

Strategic Programming of Detection and Therapy Parameters in Implantable Cardioverter-Defibrillators Reduces Shocks in Primary Prevention Patients

Results From the PREPARE (Primary Prevention Parameters Evaluation) Study

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- Objectives** Our purpose was to demonstrate that strategically chosen implantable cardioverter-defibrillator (ICD) ventricular tachycardia (VT) or ventricular fibrillation (VF) detection and therapy parameters can reduce the combined incidence of device-delivered shocks, arrhythmic syncope, and untreated sustained symptomatic VT/VF (morbidity index).
- Background** Strategically chosen ICD VT/VF detection and therapy parameters have been shown in previous studies to reduce the number of shocked episodes. In the PREPARE (Primary Prevention Parameters Evaluation) study, these prior strategies were combined with additional strategies specific to primary prevention patients.
- Methods** The PREPARE study was a prospective, cohort-controlled study that analyzed 700 patients (biventricular [Bi-V] ICD and non-Bi-V ICD) with primary prevention indications for an ICD from 38 centers followed for 1 year. VT/VF was detected for rates ≥ 182 beats/min that were maintained for at least 30 of 40 beats. Antitachycardia pacing was programmed as the first therapy for regular rhythms with rates of 182 to 250 beats/min, and supraventricular tachycardia discriminators were used for rhythms ≤ 200 beats/min. The control cohort consisted of 689 primary prevention patients from the EMPIRIC (Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter Defibrillators Trial) (non-Bi-V ICD, physician arm only) and MIRACLE ICD (Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation) (Bi-V ICD) trials for whom VT/VF detection and therapy programming were not controlled.
- Results** The PREPARE programming significantly reduced the morbidity index incidence density (0.26 events/patient-year for PREPARE study patients vs. 0.69 control cohort, $p = 0.003$). The PREPARE study patients were less likely to receive a shock in the first year compared with control patients (9% vs. 17%, $p < 0.01$). The incidence of untreated VT and arrhythmic syncope was similar between the PREPARE study patients and the control cohort.
- Conclusions** Strategically chosen VT/VF detection and therapy parameters can safely reduce shocks and other morbidities associated with ICD therapy in patients receiving an ICD for primary prevention indications. (PREPARE-Primary Prevention Parameters Evaluation; NCT00279279) (J Am Coll Cardiol 2008;52:541-50) © 2008 by the American College of Cardiology Foundation

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son, Stern, Moore, Lu, Lee, Birgersdotter-Green, Wathen, and Van Gelder all received funding for participation as investigators for the PREPARE study. Drs. Williamson, Stern, Lee, Birgersdotter-Green, and Wathen have served as consultants for Medtronic, Inc., the sponsor of the PREPARE study. Brooke Heubner, Dr. Brown, and Keith Holloman are employed by and own stock in Medtronic, Inc., the sponsor of the PREPARE study. Alfred E. Buxton, MD, served as Guest Editor for this article.

Manuscript received September 25, 2007; revised manuscript received April 18, 2008, accepted May 2, 2008.

**Abbreviations
and Acronyms**

ATP	= antitachycardia pacing
Bi-V	= biventricular
CI	= confidence interval
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
LVEF	= left ventricular ejection fraction
SVT	= supraventricular tachycardia
VF	= ventricular fibrillation
VT	= ventricular tachycardia

The effectiveness of implantable cardioverter-defibrillator (ICD) therapy at reducing mortality is well documented, initially as secondary prevention after aborted sudden cardiac death and more recently in primary prevention patients (1,2). However, the mortality benefit comes at the cost of some morbidity, including the pain caused by defibrillating shocks, both appropriate and inappropriate. Between 15% to 25% of patients who receive multiple shocks experience increased anxiety and depression and, therefore, have difficulty adjusting to life with an ICD (3,4).

In addition, a shock may be proarrhythmic (5). Therefore, avoidance of unnecessary shocks remains an important goal. Previous investigations have demonstrated substantial differences in frequency, rate, and mechanisms of tachycardia observed in patients with ICDs implanted for primary versus secondary prevention indications (6). The primary prevention patient population has been reported to have a lower incidence of ventricular arrhythmias compared with secondary prevention patients (6,7). Consequently, a higher proportion of ICD therapies in primary prevention patients could be due to inappropriate detections and therapies primarily due to arrhythmias such as sinus tachycardia and atrial fibrillation (6,8).

The PainFREE RX II (Pacing Fast VT REduces Shock Therapies) and EMPIRIC (Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter Defibrillators) trials demonstrated that specific ventricular tachycardia (VT) and ventricular fibrillation (VF) detection and therapy programming strategies reduced the frequency of shocked episodes (9,10). The use of detection algorithms designed to distinguish supraventricular and ventricular tachyarrhythmias and the use of antitachycardia pacing (ATP) to terminate rapid VTs have been reported to be important components of programming strategies designed to optimize ICD programming (11-14). The EMPIRIC and PainFREE RX II trials assessed ICD detection and therapy strategies to safely reduce the morbidity associated with ICD shock in a patient population that included primary and secondary prevention patients with no indication for a biventricular (Bi-V) ICD device. The purpose of the PREPARE (Primary Prevention Parameters Evaluation) study was to adapt these strategies specifically to primary prevention patients both with and without Bi-V ICD indications. A treatment rate cutoff of 188 beats/min has been used to treat primary prevention patients in several large trials (2,6,15). In the latter 2 studies, investigators recommended a treatment cutoff between 170 and 180 beats/min for primary prevention patients in order

to reduce the proportion of inappropriate therapies while still providing appropriate therapy. These recommendations were adopted for the PREPARE study, which used a rate cutoff of 182 beats/min.

Methods

Patients. THE PREPARE STUDY COHORT. Details of the PREPARE study design have been previously reported (16). The PREPARE study was a prospective 38-center study comprised of 700 patients without a history of spontaneous sustained symptomatic VT or VF (primary prevention patients), who had an indication for a single chamber, dual chamber, or Bi-V ICD.

Inclusion criteria required:

- Initial implantation for primary prevention ICD indications or
- Prior ICD implantation within 6 months without subsequent spontaneous VT/VF episodes

Patients were excluded for:

- History of spontaneous sustained symptomatic ventricular arrhythmias
- An electrophysiology test in the past, with inducible sustained VT <180 beats/min
- Any ICD implanted >6 months before the study
- An ICD implanted within the previous 6 months, with subsequent history of a spontaneous episode of VT or VF appropriately treated with either ATP or shock

Patients were not excluded for a history of supraventricular tachycardia (SVT) or other nonventricular tachycardia or a ventricular fibrillation event. Enrollment was conducted between October 2003 and May 2005. The institutional review board at each center approved the study protocol, and written informed consent was obtained from each patient.

CONTROL COHORT. The control cohort was a historical control group comprised of the entire subset of patients from the previously conducted MIRACLE ICD (Multi-center InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation) and EMPIRIC trials who met the primary prevention definition and had VT/VF detection and therapy parameters programmed at the discretion of the physician.

The MIRACLE ICD trial was a randomized study of cardiac resynchronization therapy and ICD (Bi-V) effectiveness in 978 patients with New York Heart Association functional class II, III, or IV, left ventricular ejection fraction (LVEF) <35%, QRS duration >130 ms, and an ICD indication. Patients were enrolled from October 1999 to July 2002 and followed for a minimum of 12 months (17). The primary prevention subset of these patients (n = 415) provided the control cohort representing primary prevention patients receiving Bi-V ICD.

In the EMPIRIC trial, 900 patients with indications for an ICD were randomized to either standardized empiric or physician-tailored VT/VF programming. Patients implanted with dual chamber ICDs were enrolled from August 2002 to October 2003 and followed for 12 months. The primary prevention subset of the physician-tailored VT/VF programmed patients from the EMPIRIC trial (n = 276) provided the control cohort representing non-Bi-V ICD patients.

The control cohort was, therefore, made up of 415 primary prevention patients from the MIRACLE ICD trial and 276 patients from the EMPIRIC trial, for a total of 691 patients.

Programming. Tachyarrhythmia detection and therapy settings were strategically chosen in the PREPARE study cohort to safely reduce shocks for VT/VF and SVTs (Table 1). The key strategies included: 1) detecting only fast tachycardias; 2) detecting only sustained tachycardias; 3) applying ATP as first therapy for fast VTs; 4) employing SVT discriminators; and 5) employing high-output first shock. A more detailed discussion of these strategies can be found in a report outlining the rationale for the study design (16). Bradycardia pacing settings were programmed at the discretion of the investigators. Detection and tachycardia therapy programming changes were allowed after enrollment but required documentation of medical justification. Programming of the VT/VF detection and therapy parameters in the control cohort was not specified and was at the discretion of the investigators.

Data collection. The PREPARE cohort patients were followed for 12 months, with device interrogations and clinical evaluations at 6 and 12 months. Data collection included VT/VF and SVT episodes, device programming, medical justifications for VT/VF programming changes, cardiovascular medications, and cardiovascular adverse events. The device-detected VT/VF and SVT episodes were classified by the investigator and then classified by another expert blinded to the patients' clinical information. Any discrepancies between these 2 classifications resulted in additional review and final classification by an electrophysiologist study investigator.

All cardiovascular adverse events were collected. These events, which included but were not limited to dizziness, near-syncope, and syncope, were reviewed by an adverse event review committee. Syncope diaries, clinical summa-

ries, and device-stored electrograms, interval plots, and episode logs were reviewed. If a syncopal event occurred within 24 h of an arrhythmic event, it was considered related to 1 or more VT/VF or SVT episodes.

Data collected in control patients included VT/VF and SVT episodes, device programming and justification for VT/VF programming changes, cardiovascular medications, and adverse events. All adverse events were reviewed and adjudicated by an adverse event review committee. Though adverse events committees for the 3 studies were different, decisions for all were made by consensus of 3 to 6 physicians, or, in the event no consensus was reached, a decision was made by the committee chair. VT/VF and SVT episodes stored by the device were evaluated to determine if device detection was appropriate. The EMPIRIC trial patients had device interrogations and clinical evaluations performed at 3, 6, and 12 months. The MIRACLE ICD trial patients were evaluated at 1, 3, 6, and 12 months.

End points. The primary end point of the study (the morbidity index) was designed to measure not only the beneficial effect of avoiding shocks but also to account for the potential adverse effects of the PREPARE study ICD programming. The morbidity index was comprised of the following events: 1) spontaneous episodes treated with device-delivered cardioversion or defibrillation, including appropriate and inappropriate shocks; 2) syncope secondary to arrhythmia or presumed arrhythmia; and 3) untreated sustained symptomatic VT/VF events (defined as untreated symptomatic episodes of at least 30 beats). Syncopal arrhythmias that were either shocked or untreated VT/VF were counted only once in the total number of morbidity index events. The morbidity index incidence density was calculated by dividing the morbidity index by the total patient-years of follow-up through the first 12 months. For the PREPARE study patients, Time 0 was the date of programming to the PREPARE study VT/VF programming parameters. For control patients, Time 0 was the date of implant.

The secondary end point was the morbidity tachycardia index, which was an extension of the morbidity index. The morbidity tachycardia index was composed of 3 types of events evaluated in the morbidity index: 1) spontaneous episodes treated with device-delivered cardioversion or defibrillation, including appropriate and inappropriate shocks; 2) syncope secondary to arrhythmia or presumed arrhyth-

Table 1 PREPARE VT/VF Programming Parameters

	Detection	Threshold	Beats to Detect	Therapies
VF	On	250 beats/min	30 of 40	30 to 35 J (max output) × 6
FVT	via VF	182 beats/min	30 of 40	Burst (1 sequence), 30 to 35 J (max output) × 5
VT	Monitor	167 beats/min	32	Off

Supraventricular tachycardia criteria on (dual chamber, biventricular implantable cardioverter-defibrillator): atrial fibrillation/flutter, sinus tachycardia (1:1 VT-ST boundary = 66%); supraventricular tachycardia criteria on (single chamber): wavelet morphology discrimination (match threshold = 70%); supraventricular tachycardia limit = 300 ms; burst antitachycardia pacing: 8 intervals, pacing cycle length = 88% of tachycardia cycle length. FVT = fast ventricular tachycardia; PREPARE = Primary Prevention Parameters Evaluation study; VF = ventricular fibrillation; VT = ventricular tachycardia; VT-ST = ventricular tachycardia-sinus tachycardia.

mia; 3) untreated sustained symptomatic VT/VF events (defined as untreated symptomatic episodes of at least 30 beats); and also included 4) spontaneous episodes treated only with ATP.

Statistical analyses. Statistical analyses were performed according to intention to treat and included all the PREPARE study patients and control patients with follow-up data. The primary hypothesis—that patients programmed using the PREPARE study parameters experience a lower rate of morbidity index events compared with patients programmed using physician-tailored programming—was tested with a Poisson regression analysis using generalized estimating equation methodology with an independent working correlation structure to account for within-patient correlation (18). Each patient’s outcome was the number of events, with patient-specific follow-up time treated as an offset. A propensity score analysis was used to compare event rates between the PREPARE study patients and control patients in 5 strata such that the PREPARE study patients and control patients in the same stratum had similar distributions of baseline characteristics (19): age at consent, gender, device type (Bi-V ICD/non-Bi-V ICD), baseline LVEF, use of beta-blockers, use of antiarrhythmic agents, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, New York Heart Association functional classification, atrial arrhythmias, myocardial infarction, valvular disease, hypertension, coronary artery bypass graft, cardiovascular syncope, and ischemic

cardiomyopathy. Propensity scores were estimated using logistic regression with baseline variables and their 2-way interactions as covariates. The generalized estimating equation Poisson analysis was repeated within strata defined by quintiles of the propensity score and averaged across these strata for the propensity score-adjusted analysis of the primary hypothesis. Analysis of variance (ANOVA) and Cochran-Mantel-Haenszel tests were used to assess balance of baseline covariates across quintiles of the propensity score. Analysis of the morbidity tachycardia index was also performed using this methodology.

All statistical analyses were performed using SAS (version 9.1, SAS Institute Inc., Cary, North Carolina). Comparisons of baseline characteristics were done using 2-sample *t* tests and chi-square tests. Kaplan-Meier estimates with log-rank tests and multivariable Cox proportional hazards models were used to compare the PREPARE study participants with the control cohort for patient mortality, all-cause shock, shock for true VT/VF, and shock for true SVT/other.

Results

Patient demographics. A total of 700 patients were enrolled in the PREPARE study. The control cohort was made up of 415 primary prevention patients from the MIRACLE ICD trial and 276 patients from the EMPIRIC trial, for a total of 691 patients. There were

Table 2 Baseline Patient Characteristics

	PREPARE (n = 700)	Control: Bi-V ICD* (n = 415)	Control: Non-Bi-V ICD† (n = 276)	Combined Control (n = 691)	p Value‡
Age, yrs, mean (SD)	67.4 (12.2)	65.4 (11.5)	65.6 (12)	65.5 (11.7)	0.003
Male gender	79%	75%	80%	77%	0.3
NYHA functional class					0.06
No heart failure or class I/II	59%	3%	86%	54%	
Class III/IV	41%	67%	14%	46%	
QRS duration, ms, mean (SD)	126.8 (35.4)	164.8 (22.2)	N/A	164.8 (22.2)	<0.0001
LVEF, %, mean (SD)	27.6 (10.4)	21 (6.8)	30.3 (11.0)	24.7 (9.8)	<0.0001
Ischemic cardiomyopathy§	70%	57%	56%	57%	<0.0001
Myocardial infarction§	60%	47%	70%	56%	0.11
Valvular heart disease§	26%	8%	21%	13%	<0.0001
Hypertension§	57%	44%	55%	48%	<0.001
CABG	44%	41%	49%	44%	0.98
Atrial arrhythmia history¶	33%	17%	23%	20%	<0.0001
Syncope or near-syncope#	31%	27%	43%	33%	0.32
Syncope	13%	N/A	29%	29%	<0.0001
Baseline medications					
ACE inhibitors or ARBs	84%	93%	69%	83%	0.91
Beta-blockers	84%	70%	76%	73%	<0.0001
Any antiarrhythmic agent	12%	23%	14%	20%	<0.0001

*The MIRACLE ICD trial primary prevention patients; †the EMPIRIC trial physician-tailored, primary prevention patients; ‡p value comparison of the PREPARE study cohort and combined control cohort comes from a *t* test, chi-square test, or Fisher exact test as appropriate; §1 MIRACLE ICD trial patient did not complete the Cardiovascular History section of the case report form. Therefore, the denominator used in the calculation of percentage is 414 instead of 415; ||10 patients in the MIRACLE ICD trial did not complete the Cardiovascular Surgical History section of the case report form. Therefore, the denominator used in the calculation of percentages is 405 instead of 415; ¶2 MIRACLE ICD trial patients did not complete the Spontaneous Arrhythmia section of the case report form. Therefore, the denominator used in the calculation of percentages is 413 instead of 415; #1 MIRACLE ICD trial patient did not complete the Syncope History section of the case report form. Therefore, the denominator used in the calculation of percentage is 414 instead of 415.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; Bi-V = biventricular; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PREPARE = Primary Prevention Parameters Evaluation study.

significant differences in baseline characteristics between groups (Table 2). Statistically significant differences were evident for baseline age, LVEF, history of ischemic cardiomyopathy, valvular heart disease, hypertension, atrial arrhythmias, syncope, baseline use of beta-blockers, and baseline use of antiarrhythmic agents. A greater proportion of patients enrolled in the PREPARE study were implanted with non-Bi-V ICD systems. Refer to Table 3 for details of implant and device characteristics. Because no record of patients excluded from the PREPARE study for inducible sustained VT <180 beats/min was maintained, an estimate of patients at risk for nondetection of slow VT was derived by finding the percentage of patients in the control cohort who received therapy for at least 1 VT <180 beats/min. Among control patients, 79 of 689 (11.5%) had at least 1 episode of VT <180 beats/min treated with ATP or shock.

Of the 700 patients, 452 (65%) received new implants at the time of enrollment, 145 (21%) were enrolled within 30 days of implant, and 103 (15%) were enrolled between 31 days and 6 months after implant. Nearly all, 689 of 691 (99.7%), of the control patients had follow-up data and were included in all analyses.

Programming. Figure 1A highlights important differences in programming between the PREPARE study patients and control patients. The PREPARE study patients were programmed according to protocol to detect and treat tachycardias faster than 182 beats/min while control patients had varying rate thresholds that were slower than 182 beats/min for the majority of patients. Figure 1B summarizes the cumulative percentage of treated patients programmed to ATP ON. Other differences in programming at baseline between the PREPARE study patients and control patients are detailed in Table 4. Of 700 PREPARE study patients enrolled, 658 (94%) were programmed correctly to the PREPARE study VT/VF parameters during the study.

Primary end point. The morbidity index incidence density (defined as the total number of morbidity index events divided by the total years of follow-up in the first 12 months) for the PREPARE study patients was significantly lower compared with that seen in the control cohort, (0.26 vs. 0.69, ratio = 0.38, 95% confidence interval [CI]: 0.20 to 0.72, $p = 0.003$) (Fig. 2).

The total number of morbidity index events is adjusted for events that count in more than 1 category. Shocked events and untreated VT/VF events that led to subsequent

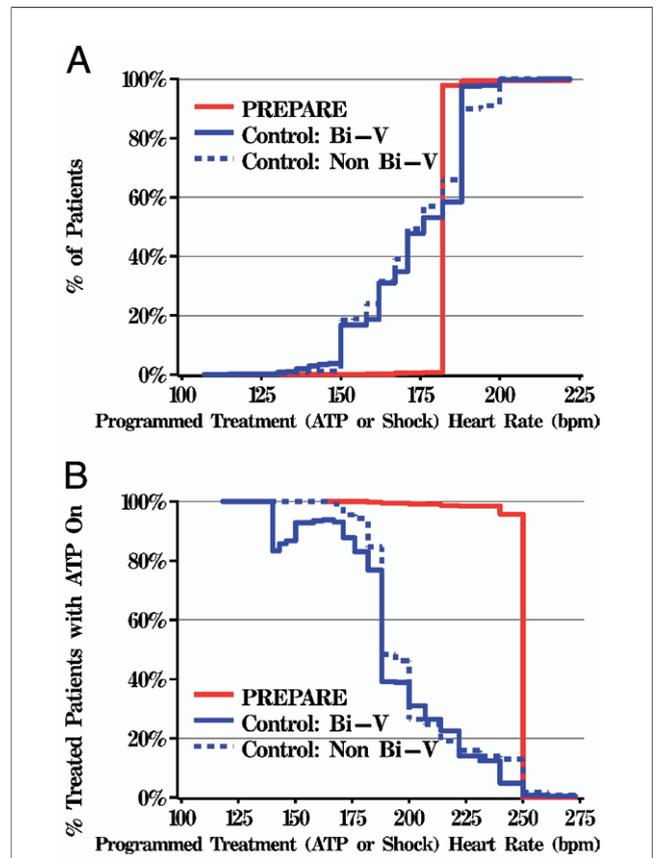


Figure 1 Programmed ICD Therapies Versus Heart Rate

(A) Cumulative percentage of patients programmed to antitachycardia pacing (ATP) and/or shock therapy (number of patients with ATP or shock therapy on at each heart rate/total number of patients in the cohort). The solid red line illustrates that nearly all PREPARE study patients had their implantable cardioverter-defibrillator (ICD) enabled to treat tachycardias >182 beats/min. In contrast, programming for the control cohort was enabled to treat slower tachycardias for the majority of patients. (B) Cumulative percentage of treated patients programmed to ATP on (number of patients with ATP programmed on at each heart rate/number of patients with ATP or shock therapy programmed on at each heart rate). The solid red line illustrates that nearly all PREPARE study patients who were programmed to be treated were programmed to be treated with ATP up to 250 beats/min. In marked contrast, a large proportion of control patients were programmed to be treated with shock, not ATP. For example, only about 40% of control patients programmed to be treated at heart rates faster than 200 beats/min were treated with ATP, while the remaining 60% were programmed to deliver shock without ATP. Bi-V = biventricular implantable cardioverter-defibrillator; bpm = beats/min.

Table 3 Implant and Device Characteristics		
	PREPARE (n = 700)	Combined Control (n = 691)
Device type		
Nonbiventricular	452 (65%)	276 (40%)
Single chamber	110 (24%)	0
Dual chamber	342 (76%)	276 (100%)
Biventricular	247 (35%)	415 (60%)
Unsuccessful implant	1 (<1%)	N/A

N/A = not applicable; PREPARE = Primary Prevention Parameters Evaluation study.

syncope events were counted only once in the total number of morbidity index events. The PREPARE study patients experienced 178 events of which 167 were included in the morbidity index. Not included were 11 morbidity index events that were not considered unique. These included 3 arrhythmic syncope events related to untreated VT/VF events and 8 arrhythmic syncope events related to shocked events. Patients in the control cohort experienced 351 morbidity index events of which 349 were included in the morbidity index. There were 2 morbidity index events not considered unique. These events were classified as arrhythmic syncope and were related to shocked events.

Table 4 ICD Detection and Therapy Programming

	PREPARE (n = 700)*	Combined Control (n = 689)
Treated rate threshold, † beats/min, median (25%, 75%)	182 (182, 182)	176 (162, 188)
VF number of intervals to detect, n (%)		
12 of 16	7 (1%)	397 (58%)
18 of 24	4 (<1%)	291 (42%)
24 of 32	0	1 (<1%)
30 of 40 ‡	687 (99%)	0
SVT discriminators ON, n (%) ‡	690 (99%)	518 (75%)
Therapy		
At least 1 ATP attempt for ventricular rates, n (%)		
In VT zone §	1 (<1%)	203 (29%)
In FVT zone †	693 (>99%)	171 (25%)
First VF therapy, J, n (%)		
<20	1 (<1%)	82 (12%)
20 to 29	10 (1%)	187 (27%)
30 to 35 ‡	687 (98%)	420 (61%)

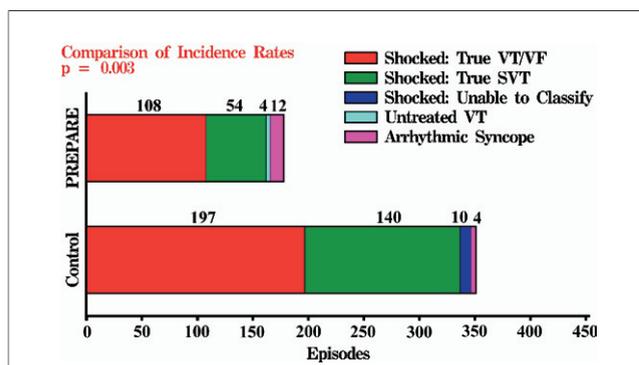
*Reported values are based on 698 PREPARE study patients with available baseline programming information; †PREPARE study patients were required to be programmed with a treated rate threshold of 182 beats/min. One patient had all detection programmed OFF at the programmed parameters visit. Eight days later the patient returned for an unscheduled visit and therapies were turned ON. This patient is not included in the calculation of treated rate threshold; ‡protocol-required PREPARE study programmed parameter; §PREPARE study patients were required to be programmed to VT monitor only.

ATP = antitachycardia pacing; ICD = implantable cardioverter-defibrillator; SVT = supraventricular tachycardia; other abbreviations as in Table 1.

There was no evidence this result was due to imbalance in baseline characteristics. The difference in morbidity index incidence density between the PREPARE study patients and control patients remained significant (ratio = 0.44, 95% CI: 0.26 to 0.75, $p = 0.002$) after stratifying by propensity score quintile (Table 5). The propensity score model discriminated the PREPARE study patients and control patients well ($C = 0.82$) resulting in ANOVA and Cochran-Mantel-Haenszel tests finding no imbalance of baseline variables between the PREPARE study participants and the control group across the 5 strata.

Analysis of the PREPARE study patients comparing patients with a new implant at time of enrollment and those patients with a previous implant up to 6 months before enrollment shows that there was no difference in the morbidity index densities between the 2 subgroups (0.24 vs. 0.31, ratio = 0.77, 95% CI: 0.35 to 1.69, $p = 0.52$).

Secondary end points. MORBIDITY TACHYCARDIA INDEX. The morbidity tachycardia index included the addition of episodes receiving only device-delivered ATP therapy but was otherwise identical to the morbidity index. The PREPARE study patients experienced 273 additional events that received device-delivered ATP therapy, while patients in the control cohort experienced

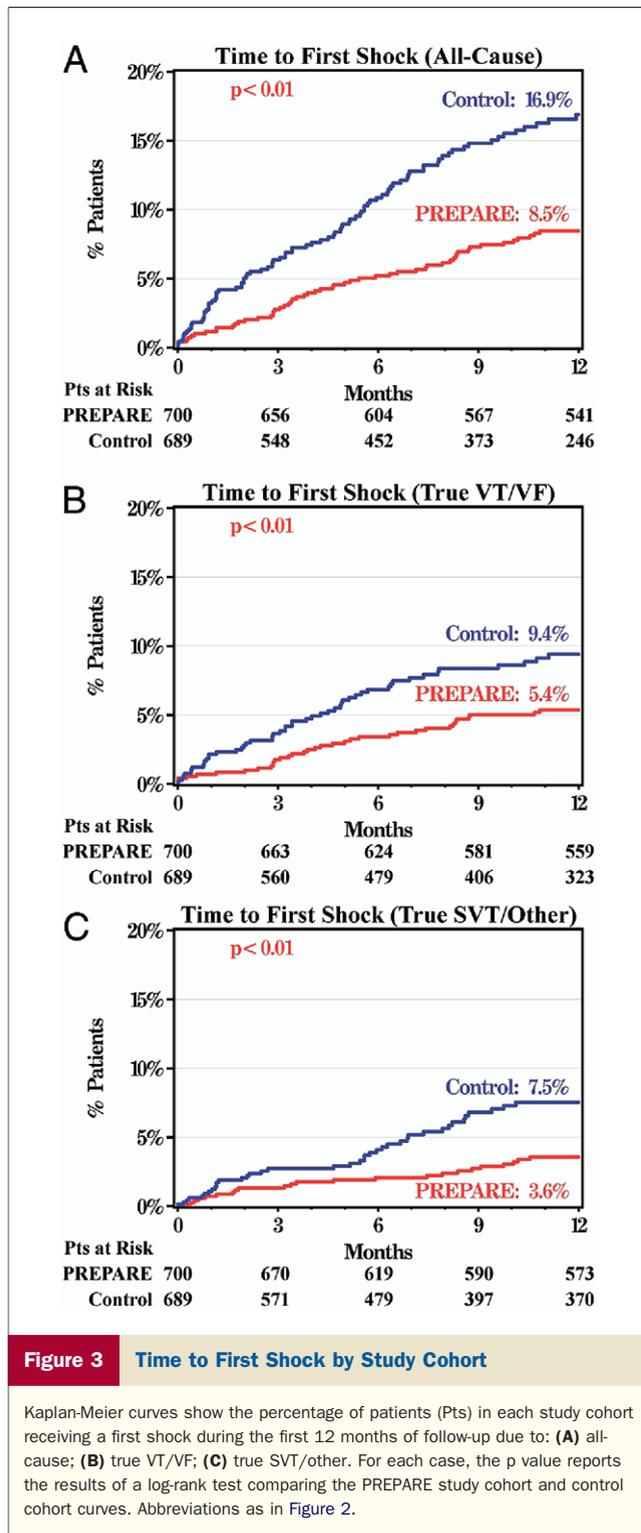
**Figure 2** Morbidity Index for the PREPARE Study Patients Versus the Control Cohort

The PREPARE study patients had fewer morbidity index events (primary end point) as compared with the control cohort. Both appropriate and inappropriate shocks were substantially reduced in the PREPARE study programmed patients. There were relatively few syncopal events that contributed to the primary end point. SVT = supraventricular tachycardia or other nonventricular tachycardia or ventricular fibrillation event; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 5 Primary and Secondary End Point Analyses by Propensity Score Quintile

Quintile	PREPARE	Control	Ratio (95% CI)
Morbidity index			
1	0.30	0.84	0.35 (0.13-0.98)
2	0.20	0.89	0.23 (0.04-1.22)
3	0.39	0.46	0.85 (0.35-2.05)
4	0.28	0.42	0.66 (0.22-2.04)
5	0.20	0.54	0.37 (0.13-1.00)
Overall ratio 0.44, 95% CI: 0.26 to 0.75, $p = 0.002$			
Morbidity tachycardia index			
1	0.45	2.63	0.17 (0.04-0.71)
2	0.39	2.09	0.19 (0.05-0.64)
3	0.82	0.76	1.08 (0.43-2.71)
4	1.19	2.55	0.47 (0.08-2.57)
5	0.36	1.28	0.28 (0.07-1.07)
Overall ratio 0.34, 95% CI: 0.19 to 0.62, $p < 0.001$			

Values are events/patient-year.
CI = confidence interval.



639 additional events treated with ATP. The morbidity tachycardia index incidence density for PREPARE patients was significantly lower than the incidence density for the control cohort (0.70 vs. 1.96, ratio = 0.36, 95% CI: 0.15 to 0.83, p = 0.02). There was no evidence this result was due to imbalance in baseline characteristics. The difference in morbidity tachycardia index incidence

density between the PREPARE study patients and control patients remained significant (ratio = 0.34, 95% CI: 0.19 to 0.62, p < 0.001) after stratifying by propensity score quintile (Table 5).

In the PREPARE study group, there were 753 episodes of nonsustained tachycardia lasting 12 to 29 beats. Approximately 290 of these were nonsustained VT based upon the criteria of ventricular rate > atrial rate. There were 29 monitored VT episodes in addition to the 290 nonsustained VT episodes that would likely have received ATP therapy had these patients been programmed to treat slower, shorter duration episodes as in the control cohort. Adding together the 290 nonsustained VTs, 29 monitored VTs, and 273 VTs treated with ATP yields 592 slow VTs in the PREPARE study patients, which is not appreciably different than the 639 in the control cohort.

Other shock analysis. The PREPARE study patients were less likely to receive a shock for any cause in the first year as compared with the control cohort (8.5% vs. 16.9%, hazard ratio [HR]: 0.48, 95% CI: 0.34 to 0.67, p < 0.01) (Fig. 3A). This finding remained significant when controlling for differences in baseline characteristics using a Cox proportional hazards model (HR: 0.49, 95% CI: 0.29 to 0.82, adjusted p < 0.01). The PREPARE study patients were less likely to receive a shock for true VT/VF in the first year as compared with the control cohort (5.4% vs. 9.4%, HR: 0.55, 95% CI: 0.36 to 0.84, p < 0.01) (Fig. 3B), although this finding became nonsignificant when controlling for differences in baseline characteristics (HR: 0.58, 95% CI: 0.30 to 1.12, adjusted p = 0.11). The PREPARE study patients were less likely to receive a shock for true SVT/other in the first year as compared with the control cohort (3.6% vs. 7.5%, HR: 0.46, 95% CI: 0.28 to 0.78, p < 0.01) (Fig. 3C). This finding remained significant when controlling for differences in baseline characteristics (HR: 0.38, 95% CI: 0.16 to 0.86, adjusted p = 0.02).

Safety. Of the 290 lightheaded or syncopal adverse events (including syncope, near-syncope, and dizziness) that occurred in the PREPARE study patients, 31 (11%) were classified as related to arrhythmia (Table 6). Of those, 15 were judged to be related specifically to the PREPARE study programming. A total of 40 true syncopal events were reported, 12 of which were considered related to arrhythmia and included in the morbidity index. Of these 12, 10 were judged to be related to the PREPARE study programming

Table 6 Syncopal Adverse Events in the PREPARE Study Patients

Adverse Event	PREPARE (n = 700)		
	Arrhythmic	Nonarrhythmic	Total
Syncope	11 (1.6%) 12	23 (3.3%) 28	31 (4.4%) 40
Near syncope	6 (0.9%) 6	14 (2.0%) 20	19 (2.7%) 26
Dizziness	12 (1.7%) 13	93 (13.3%) 211	101 (14.4%) 224
Total	27 (3.9%) 31	117 (16.7%) 259	131 (18.7%) 290

Values are patients (%) events.

parameters. Of the 11 patients who experienced these 12 events, 8 completed the study and 3 withdrew from the study. There were no injuries or deaths associated with these events. In the control cohort, cardiovascular adverse events were collected, but there was no systematic collection of syncope events. Even so, there were 4 true syncope or untreated symptomatic sustained VT/VF episodes reported in the first year of control patients' follow-up.

Over the course of follow-up in the PREPARE cohort, 7 patients had a total of 29 monitored VT episodes with an incidence density of 0.046 episodes per patient-year (95% CI: 0.011 to 0.195). There was 1 reported adverse event of dizziness associated with these episodes.

The PREPARE study patients had a lower mortality rate compared with the control cohort (4.9% PREPARE study patients vs. 8.7% control patients, HR: 0.55, 95% CI: 0.35, 0.86, $p = 0.01$) (Fig. 4). However, when taking into account imbalances in baseline characteristics, the difference between study cohorts in time to mortality was not statistically significant (HR: 0.57, 95% CI: 0.29 to 1.11, adjusted $p = 0.10$).

One patient death was adjudicated as being possibly related to the PREPARE study programming. This patient experienced an episode of slow VT detected in the monitor zone that accelerated to VF and was terminated with the sixth shock. The cause of death was determined to be possibly related to the prolonged ventricular arrhythmia.

Discussion

The PREPARE study programming significantly reduced the rate of morbidity index events in primary prevention patients when compared with the rate of events for patients in the historical physician-tailored control cohort. Programming strategies that prolong detection duration (30 of 40

ventricular beats), increase the heart rate threshold of tachycardia detection (182 beats/min), use supraventricular detection discrimination algorithms and ATP, and encourage first shock termination of tachyarrhythmias can safely and substantially reduce the number of tachyarrhythmias subjected to shock therapy.

The goal of the PREPARE study was not only to reduce the number of treated, particularly shocked, episodes, but to do so safely. Reducing the number of episodes subject to therapy does not predictably reduce or improve safety. While slow and brief arrhythmias usually do not lead to syncope or death, there can be slow ventricular arrhythmias that can cause hemodynamic compromise even with surprisingly brief durations (20). However, while not specifically assessed as an end point in this study, ATP and/or shocks for sinus tachycardia or atrial fibrillation with a relatively rapid ventricular response can themselves lead to hemodynamically compromising rhythms, ischemia, electromechanical dissociation, and occasionally to syncope, myocardial infarction, or death (21).

Overall safety in the PREPARE study was excellent as measured by arrhythmic syncope, untreated VT, and mortality. Nonarrhythmic syncope events were common, occurring in 16.7% of patients; however, arrhythmic syncope was rare (1.6%). All-cause mortality in the PREPARE study group was relatively low (Kaplan-Meier estimated 12-month mortality: 4.9%). One patient death was adjudicated as possibly related to the PREPARE study programming. This death followed a monitored VT lasting 1.5 min before accelerating into the therapy zone where 6 shocks were required to terminate the tachycardia. It is likely that the patient outcome would have been no different with nominal programming for primary prevention patients, which consists of a single high-rate therapy zone with or without low-rate monitoring.

Historically, mortality estimates based on ICD-detected episodes are elevated (22). This bias is related, in part, to the treatment of nonsustained and nonlife-threatening arrhythmias before they have an opportunity to self-terminate. In the PREPARE study, the number of sustained and treated ICD episodes probably better estimates the number of patients that are actually rescued from death by the ICD. The PREPARE study data clearly demonstrate that by waiting and permitting nonsustained and slower arrhythmias to self-terminate, there are fewer shocked and treated ventricular and SVTs. The magnitudes of these differences are remarkable with the PREPARE morbidity index incidence rate 38% and the morbidity tachycardia index incidence rate 36% of that observed in the control cohort. Clearly, the power to reduce the number of shocked and treated tachycardias in primary prevention patients with and without the need for cardiac resynchronization therapy is in the hands of the programming physician.

The primary value of the ICD, especially in the setting of primary prevention, is to prolong life. However, many have asked the question, at what cost? The cost is not just

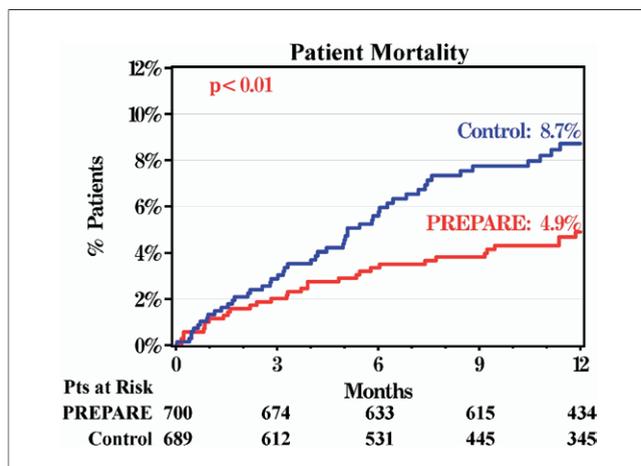


Figure 4 Patient Mortality by Study Cohort

Kaplan-Meier curves show the mortality rate in patients (Pts) from each study cohort during the first 12 months of follow-up. The p value reports the results of a log-rank test comparing the PREPARE study cohort and control cohort curves.

financial but also relates to the morbidity of the therapy, which has a significant influence on patients' and physicians' perceptions. A programming strategy that dramatically reduces the number of painful therapies that a patient receives will favorably affect the perceived value of the device. Since the PREPARE study demonstrates that it is within the physician's control to reduce this morbidity, these findings are important to advancing the implementation of ICD therapy. The choice to strategically select the programming of VT/VF detection and termination parameters, all under physician control, can make ICD therapy more comfortable and acceptable while still remaining safe and effective.

Study limitations. The major limitation of this clinical investigation was the use of a historical control cohort instead of a randomized control design. The considerations in using the combination of primary prevention patients enrolled in the MIRACLE ICD and EMPIRIC trials are discussed in detail in the PREPARE study design report (16). The differences in baseline characteristics between the 2 groups were considerable. Antiarrhythmic agents may slow down the rate of ventricular arrhythmias and increase the risk of underdetection of arrhythmias. Only 12% of the PREPARE study patients were treated with antiarrhythmic agents; therefore, extrapolation of our results to patients on antiarrhythmic agents may not be warranted.

These differences are, in part, related to the expansion of the primary prevention ICD indications to include patients without ischemic heart disease. However, these baseline imbalances do not appear to explain the substantial reduction in event rates based on the propensity score-adjusted analysis. Mortality rates were not increased in the PREPARE study patients, and although arrhythmic syncope was slightly increased in the PREPARE study patients, the methodology for collecting the syncopal events in the control cohort almost certainly underestimated the true event rate. Finally, it must be emphasized that the PREPARE study programming strategy was tested only in patients without a prior history of sustained ventricular arrhythmias. In addition, patients with induced VT slower than 180 beats/min were excluded. Our screening process did not document how many patients were excluded from enrollment by this exclusion criteria. Enrollment was limited to patients classified as primary prevention patients. Extrapolation of our results to patients with previously known arrhythmias before enrollment is not warranted.

Conclusions

Strategically chosen tachycardia detection and therapy options targeting primary prevention patients can safely reduce the morbidity related to ICD therapy. By moderately extending the detection duration, using fast rate cutoffs, ATP in faster rate zones, and existing SVT discrimination algorithms, the PREPARE study programming can safely

be used to reduce the combined morbidity of spontaneous shocked episodes, arrhythmic syncope, and untreated sustained symptomatic VT/VF events in primary prevention patients. These same strategically chosen parameters can also reduce morbidity when ATP therapy is taken into account and reduce the proportion of patients shocked in the first year by all-cause, appropriate, and inappropriate shocks. Multiple strategies were tested in aggregate to achieve the desired result of reduced morbidity in primary prevention patients. Subsequent clinical trials are needed to evaluate the contribution of each programming component independently.

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REFERENCES

1. Moss AJ, Zareba W, Hall WJ, et al., for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.
2. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.
3. Sears SF, Todaro JF, Urizar G, et al. Assessing the psychosocial impact of the ICD: a national survey of implantable cardioverter defibrillator health care providers. *Pacing Clin Electrophysiol* 2000; 23:939-45.
4. Lüderitz B, Jung W, Deister A, Marneros A, Manz M. Patient acceptance of the implantable cardioverter defibrillator in ventricular tachyarrhythmias. *Pacing Clin Electrophysiol* 1993;16:1815-21.
5. Mofrad PS, Ottoboni L, Zei PC, et al. VF and fatal cardiac arrest following ICD therapy delivery: what is the cause? *Pacing Clin Electrophysiol* 2007;30:551-3.
6. Wilkoff BL, Hess M, Young J, Abraham WT. Differences in tachyarrhythmia detection and implantable cardioverter defibrillator therapy by primary or secondary prevention indication in cardiac resynchronization therapy patients. *J Cardiovasc Electrophysiol* 2004;15:1002-9.
7. Ousdigian KT, Wilkoff BL, Morgan JM, et al. ICD patients with a history of spontaneous sustained VT have different outcomes than other secondary or primary prevention patients. *Circulation* 2005; 112:17.
8. Sweeney MO, Wathen MS, Volosin K, et al. Appropriate and inappropriate ventricular therapies, quality of life, and mortality among primary and secondary prevention implantable cardioverter defibrillator patients: results from the Pacing Fast VT REduces Shock Therapies (PainFREE Rx II) trial. *Circulation* 2005;111:2898-905.
9. Wathen MS, DeGroot PJ, Sweeney MO, et al. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock therapies (PainFREE Rx II) trial results. *Circulation* 2004;110:2591-6.
10. Wilkoff BL, Ousdigian KT, Sterns LD, Wang ZJ, Wilson RD, Morgan JM, for the EMPIRIC Trial Investigators. A comparison of EMPIRIC to Physician-tailored programming of Implantable Cardioverter-defibrillators: results from the prospective randomized multicenter EMPIRIC trial. *J Am Coll Cardiol* 2006;48:330-9.
11. Wathen MS, Sweeney MO, DeGroot PJ, et al. Shock reduction using antitachycardia pacing for spontaneous rapid ventricular tachycardia in patients with coronary artery disease. *Circulation* 2001;104:796-801.
12. Schaumann A, von zur Muhlen F, Herse B, Gonska BD, Kreuzer H. Empirical versus tested antitachycardia pacing in implantable cardio-

- verter defibrillators: a prospective study including 200 patients. *Circulation* 1998;97:66-74.
13. Wilkoff BL, Kuhlkamp V, Volosin K, et al. Critical analysis of dual-chamber implantable cardioverter-defibrillator arrhythmia detection: results and technical considerations. *Circulation* 2001;103:381-6.
 14. Gehi AK, Mehta D, Gomes JA. Evaluation and management of patients after implantable cardioverter-defibrillator shock. *JAMA* 2006;296:2839-47.
 15. Russo AM, Nayak H, Verdino R, et al. Implantable cardioverter defibrillator events in patients with asymptomatic nonsustained ventricular tachycardia: is device implantation justified? *Pacing Clin Electrophysiol* 2003;26:2289-95.
 16. Wilkoff BL, Stern R, Williamson B, et al. Design of the Primary Prevention Parameters Evaluation (PREPARE) trial of implantable cardioverter defibrillators to reduce patient morbidity. *Trials* 2006;7:18.
 17. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA* 2003;289:2685-94.
 18. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13-22.
 19. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-81.
 20. Bansch D, Castrucce M, Bocker D, Breithardt G, Block M. Ventricular tachycardias above the initially programmed tachycardia detection interval in patients with implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2000;36:557-65.
 21. Pinski SL, Fahy GJ. The proarrhythmic potential of implantable cardioverter-defibrillators. *Circulation* 1995;92:1651-64.
 22. Sweeney MO, Ruskin JN. Mortality benefits and the implantable cardioverter-defibrillator. *Circulation* 1994;89:1851-8.
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- Key Words:** defibrillators ■ implantable ■ tachyarrhythmias ■ defibrillation ■ cardioversion.
-  **APPENDIX**
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- For a complete list of investigators, coordinators, and institutions participating in the PREPARE study, please see the online version of this article.**