Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results

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BACKGROUND The benefits of implantable cardioverter-defibrillators (ICDs) have been well demonstrated in many clinical trials, and ICD shocks for ventricular tachyarrhythmias save lives. However, inappropriate and unnecessary shock delivery remains a significant clinical issue with considerable consequences for patients and the healthcare system.

OBJECTIVE The purpose of the PainFree SmartShock Technology (SST) study was to investigate new-generation ICDs to reduce inappropriate and unnecessary shocks through novel discrimination algorithms with modern programming strategies.

METHODS This prospective, multicenter clinical trial enrolled 2790 patients with approved indication for ICD implantation (79% male, mean age 65 years; 69% primary prevention indication, 27% single-chamber ICD, 33% replacement or upgrade). Patients were followed for a minimum of 12 months, and mean follow-up was 22 months. The primary end-point of the study was the percentage of patients remaining free of inappropriate shocks at 1 year postimplant, analyzed separately for dual/triple-chamber ICDs (N = 2019) and single-chamber ICDs (N = 751).

RESULTS The inappropriate shock rate at 1 year was 1.5% for patients with dual/triple-chamber ICDs and 2.5% for patients with single-chamber devices. Two years postimplant, the inappropriate shock rate was 2.8% for patients with dual-/triple chamber ICDs and 3.7% for those with single-chamber ICDs. The most common cause of an inappropriate shock in both groups was atrial fibrillation or flutter.

CONCLUSION In a large patient cohort receiving ICDs for primary or secondary prevention, the adoption of novel enhanced detection algorithms in conjunction with routine implementation of modern programming strategies led to a very low inappropriate shock rate.

KEYWORDS Implantable cardioverter-defibrillator; Cardiac resynchronization therapy; Heart failure; Atrial fibrillation; Inappropriate shock

ABBREVIATIONS **AF** = atrial fibrillation; **ATP** = antitachycardia pacing; **CI** = confidence interval; **EGM** = electrogram; **ERC** = episode review committee; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **LVEF** = left ventricular ejection fraction; **NID** = number of intervals to detect; **RV** = right ventricle; **SST** = SmartShock Technology; **SVT** = supraventricular tachycardia; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

Implantable cardioverter-defibrillator (ICD) therapy is the standard of care for secondary prevention of sudden cardiac death and for primary prevention of cardiac arrest in appropriately selected patients with established risk.[1] Although ICD shocks are lifesaving in the case of sustained ventricular tachyarrhythmias, shocks can also be delivered unnecessarily for nonsustained episodes or inappropriately for supraventricular arrhythmias, nonarrhythmic noise, or artifacts.[2,3] These avoidable ICD shocks result in unnecessary hospital admissions and may have a negative impact on patient quality of life[4–6] as well as on morbidity and mortality.[7,8]

Although the reported frequency of ICD shocks varies according to patient population, device type, and specific ICD programming, a substantial proportion of patients consistently receive inappropriate shocks after ICD implantation. Recent studies have reported inappropriate shocks rates of up to 10%, but have largely excluded single-chamber devices that have been associated with inappropriate therapy rates between 14% and 27%.[9–12] Shock reduction strategies have included selective implantation of atrial leads for improved supraventricular tachycardia (SVT) diagnosis, widespread use of empiric antitachycardia pacing (ATP) for relatively rapid arrhythmias, strategic programming to delay ICD detection or treatment, and development of improved arrhythmia discrimination algorithms.

A strategy for reducing inappropriate shocks combining improved arrhythmia discrimination algorithms and longer detection times was previously evaluated through the use of archived patient electrograms and "virtual ICD" computer modeling.[13] In the PainFree SST (SmartShock Technology) study, we sought to prospectively validate the prediction that a novel suite of new detection algorithms in conjunction with routine implementation of a proven programming strategy would improve freedom from inappropriate shocks in a large and heterogeneous "real-world" population of ICD patients.

Methods

Study design

The study design of the PainFree SST trial has previously been described.[14] In brief, the PainFree SST study was a prospective, multicenter clinical trial conducted in 2 consecutive phases. All subjects were followed until study closure but not less than 1 year. Total study duration was 4 years, from September 2009 until August 2013. After implantation, subjects were required to have a follow-up visit every 6 months. Data were collected at the time of enrollment, at scheduled and unscheduled follow-up visits, and at study exit.

Study population

Patients were eligible for the study if they had a clinical indication for an ICD for either primary or secondary prevention of sudden cardiac death and intended to receive a single-chamber or, dual/triple-chamber Protecta device (Medtronic Inc, Minneapolis, MN). This included new implants, system upgrades, and generator replacements. Exclusion criteria included, among others, participation in another study that could confound results, life expectancy less than 12 months, or the presence of a mechanical tricuspid heart valve. The study was performed in compliance with the Declaration of Helsinki. The institutional review board of each participating center approved the study protocol, and all patients gave written informed consent.

Study end-points

The primary study end-point was the percentage of patients receiving at least 1 inappropriate shock at 12 months. Secondary end-points included the percentage of patients receiving any inappropriate device therapy (ie, shocks and/or overdrive pacing (ATP)) at 12 months, the causes of inappropriate shocks, the incidence of appropriate device therapy, and evaluation of any undertreatment of ventricular arrhythmias. All-cause mortality also was reported.

Algorithm description

SmartShock Technology consists of 6 discrimination algorithms that are activated by the device when rate-based arrhythmia detection criteria are met in order to distinguish between true ventricular arrhythmias and other rhythms. This technology has demonstrated clinical safety and ventricular fibrillation (VF) detection efficacy and sensitivity.[15] Detailed descriptions of the new and updated algorithms can be found elsewhere.[14] (1) Wavelet morphology algorithms were integrated with atrioventricular timing discrimination (PR Logic) in dual/triple-chamber ICDs to help differentiate ventricular tachycardia (VT) from SVT based on QRS morphology. This discrimination applies to all VT with rates slower than a programmable limiting rate (SVT Limit). (2) The nominal SVT Limit has been changed from 320 to 260 ms to allow SVT discriminators to withhold detection and therapy for atrial rhythms that are faster than the VF detection interval. (3) Confirmation+ improves recognition of VT/VF termination to prevent inappropriate shock by using confirmation intervals based on ventricular cycle length + 60 ms instead of the slowest programmed therapy zone. (4) T-Wave Oversensing algorithm withholds detection and therapy when T-wave oversensing is occurring based on information from the sensing channel and a parallel signal path that attenuates lower-frequency signals such as T-waves while minimally attenuating R waves. (5) Lead Noise Discrimination algorithm discriminates sensed rhythms that are due to lead noise from those due to VT/VF and provides the ability to withhold therapy delivery. (6) RV Lead Integrity Alert provides early indication of potential lead fracture by an audible alert and automatically extends VF number of intervals to detect (NID) to 30/40 (if it was less).

Device programming

VF zones were programmed with a detection interval of 320 ms, and programming of a VT therapy zone was left up to the

physician's discretion. Discrimination algorithms were programmed ON, per the nominal "out of box" settings of the device. SVT discrimination algorithms were active for median ventricular intervals ≥260 ms. In primary prevention patients, the NID was programmed at 30/40, requiring 30 of 40 subsequent intervals to be <320 ms, which is clinically proven to safely reduce shocks.[16] The secondary prevention patients were randomized between NID 30/40 and 18/24 with further analysis to be reported at a later time. ATP during charging was programmed in the VF zone. VT detection and therapy was left to the physician's discretion. Further details are described in the design paper of this trial.[14]

Rhythm classification

All ICDs were programmed to store a near-field and a far-field electrogram (EGM) for spontaneous device-detected episodes. Episodes were adjudicated by an episode review committee (ERC) comprising 9 independent physicians who were not study investigators (Appendix B). Each spontaneous episode with stored EGM was reviewed by 2 ERC members and by a third reviewer in the case of disagreement. If concordance was not achieved between 2 of 3 reviewers, the episode was reviewed by the full ERC to reach consensus. All episodes resulting in therapy delivery were classified as appropriate or inappropriate. An episode was considered inappropriate when any therapy was delivered in a rhythm that was not a true ventricular arrhythmia, including a nonsustained episode that self-terminated before shock. Untreated episodes also were adjudicated to assess sensitivity.

Statistical analysis

Continuous variables are reported with mean and standard deviation and categorical variables with count and percentage. Therapy rates were analyzed using competing risks survival analysis methods, accounting for death as a competing risk. Therapy incidence rates were estimated using cumulative incidence functions[17] and reported with 95% confidence interval (CI). Incidence rates thus represent the percentage of patients with at least 1 therapy event in the specified time window. All inappropriately shocked episodes were included in the analysis. A sensitivity analysis was performed by counting shocked episodes with incomplete data (only EGM missing) as inappropriate. The relationship between inappropriate shocks and patient baseline characteristics was analyzed using a multivariable Fine and Gray regression model.[18] Age and left ventricular ejection fraction (LVEF) were included in the model as continuous variables, but QRS duration was dichotomized with a cutoff value of 120 ms because of observed nonlinearity of the effect. Other variables included were device type, gender, indication (primary vs secondary prevention), previous device, history of myocardial infarction, atrial fibrillation (AF), VT, and the prescription of antiarrhythmic drugs. There were missing values for gender (0.2%), age (0.2%), LVEF (7.4%), QRS duration (12.3%), and indication (0.2%). Multiple imputation using the fully conditional specification method was used to create 10 imputed datasets that were analyzed separately.[19] Results were combined using the Rubin rule. Statistical comparison of subgroups defined by programming of VT therapies used a 2-sided Gray test.[17]

Episodes that met ventricular rate criteria, but had device therapy withheld due to the discrimination algorithms were all reviewed by the ERC and classified as appropriately or inappropriately rejected. Relative sensitivity was calculated as the quotient between the number of true VT/VF episodes that appropriately received therapy and the number of all true VT/VF episodes.

The study was designed to include at least 1131 patients with dual/triple-chamber devices in order to estimate the inappropriate shock rate at 1 year postimplant with 1% precision. This was based on the assumption that the inappropriate shock rate would be 4%.[3,14] Similarly, inclusion of at least 610 patients with single-chamber devices would achieve 2% precision in case of a true inappropriate shock rate of 7.5% at 1 year. $P < .05$ was considered significant. All analyses were performed with SAS versions 9.3 and 9.4 (SAS Institute Inc, Cary, NC).

Results

Study population

Between September 2009 and August 2012, a total of 2790 patients were enrolled by 126 centers in North and South America, Europe, Asia, and Africa. Twenty patients were excluded from analysis, because they did not meet the eligibility criteria; 1 patient did not sign consent, 1 patient participated in a confounding trial, 8 patients did not have an implant attempted, 5 patients failed implant, and 5 patients received a device other than the Protecta. Baseline characteristics for the remaining 2770 patients, including 751 recipients of a single-chamber, 948 of a dual-chamber, and 1,071 of a triple-chamber ICD, are given in Table 1.

Patients were followed for a mean of 22 ± 9 months with min–max range of 0 to 46 months for dual/triple-chamber ICDs and 0 to 35 months for single-chamber ICDs. During this period, 230 patients died and 438 patients exited the study early. Postimplant device data were available for 2598 patients. Figure 1 shows the analysis cohort and the data available for analysis.

Inappropriate therapies

The inappropriate shock incidence for dual/triple-chamber ICDs was 1.5% at 1 year (CI 1.0%–2.1%), 2.8% at 2 years (CI 2.1%–3.8%), and 3.9% at 3 years (CI 2.8%–5.4%; Figure 2A). Incidence of any inappropriate therapy in dual-/triple chamber devices, including shock and/or ATP therapy, was 2.3% at 1 year (CI 1.7%–3.1%), 3.7% at 2 years (CI 2.8%–4.8%), and 5.7% at 3 years (CI 4.0%–7.6%; Figure 2A). During the entire follow-up period, 48 of the 2019 patients with a dual-/triple-chamber device had 84 episodes with inappropriate shocks.

Single-chamber devices showed an inappropriate-shock incidence of 2.5% at 1 year (CI 1.5%–3.9%) and 3.7% at

Table 1 Baseline characteristics

Subject characteristics	All patients (N = 2770)	Single-chamber ICD (N = 751)	Dual-chamber ICD (N = 948)	Triple-chamber ICD (N = 1071)
Demographics and clinical presentation				
Geography (%)				
North America	41	40	42	40
Europe	38	38	33	43
Other	21	22	25	17
Male (%)	79	81	79	78
Age (years)	65 ± 12	62 ± 12	63 ± 13	68 ± 11
Left ventricular ejection fraction (%)	32 ± 13	33 ± 14	36 ± 15	28 ± 9
QRS (ms)	126 ± 33	107 ± 22	114 ± 27	153 ± 28
Secondary prevention (%)	31	34	41	19
Device replacement or upgrade (%)	33	21	30	45
New York Heart Association functional class (%)				
I	15	25	20	4
II	40	46	44	31
III	31	13	15	57
IV	1	1	0	2
No heart failure	13	15	21	4
History (%)				
Cardiomyopathy, ischemic	44	43	45	43
Congestive heart failure	38	30	29	53
Coronary artery disease	45	47	44	45
Familial or inherited conditions with high risk for ventricular tachycardia	5	5	6	3
Hypertension	52	46	54	55
Myocardial infarction	38	43	39	33
Valve dysfunction	25	18	21	33
Coronary artery bypass graft	24	21	22	27
Coronary artery intervention	28	30	30	24
Arrhythmias and conduction defects (%)				
Atrial fibrillation	30	22	27	37
Atrial flutter	5	2	7	5
Atrial tachycardia	2	1	3	3
Ventricular tachycardia (including nonsustained)	36	34	47	27
Atrioventricular block	15	7	15	20
Left bundle branch block	25	6	9	53
Right bundle branch block	8	5	9	8
Medication (%)				
Angiotensin-converting enzyme inhibitor or sartan	77	76	72	82
Beta-blocker	86	86	84	87
Diuretic	68	57	59	84
Calcium channel blocker	11	12	13	9
Statin	60	66	59	58
Antiarrhythmic drug	19	13	24	18

ICD = implantable cardioverter-defibrillator.

2 years (CI 2.2%–5.7%). Incidence of any inappropriate single-chamber device therapy, including shock or ATP therapy, was 3.4% at 1 year (CI 2.2%–5.0%) and 4.8% at 2 years (CI 3.2%–7.0%; Figure 2B). During the entire follow-up period, 22 of 751 patients with a single-chamber ICD had 31 episodes with inappropriate shocks.

The most frequent cause of an inappropriate shock was AF for all device types, followed by oversensing due to EGM noise (Table 2). The relationship between patient baseline characteristics and the incidence of inappropriate shocks at 2 years is shown in Figure 3. Multivariable analysis identified a history of AF (hazard ratio [HR] 2.9, $P = .0001$), history of VT (HR 2.2, $P = .001$), and absence of prior myocardial infarction (HR 2.3, $P = .009$) as independent predictors of inappropriate device shocks.

VT zone shocks were enabled at the physician's discretion in 1646 study patient (59% of the total). Typically, VT detection required 24 consecutive R-R intervals (median, quartiles: 16–24) to be ≤350 ms (median, quartiles: 340–360 ms). Inappropriate shock incidence in patients with VT shocks enabled was 2.8% at 2 years, which was not significantly different from the 3.4% inappropriate shock incidence in the 41% of patients who did not have VT zone shocks programmed ($P = .83$; Figure 4).

There were 111 shocked episodes in 17 patients in whom EGMs were overwritten due to limited device memory, including patients with VT storms. If all shocked episodes without reviewable EGMs were classified as inappropriate, the inappropriate shock rate at 1 year would be 1.7% in dual/triple-chamber ICD patients and 3.3% in single-chamber patients.

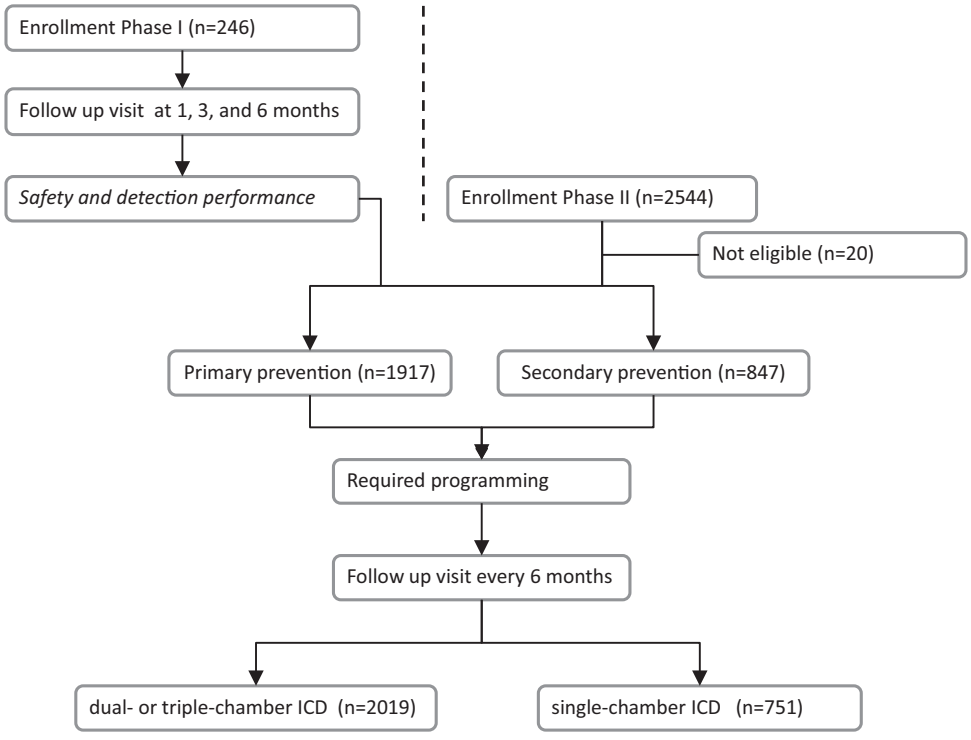

Figure 1 Flow diagram.

Appropriate therapy

There were 4028 episodes in which only appropriate therapies were delivered, including 689 episodes in 234 patients who received appropriate shocks and 3339 episodes in 363 patients who received appropriate ATP only. The respective 1- and 2-year incidence rates of appropriate shocks were 5.9% (CI 4.9%–7.1%) and 10.1% (CI 8.6%–11.7%) for the dual/triple-chamber ICD group and 6.5% (CI 4.8%–8.5%) and 10.4% (CI 7.8%–13.3%) for the single-chamber ICD group. For all appropriate therapy (ie, both shocks and ATP), the respective 1- and 2-year incidence rates were 13.7% (CI 12.2%–15.3%) and 20.1% (CI 18.1%–22.1%) for the dual/triple-chamber ICD group and 10.8% (CI 8.6%–13.3%) and 17.6% (CI 14.4%–21.2%) for the single-chamber ICD group.

Combining appropriate and inappropriate therapies, the all-cause therapy-free rate was 85.3% at 1 year (84.7% for dual/triple-chamber ICD and 86.9% for single-chamber ICD), and the all-cause shock free rate was 92.5% at 1 year (92.8% for dual/triple-chamber ICD and 91.7% for single-chamber ICD). Of note, of 804 episodes receiving shocks, 115 (14%) received any inappropriate shock.

Mortality

In total, 230 patients died during the study. None of the patients for whom device data were available died because of inappropriately withheld device therapy or in relationship with inappropriate therapy. The estimated mortality at 2 years was 10.2% (CI 8.7%–11.6%) in dual/triple-chamber ICD patients [6.9% (CI 5.1%–8.7%) for dual-chamber ICD and 13.0% (CI 10.7%–15.2%) for triple-chamber ICD] and 6.0% (CI 3.9%–8.0%) in single-chamber ICD patients.

Sensitivity of discrimination algorithms

The discrimination algorithms withheld therapy for 9863 episodes. The ERC reviewed the 3339 episodes with EGM for which therapy was withheld and considered therapy to be appropriately withheld for 3291 episodes (98.6%). As indicated earlier, the ERC also reviewed all treated episodes and identified episodes with EGM that were true ventricular arrhythmias for which therapy was delivered. The total number of true ventricular arrhythmias was then 3901 episodes and relative sensitivity was 98.8%. None of the 48 sustained true ventricular arrhythmias for which therapy was withheld led to death or major adverse events. In addition, 13 episodes with detection delayed for more than 2 minutes did not have serious adverse consequences.

Discussion

The PainFree SST study demonstrated that novel ICD discrimination algorithms and routine use of contemporary evidence-based ICD programming will result in a low inappropriate shock rate. Shock rates were uniformly low across a heterogeneous, real-world population representing a variety of clinical ICD device indications, treated with different types of ICDs (single-, dual-, and triple-chamber ICDs), and afflicted by a multitude of comorbidities including AF. Notably, the inappropriate shock rate in our study was unaffected by physician-tailored treatment of ventricular arrhythmias slower than 188 bpm.

Inappropriate ICD interventions

Implementation of a strategy that combines evidence-based programming and enhanced discrimination algorithms may be an effective way to reduce inappropriate and unnecessary ICD

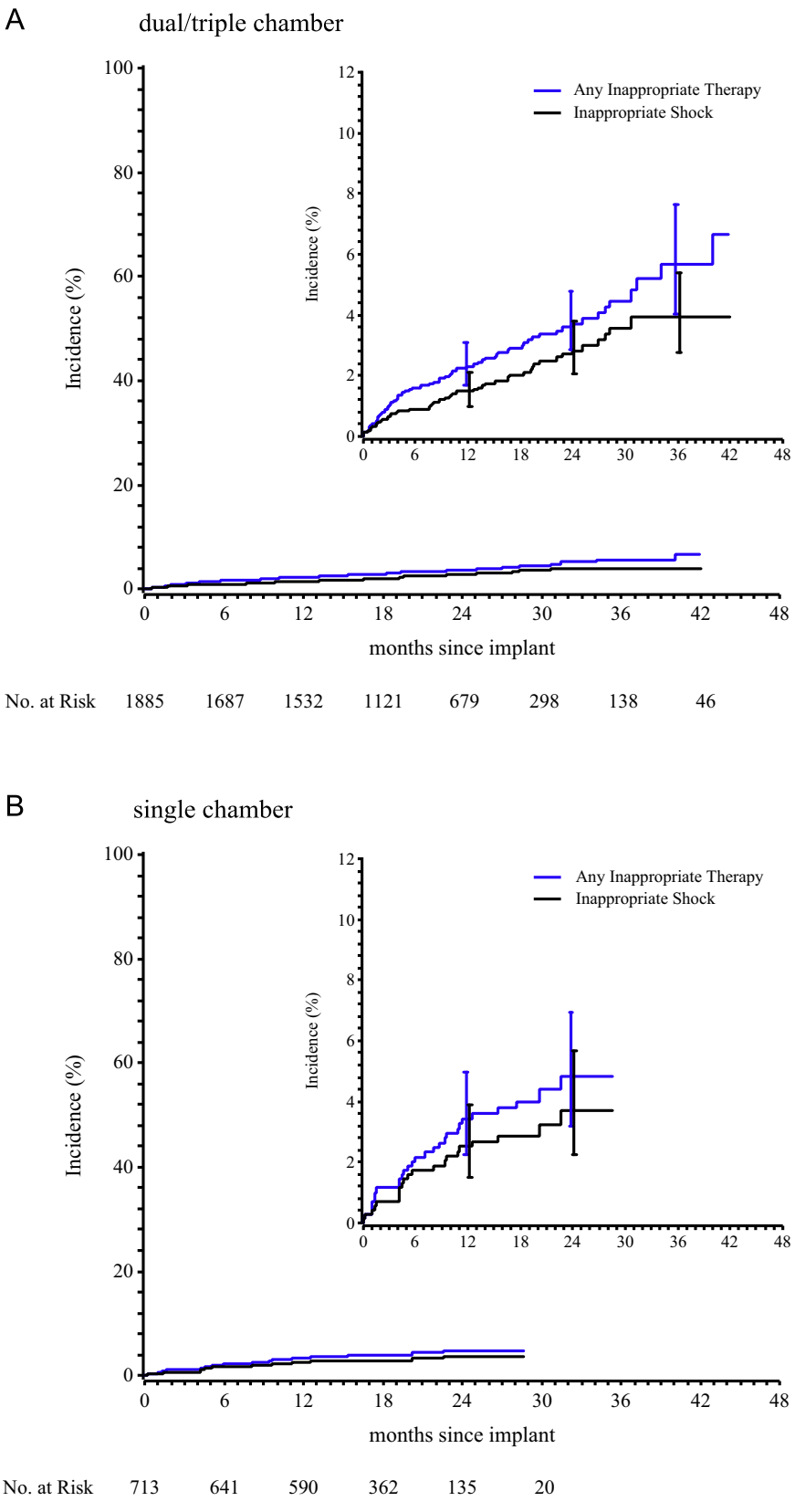

Figure 2 Inappropriate shocks and inappropriate therapy in dual/triple-chamber devices **(A)** and single-chamber devices **(B)**. The main figure and the inset show the same curves on a different scale in both panels.

Table 2 Causes of inappropriate shocks

Cause of inappropriate shock	Dual/triple-chamber ICD		Single-chamber ICD	
	No. of shocked episodes (%)	No. of patients with inappropriate shock(s)	No. of shocked episodes (%)	No. of patients with inappropriate shock(s)
Atrial fibrillation/atrial flutter	41 (49%)	26	25 (81%)	16
Other supraventricular tachycardia (eg, sinus tachycardia, atrial tachycardia)	11 (13%)	8	3 (10%)	3
Committed shock after appropriate therapy	7 (8%)	7	0 (0%)	0
Ablation procedure	0 (0%)	0	1 (3%)	1
Electrogram noise	21 (25%)	6	2 (6%)	2
T-wave oversensing	4 (5%)	4	0 (0%)	0
Total	84 (100%)	48	31 (100%)	22

Patient counts are not mutually exclusive as some patients had shocks for multiple causes. Twenty-one patients had >1 episode with inappropriate shocks (maximum 8 episodes). In total, the 115 inappropriately shocked episodes received 220 shocks (maximum 6 shocks for a single episode).

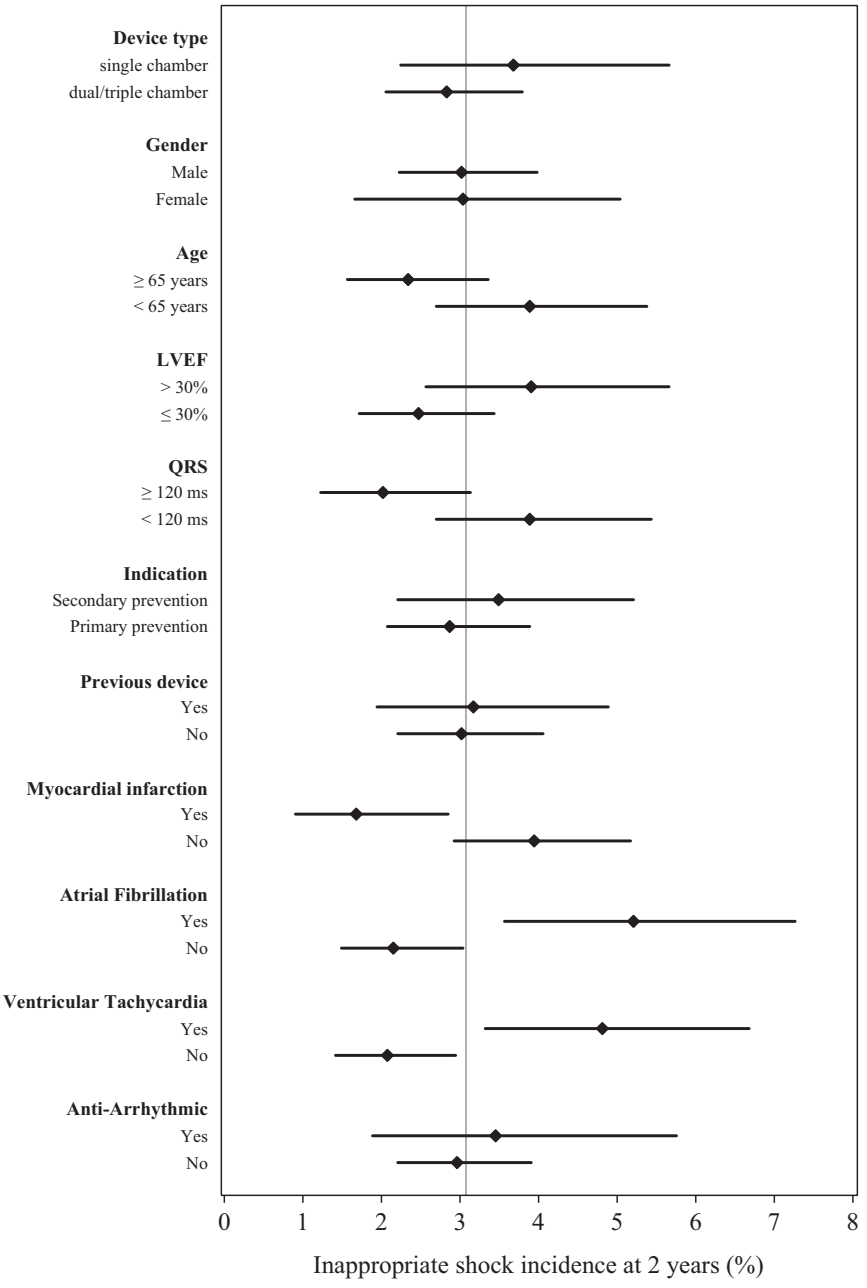

Figure 3 Incidence of inappropriate shocks for subgroups. The *vertical line* at 3.1% represents the inappropriate shock rate at 2 years in the full study cohort. LVEF = left ventricular ejection fraction.

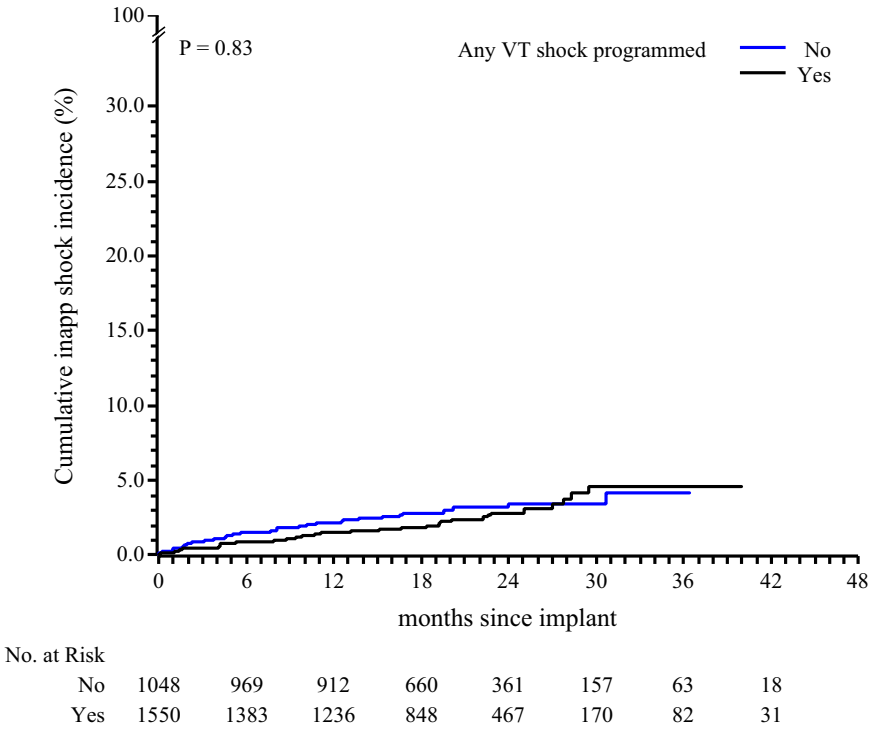

Figure 4 Inappropriate shocks in relation to ventricular tachycardia (VT) therapy programming.

interventions. PainFree SST patients experienced 1-year inappropriate shock rates of 1.5% in the dual/triple-chamber ICD group and 2.5% in the single-chamber ICD group. One-year inappropriate therapy (ie, shocks and ATP) rates were 2.3% and 3.4% in the dual/triple-chamber ICD group and single-chamber ICD group, respectively. To our knowledge, the inappropriate shock and therapy rates demonstrated with this strategy are the lowest reported in the literature. The 1-year inappropriate shock rates of PainFree Rx II, EMPIRIC, and PREPARE were 9.3%, 10.7%, and 3.6%, respectively.[3,16] MADIT-RIT reported a 5% probability of inappropriate therapy in the delayed therapy arm and a 4% probability of inappropriate therapy at 1 year of follow-up in the high-rate therapy arm.[9] Similarly, the ADVANCE III study showed a 3% probability of inappropriate shocks and 11.5% probability of inappropriate therapies at 1 year.[10] Of note, in PainFree SST only 14% of shocked episodes had any inappropriate shock. In comparison, the MADIT-RIT study reported that the proportion of shocks that was inappropriate was 48% in the delayed therapy arm and 26% in the high-rate arm.[9] In Advance III, 40% of all shocks were inappropriate in the standard-detection arm and 28% in the long-detection interval arm.[10] Our results are even more remarkable when we consider the fact that MADIT-RIT did not include single-chamber devices, which are generally less capable of withholding inappropriate therapy for atrial tachyarrhythmias.

Causes of inappropriate shocks

Underlying causes of inappropriate ICD interventions include supraventricular tachyarrhythmias (especially AF with rapid ventricular response), lead or signal or noise oversensing, and lead or connector malfunction.[2,3] As in prior trials,[8,9] AF was the most common cause of an inappropriate therapy, and a baseline history of AF was a predictor of receiving an inappropriate therapy. Our inappropriate therapy rate was $<3\%$ at 1 year, despite a 30% prevalence of AF. In comparison, the high-rate arm of MADIT-RIT reported a 1-year inappropriate therapy rate of 5% despite an only 11% prevalence of AF and a higher ICD therapy rate cutoff ≥ 200 bpm with no SVT discriminators enabled. Our nearly 3-fold higher prevalence of AF and lower rates of inappropriate therapy in PainFree SST suggest to us the potential importance of applying discrimination algorithms at higher rates to prevent unnecessary ICD interventions. A small minority of patients in our study remained subject to inappropriate shocks due to AF despite programming enhancements, so there remains an appropriate role for both pharmacologic and nonpharmacologic treatment measures in these patients.

Use of multiple VT zones does not affect inappropriate shock rate

In the MADIT-RIT trial, a VT zone with therapies was programmed ON in the standard-interval detection group and OFF in the high-rate group.[9] The incidence of inappropriate therapy in the standard-interval and high-rate groups after 2 years of follow-up were 25% and 6%, respectively. In the PainFree SST study, the VT zone was recommended per protocol to be programmed OFF, unless the patient had a history of sustained VT or the physician considered it appropriate to program it ON. In total, 59% of our patients had VT zone shock therapies enabled, but without an apparent increase in inappropriate shocks. It is reassuring to note that the use of discrimination algorithms in

programmed VT zones did not result in any meaningful difference in the inappropriate shock rate.

Study limitations

Some limitations of the PainFree SST trial deserve further consideration. All patients enrolled in this study received devices with proprietary discrimination algorithms produced by a single manufacturer. Although the results may be generalizable in the sense that a strategy of applying discrimination algorithms to high ventricular rates, treating only faster rhythms with longer duration, and using ATP more aggressively may be used to minimize the risk of inappropriate shocks, our results might prove specific to patients with an ICD from this manufacturer. Some episode EGMs were overwritten during VT/VF storms and consequently lost to final analysis. However, any such loss of follow-up data was limited, and a sensitivity analysis classifying all therapy episodes with missing EGMs as inappropriate revealed no major impact on our primary end-points or conclusions. Because the study end-point was not mortality and in absence of a control group, no strong claim on the cause of mortality can be made. Finally, because of the absence of a control group in this design, direct comparison to alternative shock reduction strategies may be limited. We believe that the inclusive nature of the study protocol allowed us to achieve a representative real-world population.

Conclusion

Routine implementation of a predefined ("out-of-the box") programming strategy in conjunction with the adoption of novel discrimination algorithms led to a very low rate of inappropriate shocks in ICD patients at 1 and 2 years. Flexible programming of the VT zone did not affect the inappropriate shock rate.

Acknowledgments

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Appendix A. PainFree SST Investigators

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Appendix B. Episode Review Committee

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References

1. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–2329.
2. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
3. Wilkoff BL, Ousdigian KT, Sterns LD, Wang ZJ, Wilson RD, Morgan JM. 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;48:330–339.
4. Passman R, Subacius H, Ruo B, Schaechter A, Howard A, Sears SF, Kadish A. Implantable cardioverter defibrillators and quality of life: results from the defibrillators in nonischemic cardiomyopathy treatment evaluation study. Arch Intern Med 2007;167:2226–2232.
5. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, Kutalek SP, Friedman PL, Bubien RS, Page RL, Powell J. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation 2002;105:589–594.
6. Freedenberg V, Thomas SA, Friedmann E. Anxiety and depression in implanted cardioverter-defibrillator recipients and heart failure: a review. Heart Fail Clin 2011;7:59–68.
7. Mishkin JD, Saxonhouse SJ, Woo GW, Burkart TA, Miles WM, Conti JB, Schofield RS, Sears SF, Aranda JM Jr. Appropriate evaluation and treatment of heart failure patients after implantable cardioverter-defibrillator discharge: time to go beyond the initial shock. J Am Coll Cardiol 2009;54:1993–2000.
8. Daubert JP, Zareba W, Cannom DS, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. J Am Coll Cardiol 2008;51:1357–1365.

9. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275–2283.
10. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JB, Hersi A, Gulaj M, Wijfels MC, Santi E, Manotta L, Arenal A. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. JAMA 2013;309:1903–1911.
11. Ruwald AC, Sood N, Ruwald MH, Jons C, Clyne CA, McNitt S, Wang P, Zareba W, Moss AJ. Frequency of inappropriate therapy in patients implanted with dual- versus single-chamber ICD devices in the ICD arm of MADIT-CRT. J Cardiovasc Electrophysiol 2013;24:672–679.
12. Theuns DA, Rivero-Ayerza M, Boersma E, Jordaens L. Prevention of inappropriate therapy in implantable defibrillators: a meta-analysis of clinical trials comparing single-chamber and dual-chamber arrhythmia discrimination algorithms. Int J Cardiol 2008;125:352–357.
13. Volosin KJ, Exner DV, Wathen MS, Sherfesee L, Scinicariello AP, Gillberg JM. Combining shock reduction strategies to enhance ICD therapy: a role for computer modeling. J Cardiovasc Electrophysiol 2011;22:280–289.
14. Auricchio A, Meijer A, Kurita T, Schloss E, Brinkman K, Claessens-van Ooijen M, Sterns L. Safety, efficacy, and performance of new discrimination algorithms to reduce inappropriate and unnecessary shocks: the PainFree SST clinical study design. Europace 2011;13:1484–1493.
15. Wollmann CG, Lawo T, Kűhlkamp V, Becker R, Garutti C, Jackson T, Brown ML, Mayr H. The Protecta XT implantable defibrillator. Detection performance and safety results from the PainFree SST Study. Pacing Clin Electrophysiol 2014;37:1198–1209.
16. Wilkoff BL, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW, Birgersdotter-Green UM, Wathen MS, Van Gelder IC, Heubner BM, Brown ML, Holloman KK. 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. J Am Coll Cardiol 2008;52:541–550.
17. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141–1154.
18. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2010;30:377–399.

CLINICAL PERSPECTIVES

Much focus has been placed recently on the prevention of unnecessary ICD shocks, both appropriate and inappropriate. Strategies used to reduce shocks have included reprogramming to detect only faster rhythms that exceed a threshold duration and providing antitachycardia pacing to painlessly terminate the arrhythmia without a shock. However, less attention has been given to the nonprogrammable qualities of the arrhythmia discriminators in reducing shocks. Arrhythmia discrimination algorithms play an important role in withholding inappropriate shocks after detection thresholds are met and reducing the risk of an inappropriate shocks for patients with slower symptomatic ventricular tachycardia, which may require deviation from evidence-based shock reduction programming. In the PainFree SST study, we demonstrated that the combination of arrhythmia discrimination algorithms and evidence-based shock reduction programming results in very low inappropriate shock rates. Furthermore, we demonstrated that the risk of an inappropriate shock is not increased when therapies for slow VT are enabled, which occurred in 59% of enrolled subjects. The algorithms and programmed settings used in the PainFree SST study were nominal settings for the ICDs used in the study, with the exception of the number of intervals to detect ventricular fibrillation. Thus, the shock reduction benefit seen with the algorithms and programming in this "real-world" clinical study can be easily extrapolated to the clinical setting, which in turn will benefit patients by reducing shocks and improving quality of life.