

## Heart Rhythm Disorders

# Predictive Value of Ventricular Arrhythmia Inducibility for Subsequent Ventricular Tachycardia or Ventricular Fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Patients

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<b>OBJECTIVES</b>	We correlated electrophysiologic inducibility with spontaneous ventricular tachycardia (VT) or ventricular fibrillation (VF) in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II.
<b>BACKGROUND</b>	In the MADIT II study, 593 (82%) of 720 implantable cardioverter-defibrillator (ICD) randomized patients underwent electrophysiologic testing. Patients received an ICD whether they were inducible or not.
<b>METHODS</b>	A "standard" inducibility definition included sustained monomorphic or polymorphic VT induced with three or fewer extrastimuli or VF induced with two or fewer extrastimuli. We compared a narrow inducibility definition (only monomorphic VT) and a broad definition (standard definition plus VF with three extrastimuli). We used ICD-stored electrograms to categorize spontaneous VT or VF.
<b>RESULTS</b>	Inducible patients (standard definition) had a greater likelihood of experiencing ICD therapy for VT than noninducible patients ( $p = 0.023$ ). Unexpectedly, ICD therapy for spontaneous VF was less common ( $p = 0.021$ ) in inducible patients than in noninducible patients. The two-year Kaplan-Meier event rate for VT or VF was 29.4% for inducible patients and 25.5% for noninducible patients. Standard inducibility did not predict the combined end point of VT or VF ( $p = 0.280$ , by log-rank analysis). The narrow inducibility definition outperformed the standard definition, whereas the broad definition appeared inferior to the standard definition.
<b>CONCLUSIONS</b>	In the MADIT II study patients, inducibility was associated with an increased likelihood of VT. Noninducible MADIT II study subjects using this electrophysiologic protocol had a considerable VT event rate and a higher VF event rate than inducible patients. Induction of polymorphic VT or VF, even with double extrastimuli, appears less relevant than induction of monomorphic VT. (J Am Coll Cardiol 2006;47:98-107) © 2006 by the American College of Cardiology Foundation

Implantable cardioverter-defibrillator (ICD) therapy in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II reduced the risk of all-cause mortality

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by 31% in patients after myocardial infarction (MI) with an ejection fraction of 0.30 or less (1). This trial was the first to enroll patients without a previous incident of sustained

ventricular arrhythmia or inducibility as a requirement. Unlike the MADIT II study, previous prophylactic ICD trials (2,3) excluded noninducible patients on the basis of the belief that electrophysiologic (EP) inducibility identified a group at increased risk for sudden death. The Multicenter UnSustained Tachycardia Trial (MUSTT) substudy results (4) did demonstrate a significantly increased risk of mortality in EP-inducible patients compared with noninducible patients. However, the two-year total mortality of inducible patients (28%) was only 1.33-fold greater than for noninducible patients (21%), implying that inducibility had modest clinical relevance in these post-MI patients (4). Furthermore, EP testing was even less predictive in patients with an ejection fraction of 0.30 or less (5). Thus, it is unclear how well EP inducibility functions as a screening test to select postinfarction patients fitting the MADIT II study criteria for ICD implantation.

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#### Abbreviations and Acronyms

ATP	= anti-tachycardia pacing
EP	= electrophysiologic
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
MADIT	= Multicenter Automatic Defibrillator Implantation Trial
MI	= myocardial infarction
RV	= right ventricular
VF	= ventricular fibrillation
VT	= ventricular tachycardia

The evaluation of inducibility as a predictor of arrhythmic events was a prespecified secondary objective of the MADIT II study. Thus, the MADIT II study protocol strongly encouraged patients randomly assigned to the ICD arm of the MADIT II study to undergo EP inducibility testing but for ICD implantation to be performed regardless of inducibility status. To maximize statistical power to address the role of EP testing, ICD to conventional randomization was 3:2 (1,6). Arrhythmia end points, i.e., ventricular tachycardia (VT) or ventricular fibrillation (VF), were determined using ICD interrogation data. We then evaluated the association between EP inducibility and subsequent ventricular arrhythmia and also with mortality. We evaluated whether classification of patients by inducibility status and baseline QRS duration (7–10) would predict arrhythmic events as well. Therefore, this study addressed whether ICD implantation in post-MI patients with an ejection fraction of 0.30 or less should be limited to those found to be inducible or whether otherwise-similar but noninducible patients also are at significant risk of life-threatening ventricular arrhythmia.

## METHODS

The MADIT II study (1) prospectively enrolled 1,232 patients with a previous MI and an ejection fraction of 0.30 or less. Of the 742 patients randomized to the ICD arm of the trial, 720 subjects actually received an implanted defibrillator. Electrophysiologic testing for ventricular tachycardia inducibility was recommended before the implantation of the ICD but was not a mandatory protocol requirement. Of the 720 ICD implant patients, 593 underwent EP testing, and this latter group is the cohort used in the present study.

**EP testing and inducibility definitions.** The EP testing protocol used 400-ms and 600-ms drive trains followed by one to three ventricular extrastimuli that were 2 ms in duration at twice the diastolic threshold (1,6,11). Extrastimuli were decremented down to a coupling interval no shorter than 180 ms. Stimulation was performed at one right ventricular (RV) site and then repeated at a second RV site. Rapid burst pacing was not used for induction. A catheter-based EP testing study was recommended, but inducibility was determined through the ICD in 13% of the

group. The EP study end point included the induction of a sustained monomorphic VT, polymorphic VT, or VF episode or completion of the protocol. A sustained ventricular arrhythmia was defined as one lasting 30 s or requiring termination sooner because of hemodynamic compromise.

Monomorphic VT was defined as a VT with a uniform beat-to-beat surface QRS morphology. Polymorphic VT had a variable surface QRS morphology, and VF was defined as a rapid, disorganized rhythm without consistently identifiable complexes. A prespecified definition, i.e., standard inducibility, included sustained monomorphic VT induced with three or fewer extrastimuli, polymorphic VT induced with three or fewer extrastimuli, and VF induced with two or fewer ventricular extrastimuli. We also evaluated two alternative inducibility definitions, narrow inducibility (also prespecified), which included only sustained monomorphic VT, and a broad definition, which included the standard inducibility criteria plus VF induced with three extrastimuli.

**Analysis of ICD therapy.** Patients in the MADIT II ICD study arm underwent quarterly ICD interrogation as well as interim visits if their symptoms dictated (1). Centers completed ICD follow-up data forms describing each ICD therapy (anti-tachycardia pacing [ATP] or shock) and downloaded ICD interrogation to discs. All ICD interrogation data were reviewed by an ICD end point committee composed of three of the authors (J.P.D., W.Z., and A.C.), who adjudicated each ICD event. The ICD end point committee was blinded to the results of the EP study results. We classified ICD therapy occurring for VT or VF as appropriate. Inappropriate therapy, due to atrial fibrillation, supraventricular tachycardia, or abnormal sensing, amounting to 35.4% of ICD events or therapy events that could not be classified (2.3% of total ICD events), was not included in this analysis.

The ICD end point committee reviewed all available information, including the ICD episode summary, stored intracardiac electrograms, and the enrollment center's rhythm classification. If applicable, the event was considered in the context of other episodes for the same patient. The triggering arrhythmia was characterized as VT if the rate was between 140 and 250 beats/min and the complexes were uniform and regular. The arrhythmia was characterized as VF if the rate was >200 beats/min, if the rhythm was irregular, and if the electrogram complexes were indistinct. Polymorphic VT was included with VT when <200 beats/min and with VF if the rate was >200 beats/min. Ventricular tachycardia was differentiated from supraventricular tachycardia using standard criteria, including a change in electrogram morphology, sudden onset, and the atrial-ventricular relationship if atrial electrograms were available.

**Statistical analysis.** The primary end point for this study was the incidence of spontaneous VT or fibrillation requiring treatment by the ICD in relationship to EP inducibility at electrophysiologic testing. Clinical characteristics of the inducible and noninducible groups were compared using the

*t* test or F test, chi-square method, or Wilcoxon/Kruskal-Wallis rank sum test where appropriate. Kaplan-Meier survival curves with log-rank test evaluated univariate associations between EP inducibility and outcome events (12). To test the combined predictive value of inducibility plus QRS width, QRS duration was dichotomized into <0.12 s (n = 286) and QRS ≥0.12 s (n = 307). We used Cox proportional hazards modeling to analyze the association between inducibility and outcome after adjustment for clinical covariates (13). Significance was evaluated by p < 0.05.

## RESULTS

**Clinical characteristics and inducibility findings.** Patients in the MADIT II ICD study arm who underwent electrophysiologic testing (n = 593) were very similar in measured clinical characteristics to those patients who did not undergo electrophysiologic testing (n = 126). Statistical differences present included more patients with a history of New York Heart Association functional class II to IV heart failure in the patients not undergoing an EP study (77% vs. 64%, p = 0.006) and more patients being on angiotensin receptor blockers (19% vs. 12%, p = 0.03). We compared the event rates in patients undergoing an EP study versus those who did not undergo an EP study. Twenty-four percent of patients undergoing an EP study versus 22% of those not undergoing an EP study reached the end point of VT or VF in follow-up. In addition, the EP study and no EP study

groups did not differ in the subsequent occurrence of hospitalization for CHF, recurrent MI, cardiac death, sudden death, or total mortality.

Sustained monomorphic VT was induced in 169 (29%) patients, sustained polymorphic VT in 26 (4%) patients, VF with single or double extrastimuli in 16 (3%) patients, and VF with triple extrastimuli in 32 (5%) of patients. Thus, 29% of patients met narrow inducibility, 36% of patients met the standard inducibility definition, and 41% of patients had broadly defined inducibility.

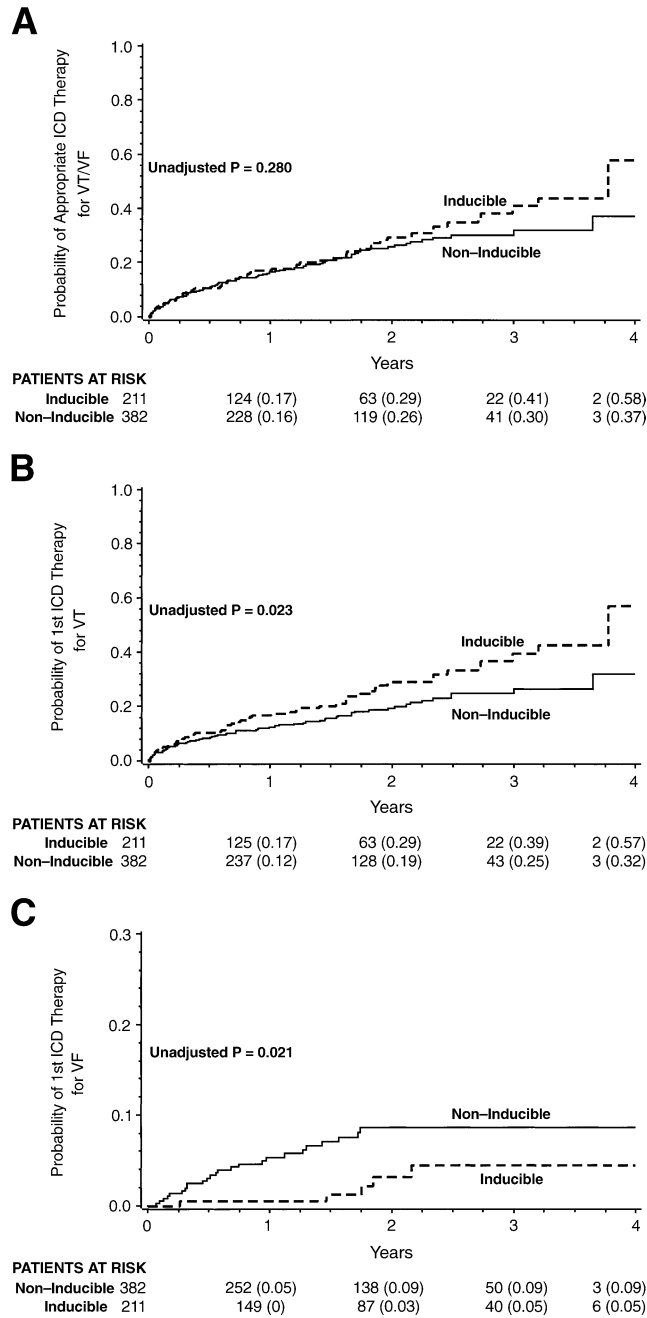
The clinical characteristics for the noninducible and inducible patients by the type of arrhythmia induced are shown in Table 1. Sesselberg *et al.* (14) have previously shown that inducible patients, defined by the standard definition (Table 1, columns two and three), bore similar clinical characteristics to the noninducible patients (Table 1, columns four and five). They found that the inducible group had a slightly slower heart rate, a tendency towards lower New York Heart Association functional class status, a slightly higher percent of patients on angiotensin-converting enzyme inhibitor therapy and a slightly longer time from most recent MI to date of EP study as compared with the noninducible group (14). Using the more detailed breakdown of inducibility, *i.e.*, Table 1, differences in clinical characteristics between the four subgroups regarding inducibility were similar to the previous analysis (14) and included interval after infarction, heart rate at enrollment, frequency of previous non-coronary artery bypass grafting revascularization, and treatment with angiotensin-converting enzyme inhibitors (Table 1).

**Table 1.** Clinical Characteristics of Patients by Inducibility Type

Clinical Characteristics	Monomorphic VT (n = 169)	Polymorphic VT or VF With S2-3 (n = 42)	VF With S4 (n = 32)	Neither VT Nor VF Induced (n = 350)
Male	151 (89%)	33 (79%)	25 (78%)	289 (83%)
Age (yrs)	62 ± 12	62 ± 11	65 ± 10	64 ± 10
Months post-MI*	90 (33, 164)	34 (16, 75)	54 (29, 128)	61 (17, 117)
Whites	154 (91%)	33 (79%)	29 (91%)	303 (87%)
Diabetes	53 (31%)	13 (31%)	9 (28%)	127 (36%)
Hypertension	81 (48%)	24 (57%)	19 (59%)	187 (54%)
Smoking	139 (82%)	34 (81%)	24 (75%)	274 (79%)
NYHA functional class I or II†	122 (73%)	37 (88%)	20 (63%)	232 (67%)
Previous CABG	97 (57%)	22 (52%)	18 (56%)	209 (60%)
Previous PTCA†	74 (44%)	24 (57%)	21 (68%)	142 (41%)
Heart rate (beats/min)*	70 ± 13	69 ± 10	70 ± 12	74 ± 13
Systolic BP (mm Hg)	121 ± 17	122 ± 18	124 ± 14	123 ± 19
Diastolic BP (mm Hg)	70 ± 10	71 ± 11	71 ± 10	72 ± 11
BUN (mg/dl)	22 ± 10	21 ± 9	23 ± 16	24 ± 13
QRS (ms)	121 ± 29	123 ± 35	117 ± 29	120 ± 31
Ejection fraction ×100	22 ± 5	23 ± 5	24 ± 5	23 ± 6
Enrollment medications				
Beta-blockers	114 (67%)	30 (71%)	26 (81%)	215 (61%)
Digitalis	103 (61%)	20 (48%)	16 (50%)	213 (61%)
ACE inhibitors†	145 (86%)	33 (79%)	22 (69%)	268 (77%)
Lipid agents	114 (67%)	31 (74%)	26 (81%)	229 (65%)

Values shown are numbers of patients with percent of group in parentheses, or means ± standard deviation, except for months post-myocardial infarction (MI) where the 50% median values, and in parentheses, the interquartile range, are shown. NYHA functional class represents the most severe NYHA class within the three months before enrollment. \*p ≤ 0.001 and †0.001 < p < 0.05; p values for any differences among the four groups.

ACE = angiotensin-converting enzyme; BP = blood pressure; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; VF = ventricular fibrillation; VT = ventricular tachycardia.



**Figure 1.** Cumulative probability of first appropriate therapy for (A) ventricular tachycardia (VT) or ventricular fibrillation (VF); (B) VT only; and (C) VF only in patients with and without inducible arrhythmias according to standard definition of inducibility. Determination of p values was from the log rank test.

**ICD therapy events related to standard inducibility definition.** At least one appropriate ICD therapy was delivered in 141 (24%) of the 593 ICD arm patients who underwent EP testing. A total of 963 appropriate ICD events occurred in these 593 patients. Figure 1A shows the cumulative probability of first appropriate ICD therapy (for either VT or VF) related to inducibility per the standard definition. Using log-rank analysis of the cumulative probability of a VT or VF event, inducible patients were not

more likely to receive appropriate ICD therapy than non-inducible patients ( $p = 0.28$ ). The two-year point estimate of the incidence of at least one therapy for either VT or VF, 29.4% and 25.5% respectively, also was not significantly different between inducible and noninducible patients by the z-test ( $p = 0.407$ ).

Considering ICD treatment for VT only (versus either VT or VF), inducible patients defined by the standard definition were significantly more likely by log-rank analysis to experience a first ICD therapy for VT ( $p = 0.023$ ). For example, at two years, 29.0% of the inducible patients and 19.3% of the noninducible patients received at least one therapy for VT using Kaplan-Meier analysis (Fig. 1B).

Unexpectedly, the noninducible group had a significantly higher cumulative likelihood of ICD treatment for a VF episode than the inducible group by log-rank analysis ( $p = 0.021$ ) (Fig. 1C). The two-year Kaplan-Meier event rate for a first therapy for VF was 3.2% for the inducible patients and 8.6% for the noninducible patients.

The aforementioned univariate associations were tested in the multivariate Cox model adjusting for relevant clinical covariates (Table 2). According to this proportional hazards analysis, EP inducibility by the standard definition was not associated with the combined end point of VT or VF (hazard ratio [HR] 1.34;  $p = 0.094$ ). However, ICD therapy for VT only was predicted by EP inducibility with a HR of 1.66 ( $p = 0.007$ ), whereas inducibility was associated with a trend toward a decreased risk of therapy

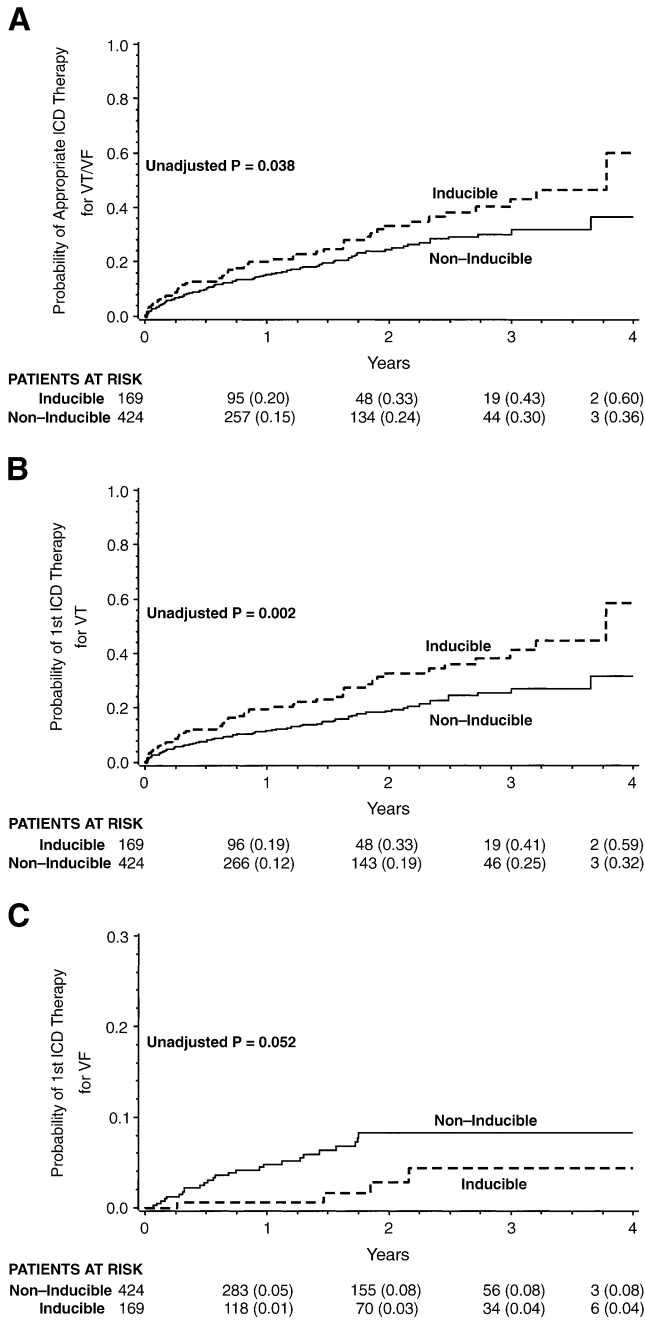
**Table 2.** Hazard Ratio for Outcomes by Definition of Inducibility Using Multivariate Cox Models

Outcome:	Hazard Ratio	95% Confidence Intervals	p Value
<b>VT or VF</b>			
Narrow	1.56	1.10-2.21	0.012
Standard	1.34	0.95-1.90	0.094
Broad	1.27	0.90-1.79	0.16
<b>VT</b>			
Narrow	1.89	1.31-2.74	0.001
Standard	1.66	1.15-2.40	0.007
Broad	1.63	1.13-2.35	0.009
<b>VF</b>			
Narrow	0.41	0.14-1.17	0.096
Standard	0.41	0.16-1.09	0.073
Broad	0.40	0.16-0.99	0.049
<b>Death</b>			
Narrow	0.68	0.39-1.18	0.17
Standard	0.58	0.34-0.99	0.045
Broad	0.59	0.36-0.97	0.039
<b>VT, VF, or death</b>			
Narrow	1.31	0.97-1.79	0.08
Standard	1.12	0.83-1.52	0.45
Broad	1.03	0.77-1.39	0.85

Clinical variables entering the models along with inducibility included heart rate  $\geq 80$  beats/min, NYHA functional class  $>II$ , absence of treatment with beta-blockers, and BUN  $>25$ . Results for VT or VF, VT and VF are not fully reliable due to the necessity of having to censor patients without events upon death.

BUN = blood urea nitrogen; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.





**Figure 2.** Cumulative probability of first appropriate therapy for (A) ventricular tachycardia (VT) or ventricular fibrillation (VF); (B) VT only; and (C) VF only in patients with and without inducible arrhythmias according to narrow definition of inducibility. Determination of p values was from the log rank test.

for VF (HR 0.41;  $p = 0.073$ ) after adjusting for the same clinical variables.

**ICD therapy events related to alternative definitions of inducibility.** The narrow definition of inducibility (monomorphic VT only) predicted the occurrence of the composite event, VT or VF, better than the standard definition ( $p = 0.038$ ), as illustrated by comparing Figure 2A with Figure 1A. This was mainly a result of the strong association between narrow inducibility and VT ( $p = 0.002$ ) (Fig. 2B).

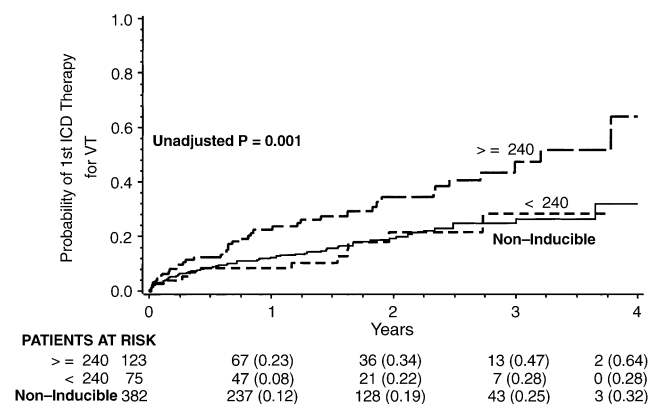
Narrow inducibility was not significantly associated with the occurrence of VF only (Fig 2C), but a trend was nevertheless still present for inducible patients to have less VF.

On the other hand, analogous graphs, such as Figures 1 and 2, that use the broad definition (not shown) were similar to the standard definition, but with slightly less separation in the inducible and noninducible curves both for VT only or for VT and VF events. The broad definition appeared to perform inferiorly to the standard definition for predicting VT or VF ( $p = 0.45$ ) or for predicting VT only ( $p = 0.06$ ) using log-rank analysis. For predicting the occurrence of VF therapy, broad inducibility, like the other two definitions, was associated with a lower risk of VF ( $p = 0.04$ ), which in this case was statistically significant.

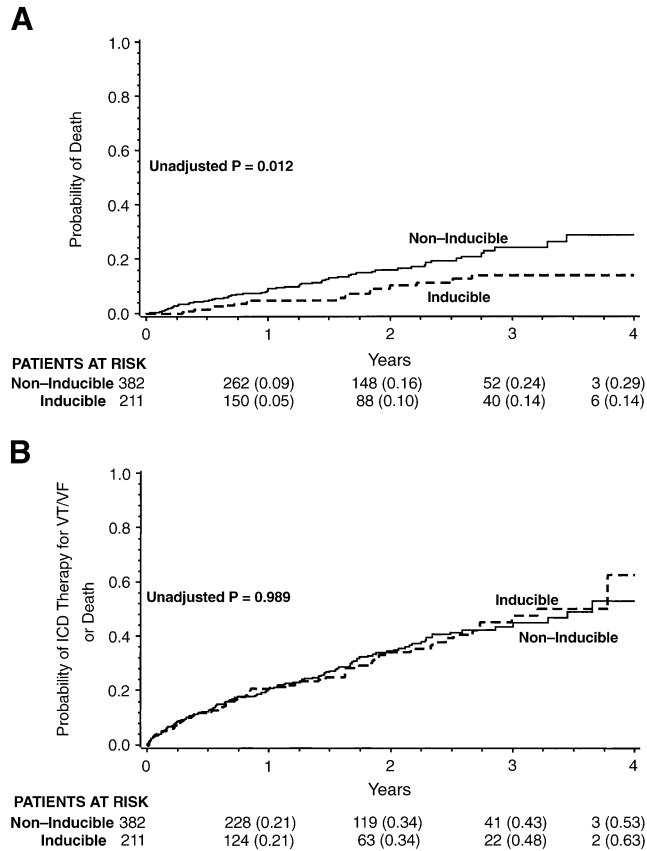
Table 2 also shows results of multivariate Cox analyses testing the association between alternative definitions of EP inducibility and outcome. Therapy for VT or VF was significantly predicted by inducibility per the narrow definition (HR 1.56;  $p = 0.012$ ), which was mainly the result of better performance of narrow inducibility for predicting ICD therapy for VT (HR 1.89;  $p = 0.001$ ).

The relationship between the broad definition of inducibility and outcome (Table 2) did not show a significant association for the composite end point of VT plus VF. Broad inducibility was associated with VT (HR 1.63;  $p = 0.009$ ) but not as strongly as narrow or even standard inducibility. Broad inducibility was associated with a lower risk of VF (HR 0.40;  $p = 0.049$ ).

Analogous to refining the definition of inducibility, we examined whether the cycle length of the induced VT impacts on the subsequent likelihood for the occurrence of VT. Previous studies in the early post-MI period (15–17) have suggested that inducible monomorphic VT with a very short cycle length may be less likely to predict subsequent VT. We subdivided the arrhythmias categorized as inducible by cycle length of the induced arrhythmia. Figure 3 demonstrates that the induction of extremely rapid VT



**Figure 3.** Cumulative probability of first therapy for ventricular tachycardia (VT) in relationship to cycle length of induced VT. The cycle length of induced VT is divided at median value of 240 ms. The induction of a slower VT ( $\geq 240$  ms) was more predictive of the subsequent clinical occurrence of VT than the induction of rapid VT ( $< 240$  ms), or noninducibility (solid line).



**Figure 4.** The cumulative probability of (A) mortality and (B) combined end point of ventricular tachycardia or ventricular fibrillation or death in patients with and without inducible tachyarrhythmias according to standard definition of inducibility.

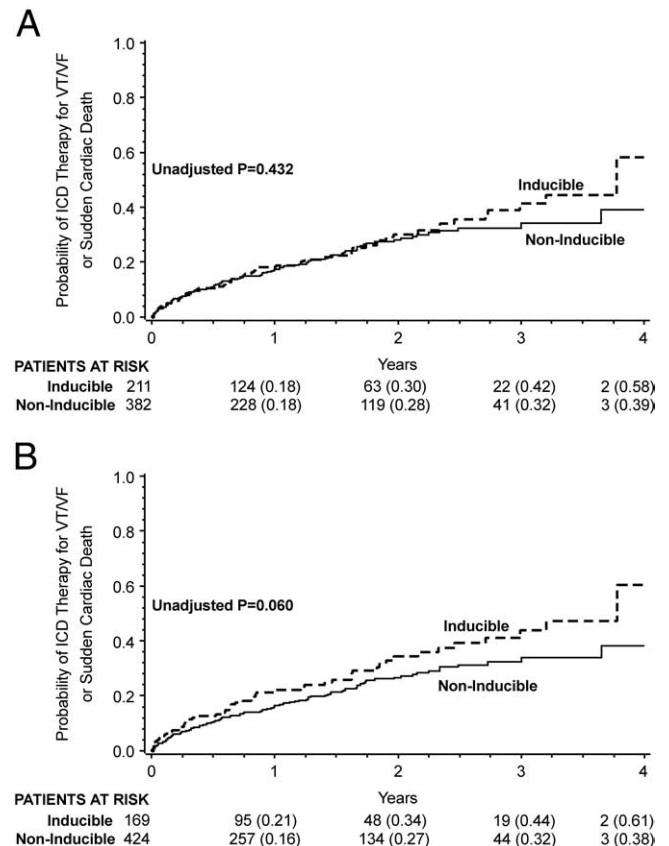
(<240 ms) did not predict the subsequent occurrence of VT better than noninducibility, whereas induction of VT with a CL  $\geq$ 240 ms led to a higher chance of subsequent VT ( $p = 0.001$ ).

**ICD therapy events related to mortality and combined end point of VT/VF/death.** Inducible patients (by the standard definition) had a lower mortality than noninducible individuals ( $p = 0.012$ ), as shown in Figure 4A. Using multivariate analysis (Table 2), we also found inducibility to be independently, although weakly, associated with improved survival (HR 0.58;  $p = 0.045$ ). Because inducibility correlated positively with VT events but inversely with both VF and mortality, inducibility did not predict the composite end point of VT, VF, or death by either univariate (Fig. 4B) or multivariate analysis (Table 2). Using the narrow inducibility definition, we discovered that mortality in the inducible group was not significantly lower by multivariate analysis (Table 2).

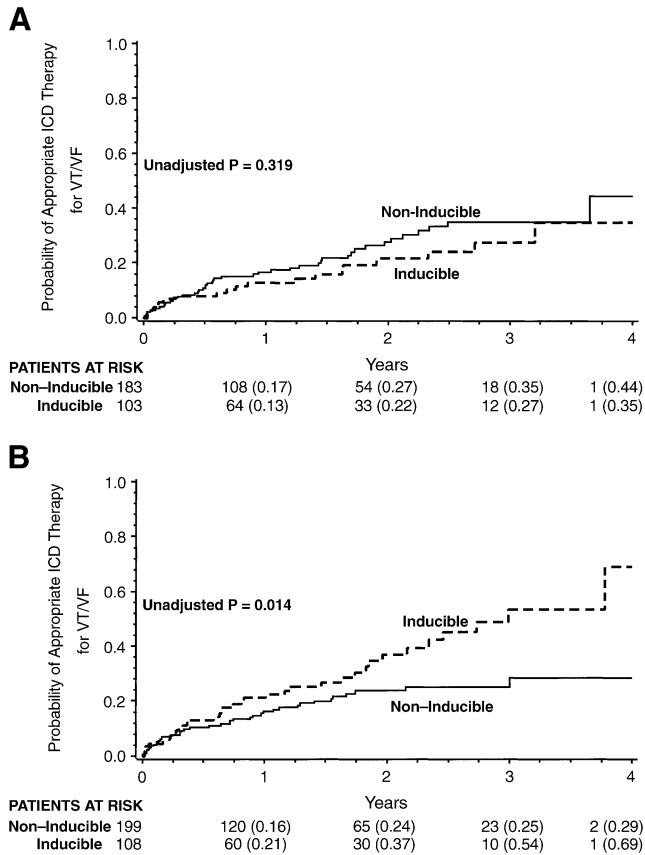
Because ICD interrogations were infrequently available postmortem, we compiled another composite end point consisting of ICD therapy for VT, ICD therapy for VF, or sudden death (without previous appropriate ICD therapy) to ensure that a fatal first arrhythmic event was not excluded. However, using deaths classified as sudden is well known to overestimate true arrhythmic events because of the potential

for other vascular events (e.g., cerebral hemorrhage, aortic aneurysm, pulmonary embolism) to present suddenly. Figure 5 shows the event rates for this composite end point for inducible and noninducible patients, using the standard as well as the narrow definition. As shown, this analysis is not appreciably different from that for the composite end point of VT or VF (shown in Figs. 1A and 2A) because total sudden deaths in patients with ICDs were low and similar in noninducible and inducible patients (5.7% and 4.3% at four years for noninducible and inducible subsets, respectively).

**ICD therapy events related to the combination of QRS duration and EP inducibility.** Figure 6A shows the ICD event rates for the combined end point of VT/VF for patients with a narrow QRS (<0.12 s) by inducibility status according to the standard definition. Figure 6B shows the ICD event rates for patients with a wide QRS ( $\geq$ 0.12 s). Inducibility was predictive for VT/VF only in the patients with prolonged baseline QRS duration. Unfortunately, the combination of QRS duration and inducibility status failed to identify a subgroup of patients at low arrhythmic risk in whom ICD implantation could be deferred (Figs. 6A and 6B). Because the analysis of QRS duration and inducibility was not prespecified, we did not subject this data to



**Figure 5.** The cumulative probability of the composite end point of appropriate implantable cardioverter-defibrillator (ICD) therapy for ventricular tachycardia (VT), appropriate ICD therapy for ventricular fibrillation (VF), or sudden death for inducible versus noninducible patients using (A) the standard definition and (B) the narrow definition.



**Figure 6.** Cumulative probability of first appropriate therapy for either ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with and without inducible arrhythmias according to standard definition of inducibility in (A) patients with QRS < 0.12 s and (B) patients with QRS ≥ 0.12 s. Determination of p values was from the log rank test.

proportional hazards analysis. The conclusions above apply whether we use the standard definition of inducibility (Figs. 6A and 6B) or the narrow definition (data not shown).

## DISCUSSION

In summary, EP inducibility in post-MI patients with ejection fraction of 0.30 or less did correlate with the subsequent occurrence of VT. However, inducibility had an inverse relationship with VF requiring ICD therapy. The inverse relationship with VF decreased the association between EP inducibility and the combined end point of VT or VF. Because both inducible and noninducible patients received ICD therapy, this MADIT II substudy is unique in being able to compare arrhythmic events broken down into either VT or VF in patients with differing inducibility status.

Previous studies have found that EP inducibility is best defined by the induction of sustained monomorphic VT, as opposed to VF (4,18–20). Thus, our finding that VT inducibility predicts the occurrence of VT but not VF is not entirely unexpected. In fact, restricting the definition of inducibility to only include induction of monomorphic VT (the narrow definition) improves the correlation of induc-

ibility with the subsequent occurrence of VT (Fig. 2B vs. Fig. 1B). Conversely, the broad definition was least strongly associated with subsequent VT episodes. It appears, therefore, that future studies seeking to predict VT events should use this “narrow” definition of inducibility. Moreover, induction of ventricular arrhythmia with a cycle length ≥ 240 ms was associated with a higher incidence of VT events in follow-up (Fig. 3) than induction of ventricular arrhythmia with a cycle length shorter than 240 ms. Although inducibility correlates with subsequent VT, only 39% of inducible patients were estimated to experience a clinical VT episode by three years, compared with 25% of noninducible patients.

Inducible MADIT II study patients tended toward a lower likelihood of experiencing a spontaneous clinical ventricular fibrillation episode requiring ICD intervention (Figs. 1C and 2C). However, using multivariate analysis, we discovered that inducibility was not significantly associated with a reduced incidence of VF except by the broad definition (Table 2). At three years, 9% of noninducible patients required treatment for at least one episode of clinical ventricular fibrillation by their defibrillator compared with 5% of inducible patients, using the standard inducibility definition. Although this inverse relationship or trend is seemingly paradoxical, EP inducibility relates best to the stable, reentrant arrhythmia monomorphic VT and less well to VF. Ventricular fibrillation, especially in the setting of advanced congestive heart failure, may rely on focal or triggered mechanisms in addition to re-entry (21–24). Ischemia is very likely to be implicated in spontaneous VF episodes in patients with coronary artery disease (25).

Indeed, a recent paper from the MADIT II study database found that patients who experienced VF in follow-up were more likely than VT patients or patients without ICD therapy to be hospitalized for congestive heart failure (26). Such arrhythmias brought on by advanced congestive heart failure are perhaps more likely in patients having an ejection fraction ≤ 0.30. Thus, the presence of advanced congestive heart failure predicted VF as opposed to VT in multivariate analysis whereas inducibility was inversely related to subsequent VF. Electrophysiologic inducibility evaluates the substrate for a reentrant arrhythmia, which is one contributor to the risk for sudden death, along with triggering factors, such as premature beats, autonomic tone and other factors. This inverse relation between inducibility and occurrence of clinical ventricular fibrillation in a way is not paradoxical when seen in this context. Thus, patients who have a triggering event and go on to have a clinical ventricular arrhythmia are more likely to have VT as their arrhythmia if they are found to have a substrate for VT at EP study, whereas those without such a demonstrated substrate would be more likely to have clinical VF if a triggering event initiated an arrhythmia.

Recent work has ascribed VF to a two-part process involving VT (spiral wave) initiation, and then spiral wave disorganization dependent upon the slope of the action potential duration–diastolic interval relationship, also called

the restitution slope (24,27,28), although this concept is controversial (29–32). One could speculate that if stable monomorphic VT were induced in the EP laboratory, and did not degenerate to VF in that setting, that a spontaneous ventricular arrhythmia might be less likely to (rapidly) degenerate into VF. Patients who maintain a stable rotor or reentry circuit in the EP laboratory could conceivably have a different restitution slope than those who do not exhibit inducible monomorphic VT. Inducibility of a monomorphic VT might identify a patient whose arrhythmia is less likely to deteriorate into VF (at least early after onset).

Although these data demonstrate shortcomings of EP inducibility, recent data from the MUSTT study are in fact quite concordant (5). In the MUSTT study (5), the two-year total mortality in patients with an ejection fraction  $<0.30$  was 33% in inducible patients and 26% in noninducible patients, yielding an unadjusted risk ratio of 1.27, which is very similar to the HR of 1.34 for the combined VT and VF end point we found (Table 2). Using the MUSTT study data on arrhythmic death or cardiac arrest also yields a similar unadjusted risk ratio of 1.4 for inducibility in the low ejection fraction subgroup (5). In the MUSTT study, EP inducibility was less predictive of mortality or arrhythmic death in the lower ejection fraction strata, the MADIT II-like subset of the MUSTT study, than in the patients whose ejection fraction was between 0.30 and 0.40. Unlike the MADIT II study, the relative contribution of VT as opposed to VF to sudden death mortality could not be differentiated in the MUSTT study because noninducible patients and nontreatment arm patients did not receive an ICD. Unlike the data in this MADIT II substudy or those from the MUSTT study, many earlier publications supporting the role of EP testing suffer one or more limitations, including the use of sudden death as opposed to total mortality as an end point, inhomogeneous populations with varying severity of structural heart disease, and differing treatments for inducible and noninducible patients at a time before recognition of the proarrhythmic effects of pharmacologic agents (11,15–18,33).

In the MADIT II study, inducibility did not correlate with increased mortality; in fact inducible patients tended to have a lower mortality rate (Fig. 4A), although this finding was of only borderline significance using multivariate analysis (Table 2). The (slightly) reduced, as opposed to increased mortality associated with inducibility in this study, is not paradoxical because both inducible and noninducible MADIT II study groups were treated with an ICD as opposed to the MUSTT study. Electrophysiologic testing did predict a greater occurrence of VT, but VT is virtually always successfully treated by the ICD and, thus, inducibility was not associated with increased mortality. Likewise, in the AVID study inducibility did not predict an inferior survival (34).

The imperfect predictability of EP testing shown in this study is not attributable to differences with previously

used EP protocols. The Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, which found EP inducibility poorly predictive, was criticized for the EP protocol being insufficiently aggressive. In the MADIT II study, however, a rigorous induction protocol consisting of triple extrastimuli at two RV sites and two cycle lengths was used. Attesting to the aggressive nature of the protocol, the MADIT II study investigators found a relatively high inducibility rate of 36% (211 of 593), similar to the 35% inducibility reported in the MUSTT study. Nevertheless, noninducible patients had 64% as great a chance of experiencing VT by three years as did inducible patients (Fig. 1B), suggesting that this well-validated protocol is relatively insensitive in patients with an ejection fraction  $<0.30$ .

**Study limitations.** This report has several possible limitations, one of which is the lack of availability of ICD programming details, which was left to investigator preference in the MADIT II study. Theoretically, this could affect the degree of detection of VT. For instance, if a slow VT were induced at EP study, this could have encouraged the investigator to program a slow detection rate, which could increase the yield of VT events in follow-up. This could conceivably increase the correlation between VT inducibility and VT events. It appears that this would have been a very infrequent occurrence, because only five patients had inducible VT at a rate  $<170$  beats/min. On the other hand, alterations in programming would be very unlikely to have affected the detection of VF events, leading to the inverse relation between inducibility and VF events. Varying the lower zone detection rate would not effect detection of VF. The detection time for VF is not programmable for the ICD devices used in this study. A self-terminating arrhythmia that did not lead to ICD therapy was not classified as either VT or VF in this study.

A second potential limitation is that not all patients underwent an EP study. As noted previously, the clinical characteristics of patients having an EP study versus those not having an EP study did not differ in clinically relevant characteristics. Moreover, patients undergoing an EP study had similar event rates for VT or VF, CHF hospitalization or death, in follow-up to those patients not undergoing an EP study. Third, the findings concerning the predictive value of the EP test for VT or VF are specific to the EP testing protocol used. Protocols using more than three extrastimuli, which may induce VT in a greater proportion of patients (35–37) or other variations could possibly have led to different findings. As noted previously, the MUSTT study, the largest other study prospectively after patients with remote MI, used a virtually identical protocol to the MADIT II study protocol. In addition, we found that the induction of VT tended to be inversely related to the occurrence of VF in follow-up, no matter which inducibility definition was used. Fourth, concerning the tendency of noninducible patients to have an increased likelihood of VF, the classification of



events as VT or as VF relies on arbitrary definitions and does involve potentially subjective electrogram data interpretation. Thus, one should not overinterpret the tendency toward more VF in the noninducible group, a trend that was not statistically significant by multivariate analysis. Finally, these data pertain to the relationship between inducibility and subsequent VT or VF episodes. The occurrence of VT or VF treatment by an ICD should not be equated with a mortal event because some episodes undoubtedly would have terminated spontaneously if the ICD had not intervened. The magnitude of this effect is observed when comparing the incidence of a first ICD therapy for VT or VF, 27% at two years (26), with the difference in total mortality between ICD and conventional groups, 6% at two years (38).

**Conclusions.** We found a limited predictive value of EP testing using a stimulation protocol using up to three extrastimuli at two sites for ruling out subsequent VT or VF events. Although noninducible patients in the MADIT II study population do have a slightly lower risk of the combined arrhythmic end point of VT or VF, their risk of VF tended to be higher than in inducible patients. Thus, for postinfarction patients with an ejection fraction of  $\leq 0.30$ , noninducibility at EP testing does not equate with a low arrhythmic risk. This study does not support excluding noninducible patients from ICD therapy.

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