Published in final edited form as:

Am J Cardiol. 2007 July 1; 100(1): 76–83. doi:10.1016/j.amjcard.2007.02.055.

Designation & Distribution of Events in the Multicenter UnSustained Tachycardia Trial (MUSTT)

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Abstract

Patients with coronary artery disease, depressed left ventricular ejection fraction (LVEF), and nonsustained ventricular tachycardia (NSVT) have a high mortality rate due to both arrhythmic (arrhythmic death/cardiac arrest) and other cardiac causes. The Multicenter UnSustained Tachycardia Trial (MUSTT) aimed to determine whether electrophysiologic study (EPS) was helpful in choosing drug or defibrillator therapy in patients induced into sustained ventricular tachycardia (VT). The Events Committee attempted to categorize follow-up events in MUSTT patients, and to present a detailed breakdown of events. A derivative of the Hinkle-Thaler classification was used, incorporating lessons from other multicenter studies. The committee was blinded as to the results of EPS and the ICD or other antiarrhythmic therapy status of the patients. The primary endpoint was cardiac arrest or death from arrhythmia. Secondary endpoints were death from all causes, from cardiac causes, and spontaneous sustained VT. Classifications were: I: Death; II: Cardiac arrest. Each of these was similarly divided: A: Arrhythmic with 14 subcategories e.g. unwitnessed or EPS-related. B: Nonarrhythmic with 10 subcategories, e.g. ischemia. Terminal VF in progressive heart failure was considered nonarrhythmic. Events were reviewed by 2 members. Disagreements were resolved by the 2 members or if needed by the full committee. Of the 2202 patients in MUSTT, there were 902 deaths. Sustained VT requiring cardioversion occurred in 182 patients. An additional 94 patients had resuscitated cardiac arrests. Events occurred in 1027 patients, and all were reviewed. The three leading events were deaths that were classed as sudden-unwitnessed (23% of 902), due to progressive heart failure (22%), or non-cardiovascular causes (18%). Arrhythmic deaths or cardiac arrest frequency: inducible patients randomized to no antiarrhythmic therapy > inducible patients receiving an ICD > patients who

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were noninducible. In conclusion, the classification system provided a detailed breakdown of events in consistent categories, showing utility for event analysis and interpretation and development of therapeutic strategies. The classifications assigned by the committee were used in all MUSTT outcomes articles, thus affecting all reported outcomes and overall interpretations of the MUSTT study.

Keywords

Clinical Trial; Ventricular tachycardias; Coronary artery disease; Ejection fraction; MUSTT; Multicenter UnSustained Tachycardia Trial; Sudden cardiac death

INTRODUCTION

The Multicenter UnSustained Tachycardia Trial (MUSTT) (1) confirmed the hypothesis that patients with coronary artery disease, left ventricular (LV) ejection fraction (EF) <0.40, and nonsustained ventricular tachycardia (NSVT) have a high mortality rate due to both arrhythmic death (arrhythmic/cardiac arrest, AD/CA) and other cardiac causes. Patients induced into sustained VT and randomized to EPS-guided AA therapy who received an implantable cardioverter-defibrillator (ICD) had significantly lower mortality during follow-up than those receiving AA drugs.

As with any trial, the results reported in MUSTT publications (1–10, and others) depend on the data provided to the events committee, the definitions used by the committee, the processes used by the committee, the actual assignment of event classification, and the statistical analyses then performed by the data coordinating center. This paper documents the processes and methods used by the MUSTT Events Committee and the Data Coordinating Center at Duke University.

The purpose of the present report is to provide details on events that are otherwise not included in other MUSTT publications. In addition, the classification methodology used in MUSTT has evolved from earlier schemes, and may be useful to those planning other trials.

METHODS

Overview

The objective was to collect necessary information in a prospective and orderly fashion; to have defined events assigned to categories by an Events Committee that was blinded to the results of the baseline EPS and treatment status of the patient; and to do this in a process complete enough to eliminate any post-hoc reassignment. The data, forms, and processes were developed as part of an evolutionary line beginning with the Hinkle-Thaler classification system (11) and incorporating lessons from the Cardiac Arrhythmia Pilot Study (CAPS) (12) and the Cardiac Arrhythmia Suppression Study (CAST) (13), with a CAST events committee member (D.S.E.) participating in the MUSTT Events Committee. The committee consisted of the authors of this paper, with K.L.L and G.E.H serving as non-voting statistical consultants.

Patient groups

Patients enrolled in MUSTT who had inducible sustained VT were randomized to EP-guided antiarrhythmic therapy or to no antiarrhythmic therapy (Randomized group); those who were not inducible were also followed prospectively (Non-Randomized or Registry group).

Protocol uniformity

Each center participating in MUSTT was required to adhere to a designated EPS protocol (1). Each laboratory was visited to validate the stimulator output calibrations, the presence of sufficient organization and study coordinator support, and to reinforce the importance of uniform data. "Inducible" in the MUSTT protocol was defined as induction of sustained monomorphic ventricular tachycardia (VT) with up to 3 extrastimuli, or polymorphic VT or ventricular fibrillation induced with 1–2 extrastimuli.

Enrollment and Follow-Up/Event forms

These were provided to each center, and periodically reviewed on site by a monitor. Enrollment data were validated by members of the MUSTT executive or steering committee, including review of the qualifying nonsustained VT, and the tracings recorded at the time of induction of sustained VT during EPS.

Follow-up was performed every three months in the office or clinic. Information collected included major events: death or resuscitated cardiac arrest (leading to a detailed subform), spontaneous sustained VT, new myocardial infarction new or changed angina, new onset heart failure (HF), heart transplantation, syncope (ascribed to medications, unprovoked, postural/situational, unknown, other), and interim hospitalization. Details of any events were extensively catalogued: number, date, and time of day; documentation of VT including rate, morphology, symptoms, ICD discharges, all medications including beta blockers, angiotensin converting enzyme inhibitors, antiarrhythmic drugs, and any changes since the previous report. Death or resuscitated cardiac arrest events were detailed in forms submitted per protocol; these elicited more information including a narrative report from the clinical center combined with relevant portions of hospital and laboratory reports (patient consent to this was a prerequisite for enrollment in MUSTT).

Information to the Events Committee

The Data Coordinating Center prepared the information described above for presentation to the Events Committee by expunging all identifiers as to reporting investigator or site, patient identity (other than sex and age), inducibility of tachyarrhythmias at the baseline EPS, randomization, treatment status or type of treatment. The committee was then presented with a new form that provided the classification options (reflected in Tables 1–3), as well as a narrative summary and supporting event forms, together with photocopied hospital, ambulance, or emergency room documents, including ECGs when available (all re-written or blacked out to assure that the committee was blinded as to the treatment limb of that patient). There were 23 deaths for which there was insufficient information for any attempt at classification.

Information was not supplied to the Events Committee on spontaneous sustained VT *not* requiring resuscitation, one of the secondary endpoints of the study. Many of these patients had therapy changes at the time of their VT, including ICD implantation. Follow up on these continued on an intention to treat basis. Similarly, the Committee was not informed about ICD interventions including monitoring, stored electrograms, antitachycardia pacing events, or shocks, except as “resuscitated cardiac arrest”. This was to ensure that the Committee remained blinded as to the treatment status of the patients.

Events Committee review

The information provided to the Events Committee on each patient was reviewed by the full Committee at a periodic meeting, or was sent in rotation to two committee members. If there was agreement between the two reviewers on classification, this was the classification assigned for data analysis. Attempts were made to resolve disagreements between the two reviewers, e.g. by telephone conference. Otherwise these were resolved by consensus of the entire Events Committee, which met face to face two-three times yearly. The full Events Committee also dealt with any backlog of events. The Committee at times was unable to reach a clear decision due to lack of available information, even after the Data Coordinating Center had made additional efforts. All events were classified using a system of notations that had been prospectively developed to indicate the degree of reviewer confidence in the classification: straightforward, complex, uncertain, or “not an event”, each with space for comment.

Statistical methods and analysis

The data are primarily tabular. Group differences were assessed using a 2-tailed X^2 test, with significance at $p = 0.05$.

RESULTS

Tables 1–3 provide details of the categories or classifications assigned to patients by the Events Committee to illustrate the distribution of events. Figures 1–3 summarize the data for the most frequent events. Table 1 and Figure 1 show death and resuscitated cardiac arrest designations for all patients. Table 2 and Figure 2 show this information for the Randomized group; and Table 3 and Figure 3 show this for the Nonrandomized (Registry) group. The Committee was blinded as to the inducibility, randomization and treatment status of the patients, but based on the Committee’s designations, the Coordinating Center subsequently compiled the information. The inducible Registry patients in Table 3 were patients who declined randomization. There were 21 Registry patients and 2 Randomized patients who had events that could not be classified due to insufficient information. These represented 1.0 % of the 2202 patients enrolled in MUSTT, and 2.2% of patients having events as defined.

Cardiac mortality was high in both major groups: Randomized 41% (290/704), Registry 41% (612/1498) $p=NS$. Cardiac death, whether arrhythmic or nonarrhythmic, accounted for 74% of the deaths. Sudden cardiac death accounted for (44% of deaths). Of these, the largest subgroup was *unwitnessed* sudden arrhythmic death (I-A-1, see tables) with 209 (23% of 902 deaths, 9% of all enrolled patients). *Witnessed* sudden arrhythmic death (I-A-3-a)

accounted for 105 (12%). Sudden deaths were followed by deaths ascribed to progressive heart failure (HF) in 201 (22%) (I-B-3), Table 1. Nonarrhythmic death occurred in 483 (53%) with noncardiac deaths in 218 of these, or 24% of the total.

Event distribution was mostly similar for Randomized and Registry patients taken as a whole (Tables 1–3, Figures 1–3). There were 290 deaths in the Randomized group, 65 (22%) of them sudden unwitnessed, vs 144/612 (24%) in the Registry group ($p=NS$). Witnessed sudden death without symptoms of ischemia occurred in 56 (19%) of Randomized vs. 85 (14%) of Registry patients ($p=NS$), and deaths due to progressive CHF were also similar (20 vs. 23%, $p=NS$). Noncardiac death was insignificantly less in the Randomized group (59 vs. 149; 20% vs. 24%, $p=NS$).

Among the treatment arms of the Randomized patients, gross mortality rates were concordant with the time-adjusted mortality previously reported (1). Overall, the lowest mortality was 21% in patients receiving an ICD. This was significant at $p<0.001$ vs all and each of the other arms: a) no antiarrhythmic therapy 45%, b) all EP-guided therapy 38%, and c) antiarrhythmic drug therapy 52%. Further, arrhythmic mortality was also lowest (6%, $p<0.002$) in patients receiving an ICD (Table 2).

Further analysis of the treatment arms based on the classification system revealed dramatic findings (Figure 4). Although event distribution was generally similar for Randomized and Registry patients taken as a whole, breakdown of the Randomized group into treatment arms showed large differences. Arrhythmic death or cardiac arrest occurred in 27% of 353 patients who were inducible and randomized to no antiarrhythmic therapy, vs. 8% of 167 inducible patients who received an ICD ($p<0.0001$). Further, arrhythmic death or cardiac arrest occurred in “only” 20% of 1397 noninducible (Registry) patients vs. 27% of 353 patients who were inducible and randomized to no antiarrhythmic therapy ($p<0.005$). (Figure 4, Tables 1–3). This indicates that inducibility by electrophysiologic studies has value as part of a risk-stratification schema.

Ease of classification

Of 1027 events, 625 (61%) events were initially reviewed independently by two members. The other 402 (39%) were reviewed initially by 2 reviewers at one of the periodic meetings. In both scenarios, if 2 reviewers did not agree, the issue was resolved between the reviewers, or by the entire committee. The Individual Events Committee members felt challenged (ease = complex or uncertain) in 251 of 1027 (24 %). Disagreements between reviewers were considered “major” if the issue was “arrhythmic vs. nonarrhythmic” ($N=70$), or “minor” (subcategory of arrhythmic or nonarrhythmic, $N=126$). As an example, in an unwitnessed sudden death, there may have been uncertainty whether this was primarily arrhythmic (Class IA1, Table 1) or the result of progressive HF (Class IB1c). Similarly, an expected death from HF in <4 months, or a clinical history of rapidly progressive HF (e.g. patient unable to leave hospital, on dobutamine drip) led to a HF designation, even if the final event was VF. If still uncertain, it was attributed to anarrhythmia. Most disagreements between reviewers were resolved between the two members. The disagreements were resolved by provision of new data (additional information from the hospital or family), by information or insights of

one of the reviewers convincing the Committee, or by Committee consensus on the best choice.

DISCUSSION

Interpretation of data from large trials depends on an understanding of the event classification system used during the trial. This article outlines the structure and use of an events classification scheme developed by the MUSTT study. It was evolved from previous classifications. As the data emerged, it was possible to establish important outcomes differences based on differing treatment strategies. The *utility* of the events classification system is that analysis is possible far beyond a simple “dead or alive” notation, and this can lead to more a informed planning process for subsequent therapeutic trials.

Event classifications for arrhythmia-related events traditionally focus on sudden arrhythmic death (SAD) or sudden cardiac death (SCD) defined by time from onset of event to death, but there are many variations (14–26), some of which are summarized in Table 4. Many of these do not permit easy distinctions between cardiac and noncardiac causes of death; or between cardiac events that are primarily ischemic or hemodynamic vs. primarily arrhythmic.

The Hinkle-Thaler article of 1982 (11) attempted to impose some order and discrimination capability (Table 5) by defining deaths as either arrhythmic or due to circulatory failure, but problems remained. Arrhythmic death was defined as an unexpected fatal collapse; but the sequence of ventricular tachycardia causing progressive deterioration and ultimate death would be classified as circulatory failure. Cardiac death was defined as “occurring when the rhythmic contractions of the ventricles ceased and did not return spontaneously”, but noncardiac death was not included in the classification. This led to anomalies such as 44% of the deaths attributed to “circulatory failure” occurring as the terminal event in cancer patients (11).

Subsequent iterations to improve or modify the Hinkle-Thaler system have evolved through multicenter trials such as CAPS (16) CAST (13) and MUSTT in efforts to achieve greater precision in the classification of events in randomized prospective clinical trials. In MUSTT as well as most arrhythmia-oriented trials designed up to that point, the primary endpoint was arrhythmic death or cardiac arrest, with secondary endpoints of overall or “total” mortality, recurrent ventricular tachycardia, and noncardiac death. The inescapable limitations of data interpretation have been discussed and pondered (23). Even protocols that pay particular homage to the Hinkle-Thaler system (27) find that allowances, adjustments, and changes must be made. In spite of these efforts, reviews of additional data from sources such as autopsies and ICD stored electrograms have often revealed that an event committee’s classification was in error (25,26). In MUSTT, every attempt was made to acquire all relevant information *prior* to review by the Events Committee so that *post-hoc* classification changes would be minimized, and indeed none were used. In MUSTT patients with an ICD, the low incidence of fatal events classified as arrhythmic by the (blinded) Events Committee is a further validation of the classification scheme. In addition, the review process described seemed to achieve a greater degree of agreement than reported in other

studies (25,26). Compared to designations in other trials, there were relatively more noncardiac deaths in MUSTT (1, 11, 13, 27–29) (Table 6). This is likely due to the more complete classification scheme in MUSTT; some of the other schemes omitted noncardiac events.

The ultimately subjective nature of any classification scheme was all too apparent in the early literature related to interpretation of ICD data, with the attendant lexicon of “virtual saves”, and “hypothetical vs. actual mortality”. This situation prompted a Policy Conference and Statement by the North American Society of Pacing and Electrophysiology (NASPE, now HRS) (30). Henceforth total mortality (alive or dead) would be generally accepted as the primary endpoint for prospective trials (28,29), but MUSTT was initiated prior to this new convention. Nevertheless, the rigorous criteria used by the Events Committee produced a detailed tabulation of events based as far as possible on objective information analyzed in a blinded fashion.

The primary endpoint of MUSTT was arrhythmic death or cardiac arrest, with total mortality as a secondary endpoint. The data reviewed by the Events Committee consisted of data forms, narratives, and other information that was censored to keep the committee blinded as to patient study site, inducibility, randomization, or treatment status. The advantages of this type of blinded analysis outweigh the possibility of bias introduced into the narratives and other documents selected for presentation to the Events Committee by the experienced research coordinating center.

Acknowledgments

Supported by grants from the National Heart Lung and Blood Institute (NHLBI, U01 HL45700 and U01 HL45726), C.R. Bard Inc, Berlex Laboratories, Boehringer-Ingelheim Pharmaceuticals, Guidant Corporation, Knoll Pharmaceuticals, Medtronic Inc, G.D. Searle Inc, St. Jude Medical Inc, and Wyeth-Ayerst Laboratories

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Figure 1.

All Patients: Deaths (N=902) & Resuscitated Cardiac Arrests (CA) (N=99).

Figure 2.

Randomized Patients: Deaths (N=290) and Resuscitated Cardiac Arrests (CA) (N=37).

Figure 3.
Nonrandomized (Registry) Patients: Deaths (N=612) & Resuscitated Cardiac Arrests (CA) (N=62).

Figure 4.

Percent of patients with arrhythmic death (Arrhy D) or cardiac arrest (CA) or death due to progressive heart failure (HF). Inducible patients are Randomized; Non-Inducibles are the Registry Group.

Table 1

All Patients: Deaths (D) & Resuscitated Cardiac Arrests (CA)

Numbers and letters were used to code classifications assigned by the Events Committee.

	Randomized (N=704)		Nonrandomized (N=1498)*		All Patients (N=2202)	
	D / CA	D / CA	D / CA	D / CA	D / CA	D / CA
I. Deaths/Resuscitated Cardiac Arrests**	290 / 37	612 / 62	902 / 99			
A. Arrhythmic Deaths/Resuscitated Cardiac Arrests**	140 / 29	256 / 45	396 / 74			
1. Arrhythmic – Unwitnessed; patient stable then not seen >5 minutes,	65 / 3	144 / 4	209 / 7			
2. Arrhythmic – Instant, after symptoms or signs of ischemia	7 / 5	6 / 1	13 / 6			
3. Arrhythmic – Sudden, no known symptoms of ischemia:						
a. Without preceding symptoms	42 / 9	63 / 23	105 / 32			
b. Immediately following dyspnea, lightheadedness, or palpitations	4 / 0	14 / 4	18 / 4			
c. Immediately following ECG documented sustained VT or VF	10 / 11	8 / 13	18 / 24			
4. Arrhythmic – Nonsudden:						
a. Incessant VT	2 / 0	2 / 0	4 / 0			
b. Sequelae of cardiac arrest	7 / 0	17 / 0	24 / 0			
c. Consistent with pharmacologic antiarrhythmic drug treatment	2 / 1	1 / 0	3 / 1			
d. ICD post-op mortality (within 30 days of surgery)	1 / 0	0 / 0	1 / 0			
e. Other arrhythmia surgery post-op mortality	0 / 0	0 / 0	0 / 0			
f. EPS related death	0 / 0	0 / 0	0 / 0			
g. If patient had received an ICD, then due to failed ICD therapy***	0 / 0	1 / 0	1 / 0			
B. Nonarrhythmic Deaths/Resuscitated Cardiac Arrests	148 / 8	335 / 17	483 / 25			
1. Cardiac Nonarrhythmic:						
a. Pulmonary Edema not due to VT	5 / 0	15 / 1	20 / 1			
b. Precipitated by bradyarrhythmia	8 / 0	5 / 4	13 / 4			
c. Progressive Heart Failure with est. survival <4mo.****	58 / 2	143 / 5	201 / 7			
d. Possibly Ischemic, MI within 48 hours	10 / 0	10 / 5	20 / 5			
e. Possibly Ischemic, non-MI, e.g. during unstable angina or exercise.	2 / 0	6 / 1	8 / 1			
f,g. Event within 48 h (f) to 30 days (g) of cardiovascular procedure	2 / 3	7 / 0	9 / 3			

	Randomized (N=704)		Nonrandomized (N=1498)*		All Patients (N=2202)	
	D / CA		D / CA		D / CA	
h. Other nonarrhythmic cardiac event (e.g. tamponade)	4 / 1		0 / 0		4 / 1	
2. Noncardiac:						
a. Vascular (pulmonary embolism, CVA, etc)	14 / 2		32 / 0		46 / 2	
b. Non-cardiovascular (e.g. trauma, renal failure, etc)	45 / 0		117 / 0		162 / 0	
C. Unknown Cause of Death/Resuscitated Cardiac Arrest	2 / 0		21 / 0		23 / 0	
X. Sustained ventricular tachycardia (VT)*****	110		72		182	

D / CA = Deaths/Resuscitated Cardiac Arrests, MI = myocardial infarction. VT = ventricular tachycardias, VF = ventricular fibrillation. CVA = cerebro-vascular accident. ICD = implantable cardioverter-defibrillator.

* Nonrandomized patients are primarily those not inducible into sustained monomorphic VT (N=1397), together with a smaller number who refused randomization (N=101). All were followed prospectively.

** Five patients had 2 cardiac arrests (all five were registry patients). Thus, 94 patients experienced a cardiac arrest.

*** The Events Committee was officially blinded to randomization & treatment. This classification was thus used only for this patient whose data was inadvertently apparent.

**** Thus VT or ventricular fibrillation as a final event in a patient moribund due to HF would not be classified as an arrhythmic death.

***** Information on VT that did not require external cardioversion was not reviewed by the Events Committee, but is provided here to complete the Assigned endpoint classifications. See text.

Table 2

Randomized Patients: Deaths (D) and Resuscitated Cardiac Arrests (CA) by randomization groups and subgroups*.

	No AA Therapy (N=353)	EP-Guided: Total (N=351)	EP-Guided: AA Drugs (N=151)	EP-Guided: ICD patients (N=167)	“EP- Guided” but not treated (N=33)	All Randomized Patients (N=704)
	D / CA	D / CA	D / CA	D / CA	D / CA	D / CA
I. Deaths/CA	158 / 21	132 / 16	79 / 10	35 / 3	18 / 3	290 / 37
A. Arrhythmic Deaths/CA	81 / 15	59 / 14	35 / 8	11 / 3	13 / 3	140 / 29
1. Arrhythmic - Unwitnessed; patient stable then not seen >5 minutes,	39 / 2	26 / 1	15 / 0	4 / 1	7 / 0	65 / 3
2. Arrhythmic - Instant, after symptoms or signs of ischemia	4 / 3	3 / 2	3 / 2	0 / 0	0 / 0	7 / 5
3. Arrhythmic - Sudden, no known symptoms of ischemia:						
a. Without preceding symptoms	27 / 6	15 / 3	7 / 2	3 / 0	5 / 1	42 / 9
b. Immediately following dyspnea, lightheadedness, or palpitations	2 / 0	2 / 0	1 / 0	1 / 0	0 / 0	4 / 0
c. Immediately following ECG documented sustained VT or VF	2 / 3	8 / 8	6 / 4	1 / 2	1 / 2	10 / 11
4. Arrhythmic - Nonsudden:						
a. Incessant VT	1 / 0	1 / 0	1 / 0	0 / 0	0 / 0	2 / 0
b. Sequelae of cardiac arrest	5 / 0	2 / 0	1 / 0	1 / 0	0 / 0	7 / 0
c. Consistent with pharmacologic antiarrhythmic drug treatment	1 / 1	1 / 0	1 / 0	0 / 0	0 / 0	2 / 1
d. ICD post-op mortality (within 30 days of surgery)	0 / 0	1 / 0	0 / 0	1 / 0	0 / 0	1 / 0
e. Other arrhythmia surgery post-op mortality	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
f. EPS related death	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
g. If patient had received an ICD, then due to ineffective ICD therapy	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
B. Nonarrhythmic Deaths/CA	76 / 6	72 / 2	43 / 2	24 / 0	5 / 0	148 / 8
1. Cardiac Nonarrhythmic:						
a. Pulmonary Edema not due to VT	3 / 0	2 / 0	2 / 0	0 / 0	0 / 0	5 / 0

	No AA Therapy (N=353)	EP-Guided: Total (N=351)	EP-Guided: AA Drugs (N=151)	EP-Guided: ICD patients (N=167)	“EP- Guided” but not treated (N=33)	All Randomized Patients (N=704)
	D / CA	D / CA	D / CA	D / CA	D / CA	D / CA
b. Precipitated by bradyarrhythmia	3 / 0	5 / 0	4 / 0	1 / 0	0 / 0	8 / 0
c. Progressive Heart Failure with est. survival <4mo.*	32 / 1	26 / 1	12 / 1	11 / 0	3 / 0	58 / 2
d. Possibly Ischemic, MI within 48 hours	4 / 0	6 / 0	5 / 0	0 / 0	1 / 0	10 / 0
e. Possibly Ischemic, non-MI, e.g. during unstable angina or exercise.	1 / 0	1 / 0	1 / 0	0 / 0	0 / 0	2 / 0
f.g. Event within 48 h (f) to 30 days (g) of cardiovascular procedure	0 / 2	2 / 1	2 / 1	0 / 0	0 / 0	2 / 3
h. Other nonarrhythmic cardiac event (e.g. tamponade)	3 / 1	1 / 0	0 / 0	1 / 0	0 / 0	4 / 1
2. Noncardiac: Deaths/CA						
a. Vascular (pulmonary embolism, CVA, etc)	9 / 2	5 / 0	3 / 0	2 / 0	0 / 0	14 / 2
b. Non-cardiovascular (e.g. trauma, renal failure, etc)	21 / 0	24 / 0	14 / 0	9 / 0	1 / 0	45 / 0
C. Unknown Cause of Death/CA	1 / 0	1 / 0	1 / 0	0 / 0	0 / 0	2 / 0
X. Sustained ventricular tachycardia (VT)**	52	58	29	24	5	110

D / CA = Deaths/Resuscitated Cardiac Arrests. MI = myocardial infarction. VT = ventricular tachycardias. VF = ventricular fibrillation. CVA = cerebro-vascular accident. ICD = implantable cardioverter-defibrillator. EP = electrophysiological testing.

* The Events Committee was blinded as to treatment groups & subgroups. The data in this table was subsequently tabulated by the data coordinating center.

** Information on VT that did not require external cardioversion was not reviewed by the Events Committee but is provided here to complete the assigned endpoint classifications. See text.

Table 3

Nonrandomized (Registry) Patients: Deaths (D) & Resuscitated Cardiac Arrests (CA).

	Non-Inducible* (N=1397)	Inducible* (N=101)	All Nonrandomized (N=1498)
I. Deaths/Resuscitated Cardiac Arrests**	572 / 59	40 / 3	612 / 62
A. Arrhythmic Deaths/Resuscitated Cardiac Arrests	237 / 42	19 / 3	256 / 45
1. Arrhythmic - Unwitnessed; patient stable then not seen >5 minutes,	133 / 3	11 / 1	144 / 4
2. Arrhythmic - Instant, after symptoms or signs of ischemia	5 / 1	1 / 0	6 / 1
3. Arrhythmic - Sudden, no known symptoms of ischemia:			
a. Without preceding symptoms	60 / 22	3 / 1	63 / 23
b. Immediately following dyspnea, lightheadedness, or palpitations	12 / 3	2 / 1	14 / 4
c. Immediately following ECG documented sustained VT or VF	8	0	8
4. Arrhythmic - Nonsudden:			
a. Incessant VT	2 / 0	0 / 0	2 / 0
b. Sequelae of cardiac arrest	16 / 0	1 / 0	17 / 0
c. Consistent with pharmacologic antiarrhythmic drug treatment	0 / 0	1 / 0	1 / 0
d. ICD post-op mortality (within 30 days of surgery)	0 / 0	0 / 0	0 / 0
e. Other arrhythmia surgery post-op mortality	0 / 0	0 / 0	0 / 0
f. EPS related death	0 / 0	0 / 0	0 / 0
g. If patient had received an ICD, then due to ineffective ICD therapy	1 / 0	0 / 0	1 / 0
B. Nonarrhythmic Deaths/Resuscitated Cardiac Arrests	316 / 17	19 / 0	335 / 17
1. Cardiac Nonarrhythmic:			
a. Pulmonary Edema not due to VT	14 / 1	1 / 0	15 / 1
b. Precipitated by bradyarrhythmia	5 / 4	0 / 0	5 / 4
c. Progressive Heart Failure with est. survival <4mo.	134 / 5	9 / 0	143 / 5
d. Possibly Ischemic, MI within 48 hours	9 / 5	1 / 0	10 / 5
e. Possibly Ischemic, non-MI, e.g. during unstable angina or exercise.	6 / 1	0 / 0	6 / 1
f,g. Event within 48 h (f) to 30 days (g) of cardiovascular procedure	7 / 0	0 / 0	7 / 0
h. Other nonarrhythmic cardiac event (e.g. tamponade)	0 / 0	0 / 0	0 / 0
2. Noncardiac:			

	Non-Inducible* (N=1397)	Inducible* (N=101)	All Nonrandomized (N=1498)
a. Vascular (pulmonary embolism, CVA, etc)	30 / 0	2 / 0	3 / 0
b. Non-cardiovascular (e.g. trauma, renal failure, etc)	111 / 1	6 / 0	117 / 1
C. Unknown Cause of Death/Resuscitated Cardiac Arrests	19 / 0	2 / 0	21 / 0
X. Sustained ventricular tachycardia (VT)***	64	8	72

D / CA = Deaths/Resuscitated Cardiac Arrests. MI = myocardial infarction. VT = ventricular tachycardias. VF = ventricular fibrillation. CVA = cerebro-vascular accident. ICD = implantable cardioverter-defibrillator. EP = electrophysiological testing.

* Inducible sustained monomorphic ventricular tachycardia (VT) with up to 3 extrastimuli, or polymorphic VT or ventricular fibrillation induced with 1–2 extrastimuli as per the MUSTT protocol. The inducible patients in this table declined randomization.

** Five patients had 2 cardiac arrests (all five were registry patients). Thus, 57 of patients in this table experienced a cardiac arrest.

*** Information on VT that did not require external cardioversion was not reviewed by the Events Committee but is provided here to complete the assigned endpoint classifications. See text.

Table 4**Sudden Cardiac Death Definitions**

Author or study	Year	Reference	Definition
Kuller	1967	14	Unexpected, death within 2 hours of symptom onset
World Health Organization (“old”)	1970	15	Unexpected, death within 24 hours of symptom onset
Ruberman	1973	16	Unexpected, death within few minutes of symptom onset
Meyerburg	1978	17	Unexpected, death within 1 hour of symptom onset
Goldstein	1982	18	Witnessed unexpected death within 1 hour of symptom onset
Cummins/Task Force	1991	20	“No comment” recommended on time or suddenness
(Many, e.g.)	1982–1998	21–26	(Pleas for uniformity)

Table 5**Hinkle-Thaler Classification of Cardiac Deaths (11).**

I. Arrhythmic: abrupt loss of consciousness and collapse.

- 1** No prior circulatory impairment; collapse witnessed or not.
- 2** Prior stable HF; collapse witnessed or not.
- 3** Prior HF, worsening; collapse witnessed or not.

II. Progressive circulatory failure.

- 1** Primarily peripheral failure; event witnessed or not.
- 2** Primarily myocardial failure (including acute infarction); event witnessed or not.

III. Events not classifiable.

Note: Classification not limited to ischemic heart disease; noncardiac causes were not part of the classification system.

Table 6

Distribution of modes of death in some arrhythmia trials involving patients with ischemic heart disease.

Events as %	Hinkle-Thaler (11)	CAST (13)	CABG-Patch (27)	AVID (29)	MADIT (28)	MUSTT (1 & Present)
Arrhythmic	58	53	29	39	NR	44
Non-arrhythmic	42	47	48	39	NR	30
Non-cardiac	(1)	0	18	22	NR	23

Trial acronyms: CAST = Cardiac Arrhythmia Suppression Trial. CABG = Coronary Artery Bypass Graft. AVID = Antiarrhythmic drugs Versus Implantable Defibrillator. MADIT = Multicenter Automatic Defibrillator Implantation Trial. MUSTT = Multicenter Unsustained Tachycardia Trial.

Note that Hinkle-Thaler and CAST were limited to cardiac mortality endpoints. Hinkle-Thaler and AVID also included non-ischemic cardiac deaths. Other differences in reporting (see text) also make comparisons difficult. NR: Not reported. For MUSTT, non-arrhythmic in this table excludes non-cardiac (they are combined as major heading in Tables 1–3).