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Prognostic Importance of Defibrillator-Appropriate Shocks and Antitachycardia Pacing in Patients With Mild Heart Failure

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Background—Patients with heart failure and an implantable cardioverter-defibrillator (ICD) for primary prevention are at increased mortality risk after receiving shock therapy. We sought to determine the prognostic significance of ICD therapies, both shock and antitachycardia pacing, delivered for different ventricular arrhythmia (VA) rates.

Methods and Results—We evaluated mortality risk among 1790 ICD-implanted patients from MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). For the first analysis, patients were divided into mutually exclusive groups by the rate of treated VA only: slow VA (<200 beats per minute) and fast VA (≥200 beats per minute or ventricular fibrillation). In a secondary analysis, both the type of ICD therapy and VA rate were used. The reference group was always patients who had no ICD therapy. ICD therapy for fast VA was associated with increased mortality risk (hazard ratio [HR], 2.27; 95% CI, 1.48–3.48; *P*<0.001). However, mortality risk after ICD therapy for slow VA was similar to the risk related to no ICD therapy (HR, 1.45; 95% CI, 0.86–2.44; *P*=0.162). Consistently, shocks (HR, 2.96; 95% CI, 1.91–4.60; *P*<0.001) and antitachycardia pacing (HR, 2.22; 95% CI, 0.96–5.14; *P*=0.063) for fast VA were both associated with increased mortality risk. Shocks and antitachycardia pacing for slow VA were not significantly associated with increased mortality risk (HR, 1.43 [95% CI, 0.52–3.92; *P*=0.489]; and HR, 1.43 [95% CI, 0.80–2.56; *P*=0.232], respectively).

Conclusions—In patients with mild heart failure receiving ICD for primary prevention, mortality is associated with the rate of underlying VA rather than the type of therapy. These findings suggest that fast VA is a marker for increased mortality rather than shock therapy directly contributing to increased risk.

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Patients with heart failure (HF) are at increased risk of developing ventricular arrhythmias (VAs) that predispose to sudden death. Previous studies established that implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) are effective in reducing the risk of mortality and VAs, respectively, among patients with HF.[1,2]

Later research, however, indicated that ICD shocks, whether appropriate or inappropriate, are associated with greater mortality risk in the long-term.[3–11] Although there is evidence that shocks may induce myocardial damage, it remains unknown whether ICD shocks directly lead to mortality.[12–14] High-rate cutoff and delayed ICD programming strategies have been shown to reduce unnecessary shocks.[15–17] In MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial—Reduction in Inappropriate Therapy), novel programming was associated with a trend toward decreased mortality, although other studies have suggested no mortality benefit.[17–19]

Using the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study population of patients with mild HF,[20] we therefore aimed to assess whether shock therapy itself is responsible for increased mortality or, alternatively, the underlying rate of

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Clinical Perspective

What Is New?

- Fast ventricular arrhythmias (>200 beats per minute) but not slow ventricular arrhythmias are associated with increased mortality in patients with mild heart failure and reduced left ventricular function (left ventricular ejection fraction <30%).
- Implanted cardioverter-defibrillator shocks are not associated with increased mortality if rendered for slow ventricular arrhythmias and supraventricular tachycardia.
- Fast ventricular arrhythmias are a marker of severe myocardial disease and probably represent advanced substrate (diffuse scar).

What Are the Clinical Implications?

- These patients should be evaluated early for advanced therapies.

VA (fast versus slow) is an indicator of disease severity and, thus, a marker of mortality risk. This aim seeks to further clarify findings observed in MADIT-RIT, in which high-rate programming and delayed programming strategies showed a mortality benefit (hazard ratio, 0.45 [P=0.01]; and hazard ratio, 0.56 [P=0.06], respectively) in a population of patients with mild to moderate HF.[17]

Methods

Study Population

The study population comprised the entire cohort of the original MADIT-CRT. The protocol and results of the study have been detailed previously.[20,21] Briefly, 1820 patients with left ventricular ejection fraction <30%, QRS duration of at least 130 ms, and either ischemic cardiomyopathy and New York Heart Association (NYHA) class I to II symptoms or nonischemic cardiomyopathy and NYHA class II were randomly assigned to CRT-D or ICD treatment arms (both arms had a defibrillator). Patients from both treatment arms received optimal medical therapy for HF. Exclusion criteria included NYHA class III or IV symptoms, coronary artery bypass graft surgery, percutaneous coronary intervention, or myocardial infarction within 90 days before enrollment; second- or third-degree heart block; chronic atrial fibrillation; and comorbidities, such as uremia (blood urea nitrogen >70 mg/dL or creatinine >3.0 mg/dL) and liver failure.

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Heart Research Follow-Up Program at the University of Rochester Medical Center (Rochester, NY).

Follow-Up

MADIT-CRT was conducted between December 22, 2004, and June 22, 2009. The institutional review board of each participating center approved the posttrial follow-up. All patients provided written informed consent.

Device Programming and Interrogation

Device programming and interrogation were previously reported.[21] Devices were programmed to monitor and deliver therapy. A 2-zone configuration was used. The ventricular tachycardia (VT) zone was set at 180 beats per minute (bpm), whereas the ventricular fibrillation (VF) zone was set at 250 bpm. Detection was 2.5 seconds for the VT zone and 1.0 second for the VF zone. VT zone first therapy was burst-type antitachycardia pacing (ATP) with 8 pulses at 88% of the measured cycle length and a 10-ms decrement between bursts, then shock therapy. Second therapy was shock at the defibrillation threshold plus at least 10 J (if possible). The remaining therapies were maximal energy shocks.

Definitions and End Points

In this substudy, the original MADIT-CRT study population was reclassified into 3 prespecified subgroups: no ICD therapy (no VT or VF), ICD therapy for VT <200 bpm, and ICD therapy for VT ≥200 bpm or VF. Those experiencing ICD therapy for VT <200 bpm were characterized as the slow VA group, whereas those experiencing ICD therapy for VT ≥200 bpm or VF were described as the fast VA group. The definition of fast VA was chosen on the basis of MADIT-RIT, which suggested that treatment of VT <200 bpm may not be lifesaving.[17]

For the primary analysis, patients were divided into mutually exclusive groups by the rate of treated VA: slow VA or fast VA. For the secondary analysis, both the type of therapy and underlying VA rate (ATP for slow VA, shock for slow VA, ATP for fast VA, and shock for fast VA) were used. The reference group was always patients who had no ICD therapy. The heart rate at the beginning of each arrhythmic episode was used in the categorization of fast versus slow episodes.

If a patient received ≥2 therapies within a single episode, only the heart rate that initiated the cycle was captured, whereas additional heart rate data within the episode were not assessed by the interrogation committee. A total of 28 (9.7%) of the patients in MADIT-CRT had multiple therapies within a single event (ie, ATP followed by shocks or multiple shocks); for this subset of patients, only the heart rate that initiated the episode was captured.

To allow categorization with multiple therapies for a patient within different episodes (in different time frames), the

Distribution of Heart Rate for VT/VF
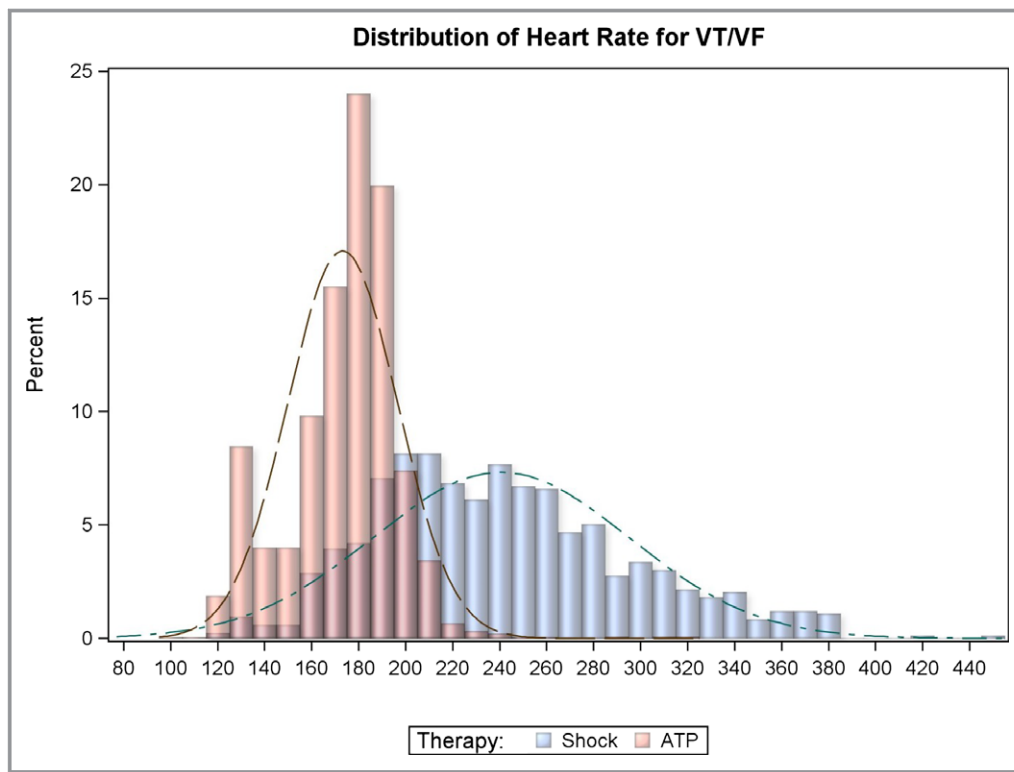
Figure. The distribution of appropriate implanted cardioverter-defibrillator–rendered therapy, as separated by the rate of ventricular arrhythmia, in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). The dark purple area represents overlap between antitachycardia pacing (ATP) and shocks. VF indicates ventricular fibrillation; VT, ventricular tachycardia.

therapy groups were created to be mutually exclusive by prioritizing increasing risk among groups in the following rank order: ATP for slow VA, shock for slow VA, ATP for fast VA, and shock for fast VA. For example, if a subject had ICD therapies for both shock for slow VA and shock for fast VA, the higher-risk event (ie, shock for fast VA) was considered for the analysis. Likewise, if a subject had therapies that included both ATP for slow VA but also shock for fast VA, the shock for fast VA was analyzed. Because of the time-dependent nature of the covariates, patients developing different types of VA events during the study were moved to or kept in the group with the highest heart rate range. The end point of current the study was all-cause mortality.

Statistical Analysis

Baseline clinical characteristics were compared between patients from the 3 groups (no ICD therapy [no VT or VF], ICD therapy for slow VA, and ICD therapy for fast VA), using the χ^2 test or Fisher's exact test for categorical variables. For purposes of consistency, we used the Kruskal-Wallis test for all continuous variables. Categorical data are presented as frequencies and percentages, and continuous variables are presented as mean±SD.

Multivariate Cox proportional hazards regression analysis was used to assess the association between treated VA and the risk of long-term mortality in a time-dependent manner. The Cox model was adjusted for relevant clinical covariates using best subset regression modeling (CRT-D treatment, non–left bundle branch block configuration, CRT-D treatment by non–left bundle branch block interaction, age ≥65 years, smoking, diabetes mellitus, glomerular filtration rate ≥60 mL/min per 1.73 m², left atrial volume index, prior congestive HF hospitalization, prior hospitalization of any type, QRS duration, weight, time-dependent inappropriate ATP, and time-dependent inappropriate shock).

All statistical tests were 2 sided, and *P*<0.05 was considered statistically significant. Analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

Results

During a median follow-up of 4 years, there were 423 patients who experienced appropriate ICD therapy, with 163 receiving therapy for slow VA and 260 receiving therapy for fast VA. The distribution of the device therapies stratified by the rate of VA is shown in the Figure.

Table 1. Patient Baseline Clinical Characteristics Categorized by Shock Therapy

Clinical Characteristics	No ICD Therapy (No VT or VF) (n=1367)	ICD Therapy for VT <200 bpm (n=163)	ICD Therapy for VT ≥200 bpm or VF (n=260)
Age at enrollment, y	64.9±10.8	64.6±9.7	61.8±10.7*
Female sex	27	20	14*
White race	91	90	88
SBP, mm Hg	123.3±17.5	120.0±15.9	120.6±17.6*
Heart rate, bpm	67.7±11.0	66.8±8.2	68.7±11.3
BMI, kg/m^2	28.6±5.4	28.8±4.4	29.0±5.2
Smoking	10	20	15*
Creatinine, mg/dL	1.17±0.37	1.16±0.30	1.14±0.26
CRT-D–assigned treatment arm	62	58	54
Diabetes mellitus	31	29	26
Hypertension	65	59	62
Ischemic cardiomyopathy	54	61	57
Prior MI	41	53	52*
Survival time from MI to enrollment	9.3±8.0	11.9±7.7	11.0±7.6*
Time from revascularization	4.9±5.0	5.4±5.6	6.7±5.6*
Prior atrial arrhythmias	11	12	15
Prior ventricular arrhythmias	5	13	15*
Aspirin	65	71	59
β Blockers	94	93	91
ACE inhibitor or ARB	95	96	97
Statin	67	72	67
Antiarrhythmic agent	7	13	9
Digitalis	24	23	34*
Diuretic	67	68	71
PR interval, ms	198±33	197±34	195±32
QRS, ms	158.7±19.3	156.4±20.4	156.2±21.7*
LBBB	73	60	65*
IVCD	15	23	23*
LVEF, %	29.3±3.4	28.7±2.9	28.0±3.6*
LVEDV indexed by BSA	121.8±27.1	125.6±27.1	130.6±33.8*
LVESV indexed by BSA	86.6±21.9	89.9±21.2	94.6±27.5*
LAV indexed by BSA	45.9±9.9	48.3±10.0	49.2±10.3*

Numbers are mean±SD or percentage. ACE indicates angiotensin-covering enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; bpm, beats per minute; BSA, body surface area; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implanted cardioverter-defibrillator; IVCD, intraventricular conduction disturbance; LAV, left atrial volume; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia.
*P<0.01.

The baseline clinical characteristics categorized by the occurrence and the rate of VA are shown in Table 1. Patients experiencing ICD therapy for fast VA were younger, more often male, and more likely to be treated with digoxin. Those not receiving ICD therapy or who had ICD therapy for slow VA had smaller chamber volumes and a greater left ventricular ejection fraction.

In a multivariable model, we adjusted our analyses for variables that were found to be predictive of mortality. For example, we adjusted for CRT-D treatment, left bundle branch

Table 2. Risk of Death by the Rate of Underlying VA (Slow and Fast)

Time-Dependent Appropriate Therapy	HR*	95% CI	P Value
VT <200 bpm vs no therapy	1.45	0.86–2.44	0.162
VT ≥200 bpm or VF vs no therapy	2.27	1.48–3.48	<0.001

Bpm indicates beats per minute; HR, hazard ratio; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
*The reference group is patients without implanted cardioverter-defibrillator therapy (either appropriate or inappropriate). The model is adjusted to cardiac resynchronization therapy with defibrillator (CRT-D) treatment, non–left bundle branch block (LBBB), CRT-D treatment by non-LBBB interaction, age ≥65 years, smoking, diabetes mellitus, glomerular filtration rate ≥60 mL/min per 1.73 m^2, left atrial volume index, prior congestive heart failure hospitalization, prior hospitalization of any type, QRS duration, weight, time-dependent inappropriate antitachycardia pacing, and time-dependent inappropriate shock.

Table 3. Risk of Death by the Rate of Underlying VA (Slow and Fast) and the Type of Rendered Therapy

Variable	HR*	95% CI	P Value
Time-dependent appropriate shock: VT <200 bpm	1.43	0.52–3.92	0.489
Time-dependent appropriate shock: VT ≥200 bpm or VF	2.96	1.91–4.60	<0.001
Time-dependent appropriate ATP: VT <200 bpm	1.43	0.80–2.56	0.232
Time-dependent appropriate ATP: VT ≥200 bpm or VF	2.22	0.96–5.14	0.063
No ICD therapy		Reference	

ATP indicates antitachycardia pacing; bpm, beats per minute; HR, hazard ratio; ICD, implanted cardioverter-defibrillator; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
*The reference group is patients without ICD therapy (either appropriate or inappropriate). The model is adjusted to cardiac resynchronization therapy with defibrillator (CRT-D) treatment, non–left bundle branch block (LBBB), CRT-D treatment by non-LBBB interaction, age ≥65 years, smoking, diabetes mellitus, glomerular filtration rate ≥60 mL/min per 1.73 m^2, left atrial volume index, prior congestive heart failure hospitalization, prior hospitalization of any type, QRS duration, weight, time-dependent inappropriate ATP, and time-dependent inappropriate shock.

block morphological features, and the interaction between the 2, since CRT-D has been shown to reduce VAs in this population.[22] Our results were consistent when we analyzed the CRT-D group alone and the ICD group alone. The analyses indicate that patients treated for fast VA were at increased risk for mortality, relative to those not receiving ICD therapy (Table 2). On the other hand, patients who received ICD therapy for slow VA had similar mortality risk compared with patients who had no ICD therapy (Table 2).

Consistently, when the patient groups were further stratified according to the type of the ICD-delivered therapy, those who had ATP and those who had shock for fast VA were at significantly increased risk for long-term mortality, whereas those who had ATP and those who had shock for slow VA did not differ from patients not receiving ICD therapy (Table 3).

Discussion

The main finding of our study is that among patients with mild HF, ICD-rendered therapy, either ATP or shock, was independently associated with increased long-term mortality only if the underlying VA was fast (VT ≥200 bpm or VF). Both shock therapy and ATP for slow VA (VT <200 bpm) were associated with the same risk as not having received any ICD-rendered therapy. These findings suggest that the type of underlying VA is a marker for increased all-cause mortality, rather than the ICD shocks or ATP directly contributing to mortality risk.

Although ICD implantation reduces the risk of death in patients with HF susceptible to life-threatening VAs, both appropriate and inappropriate ICD shocks have been associated with greater mortality during long-term follow-up.[3–11] However, the debate about cause and effect has remained controversial. Electrical shock results in myocardial damage, which was hypothesized to be the source of excess mortality in this group.[12–14] One school of thought is that ICD therapy

induces cardiomyocyte dysfunction, as evidenced by subsequent derangements in cardiac biomarkers,[23,24] which, therefore, leads to cardiac dysfunction and delayed effects on mortality. However, the subsequent debate from these studies has been whether ICD shocks themselves lead to worsened prognosis or act only as a surrogate marker for advanced underlying myocardial disease.

Prior research has not conclusively answered this question. In a MADIT II substudy, Daubert et al reported that 101 of 719 patients with ischemic heart disease and reduced ejection fraction experienced an appropriate ICD shock, which was associated with a hazard for mortality of 3.36 (P<0.01).[4] In the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), an appropriate ICD shock occurred in 182 of 811 patients and was associated with a hazard for mortality of 5.68 (P<0.01).[5] Longer follow-up (45 versus 21 months) and the exclusion of NYHA class I patients in the SCD-HeFT have been thought to account for the nearly 2-fold increase in risk of mortality from appropriate shock when compared with MADIT II. The SCD-HeFT investigators also protocolled a significantly higher ICD VT zone 1 threshold (>188 bpm) compared with MADIT II (171.9±14.5 bpm).[5] Our results suggest that the higher programmed thresholds in the SCD-HeFT may have identified faster rates of VAs at the time of appropriate ICD shock, and thus selected patients with advanced myocardial substrate disease who already carried a greater risk of mortality. Sweeney et al had shown that shock therapy may lead to greater mortality relative to ATP; however, they did not stratify the ICD therapies by the rate of the underlying VA.[25]

MADIT-RIT too sought to address this issue, by assigning patients to different programming settings for the detection of arrhythmia and delivery of ICD therapy.[17] In this trial, patients assigned to high-rate programming had a decreased rate of first occurrence of ICD therapy (*P*<0.001) and improved mortality outcomes (*P*<0.01) over those with conventional programming settings. Patient assigned to a delayed programming regimen showed similar patterns as far as first occurrence of ICD therapy (*P*<0.001) and mortality (*P*=0.06). Notably, the MADIT-RIT study population was composed almost exclusively of NYHA class II and III patients, and the follow-up was only 1.4 years. Although there was an association between increased rates of ICD therapy and higher mortality in the conventional therapy group in this trial, the patient population differed from that of the present trial, which includes only patients with NYHA class I and II HF and collected data for a significantly longer period of follow-up (2.4 years). Thus, our findings apply to patients with mild HF, and it may be possible that patients with more advanced disease, as in MADIT-RIT, are more susceptible to biomechanical stresses associated with ICD therapy.

In the present study, we show that the risk for mortality is similar for ATP and shock if they were rendered for the same rate of VA in this patient population. These findings suggest that adverse outcomes associated with appropriate ICD shocks are a manifestation of the underlying VA burden. As has been well documented in the literature, the prevalence of ventricular tachyarrhythmias is a harbinger of underlying myocardial disease. Ischemic, toxic-metabolic, and neurohormonal insults can lead to ventricular remodeling, on both gross (ie, echocardiographic) and microscopic (ie, increased cross-bridge formation within ventricular sarcomeres) levels.[26–28] Maladaptive remodeling has been shown to be a ripe substrate for life-threatening arrhythmias.[29,30] Because of ICD's ability to detect abnormal and potentially lethal VAs, the discharge of ICD shock or ATP therapy acts as a clinical surrogate for the detection of these abnormal rhythms. In this way, appropriate ICD therapy can identify signs of a high-risk myocardial substrate, and our research adds to this notion by introducing the nuance that ICD therapy rendered for fast VA but not for slow VA is a marker of a severe underlying substrate. ICD therapy for slow VAs does not carry a higher risk compared with the control group. These findings are consistent with previous reports that slow VAs are better tolerated than fast VAs. Previous reports have suggested patients with HF who have fast VT experience syncope and evidence of hemodynamic compromise at higher rates than slow VT.[31] Indeed, larger size of the myocardial arrhythmogenic substrate may predispose to fast VT or VF.[32]

Given the relationship between inappropriate ICD therapy and mortality, we further adjusted our analyses for inappropriate ICD therapy. Inappropriate therapy in our analysis was not associated with increased mortality, an observation that is consistent with other studies. This further strengthens our conclusion that higher-rate VAs are a marker for advanced underlying myocardial disease and increased mortality, whereas the type of therapy (ATP or shocks) is less likely to be a direct contributor to mortality risk. Despite the fact that shocks themselves are not directly associated with mortality in patients with mild HF, therapies for the management of slow VA should be programmed according to the findings of MADIT-RIT, given the improvements seen in rates of both mortality and inappropriate therapy delivery.[17]

ICD shocks are concerning because of the pain involved and the association with psychological distress.[33–37] Thus, the prognostic significance of the type of VA is highly important for patients. Specifically, it is imperative to explain to those who experienced a shock or ATP for slow VA that they are not at increased risk for mortality.

Study Limitations

As stated, MADIT-CRT considered only patients with mild HF, limiting our ability to assess patients with more advanced HF. Data related to cardiac biomarkers were not collected, and we were thus unable to assess myocardial damage subsequent to ICD shock. Because a measurement of cardiac scar tissue was also not available, the extent of myocardial substrate disease could not be assessed, limiting our ability to distinguish between the potential causes of fast versus slow VAs. Furthermore, this is a retrospective, nonrandomized post hoc study. MADIT-CRT was not randomized to assess the type of the ICD therapy on outcome. Although we used multivariate analysis with adjustments for many confounders, possible unmeasured confounders may have biased the results.

Conclusions

In conclusion, in patients with mild HF who receive ICD for primary prevention, mortality is associated with the rate of underlying VA rather than the device-rendered therapy. This finding supports the hypothesis that shocks represent a marker of disease severity rather than a direct contributor to mortality in patients with HF.

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