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A Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter-Defibrillators

Results From the Prospective Randomized Multicenter EMPIRIC Trial

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OBJECTIVES The purpose of this randomized study was to determine whether a strategically chosen standardized set of programmable settings is at least as effective as physician-tailored choices, as measured by the shock-related morbidity of implantable cardioverter-defibrillator (ICD) therapy.

BACKGROUND Programming of ventricular tachyarrhythmia (ventricular tachycardia [VT] or ventricular fibrillation [VF]) detection and therapy for ICDs is complex, requires many choices by highly trained physicians, and directly influences the frequency of shocks and patient morbidity.

METHODS A total of 900 ICD patients were randomly assigned to standardized (EMPIRIC, n = 445) or physician-tailored (TAILORED, n = 455) VT/VF programming and followed for 1 year.

RESULTS The primary end point was met: the adjusted percentages of both VT/VF (22.3% vs. 28.7%) and supraventricular tachycardia or other non-VT/VF event episodes (11.9% vs. 26.1%) that resulted in a shock were non-inferior and lower in the EMPIRIC arm compared to the TAILORED arm. The time to first all-cause shock was non-inferior in the EMPIRIC arm (hazard ratio = 0.95, 90% confidence interval 0.74 to 1.23, non-inferiority $p = 0.0016$). The EMPIRIC trial had a significant reduction of patients with 5 or more shocks for all-cause (3.8% vs. 7.0%, $p = 0.039$) and true VT/VF (0.9% vs. 3.3%, $p = 0.018$). There were no significant differences in total mortality, syncope, emergency room visits, or unscheduled outpatient visits. Unscheduled hospitalizations occurred significantly less often ($p = 0.001$) in the EMPIRIC arm.

CONCLUSIONS Standardized empiric ICD programming for VT/VF settings is at least as effective as patient-specific, physician-tailored programming, as measured by many clinical outcomes. Simplified and pre-specified ICD programming is possible without an increase in shock-related morbidity. (J Am Coll Cardiol 2006;48:330–9) © 2006 by the American College of Cardiology Foundation

The Center for Medicaid and Medicare Services recently published expanded coverage for implantable cardioverter-defibrillator (ICD) therapy based on the mortality benefit demonstrated in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trial, the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II), and the COMPANION (Comparison of Medical Therapy, Resynchronization, and Defibrillation Therapies in Heart Failure) trial (1–5). However, ICDs can be associated with patient morbidity and worse quality of life when the patient receives painful shocks, especially multiple shocks (6–9). With expanded indications for ICD implantation, concern has developed about who should implant, program, and follow these devices and what kind of training is required for these individuals (10–13). More importantly, how can consistent expert care be delivered to every patient in order for them to receive the benefits of ICDs without substantial morbidity?

Implantable cardioverter-defibrillator therapy can involve many complex choices, including more than 100 programmable parameter values that determine the detection and treatment of rhythms presented to the device. There are multiple programming strategies for reducing the number of morbid events related to shocks. Some publications have suggested that antitachycardia pacing (ATP) is not needed for patients without a prior history of a clinical tachycardia (2,10), whereas others have suggested that more than 70% of ventricular tachyarrhythmias can be terminated safely without a shock if ATP is given a chance (7,14,15). It has been assumed that patient-specific customization of all these parameters is crucial to the ICD's appropriate response, so that all life-threatening arrhythmias are treated with minimal shocks delivered to the patient for non–life-threatening arrhythmias. This assumption is based on two premises: 1) the physician programming the ICD knows which strategies will produce the best results, and 2) a patient-specific customization of the programming will produce the best protection with the least morbidity.

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Abbreviations and Acronyms

AF	= atrial fibrillation
AFL	= atrial flutter
AT	= atrial tachycardia
ATP	= antitachycardia pacing
CI	= confidence interval
EMPIRIC	= Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter-Defibrillators trial
GEE	= general estimating equation
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
RR	= relative risk
SVT	= supraventricular tachycardia or other non-VT/VF event
VF	= ventricular fibrillation
VT	= ventricular tachycardia

This investigation tests the hypothesis that, as measured by shock-related morbidity, an initial programming strategy using a well-constructed set of tachyarrhythmia detection and therapy parameters (EMPIRIC parameters), when consistently applied to a large group of unselected ICD patients, would be as successful as an individualized patient-specific, physician-tailored (TAILORED) set of parameters. The hypothesis requires that the EMPIRIC parameters perform as well as the control group in two ways: 1) percentage of ventricular arrhythmias that are shocked, and 2) percentage of supraventricular tachycardia or other non-ventricular tachycardia (VT)/ventricular fibrillation (VF) events (SVTs) that are shocked.

METHODS

The EMPIRIC (Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter-Defibrillators) trial was a worldwide, multicenter, single-blind, non-inferiority, parallel-group, 1:1 randomized trial of ICD programming (16). Enrollment was conducted at 54 centers in the U.S., Canada, Europe, and the Middle East between August 2002 and October 2003. The institutional review board at each center approved the study protocol, and written informed consent was obtained from each patient.

PARTICIPANTS AND ICD PLACEMENT

All patients had standard indications for ICD placement as defined by the American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology guidelines (17). Patients were considered to have a secondary prevention indication for ICD placement if there was a history of spontaneous sustained VT/VF or syncope with suspected VT. All other patients were considered to have a primary prevention indication. Patients had to be undergoing their first placement of an ICD and be free of permanent atrial fibrillation (AF).

All patients received a Model 7274 Marquis DR ICD (Medtronic Inc., Minneapolis, Minnesota) and were randomized after successful implantation testing of the atrial and ventricular leads for sensing, capture, VF detection, and defibrillation with a 10-J safety margin.

RANDOMIZATION

Patients were randomized to have the tachyarrhythmia detection and therapy programmed to prescribed values (EMPIRIC) or to values determined by the treating physician (TAILORED). The patients were blinded to the randomization.

Randomization was done at the data-coordinating center and was stratified by the treatment center. The randomization was based on permuted blocks with a block size of 2 initially, followed by a block size of 2 or 4 with a probability of 0.5 each. Since the incidence and prevalence of spontaneous VT/VF and SVT may be different between primary prevention patients, randomization was also stratified by ICD indication (secondary vs. primary).

PROGRAMMING

Tachyarrhythmia detection and therapy settings were strategically chosen in the EMPIRIC arm to reduce shocks for VT/VF and SVTs and to avoid untreated slow VT (Table 1). The key strategies included: 1) avoid detecting non-sustained tachycardias;, 2) avoid detecting SVTs as VT; 3) empirical ATP for slow and fast VTs; and 4) high-output first shocks. A more detailed discussion of these strategies is found in a paper outlining the rationale for the study design (16). The VT/VF programming was set at the discretion of the implanting electrophysiologist in the TAILORED arm. All implanters and centers invited to participate had long-established ICD placement and programming practices. In order to provide similar data collection in both arms, the VT zone was programmed to monitor rhythms faster than 150 beats/min in the TAILORED arm if the investigator chose to have VT therapies off. Bradycardia settings were programmed at the discretion of the investigators in both arms.

Table 1. EMPIRIC Arm Programming of VT/VF Settings

Detection	Threshold	Detect Beats	Therapies
VF on	250 beats/min	18 of 24	30 J × 6
FVT via VF	200 beats/min	(18 of 24)	Burst (1 sequence), 30 J × 5
VT on	150 beats/min	16	Burst (2), ramp (1), 20 J, 30 J × 3

Supraventricular tachycardia criteria on: atrial fibrillation/atrial flutter, sinus tach (1:1 VT-ST boundary = 66%), SVT limit = 200 beats/min. Burst ATP: 8 intervals, R-S1 = 88%, 20 ms decrement. Ramp ATP: 8 intervals, R-S1 = 81%, 10 ms decrement.
ATP = antitachycardia pacing; FVT = fast ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Programming changes during follow-up were allowed if medically justified.

DATA COLLECTION

Patients were followed for 12 months, with device interrogations and clinical evaluations at 3, 6, and 12 months. Data collection included VT/VF and SVT episodes, device programming, medical justifications for VT/VF programming changes, cardiovascular medication, adverse device events, P- and R-wave measurements, and cardiovascular-related hospitalizations. The VT/VF and SVT recorded events were classified by the electrophysiologist investigator and then blindly adjudicated by another expert. Episodes without agreement were further reviewed by study key-investigator electrophysiologists for final classification. Ninety-one percent (2,753 of 3,031) of final classifications were concordant with the initial classification.

END POINTS

The percentage of recorded episodes in a therapeutic zone that produced a device shock for episodes determined to be VT/VF and those determined not to be VT/VF (i.e., SVT or ventricular oversensing) were calculated separately. The primary end point requires that both distinct measurements of efficacy not be inferior when comparing EMPIRIC to TAILORED programming. To make sure that the primary end point was not achieved at the expense of safety or health-care utilization, death, syncope, hospitalization, emergency room visits, and unscheduled outpatient visit frequency were recorded for analysis.

Planned and pre-defined secondary end points include time to first shock for all rhythms (VT/VF and SVT), only VT/VF rhythms, and only SVT rhythms. Additional pre-defined analyses include evaluating the time-to-first-shock end points as a function of baseline characteristics and the programmed parameters.

STATISTICAL ANALYSIS

The primary study outcome was evaluated according to the intent-to-treat principle. A per-protocol analysis was also carried out, in which 830 patients without any major protocol deviations were included. The EMPIRIC programming was considered non-inferior to the TAILORED programming approach if both the percentage of shocked VT/VF episodes and the percentage of shocked SVT episodes were no more than 10 percentage points greater in the EMPIRIC arm than the TAILORED arm. The chosen margin of 10% was pre-specified to represent a threshold that is considered clinically relevant.

The sample size was determined on the basis of previous trial data. It was assumed that during the 12-month follow-up period, 24% of patients would have at least one true VT/VF episode and 33% of patients would have at least one true SVT episode. The within-patient correlation coefficient for multiple episodes was assumed to be 0.3. With a shock rate of 30% for VT/VF and 14% for SVT episodes, a total of 900 patients (450 in each arm) would give at least 80% power for the VT/VF hypothesis and 90% power for the SVT hypothesis, each tested at a one-sided significance level of 0.05.

The percentage of shocked episodes was evaluated under a logistic regression model and the generalized estimating equations (GEE) method, with an exchangeable working correlation structure to account for within-patient correlation for multiple episodes (18). The confidence interval (CI) for the percentage difference between the two study arms was constructed using the bias-corrected accelerated bootstrap method (19). All statistical analyses were performed using SAS (Version 9.1, SAS Institute Inc., Cary, North Carolina) and S-Plus (Version 6.2, Insightful Corp., Seattle, Washington).

The EMPIRIC programming is considered to be non-inferior to the TAILORED for the key secondary end point, time to first all-cause shock, if the upper confidence limit for the hazard ratio (HR) is <1.5 (pre-defined in the design paper) (16).

RESULTS

Patient demographics. A total of 900 patients were enrolled and randomized in the trial. The baseline characteristics (Table 2) of the patients are reflective of the mixture

Table 2. Baseline Patient Characteristics

	EMPIRIC (n = 445)	TAILORED (n = 455)
Age, yrs, mean (SD)	65.1 (12.4)	64.8 (12.7)
Male gender, %	82.7	79.8
LVEF, %, mean (SD)	31.9 (13.1)	32.1 (12.3)
Myocardial infarction	71.2	67.7
Hypertension	57.5	49.5
Heart failure	62.0	60.7
NYHA functional class I–II	47.2	46.4
NYHA functional class III–IV	14.8	14.3
Syncope	31.9	33.6
History of AF/AFL/AT	24.7	26.4
Key cardiac medications, %		
Amiodarone	20.4	21.1
Beta-blocker	72.6	73.8
Indication for ICD, %		
Secondary prevention	51.7	55.8
Spontaneous sustained monomorphic VT	26.7	25.7
Spontaneous sustained VF	10.6	13.0
Syncope	14.4	17.1
Primary prevention	48.3	44.2
CAD, LVEF ≤40%, EP study +	23.8	22.2
CAD, LVEF ≤40%, EP study − or not done	17.5	16.0
Other primary prevention	7.0	5.9

All baseline patient characteristics were similar except for hypertension ($p = 0.016$).
AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; CAD = coronary artery disease; EP = electrophysiology; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; other abbreviations as in Table 1.

Table 3. Baseline ICD Detection and Therapy Programming

	EMPIRIC* (n = 445)	TAILORED (n = 455)	p Value†
Detection and discrimination			
Treated rate threshold‡, median, beats/min (n)			
All patients	150 (443)	171 (455)	<0.001
Patients with a history of spontaneous sustained monomorphic VT	150 (119)	162 (117)	<0.001
All other patients	150 (324)	176 (338)	<0.001
No. of beats to detect VF, % (n)			<0.001
12 of 16	6% (27)	50% (228)	
18 of 24	94% (416)	49% (225)	
24 of 32	0% (0)	0.4% (2)	
PR logic turned on, % (n)			
AF/AFL	100% (442)	77% (350)	<0.001
Sinus tachycardia	100% (442)	76% (348)	<0.001
1:1 VT-ST boundary§, % (n)			<0.001
50%	2% (10)	82% (287)	
66%	98% (432)	18% (61%)	
Stability on, % (n)	0% (0)	2% (11)	
High rate timeout, % (n)	0% (0)	0.2% (1)	
Therapy			
At least 1 ATP attempt for ventricular rates§, %, (n)			
Faster than 200 beats/min	99% (437)	25% (114)	<0.001
177–200 beats/min	99% (439)	70% (294)	<0.001
Slower than 177 beats/min	100% (436)	95% (250)	<0.001
1st VF therapy % (n)			<0.001
<20 J	1% (5)	15% (70)	
20–26 J	3% (12)	29% (130)	
28–30 J	96% (426)	56% (255)	

*One patient never returned programming information and one patient was discharged with the ICD turned off. †p values were calculated using either the Fisher exact test or the Wilcoxon rank sum test, as appropriate. ‡Treated rate threshold is the VT threshold when VT detection and therapy are turned on; otherwise, it is the VF threshold. §Only pertinent patients are included in the calculations.

Abbreviations as in Tables 1 and 2.

of patients with (n = 484) and without (n = 416) a prior documented spontaneous VT/VF or syncope with suspected VT. The mean age of the patients was 65.0 ± 12.6 years with mean left ventricular ejection fraction of 32.0 ± 12.7. Except for hypertension (p = 0.016), the baseline characteristics of the two groups were similar.

Programming demographics. There were 100 physicians from 51 centers that programmed the 455 patients in the TAILORED arm. There were substantial differences in the baseline programmed parameters for tachyarrhythmia detection and therapy between the two patient groups (Table 3) (Fig. 1). One of the most important differences is that the EMPIRIC arm devices were more frequently set to detect and treat slower tachycardias. Therefore, the patients enrolled in that study arm would be more likely to have their moderate-to-slow VTs and SVTs detected and treated by the ICD. The EMPIRIC arm also had a higher number of beats to detect VF, made greater and more sophisticated use

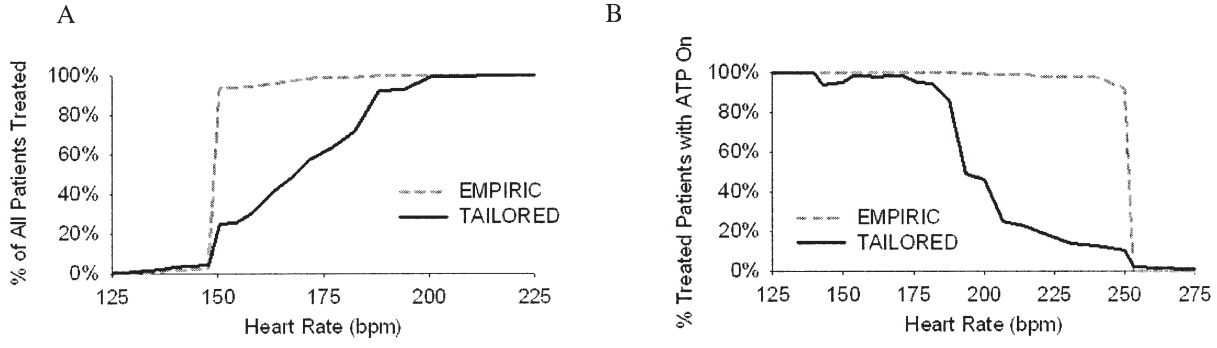

Figure 1. Programmed implantable cardioverter-defibrillator (ICD) therapies versus heart rate. **(A)** Percentage of all patients programmed to antitachycardia pacing (ATP) and/or shock therapy (number of patients with ATP or shock therapy on at each heart rate/total number of patients in the arm). The **dotted line** illustrates that nearly all EMPIRIC arm patients had their ICD enabled to treat tachycardias >150 beats/min. In marked contrast, tailored programming was enabled to treat slower tachycardias in a much smaller proportion of patients. **(B)** Percent of treated patients programmed to ATP on (number of patients with ATP on at each heart rate/number of patients with ATP or shock therapy on at each heart rate). The **dotted line** illustrates that nearly all EMPIRIC arm patients had ATP on up to 250 beats/min. In marked contrast, a small proportion of tailored arm patients had ATP on at faster heart rates.

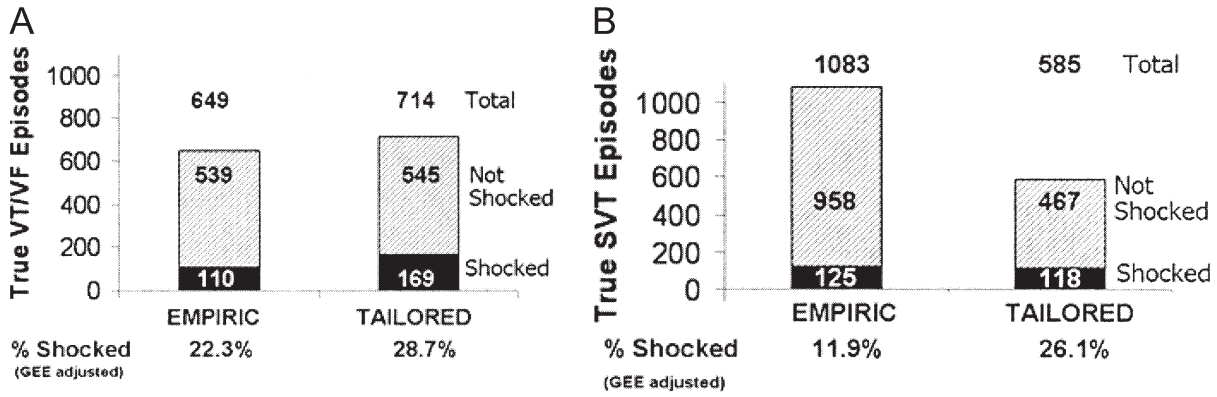

Figure 2. Number of episodes by arm. **(A)** True ventricular tachycardia/ventricular fibrillation (VT/VF) episodes. **(B)** True supraventricular tachycardia or other non-VT/VF event (SVT) episodes. **Solid bars** = shocked; **ruled bars** = not shocked. GEE = general estimating equation adjustment for multiple recurrences per patient.

of the supraventricular tachycardia detection/discrimination algorithms, used more ATP therapy, and programmed a higher VF first-shock energy. The percentage of all patients programmed for treatment with ATP and/or shocks as a function of heart rate is shown in Figure 1, as is the percentage of these patients programmed with ATP at each heart rate. The percentage of follow-up visits with any VT/VF detection or therapy programming change was significantly lower in the EMPIRIC arm compared to the TAILORED arm (13.1% vs. 20.2%, $p < 0.0001$). At the end of the follow-up, the rate threshold for treatment had been made faster than baseline programming in more EMPIRIC arm patients (5.4% vs. 2.2%) and slower in more TAILORED arm patients (4.1% vs. 8.2%).

Tachycardia and shocks. The detected and shocked tachycardia events are summarized in Figure 2. Overall, a similar number of patients received at least one shock in the EMPIRIC and TAILORED arms of the trial (18.2% vs. 19.1%). Although a similar number of true VT/VF episodes was detected in the two groups, there were more of these episodes that were treated by an ICD shock in the TAILORED arm of the study (169 vs. 110, $p = 0.20$). There were significantly more SVT episodes detected in the EMPIRIC arm (1,083 vs. 585, $p < 0.001$), but there was little difference in the number of inappropriate shock episodes (125 vs. 118).

Primary end point. The percentages of both VT/VF and SVT episodes that resulted in a shock were non-inferior in the EMPIRIC arm in comparison to the TAILORED arm (Fig. 3). The GEE-adjusted VT/VF percentage was 22.3% for the EMPIRIC arm and 28.7% for the TAILORED arm, and the difference was −6.4% with a one-sided 95% upper confidence boundary of 2.3%, which was less than the pre-specified non-inferiority margin of 10%. For SVTs, the percentages were more favorable for the EMPIRIC arm (11.9% vs. 26.1%, one-sided 95% upper confidence bound for the difference −5.0%). Results of the per-protocol analysis were consistent with the percentages of episodes shocked observed in the intent-to-treat analysis. Despite considerably more detected events in the EMPIRIC arm, there were numerically fewer shocked episodes and no evidence for an inferior outcome with EMPIRIC programming of VT/VF detection and therapy.

Time-to-first-shock secondary end points. The time to first all-cause shock was non-inferior in the EMPIRIC arm compared to the TAILORED arm based on the predefined threshold (Fig. 4A) (HR = 0.95, 90% CI 0.74 to 1.23, non-inferiority $p = 0.0016$) (16). Throughout the follow-up period, there was a modest trend toward a longer time to first VT/VF shock in the EMPIRIC arm (Fig. 4B) (HR = 0.80, 90% CI 0.56 to 1.14, superiority $p = 0.297$). The time-to-first-SVT shock curves were similar during the

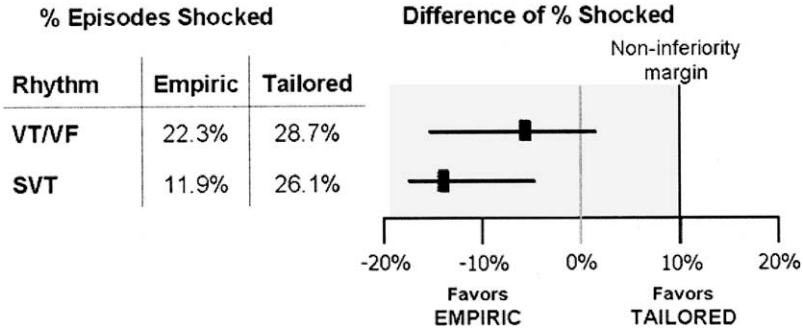

Figure 3. Percentage of episodes shocked—primary end point in the trial. The upper bound for the percentage difference is 1-sided 95% upper confidence bound. SVT = supraventricular tachycardia; other abbreviations as in Figure 2.

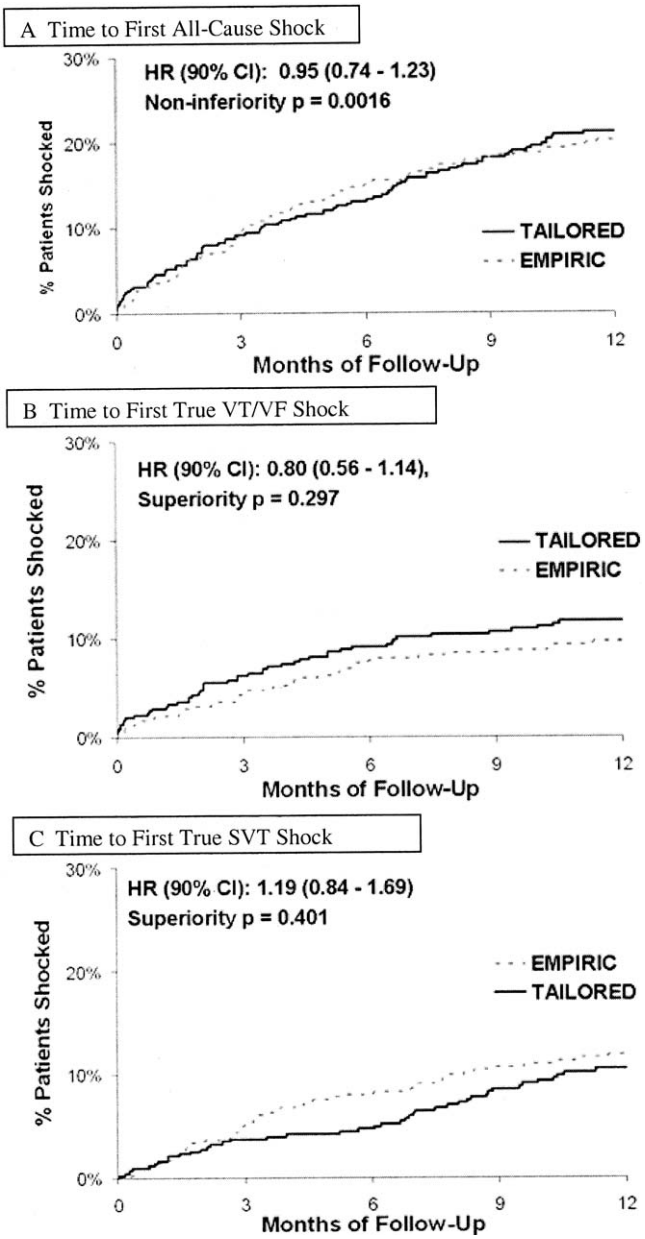

Figure 4. Time to first shock. **(A)** All-cause; **(B)** true VT/VF; **(C)** true SVT. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figures 2 and 3.

first 3 months of follow-up, and then there was a trend of more EMPIRIC arm patients receiving SVT shocks in the time period of about 3 to 6 months after implant. Toward the end of the 1 year of follow-up, the time-to-first-SVT shock curves were converging, and therefore there was no statistical difference in the time to first SVT shock (Fig. 4C) (HR = 1.19, 90% CI 0.84 to 1.69).

Safety and health-care utilization end points. Several safety and health-care utilization end points are shown in Figure 5. The overall mortality rate (24 of 445 vs. 30 of 455; HR = 0.80, 95% CI 0.47 to 1.38) was consistent with the rates seen in the recently published ICD trials and was non-inferior in the EMPIRIC arm of the trial (2–4). In addition, the syncopal rates were low and similar. There were few adverse events for untreated slower VT (0 for EMPIRIC vs. 2 for TAILORED). There were also 29 true VT episodes detected in the monitor zone of 16 TAILORED arm patients. There was no difference in emergency room visits (44 vs. 46; relative risk [RR] = 0.98, 95% CI 0.66 to 1.45) or unscheduled outpatient visits (308 vs. 293; RR = 1.07, 95% CI 0.98 to 1.18); however, the EMPIRIC arm had significantly fewer unscheduled hospitalizations (163 vs. 216; RR = 0.77, 95% CI 0.66 to 0.90, p = 0.001).

Subgroup analysis. A subgroup analysis of time to first shock was carried out with respect to main ICD indication, ejection fraction, baseline New York Heart Association functional class, amiodarone or sotalol, beta-blocker, and a history of inducible sustained VT/VF (electrophysiology study), coronary artery disease, and AF/atrial flutter (AFL)/atrial tachycardia (AT) (Fig. 6). There were no significant differences in any of these covariates; however, there was a modest trend toward a shorter time to first shock in EMPIRIC arm patients with a history of AF/AFL/AT (HR = 1.62, 95% CI 0.94 to 2.87, p = 0.082).

Additional shock and ATP analyses. Several other important metrics for evaluating programming effects on clinical outcomes are shown in Table 4. The EMPIRIC programming resulted in a statistically significant reduction in the percentage of patients with at least 5 all-cause shocks (3.8% vs. 7.0%, p = 0.039) and also those with at least 5 shocks for only true VT/VF (0.9% vs. 3.3%, p = 0.018). There was no significant difference in patients with at least 5 shocks for SVTs (2.5% vs. 3.5%, p = 0.44). Interestingly, the 5.4% (n = 49 of 900) of patients with at least 5 all-cause shocks accounted for 73.1% (EMPIRIC 32.0%, TAILORED 41.1%) of all shocks in the study.

The effect of ATP programming on shocks can be evaluated by examining only true monomorphic VT episodes that were treated with ATP or a shock. The treated monomorphic VT episodes accounted for 83.4% of all true VT/VF episodes (n = 1,363). The EMPIRIC programming approach of consistent and extensive ATP resulted in a significantly higher proportion of monomorphic VT episodes treated with ATP (94.8% vs. 87.9%, p < 0.001). This broader ATP application in the EMPIRIC arm resulted in a significant reduction in the proportion of treated monomorphic VT episodes that were shocked (12.7% vs. 21.1%, p < 0.001). The overall ATP efficacy was similar between the two arms (92.1% vs. 89.8%, p = 0.23). The ATP efficacy was higher (>90%) in both arms at heart rates of 200 beats/min or slower. This was presumably due to the programming of multiple ATP sequences to treat VT at these rates. At faster VT rates it was typical for only one ATP sequence to be programmed and delivered, thus reducing ATP efficacy to only about 75% in both arms. The EMPIRIC ATP programming trended towards a reduction in the proportion of VT/VF episodes that were accelerated by the initial ATP attempt; however, it was not significant

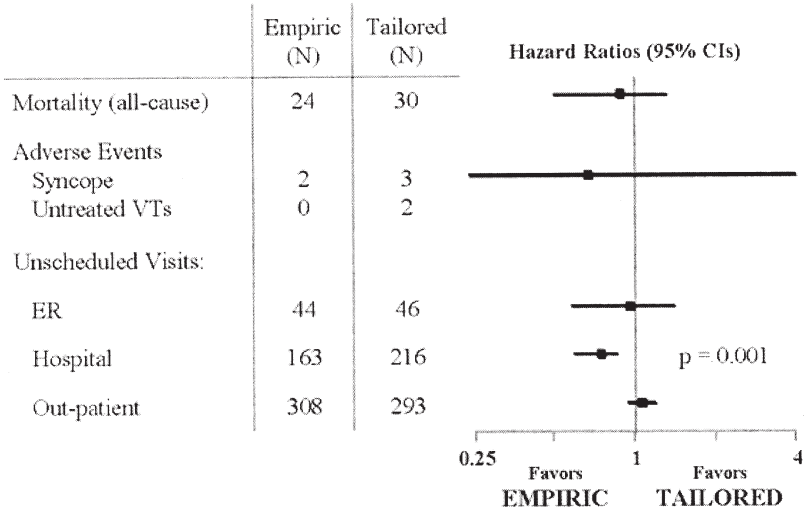

Figure 5. Safety and health-care utilization end points. ER = emergency room; other abbreviations as in Figures 2 and 4.

(2.4% vs. 7.8%; RR = 0.47, 95% CI 0.18 to 1.2, p = 0.11).

DISCUSSION

As the indications for ICD placement expand, the aspect of ICD therapy most variable and unpredictable in its application is the choice of the programmed settings. An unacceptable result of the enlarged population of patients with ICDs and the expanded cohort of implanters is poorer outcomes. The question is how to deliver ICD care with the precision of the accumulated wisdom of the electrophysiology community. Certainly this is a concern of the Centers for Medicare and Medicaid Services. The recent call for a national registry for primary prevention ICD patients associated with expanded coverage was partially motivated by a desire to assure that the outcomes demonstrated within the clinical trials can be replicated in generalized practice. The EMPIRIC trial results demonstrate that consistent strategies and an initial dramatic simplification of the programmed selections produce at least equivalent clinical outcomes to the individualized current standard of care.

ATP. This trial was not designed to make unequivocal conclusions about specific programming options. However, there were significant differences in baseline programming that appear to be associated with the outcome differences. First, ATP was programmed more consistently and extensively in the EMPIRIC arm. This EMPIRIC ATP programming strategy resulted in the significantly higher proportion of monomorphic VT episodes that were treated with ATP in the EMPIRIC arm. The consistent ATP application coupled with the high efficacy (92.1%) of ATP for spontaneous VT led to a significant reduction in the

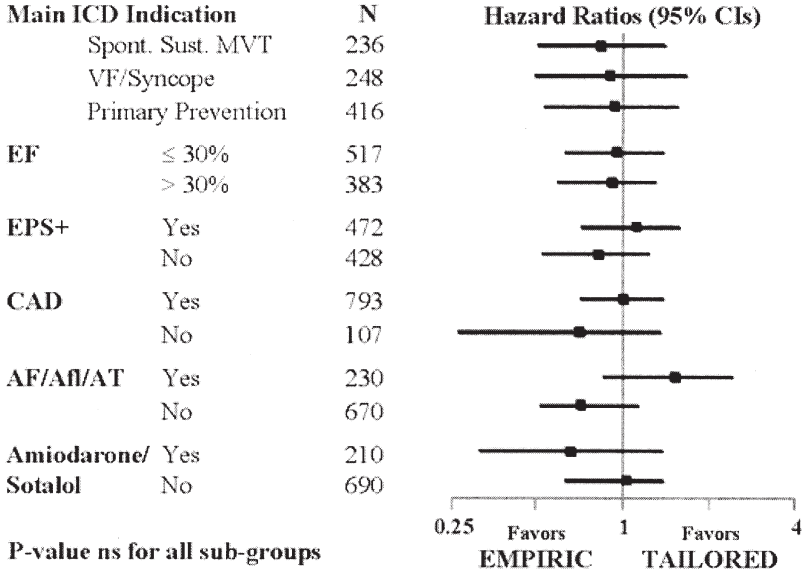

Figure 6. Subgroup analysis on time to first all-cause shock. AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; CAD = coronary artery disease; EF = ejection fraction; EPS = electrophysiologic study; MVT = monomorphic ventricular tachycardia; other abbreviations as in Figures 1 and 4.

Table 4. Additional Shock and ATP End-Points

	EMPIRIC (n = 445)	TAILORED (n = 455)	p Value
Percentage of patients with ≥5 shocks (n patients)			
All-cause	3.8% (17)	7.0% (32)	0.039
Only true VT/VF	0.9% (4)	3.3% (15)	0.018
Only true SVT	2.5% (11)	3.5% (16)	0.44
Treated monomorphic VT episodes	534	602	
Proportion treated with ATP	94.8% (506/534)	87.9% (529/602)	<0.001
Proportion shocked	12.7% (68/534)	21.1% (127/602)	<0.001
ATP efficacy for monomorphic VTs	92.1% (466/506)	89.8% (475/529)	0.23
Ventricular rate ≤200 beats/min	93.9% (431/459)	90.9% (448/493)	0.088
Ventricular rate >200 beats/min	74.5% (35/47)	75.0% (27/36)	1.0
Proportion of true VT/VF episodes accelerated by initial ATP attempt (% patients)	2.4% (2.0%)	7.8% (3.1%)	0.11

Abbreviations as in Tables 1 and 2.

shocked episodes of monomorphic VT compared to the TAILORED arm ($p < 0.001$). This EMPIRIC ATP strategy also appears to be one of the factors that resulted in a significant reduction in the percentage of patients with at least 5 all-cause or VT/VF shocks. This aspect of EMPIRIC programming may be the most clinically important because several studies have demonstrated that patients who receive 5 or more shocks have a worse quality of life (8,9). The potential drawbacks to delivering ATP include accelerations and syncope, but neither was an issue, as only 2.4% of the episodes were accelerated in the EMPIRIC arm vs. 7.8% in the TAILORED arm. There were no adverse event reports of syncope correlated with VT/VF in the EMPIRIC arm. These data and those of several other studies strongly suggest that ATP is an important aspect of ICD therapy because the majority of true VT/VF rhythms that are detected can be pace-terminated (7,14,15,20–22). The prior reports also demonstrated that empirically programmed ATP is highly effective in painlessly terminating VTs and confirm the safety of ATP therapy (e.g., low acceleration rate, no increase in syncope). Therefore, empirical ATP should be used in virtually all ICD patients.

Second, systematic use of a VT zone with aggressive SVT discriminators in the EMPIRIC arm likely led to the significant reduction in the percentage of true SVT episodes that were shocked (11.9% vs. 26.1%). This is consistent with findings by several others that have demonstrated dual-chamber SVT discriminators reduce inappropriate detections versus rate-only detection (23–25). The quantity of SVTs seen by the ICD in the EMPIRIC arm was nearly 2 times that in the TAILORED arm because the median treated rate threshold was significantly slower (150 vs. 171 beats/min, $p < 0.001$). It appears the EMPIRIC SVT discrimination approach was effective at reducing the percentage of SVT episodes shocked; however, the quantity of SVTs was so high at slower heart rates that this reduction did not translate into a reduction in the time to first SVT shock.

It is not clear that the choices employed in the EMPIRIC arm are the best or should be the ultimate choices, but it is clear that TAILORED programming is not always better. The strategies that performed well suggest that extensive ATP and use of the SVT discrimination algorithms were simple answers to a complex physiologic situation and were clinically beneficial. The initial strategy may need to be modified in a small minority of patients as their response is observed. All patients in the EMPIRIC arm had VT detection and therapy enabled for rhythms faster than 150 beats/min. Particularly as an increased percentage of ICDs are implanted in patients without a history of sustained slower VTs, raising the detection rate threshold for this large set of patients seems to be a sensible strategy to reduce shocks for SVTs and has been suggested and/or studied by others (2, 26–29). Even with the slower detection rate threshold in the EMPIRIC arm, there was no significant shock penalty paid for the dramatic increase in SVT episodes detected in the EMPIRIC arm of the trial relative to the TAILORED arm. The faster detection rate threshold in the TAILORED arm may have resulted in more untreated VTs, which may at times cause significant symptoms (30).

Implantable cardioverter-defibrillator morbidity due to shocks and the potential for shocks demand that we reduce the number and frequency of both appropriate and inappropriate shocks. This trial demonstrated that many shocks that would have been considered appropriate (e.g., monomorphic VT shocks) were in fact avoidable and thus could be considered unnecessary, since ATP could have prevented the shocks. In addition, most supraventricular tachycardia episodes overlapping with ICD therapy zones can be appropriately classified and not treated with ICD shocks. Although the mortality benefit conferred by ICD therapy in indicated populations is a critical yardstick of the therapy's efficacy, it is vital to remember that shock-related morbidity is the critical yardstick of the therapy's iatrogenic morbidity. Advances in ICD therapy must continue to focus on reducing both shock therapies for termination of life-threatening VT/VF and shock therapies delivered in response to non–life-threatening arrhythmias. There is no value in customizing the programming of the ICD if it does not improve the patient outcomes. Alternatively, there is much value in simplification of the programming strategy,

especially if, as suggested in this trial, the shock morbidity is maintained or reduced and there is no difference in mortality, syncope, or health-care utilization.

Study limitations. The shock metrics used in this trial were chosen for various reasons described in the design paper; however, there are multiple ways of assessing the shock morbidity of ICDs (16). Every attempt was made to provide an unbiased analysis, but because of detection rate settings, limitations in device memory that provide incomplete electrogram records, use of only dual-chamber devices, and the need to test a specific set of EMPIRIC parameters, these data provide only partial insight into these programming choices. Patient syncope diaries may have provided more complete documentation of syncopal events; however, recent trials have suggested very low syncope rates (7). In addition, this trial was designed only to test the empiric programming approach as the initial strategy for programming after implantation. Programming changes were needed in both arms during follow-up. Finally, the same EMPIRIC parameters were applied to all patients regardless of the clinical presentation for the implantable defibrillator. The indications for ICDs are evolving, and the optimal set of empiric parameters may also evolve differently on the basis of patient conditions.

Conclusions. A strategy of empiric ICD programming for VT/VF detection and therapy is at least as effective as patient-specific, physician-tailored programming, as measured by many patient outcome metrics. Simplified and pre-specified ICD programming is possible without an increase in shock-related morbidity.

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APPENDIX

For a list of the investigators, coordinators, and institutions that participated in the EMPIRIC trial, please see the online version of this article.