ORIGINAL ARTICLE

Reduction in Inappropriate Therapy and Mortality through ICD Programming

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ABSTRACT

BACKGROUND

The implantable cardioverter–defibrillator (ICD) is highly effective in reducing mortality among patients at risk for fatal arrhythmias, but inappropriate ICD activations are frequent, with potential adverse effects.

METHODS

We randomly assigned 1500 patients with a primary-prevention indication to receive an ICD with one of three programming configurations. The primary objective was to determine whether programmed high-rate therapy (with a 2.5-second delay before the initiation of therapy at a heart rate of ≥200 beats per minute) or delayed therapy (with a 60-second delay at 170 to 199 beats per minute, a 12-second delay at 200 to 249 beats per minute, and a 2.5-second delay at ≥250 beats per minute) was associated with a decrease in the number of patients with a first occurrence of inappropriate antitachycardia pacing or shocks, as compared with conventional programming (with a 2.5-second delay at 170 to 199 beats per minute and a 1.0-second delay at ≥200 beats per minute).

RESULTS

During an average follow-up of 1.4 years, high-rate therapy and delayed ICD therapy, as compared with conventional device programming, were associated with reductions in a first occurrence of inappropriate therapy (hazard ratio with high-rate therapy vs. conventional therapy, 0.21; 95% confidence interval [CI], 0.13 to 0.34; P<0.001; hazard ratio with delayed therapy vs. conventional therapy, 0.24; 95% CI, 0.15 to 0.40; P<0.001) and reductions in all-cause mortality (hazard ratio with high-rate therapy vs. conventional therapy, 0.45; 95% CI, 0.24 to 0.85; P=0.01; hazard ratio with delayed therapy vs. conventional therapy, 0.56; 95% CI, 0.30 to 1.02; P=0.06). There were no significant differences in procedure-related adverse events among the three treatment groups.

CONCLUSIONS

Programming of ICD therapies for tachyarrhythmias of 200 beats per minute or higher or with a prolonged delay in therapy at 170 beats per minute or higher, as compared with conventional programming, was associated with reductions in inappropriate therapy and all-cause mortality during long-term follow-up. (Funded by Boston Scientific; MADIT-RIT ClinicalTrials.gov number, NCT00947310.)

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The implantable cardioverter–defibrillator (ICD), either alone or in conjunction with cardiac-resynchronization therapy (CRT), is highly effective in reducing the rate of death due to ventricular tachyarrhythmia among high-risk cardiac patients.[1-4] However, inappropriate ICD activations, which are typically caused by supraventricular tachyarrhythmias, are frequent, despite sophisticated device-related detection algorithms that are designed to differentiate supraventricular from ventricular tachyarrhythmias; such activations have potentially life-threatening side effects.[5,6]

Inappropriate device-delivered therapy, defined as therapy delivered for nonventricular tachyarrhythmias, affects 8 to 40% of patients with ICDs.[5] The best method for programming ICD devices to reduce inappropriate therapy is unknown.[7] We conducted a large-scale, randomized study designed to evaluate specific programming features for reducing inappropriate therapy in patients with ICDs.

We hypothesized that programming ICD devices to deliver therapy at a heart rate of 200 beats per minute or higher or to increase the duration of the monitoring delay before the initiation of therapy would decrease the number of patients receiving inappropriate antitachycardia pacing or shocks without increasing morbidity or mortality, as compared with conventional programming.

Methods

Trial Design and Oversight

From September 15, 2009, through October 10, 2011, we enrolled 1500 patients at 98 hospital centers: 1017 patients at 61 centers in the United States, 35 patients at 2 centers in Canada, 277 patients at 23 centers in Europe, 103 patients at 6 centers in Israel, and 68 patients at 6 centers in Japan. Follow-up continued until trial termination on July 10, 2012.

The protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board at each of the participating centers. The investigational treatment was designed to determine whether dual-chamber ICD devices or CRT devices with ICD (CRT-D) programmed with a high heart-rate threshold or with an extended delay before initiation of antitachycardia pacing or shock delivery would be associated with a decrease in the number of patients receiving inappropriate therapies, as compared with conventional programming. Dual-chamber ICDs were used so that the two types of devices could have similar detection programming and a similar ability to identify the arrhythmia triggering the device-delivered therapy on interrogation. Details of the study design, including the definition of inappropriate therapy, have been published previously.[8] All investigators agreed to abide by the conflict-of-interest guidelines described by Healy et al.[9] All patients provided written informed consent.

The trial was designed by members of the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) executive committee. The data were gathered by the investigators at the participating centers, managed by the coordination and data center at the University of Rochester, and analyzed by the biostatistics committee, also at the University of Rochester. The first draft of the manuscript was written by the first author, with revisions by the coauthors. All the authors agreed to submit the manuscript for publication. The sponsor of the trial, Boston Scientific, was not involved in data collection, data analysis, or preparation of the manuscript. The authors vouch for the accuracy and completeness of the reported findings, as well as the fidelity of this report to the study protocol.

Recruitment and Follow-up

Patients of either sex who were at least 21 years of age could participate in the study if they had ischemic or nonischemic heart disease, were in sinus rhythm, and met approved guidelines for primary prevention with an ICD or CRT-D.[10] Patients were excluded from enrollment if they had an implanted pacemaker, ICD, or resynchronization device; had a history of permanent atrial fibrillation; had undergone coronary-artery bypass grafting or percutaneous coronary intervention or had an enzyme-positive myocardial infarction within 3 months before enrollment; or met other exclusion criteria as described in the design of the trial.[8]

Patients were seen in clinical follow-up at 3-month intervals for the first year and then at 6-month intervals until trial termination. Clinical evaluation and device testing were carried out at each follow-up visit. The treating physicians were aware of the study-group assignments. Physicians were encouraged to follow current practice guidelines for pharmacologic therapy.

RANDOMIZATION

A baseline clinical history and 12-lead electrocardiogram were obtained and a physical examination was performed for each patient. Patients were then randomly assigned (in a 1:1:1 ratio with the use of blocking and stratification) to receive an ICD with one of three programming configurations for the detection of ventricular tachycardia or ventricular fibrillation and the initiation of therapy, with similar programming for patients with an ICD alone and those with a CRT-D device, as previously reported.[8]

Briefly, the patients in the conventional-therapy group received a device programmed to two detection zones: one at a heart rate of 170 to 199 beats per minute for ventricular tachycardia, with a 2.5-second delay and atrial discriminators turned on, and a second zone beginning at 200 beats per minute for faster tachycardia, with a 1.0-second delay before delivery of antitachycardia pacing or shock. Patients in the high-rate group received a device programmed to a monitor-only zone between 170 and 199 beats per minute and to a therapy zone beginning at 200 beats per minute, after a 2.5-second monitoring delay. Patients in the delayed-therapy group received a device programmed to three detection zones: one at 170 to 199 beats per minute, with rhythm detection on and a 60-second delay before initiation of therapy; a second tachyarrhythmia-detection zone beginning at 200 beats per minute, with rhythm detection on and a 12-second delay before therapy; and a third zone at 250 beats per minute or higher, with a 2.5-second delay before initiation of therapy. In all devices, antitachycardia pacing was followed by shock therapy if pacing did not terminate the detected tachyarrhythmia. A summary diagram of the device programming in the three treatment groups is presented in Figure S1 in the Supplementary Appendix, available at NEJM.org.

DEVICE THERAPY

Commercially available transvenous devices (Boston Scientific) were used in the trial. Routine clinical methods were used for device implantation and testing, with defibrillation-threshold testing according to the Food and Drug Administration–approved labeling. The ICDs were programmed to minimize unnecessary right ventricular pacing. Details of the detection algorithms, programming, and delivered therapy for each of the three treatment groups are provided in the published design of the trial.[8] The total shock energy (in joules) accumulated over the course of the trial for appropriate and inappropriate shocks was recorded according to treatment group.

END POINTS

The prespecified primary end point was the first occurrence of inappropriate therapy (i.e., therapy delivered for nonventricular tachyarrhythmias), either antitachycardia pacing or shock. The investigators could change device programming after the first occurrence of inappropriate therapy. A three-member independent electrogram and device-interrogation committee reviewed all device interrogations with the use of electronic media downloaded from device interrogations at the enrolling centers. This core laboratory reviewed all interrogations to capture and adjudicate therapy events for appropriate or inappropriate antitachycardia pacing or shock (with appropriate therapy defined as therapy delivered for ventricular tachyarrhythmias). The classifications of specific atrial and ventricular tachyarrhythmias were based on the committee's interpretation of the device electrogram printouts, with adjudication of morphologic features, tachycardia onset, and rate stability.

The secondary end points were death from any cause and the first episode of syncope. A three-member independent morbidity and mortality committee reviewed the classification of death by the enrolling centers, including supporting source documents, and used a modified Hinkle–Thaler definition[11] to arrive at a consensus interpretation of the cause of death. Syncopal events were identified by the physicians at the enrolling centers and were adjudicated by the committee.

STATISTICAL ANALYSIS

The study was carried out as if two trials were being conducted simultaneously: one comparing high-rate therapy with conventional therapy and the other comparing delayed therapy with conventional therapy. Time zero for each patient was the date of randomization to one of the three study groups. The hypotheses were that the high-rate group, the delayed-therapy group, or both would have a reduced risk of a first occurrence of inappropriate therapy, as compared with the conventional-therapy group. The two trials were conducted in parallel, with inference made in each, and no adjustment for multiple comparisons was deemed appropriate.

Data analysis was performed according to the intention-to-treat principle. In the primary analysis, a Cox proportional-hazards regression model[12] was used to estimate the risk of a first occurrence of inappropriate therapy, with death recognized as a competing risk. The analysis was stratified according to enrolling center, status with regard to a history of paroxysmal atrial fibrillation, and device type (ICD or CRT-D). To achieve 90% power to detect a hazard ratio for inappropriate therapy of 0.5 with high-rate or delayed therapy, as compared with conventional therapy, representing a 50% reduction in the risk of inappropriate therapy, a total of 88 events were required in the two groups being compared, both in the high-rate and conventional-therapy groups together and in the delayed-therapy and conventional-therapy groups together. Additional primary analyses included Cox proportional-hazards regression for nine prespecified categorical subgroups.

The secondary analysis also used proportional-hazards regression models to evaluate all-cause mortality and first syncopal episodes in the three groups. We constructed Kaplan–Meier graphs for the primary end point and for mortality according to treatment-group assignment, with the log-rank test for significance testing.[13] Crude rates of the first occurrence and any occurrence of appropriate and inappropriate therapies were compared with the use of chi-square tests, and mean counts of total occurrences of therapy were compared with the use of negative binomial regression models.

Assumptions of proportional-hazards modeling were evaluated and were found to be valid. The analyses are based on version 1.0 of the database dated September 4, 2012.

RESULTS

STUDY POPULATION

The clinical characteristics of the 1500 patients who underwent randomization are presented in Table 1. Baseline characteristics, including the use of cardiovascular medications, were similar in the three groups. Follow-up of patients in the trial averaged 1.4 years.

Conventional therapy and delayed therapy involved prespecified arrhythmia-detection algorithms (Fig. S1 in the Supplementary Appendix). Programming deviations were identified before the first occurrence of inappropriate therapy in the prespecified therapy protocols in 51 patients in the conventional-therapy group (9.9%), 43 in the high-rate group (8.6%), and 80 in the delayed-therapy group (16.5%) (Table S1 in the Supplementary Appendix). When identified, programming deviations were corrected. Implant-related adverse events during the first 30 days, including infection, pocket hematoma, coronary venous dissection, pneumothorax, and lead dislodgement, were infrequent, and the rates did not differ significantly among the three treatment groups (Table S2 in the Supplementary Appendix). A total of 168 patients (52 in the conventional-therapy group, 66 in the high-rate group, and 50 in the delayed-therapy group) were withdrawn or were lost to follow-up during the course of the trial, and data on these patients were censored at the time of last contact.

OCCURRENCES OF APPROPRIATE AND INAPPROPRIATE THERAPY

Table 2 shows the number of patients with a first occurrence of appropriate or inappropriate therapy, the number of patients with any occurrence of device-delivered therapy, and the total occurrences of appropriate and inappropriate therapy during the trial, according to treatment group and type of therapy (antitachycardia pacing or shock). As compared with the conventional-therapy group, the high-rate and delayed-therapy groups had significantly fewer patients with a first occurrence of appropriate or inappropriate therapy and with any occurrence of device-delivered therapy, and there were fewer total occurrences of appropriate and inappropriate therapy; findings were dominated by reductions in antitachycardia pacing. First occurrences of inappropriate antitachycardia pacing were most frequent with regular supraventricular tachyarrhythmia (in 73% of the patients) and atrial fibrillation (in 19%), and first occurrences of inappropriate shocks were also most frequent with these arrhythmias (in 55% and 36% of the patients, respectively).

The total accumulated inappropriate shock energy over the course of the trial was 3714 J in the conventional-therapy group, 868 J in the high-rate group, and 1698 J in the delayed-therapy group; inappropriate shock energy was reduced in the high-rate and delayed-therapy groups by 77%

Table 1. Baseline Demographic and Clinical Characteristics According to Treatment Group.*

Variable	Conventional Therapy (N=514)	High-Rate Therapy (N=500)	Delayed Therapy (N=486)
Age — yr	63±11	63±12	62±12
Male sex — no. (%)	357 (69.5)	354 (70.8)	353 (72.6)
Race — no./total no. (%)†			
White	393/509 (77.2)	371/493 (75.3)	355/483 (73.5)
Black	84/509 (16.5)	91/493 (18.5)	97/483 (20.1)
Asian	23/509 (4.5)	27/493 (5.5)	26/483 (5.4)
Other	9/509 (1.8)	4/493 (0.8)	5/483 (1.0)
Cardiac history — no./total no. (%)			
Ischemic heart disease	271/514 (52.7)	268/499 (53.7)	252/485 (52.0)
Nonischemic heart disease	243/514 (47.3)	231/499 (46.3)	233/485 (48.0)
Cardiac risk factors — no./total no. (%)			
Hypertension	346/513 (67.4)	359/497 (72.2)	324/485 (66.8)
Diabetes mellitus	166/510 (32.5)	159/491 (32.4)	160/482 (33.2)
Current cigarette smoking	86/483 (17.8)	83/472 (17.6)	78/463 (16.8)
Atrial fibrillation	47/508 (9.3)	57/495 (11.5)	49/483 (10.1)
NYHA class II or III — no./total no. (%)	495/507 (97.6)	482/495 (97.4)	474/484 (97.9)
Body-mass index‡	29.4±7.1	28.9±6.5	29.5±6.9
Cardiac findings at enrollment			
Blood pressure — mm Hg			
Systolic	124±20	123±19	124±19
Diastolic	73±11	73±12	73±12
Resting heart rate — beats/min	72±12	72±12	73±13
Ejection fraction — %	26±6	26±7	26±7
Defibrillator type — no./total no. (%)			
ICD	258/514 (50.2)	248/499 (49.7)	236/486 (48.6)
CRT-D	256/514 (49.8)	251/499 (50.3)	250/486 (51.4)
Medications — no./total no. (%)			
ACE inhibitor	348/514 (67.7)	339/499 (67.9)	327/485 (67.4)
Aldosterone antagonist	188/514 (36.6)	190/499 (38.1)	165/485 (34.0)
Aspirin	317/514 (61.7)	334/499 (66.9)	321/485 (66.2)
Beta-blocker	476/514 (92.6)	467/499 (93.6)	460/485 (94.8)
Digitalis	62/514 (12.1)	65/499 (13.0)	66/485 (13.6)
Diuretic	336/514 (65.4)	355/499 (71.1)	316/485 (65.2)
Lipid-lowering statin	295/514 (57.4)	308/499 (61.7)	275/485 (56.7)

* Plus–minus values are means ±SD. There were no significant differences at P<0.05 between treatment groups. Conventional therapy involved a 2.5-second delay before the initiation of device therapy (antitachycardia pacing or shock) at a heart rate of 170 to 199 beats per minute and 1.0-second delay at 200 beats per minute or higher. High-rate therapy involved a 2.5-second delay at 200 beats per minute or higher. Delayed therapy involved a 60-second delay at 170 to 199 beats per minute, a 12-second delay at 200 to 249 beats per minute, and a 2.5-second delay at 250 beats per minute or higher. ACE denotes angiotensin-converting enzyme, CRT-D cardiac-resynchronization therapy with defibrillator, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.

† Race was determined by self-report.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. First Occurrence, Any Occurrence, and Total Occurrences of Appropriate and Inappropriate Device Therapy According to Treatment Group.*

Variable	Conventional Therapy (N=514)	High-Rate Therapy (N=500)	Delayed Therapy (N=486)	P Value for High-Rate Therapy vs. Conventional Therapy	P Value for Delayed Therapy vs. Conventional Therapy
First occurrence of therapy — no. of patients (%)					
Appropriate therapy	114 (22)	45 (9)	27 (6)	<0.001	<0.001
Shock	20 (4)	22 (4)	17 (3)	0.68	0.74
Antitachycardia pacing	94 (18)	23 (5)	10 (2)	<0.001	<0.001
Inappropriate therapy	105 (20)	21 (4)	26 (5)	<0.001	<0.001
Shock	20 (4)	11 (2)	13 (3)	0.12	0.28
Antitachycardia pacing	85 (17)	10 (2)	13 (3)	<0.001	<0.001
Any occurrence of therapy — no. of patients (%)					
Appropriate therapy					
Shock	28 (5)	26 (5)	19 (4)	0.86	0.25
Antitachycardia pacing	111 (22)	38 (8)	20 (4)	<0.001	<0.001
Inappropriate therapy					
Shock	31 (6)	14 (3)	15 (3)	0.01	0.03
Antitachycardia pacing	104 (20)	20 (4)	25 (5)	<0.001	<0.001
Total occurrences of therapy — no. of occurrences					
Appropriate therapy	517	185	196	<0.001	<0.001
Shock	71	72	53	0.35	0.15
Antitachycardia pacing	446	113	143	<0.001	<0.001
Inappropriate therapy	998	75	264	<0.001	<0.001
Shock	105	25	49	0.001	0.16
Antitachycardia pacing	893	50	215	<0.001	<0.001

* Crude rates of the first occurrence of therapy and any occurrence of therapy were compared with the use of chi-square tests, and mean counts of total occurrences of therapy were compared with the use of negative binomial regression models.

(P=0.01) and 54% (P=0.03), respectively. The total appropriate shock energy was similar in the three treatment groups (P=0.48).

END POINTS

Kaplan–Meier estimates of time to the first occurrence of inappropriate therapy in the three treatment groups are shown in Figure 1. Patients in the conventional-therapy group had a 29% probability of inappropriate therapy at 2.5 years, with rates of 6% in the high-rate and delayed-therapy groups during the same follow-up period. In the Kaplan–Meier estimates of all-cause mortality (Fig. 2), the conventional-treatment group had a significantly higher cumulative mortality during follow-up than did the high-rate and delayed-therapy groups.

The hazard ratios for first occurrence of inappropriate therapy as well as for death and syncope are presented in Table 3. In the comparison of the first occurrence of inappropriate therapy in the high-rate group with that in the conventional-therapy group, the hazard ratio of 0.21 indicates a 79% reduction in risk; delayed therapy was associated with a 76% reduction in the risk of a first occurrence of inappropriate therapy, as compared with conventional therapy. Mortality was reduced by 55% in the high-rate group (P=0.01) and by 44% in the delayed-therapy group (P=0.06). The frequency of a first episode of syncope was similar in the three treatment groups.

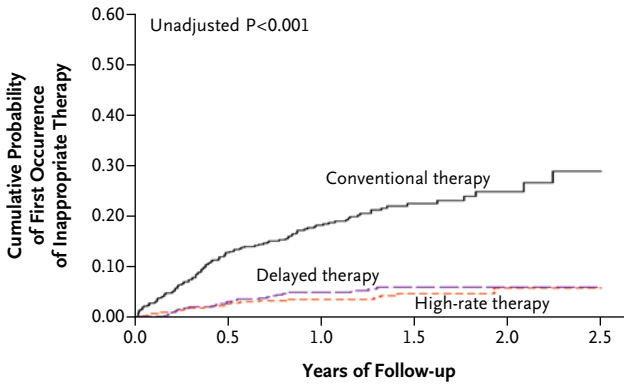
In nine prespecified subgroups, the decreases in the risk of inappropriate therapy and in mortality with high-rate therapy and delayed therapy relative to conventional therapy were consistent with those in the primary analysis (Fig. S2 in the Supplementary Appendix). No significant interactions between subgroup and treatment were identified for the inappropriate-therapy and mortality end points.

DISCUSSION

Conventional ICD programming to treat ventricular tachyarrhythmias at a heart rate of 170 beats per minute or higher has been an accepted programming strategy, although specific detection parameters have not been evaluated systematically. In a nonrandomized ICD trial, higher rate cutoffs, longer arrhythmia-detection windows, and parameters for discrimination of supraventricular tachyarrhythmias were associated with reductions in shocks and other adverse outcomes.[14] The current study was a large-scale, randomized trial comparing devices providing two specific programmed therapies with conventionally programmed therapy. High-rate therapy (delivered at a heart rate of ≥200 beats per minute) was associated with a 79% reduction in a first occurrence of inappropriate therapy, with inappropriate antitachycardia pacing decreased by a factor of approximately 6 to 8 and inappropriate shocks decreased by a factor of nearly 2. In addition, there was a 55% reduction in all-cause mortality. Similar but less significant findings were observed in the delayed-therapy group, and device programming in that group included a rhythm-detection algorithm.

The primary prespecified end point was a first occurrence of inappropriate therapy. In the design of the trial, we were concerned that the higher rate threshold or longer delay before initiation of device-delivered therapy might be associated with modest increases in mortality and syncope, but these concerns were not realized. Rather, all-cause mortality was significantly reduced with the high rate threshold of 200 beats per minute, and the frequency of syncope was similar in all three treatment groups.

The very high rate of inappropriate antitachycardia pacing with conventional therapy (delivered at a heart rate of ≥170 beats per minute) reflects frequent atrial tachyarrhythmias occurring in the range of 170 to 199 beats per minute and the failure of device algorithms to discriminate between atrial and ventricular tachyarrhythmias in this range. Some occurrences of inappropriate antitachycardia pacing converted supraventricular tachyarrhythmias to ventricular tachyarrhythmias that were then terminated by subsequent appropriate shock therapy, and our device interrogations revealed several of these sequences. In addition, appropriate antitachycardia pacing was significantly less frequent in the high-rate and delayed-therapy groups than in the conventional-therapy group, a finding that suggests that many episodes of nonsustained ventricular tachycardia that would have terminated spontaneously were treated prematurely in the conventional-therapy

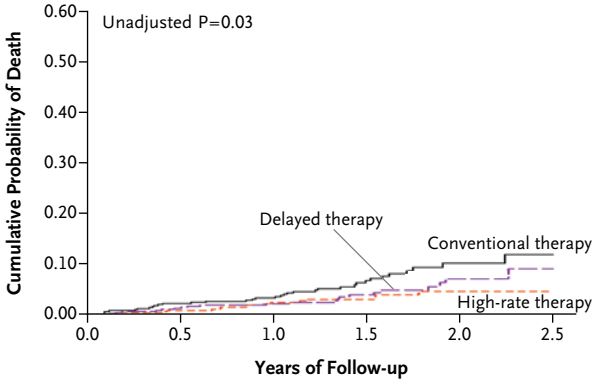


No. at Risk

Conventional therapy	514	420 (0.13)	305 (0.18)	149 (0.22)	56 (0.25)	8 (0.29)
High-rate therapy	500	454 (0.03)	339 (0.04)	191 (0.05)	70 (0.06)	17 (0.06)
Delayed therapy	486	445 (0.03)	342 (0.05)	177 (0.06)	82 (0.06)	13 (0.06)

Figure 1. Cumulative Probability of First Occurrence of Inappropriate Therapy According to Treatment Group.

The values in parentheses are Kaplan–Meier estimates of the cumulative probability of a first occurrence of inappropriate device-delivered therapy in patients randomly assigned to therapy programmed for delivery at a heart rate of 170 beats per minute or higher (conventional therapy), at a heart rate of 200 beats per minute or higher (high-rate therapy), or at a heart rate of 170 beats per minute or higher with longer tachyarrhythmia monitoring (delayed therapy).



No. at Risk

Conventional therapy	514	490 (0.02)	392 (0.03)	219 (0.07)	89 (0.10)	14 (0.12)
High-rate therapy	500	478 (0.01)	372 (0.02)	221 (0.03)	90 (0.05)	21 (0.05)
Delayed therapy	486	471 (0.01)	375 (0.02)	205 (0.04)	99 (0.07)	14 (0.09)

Figure 2. Cumulative Probability of Death According to Treatment Group.

The values in parentheses are Kaplan–Meier estimates of the cumulative probability of death.

Table 3. Hazard Ratios for a First Occurrence of Inappropriate Therapy, Death, and a First Episode of Syncope According to Treatment Group.

Variable	Conventional Therapy (N=514)	High-Rate Therapy (N=500)	Delayed Therapy (N=486)	High-Rate Therapy vs. Conventional Therapy		Delayed Therapy vs. Conventional Therapy	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	no. of patients						
First occurrence of inappropriate therapy	105	21	26	0.21 (0.13–0.34)	<0.001	0.24 (0.15–0.40)	<0.001
Death	34	16	21	0.45 (0.24–0.85)	0.01	0.56 (0.30–1.02)	0.06
First episode of syncope	23	22	22	1.32 (0.71–2.47)	0.39	1.09 (0.58–2.05)	0.80

group. In retrospect, such therapy could be considered unnecessary.

The significant reduction in appropriate and inappropriate antitachycardia pacing in the high-rate and delayed-therapy groups may have contributed to the observed mortality reduction of 44 to 55% seen in this study, and the findings raise questions about the need for and safety of empirical antitachycardia pacing. Wathen et al. evaluated the safety of initial antitachycardia pacing versus initial shock therapy in a randomized trial involving more than 300 patients in each treatment group, and they observed 10% mortality with antitachycardia pacing versus 7% with shock during a 1-year follow-up,[15] a trend that was not significant but was troubling. The marked decrease in inappropriate antitachycardia pacing with the improved programming would also be associated with fewer episodes of atrial fibrillation induced by antitachycardia pacing, which would also result in reduced mortality.[16]

Although controversial, there is evidence that defibrillator shocks can cause myocardial damage,[17-20] and the shocks have been associated with increased mortality.[21,22] Reductions in the number of inappropriate shocks and the associated significant reductions in total inappropriate shock energy delivered to the myocardium in the high-rate and delayed-therapy groups may have resulted in diminished myocardial damage and lower mortality in these two treatment groups relative to the conventional-therapy group.

The number of deaths in the present study is small, and detailed subgroup analyses of the relationship between device programming and death have limited power. The mechanisms linking diminished occurrences of inappropriate shock, antitachycardia pacing, and unnecessary therapy with reduced mortality are complex and require further investigation to determine specific causality.

Although the trial was not designed to compare the effectiveness of programmed high-rate therapy with that of delayed therapy, it is obvious from the reported findings that the overall results of these two methods of programmed therapy were similarly superior to the results of conventional programming. However, programming delayed therapy together with enhanced rhythm detection is quite complex, whereas programming therapy at a heart rate of 200 beats per minute or higher is simple.

The findings from this randomized trial add a new chapter in the ongoing evolution of ICD therapy for primary prevention, with two programming approaches that reduced potentially dangerous inappropriate therapies and increased survival among patients with ICDs.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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