 7% absolute risk reduction ($P = .04$). A similar trend was noted for total mortality.

Of importance, however: the benefit was totally due to implantable defibrillators rather than antiarrhythmic drugs. In fact, the event rate trend was actually slightly higher in patients receiving antiarrhythmic drugs without defibrillators than in patients receiving no antiarrhythmic therapy. This trend did not, however, reach statistical significance. Compared with either drug therapy without defibrillators or no antiarrhythmic therapy, defibrillators cut the rate of the combined primary end point by more than three fourths (9% vs 37%; $P < .001$) and the total mortality rate by more than half (24% vs 55%; $P < .001$; FIGURE 1).

■ IMPLICATIONS FOR PHYSICIANS

The EMIAT,⁶ CAMIAT,⁷ and CAST⁵ studies showed that antiarrhythmic drug therapy does

Implantable defibrillators, but not antiarrhythmic drugs, reduce cardiac arrests and deaths from arrhythmias...



...and reduce total mortality

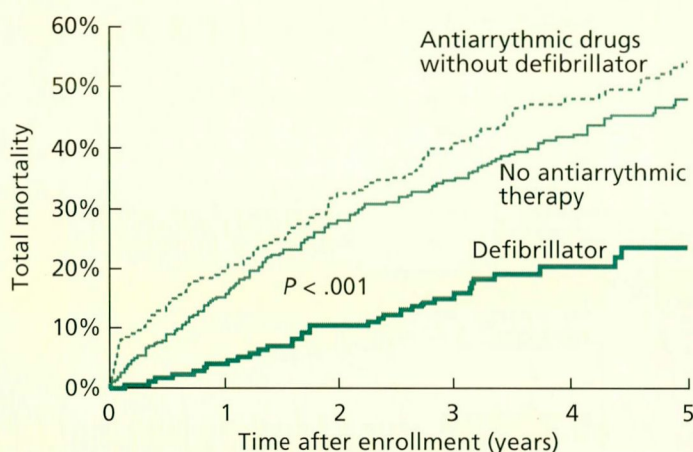


FIGURE 1. Kaplan-Meier estimates of the rates of cardiac arrest or death from arrhythmias (top) and of total mortality (bottom) among patients in the Multicenter Unsustained Tachycardia Trial (MUSTT), in which patients with positive electrophysiologic (EP) tests were randomly assigned to receive either antiarrhythmic therapy with drugs or implantable defibrillators, guided by serial EP studies, or no antiarrhythmic therapy.

FROM BUXTON AE, FISHER JD, JOSEPHSON ME, ET AL, AND THE MUSTT INVESTIGATORS. PREVENTION OF SUDDEN DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE. PROG CARDIOVASC DIS 1993; 36:215-226.



not improve survival after an MI, whether given empirically or guided by Holter monitoring or left ventricular function assessment. MUSTT now extends our knowledge by showing that EP-guided antiarrhythmic drug therapy confers no survival benefit either.

Possible reasons why antiarrhythmic drugs were not beneficial

Why should this be? After all, in MUSTT, antiarrhythmic drugs were chosen on the basis of whether they could suppress the induction of ventricular arrhythmia on serial EP tests. There are several possible explanations:

- EP testing may be an inadequate means of determining response to drug therapy.
- Coronary disease may progress, rendering an initially effective antiarrhythmic drug ineffective owing to the changed myocardial arrhythmic substrate.¹
- Class IA antiarrhythmic drugs, used by 19% of patients in the MUSTT therapy group at discharge, may have had proarrhythmic effects, attenuating any potential benefit of the antiarrhythmic drug therapy. However, the antiarrhythmic drug therapy and no-therapy groups showed no significant difference in outcomes, making this unlikely to have affected the overall outcome.

Benefit of defibrillators:

Comparing the MUSTT and MADIT studies

What is certain however is that implantable defibrillators do confer an impressive benefit. On this point, the MUSTT trial corroborates the findings of the MADIT trial.¹²

The two studies differed somewhat in their designs. MADIT was designed to compare defibrillator therapy with “conventional” therapy with class III antiarrhythmic drugs; MUSTT was designed to compare antiarrhythmic therapy (drugs or defibrillators) vs no therapy.

The antiarrhythmic drugs given were somewhat different as well: in MADIT, 74% of the patients in the conventional-therapy group were receiving the class III drug amiodarone at 1 month after enrollment, compared with 10% in MUSTT at initial discharge from the hospital. It is not known what difference this may have had on outcome.

Moreover, MADIT patients had to have a

left ventricular ejection fraction of 35% or less to enter the study, compared with 40% or less in MUSTT.

The primary end point of MADIT was all-cause mortality; in MUSTT it was the combination of arrhythmic death and cardiac arrest. Some of the MADIT patients may therefore have died of acute coronary syndromes or non-cardiac causes, diluting the significance of the results, whereas MUSTT attempted to exclude these causes of death from the analysis.

Yet both studies found implantable defibrillators to be beneficial. In MADIT, the 2-year mortality rate in the conventional-therapy group was 32%; in MUSTT, the rate was 28% in the no-therapy group and a little higher in the group that received EP-guided therapy without defibrillators. In both studies, defibrillators decreased the total mortality rate by more than half: a 54% relative risk reduction and a 17% absolute risk reduction in MADIT and a 58% relative risk reduction in MUSTT.

■ NEED TO BETTER DEFINE RISK

Given the high cost of implantable defibrillator therapy, this proven therapy must be targeted to high-risk groups to maximize the benefit from using it. Although the absolute risk reduction in these defibrillator trials was impressive in comparison to other landmark cardiovascular trials of lipid reduction, thrombolysis, and beta-blockade in heart failure, among the total population eligible for implantable defibrillator therapy, the reduction in events remains modest.¹³ Many patients would still need to receive the therapy for each life saved. Therefore, in the interest of therapeutic efficiency, we need to continue our attempts to identify more-focused risk profiles.

■ WHO SHOULD RECEIVE A DEFIBRILLATOR

The MUSTT trial convincingly demonstrated that EP-guided therapy with an implantable defibrillator significantly reduces arrhythmic deaths and cardiac arrests in patients with coronary artery disease, a left ventricular ejection fraction of 40% or less, nonsustained ventricular tachycardia, and inducible ventricular

All patients who meet the MUSTT entry criteria should undergo EP testing



arrhythmias on EP testing. All patients who meet the MUSTT inclusion criteria should undergo an EP test and, if positive, should undergo defibrillator implantation.

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