Implementation of MADIT and MUSTT in Clinical Practice: Results of an International Survey

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Background: The long-awaited dramatically positive outcome of the Multicenter Automatic Defibrillator Implantation Trial (MADIT II), just published by Moss et al.,¹⁴ has generated cardiologists' interest on the *implementation into clinical practice* of that trial. Important lessons may be learned by examining the clinical implementation of two preceding randomized, prospective, prophylactic ICD trials: the original MADIT trial, published late 1996, and the Multicenter Unsustained Tachycardia Trial (MUSTT), published late 1999. Both demonstrated that implantable cardioverter defibrillators reduce all-cause mortality by over 50% in high risk patients without previous sustained arrhythmias.

Methods: In early 2000, we surveyed 133 active electrophysiology centers (47 American, 81 European, 5 Canadian) to determine the extent to which these practices have been implemented in clinical practice during 1999, and the responses were compared to a similar survey for the year 1998.

Results: ICDs implanted for MADIT or MUSTT criteria accounted for 18% of new ICD implants in 1999, 65% greater than in 1998, increasing from 6% to 11% in Europe, and from 15% to 24% in America. During 1999, 53% of patients receiving ICDs for these indications were inpatients identified during hospitalization, 27% were outpatients referred specifically for MADIT/MUSTT indications, and 20% were identified by routine screening. Per the survey, in 1999 68% of responders were "somewhat (10-20%)" and 14% were "considerably (>20%)" more likely to implant ICDs for *all* indications.

Conclusions: Extrapolating the results of this survey to all initial ICD implants for 1999, we estimate that 8500 implants for MADIT/MUSTT criteria took place in 1999, with the overall number of such implants substantially increased over the previous year, irrespective of geographic location, and influenced significantly by the publication of MUSTT. However, screening and implant practices between centers continue to vary over a broad spectrum. It will be interesting to observe whether similar patterns will follow with MADIT II.

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The Multicenter Automatic Defibrillator Implantation Trial (MADIT)¹ and the Multicenter Unsustained Tachycardia Trial (MUSTT)² each demonstrated a greater than 50% reduction in all-cause mortality with an implantable defibrillator (ICD) compared to drug treatment or no antiarrhythmic therapy in patients with previous myocardial infarction (MI), depressed left ventricular function, nonsustained ventricular tachycardia (NSVT) and

inducible sustained ventricular tachycardia. In 1999, about two and a half years after the publication of MADIT, we conducted a survey aimed at determining the impact of MADIT on clinical practice at that time.³ One year later, following the publication of the MUSTT results, we conducted a similar survey. The purpose of this report is to summarize the findings of the latter survey, and to evaluate the evolution of physician attitudes and

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clinical practice with respect to prophylactic defibrillator implantation over time.

METHODS

In early 2000, a survey questionnaire (Appendix A) was sent to approximately 200 physicians at institutions experienced with ICD therapy. The 200 centers included all 72 who had responded to the first survey.³ The questionnaire was aimed at understanding the policies and practice with respect to patients meeting MADIT/MUSTT indications. These patients were defined as those with previous myocardial infarction, left ventricular ejection fraction ≤ 0.40 , NSVT on Holter monitoring, and inducible sustained VT. Questions 1,3,4, aimed at determining the percentage of ICD implants for MADIT/MUSTT indications, the factors influencing physician decisions for implantation, and the extent to which the MADIT/MUSTT selection criteria were extrapolated, were kept from the previous questionnaire. For the quantitative questions, centers reported their total number of first ICD implants for the previous year and the number (and/or percentage) implanted for MADIT/MUSTT. The second survey added questions 2 and 5, with the specific aim of understanding the screening methods by which potential recipients were identified, and overall impact of the MUSTT results on physician attitudes towards prophylactic ICD implantation. We received 133 completed surveys from 81 European, 5 Canadian, and 47 American centers (Appendix B). The Canadian and European responses were very similar, hence for this analysis, have been combined and referred to as "European."

RESULTS

Number/Percentage of ICD Implants for MADIT/MUSTT Indications (Question 1)

Overall, a mean of 13 patients/center received new ICDs for MADIT/MUSTT indications during 1999, representing 18% of all *initial* ICD implants. American centers (averaging 108 ICDs/year) implanted a mean of 26 patients annually (24%). In contrast, European centers (averaging 53 ICDs/year) implanted a mean of 6 patients annually (11%). Within Europe, the number of implants for MADIT/MUSTT indications varied between countries, with an average of 11 patients (13%) in Germany, and 4 patients (9%) in the remaining Euro-

pean countries. The proportion of initial ICD implants for MADIT/MUSTT indications increased from 11% in 1998 to 18% in 1999: in Europe from 6% to 11%, and in America from 15% to 24%, respectively (Fig. 1). From 1998 to 1999, as seen in Figure 1, the proportion of ICD implantations for MADIT/MUSTT indications increased from 13 to 20% in high volume centers (≥ 100 initial implants annually) and from 7 to 10% in low volume centers (≤ 40 initial implants annually). In 1999, 13% of responders reported no implants for MADIT/MUSTT indications, compared to 15% in 1998.

Source of Patients Receiving ICDs (Question 2)

"In patients who received ICDs for MADIT/MUSTT indications, give the approximate percentages for the screening methods by which the patient was identified." Overall, a majority of the patients (53%) who received ICDs were in hospital at the time of the initial screening and Holter monitor, 27% were outpatients specifically referred for MADIT/MUSTT indications, and 15% were outpatients screened for MADIT/MUSTT during a routine follow-up visit (Fig. 2). Only 5% of the implants resulted from systematic screening of patient records or chart review.

Institutional Policies for MADIT/MUSTT Screening (Question 3)

"With respect to screening for NSVT in arrhythmically asymptomatic patients late (> 30 days) post-MI, which best describes your institution's practice?" Overall, for 36% of responders, the primary policy was to perform Holter monitoring in patients with low ejection fraction who present for routine fol-

Figure 1. Evolution of ICD implants for MADIT/MUSTT indications. The light and dark bars show the number of ICD implants, as a percentage of total ICD implants in 1998 and 1999, respectively.

Figure 2. Identification of MADIT/MUSTT patients. More than half of the MADIT/MUSTT patients are hospitalized patients. Outpatients are either referred for that indication (28% total patients), screened during follow-up visits (15% total patients), or actively recruited through file records screening (5% total patients).

low-up. A similar number of responders indicated that evaluation for MADIT/MUSTT indications was limited to patients specifically referred for that reason. A small number (7%) systematically screened records and called in patients with low ejection fraction for Holter monitoring. Overall, these responses were similar to that of the 1998 survey. Geographic variation was noted in the pattern of responses. German physicians were more likely (60%) to perform Holter monitoring in patients with low ejection fraction presenting for routine follow-up, compared to 22% of other European, or 43% of American responders. Screening patients specifically referred for MADIT/MUSTT was uncommon in Germany (15%), compared to the rest of Europe (36%) or in America (43%). Systematic screening of patient records to recruit MADIT/MUSTT patients was uncommon in Europe (9%) and was not practiced in America.

Extrapolation from Specific MADIT/MUSTT Criteria (Question 4)

"Regarding the MADIT strategy, which of the following (one or more) is true in your practice?" Figure 3 provides the overview of the physicians' responses, for both 1998 and 1999. As in the survey for 1998, the two most commonly chosen answers to the survey for 1999 were: A) a patient fitting the MADIT/MUSTT criteria and inducible on baseline would receive an ICD without drug testing (75% in 1999; 61% in 1998); and C) a patient meeting the other criteria and having EF > 35% would receive an ICD (53% in 1999; 38% in 1998). These increases from 1998 to 1999 occurred in virtually all

geographic locations, but were more pronounced in America: response A increased from 69% to 86% and C, from 35% to 67%, respectively. With respect to implantation of an ICD in MADIT/MUSTT type patients without induction of a qualifying VT (VT with cycle length ≥ 230 ms, or VF induced with < 3 extrastimuli), 30% of responders followed this strategy in 1999, similar to the response in 1998. Device implantation in patients with a low ejection fraction, in the absence of spontaneous NSVT (response D), was infrequent (21% in 1999, 18% in 1998).

Indications for ICD Following Publication of MUSTT (Question 5)

"How has specifically MUSTT changed your overall (primary and secondary) indications for ICDs?" Physicians were more likely to implant ICDs for all indications following the publication of MUSTT (68% of responders were "somewhat [10-20%]" more likely, and 14% of responders were "much [> 20%]" more likely). A more favorable overall attitude toward ICD implantation was reported by 90% of American physicians and 77% of Europeans.

DISCUSSION

The results of this survey indicate that ICD implantation for MADIT/MUSTT indications in-

Figure 3. Extrapolation from MADIT/MUSTT criteria. Responders chose between the four MADIT criteria (and could indicate more than one criterion). Their specific choices are shown in Question 4 in the Appendix. From left to right: Were patients with EF > 35% accepted? If initially inducible, were patients given antiarrhythmic drugs and retested for VT inducibility? Were patients without NSVT accepted for MADIT/MUSTT screening? Were patients considered for MADIT/MUSTT even if the arrhythmia induces was not a "qualifying VT?" The paired histograms show responses from 1998 and 1999, respectively.

creased by nearly two-thirds between 1998 and 1999, comprising 1 of 4 new implants in United States and 1 of 9 new implants in Europe. Given a total worldwide implant rate of 50,000 in 1999,^{4,5} an estimated 8,500 prophylactic ICD implantations took place that year. The rapid increase in implant rates for prophylactic indications over a single year may in part reflect additional validation of the MADIT results by the outcome of MUSTT. While the populations entered into the two studies, and the final results, were nearly identical, there were of course some differences in study design. MUSTT had as its primary hypothesis that antiarrhythmic therapy—antiarrhythmic drugs if they rendered the patients noninducible or ICDs, if they remained inducible—would reduce life-threatening arrhythmic events. This contrasts to MADIT, where patients were randomized to conventional antiarrhythmic therapy or ICDs. Furthermore, MUSTT had all-cause mortality as a prespecified secondary endpoint, and planned prospectively to compare the outcomes for patients receiving antiarrhythmic drugs or ICDs. The 1998 survey indicated that a great many cardiologists and primary physicians had not accepted the MADIT results, and were waiting for the publication of the MUSTT study before deciding how they would approach the issue of prophylactic ICD implants.³ From the most recent survey, it appears that MUSTT answered many of the questions and criticisms left open following MADIT, and reinforced the patient screening suggested by MADIT.

The number of MADIT/MUSTT implants varies widely within Europe, and between Europe and America for a variety of reasons.^{4,5} The differences in implant rates between America and Europe demonstrated in the 1998 survey persisted in the second survey. Within Europe, there were major differences, with Germany continuing to implant a relatively larger number of prophylactic ICDs. However, comparing the results of this survey for 1998 and 1999, this gap seems to be diminishing with time. Similarly to 1998 results, 1999 high volume centers were more likely to apply the MADIT/MUSTT strategy than low volume centers. Among survey responders who had no or few prophylactic ICD implants, they frequently cited as contributing factors (in the "Comments" section) economic constraints as well as the nonacceptance of the MADIT/MUSTT guidelines by hospital administration/management and referring physicians.

The results of the 1999 survey confirm that, as in 1998, routine screening of outpatients with previous myocardial infarction for MADIT/MUSTT criteria remains uncommon (5% total patients). The primary source of prophylactic device recipients (53%) was patients hospitalized for other reasons (e.g., heart failure, angina). This pattern of patient selection reflects physician recruitment practices during MUSTT, where 75% of enrolled patients were initially identified during hospitalization for reasons other than the index infarction.⁶ Patients requiring hospitalization may have more advanced disease, representing an additional risk factor prompting their selection for screening and eventual ICD implantation. On the other hand, Holter monitoring and other screening are easier to perform in an inpatient setting, and concurrent hospitalization may facilitate patient acceptance of a prophylactic ICD implantation. Finally, 27% of ICD recipients were referred *specifically* for MADIT/MUSTT indications following initial screening by their primary care providers.

The substantial increase in prophylactic ICD implantation between 1998 and 1999 does not appear due to extensive extrapolation from the original MADIT criteria. Physicians seemed to anticipate the results of MUSTT: they tended to accept patients for prophylactic implantation without requiring additional drug testing (therefore, not adhering to the procainamide challenge required by the MADIT protocol), and often accepted patients with an ejection fraction greater than the 35% proscribed by MADIT (the MUSTT cut-off was 40%). In contrast, only 30% of physicians would implant a prophylactic ICD in patients who did not have induction of a qualifying VT during programmed stimulation, and only 21% would consider ICD implantation in patients without spontaneous non-sustained VT. These latter proportions were unchanged between the two surveys.

Between 1998 and 2000, virtually all countries incorporated the MADIT/MUSTT indication into Class 1 national guidelines (Table 1), moving toward global uniformity in standards for ICD implantation.⁷⁻¹² The criteria used in the MUSTT study were endorsed in the recently published "Indications for ICD Therapy" by the European Society of Cardiology.¹³ These guidelines both reflect and contributed to the increased implementation of the MADIT/MUSTT strategy for primary prevention of sudden death. In 1999, the number of implants of ICDs was 185 per million population in

Table 1. Summary of National Policy Guidelines for ICD Implantation

Indications	U.S. 1998	Spain 1999	Germany 2000	UK 2000	France 2000	Italy 1998
Resuscitated SCD	✓	✓	✓	✓	✓	✓
Sustained VT (with syncope or poorly tolerated)	✓	Struct. HD and EF ≤ 40% or EF > 40%, if AARx fail	w/o Syncope if EF ≤ 40%	w/o Syncope if EF ≤ 40%	Cardiomyopathy and LV dysfunction	✓
Unexplained syncope, inducible VT	✓	EF ≤ 35%	EF ≤ 40%	✓	Class II	Class II
Familial or inherited (without previous sust. VT, (e.g., Brugada, ARVD, HCM, LQTS)	Class II	✓	Class II	✓	Class II	Class II
LV dysfunction, previous MI, NSVT, inducible (MADIT/MUSTT)	LV dysfunction	EF ≤ 35%	EF ≤ 35%	EF ≤ 35%	EF ≤ 35%, ind. on medical Tx	EF ≤ 35%, ind. on medical Tx

All indications and those check marked (✓) indicate "Class I" indications unless otherwise indicated. SCD = sudden cardiac death; EF = Ejection fraction; ARVD = arrhythmogenic right ventricular dysplasia; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; Tx = therapy; AARx = antiarrhythmic therapy; HD = heart disease; LV = left ventricular.

America, 67 in Germany, 25 in Italy, 17 in UK, and 12 in France. The average for Western Europe was about 30. The United Kingdom recently published recommendations on the use of implantable ICDs, in which they stated that the number of implants *needs to be increased* from 17 per million population to the order of 50 per million.¹² The MADIT/MUSTT indications were an integral part of these guidelines, and hence account for some of this expected increase.

Possibly the most important lesson to be learned from these surveys is to get an insight into the implementation into clinical practice of MADIT II, just presented at the 2002 scientific sessions of the American College of Cardiology and simultaneously published in the *New England Journal of Medicine*.¹⁴ This study on 1232 patients with previous myocardial infarction and LVEF ≤ 0.30, randomized to ICD therapy versus best conventional medical therapy, showed a dramatic 31% lower risk of mortality in the ICD group ($P < 0.02$). The major difference in MADIT II compared to MADIT/MUSTT is the former's remarkably simpler screening requirements, eliminating both Holter monitoring and electrophysiological studies to induce ventricular tachycardia, both required in MADIT/MUSTT. We would expect that the elimination of

these two screening tests will accelerate the adoption of MADIT II much faster and widespread than we have reported herein for MADIT/MUSTT, but it will be interesting to observe whether this in fact takes place. We should not forget, however, that there will continue to be many chronic coronary patients—those with LVEF over 0.30 but below 0.40—which do not fit the precise indications for MADIT II, so presumably will continue to be screened as before.

LIMITATIONS

A major limitation of these findings is that the implantation volumes reflect in some cases the investigators' best estimates. In addition, the 200 institutions that received the questionnaire are not necessarily representative of all centers implanting ICDs. However, considering that the 133 responses (67%) came from large numbers of high, medium, and low volume centers, with good geographical distribution, the overall response should give a good picture of the MADIT/MUSTT practices at electrophysiology centers in North America and Europe. The second survey was conducted one year following the first one, so it is probable that some of the increased implant rates simply reflect

overall increased utilization of ICDs, as well as the impact of the MUSTT publication. It was for this reason that Question 5 was explicitly worded to ask responders on "How has specifically MUSTT changed your overall (primary and secondary) indications for ICDs?"

CONCLUSIONS

Prophylactic implantation of ICDs for patients fitting the MADIT/MUSTT criteria—impaired ventricular function following previous myocardial infarction, spontaneous nonsustained VT, and inducible sustained VT—accounted for nearly one-fifth of ICD implants in 1999, an estimated 8500 patients. The substantial increase in prophylactic ICD implantation reflects the integration of these criteria as Class I indications into national policy guidelines. The majority of current prophylactic ICD recipients continue to be identified from hospitalized patients, with another quarter specifically referred for this indication by their treating physician. However, routine and systematic screening of patients following myocardial infarction, aimed at identifying those who may benefit from prophylactic device therapy, remains infrequent. The main benefit of the knowledge gained from these two surveys may be in helping to determine current prevailing practices regarding screening and implant criteria for implanting ICDs prophylactically. It will be interesting to see how these practices continue to evolve in light of MADIT II.

APPENDIX A. QUESTIONNAIRE

MADIT and MUSTT (MADIT/MUSTT) Practice Survey

1. Over the past 12 months,
 - a) How many of your patients received ICDs for MADIT/MUSTT Indications? _____
 - b) This represents what percentage of your initial ICD implants? _____
2. In patients who received ICDs for MADIT/MUSTT indications, give the approximate percentages for the screening method by which the patient was identified (total should be 100%). If you implanted no devices for MADIT/MUSTT during these past 12 months, please leave this question blank:
 - a) out-patient, specifically referred for MADIT/MUSTT _____
 - b) out-patient, presenting for routine follow-up visit and screened for MADIT/MUSTT _____
 - c) out-patient, called in for MADIT/MUSTT screening on basis of chart or record review _____
 - d) in-patient (hospitalized for CHF, angina, etc), who was screened for MADIT/MUSTT during hospital stay) _____
3. With respect to screening for nonsustained VT (NSVT) in arrhythmically asymptomatic patients late (≥ 30 days) postmyocardial infarction, which best describes your institution's practice:
 - a) We systematically screen patient records, and call in patients with low LVEF for 24-hour Holters and follow the MADIT/MUSTT cascade for those with NSVT _____
 - b) Patients with low EF in for routine follow up are Holter monitored, and we follow the MADIT/MUSTT cascade for those with NSVT _____
 - c) We never (or very rarely) follow the MADIT/MUSTT cascade with our patients _____
 - d) We follow the MADIT/MUSTT cascade only when physicians refer patients specifically for that indication _____
4. Regarding the MADIT/MUSTT strategy, which of the following (one or more) is true in your practice:
 - a) We do not routinely perform drug testing if a MADIT/MUSTT type patient has qualifying inducible VT, but proceed directly to ICD implantation _____
 - b) We would implant an ICD in MADIT/MUSTT type patients even if nonqualifying VT was induced (cycle length < 230 ms or VF with 3 extrastimuli) _____
 - c) We study selected patients with nonsustained VT and EF $\geq 35\%$, and would implant an ICD if qualifying VT was induced _____
 - d) We study selected patients with low ejection fraction even in the absence of NSVT, and would implant an ICD if qualifying VT was induced _____
 - e) None of the above _____
5. Specifically, how has MUSTT changed your overall (primary & secondary) indications for ICDs:
 - a) Not at all _____

- b) Somewhat (10-20% more aggressive than before) _____
c) A lot (over 20% more aggressive than before) _____

Comments:

APPENDIX B. CONTRIBUTING INVESTIGATORS

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