

Algorithm-based reduction of inappropriate defibrillator shock: Results of the Inappropriate Shock Reduction with PARAD+ Rhythm Discrimination-Implantable Cardioverter Defibrillator Study



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BACKGROUND Inappropriate shocks (IS) continue to have a major negative impact on patients implanted with defibrillators.

OBJECTIVE The purpose of this study was to assess IS reduction with the PARAD+ discrimination algorithm in a general population implanted for primary or secondary prevention.

METHODS ISIS-ICD (Inappropriate Shock Reduction with PARAD+ Rhythm Discrimination-Implantable Cardioverter Defibrillator) was a 2-year international, interventional study in patients implanted with a dual implantable cardioverter-defibrillator (ICD) or triple-chamber defibrillator (cardiac resynchronization therapy-defibrillator [CRT-D]) featuring PARAD+. IS (shocks not delivered for ventricular tachycardia or fibrillation) were independently adjudicated. The primary endpoint was percentage of IS-free patients at 24 months. Primary and worst-case analyses of annual incidence rates of patients with ≥ 1 IS, overall and per defibrillator type, were conducted.

RESULTS In total, 1013 patients (80.7% male; age 67.1 ± 11.4 years; 68%/30%/2% primary/secondary/other indication) were enrolled and followed for a median of 552 days (interquartile range 354; 725). Of

993 analyzed patients programmed with PARAD+, 14 had ≥ 1 IS, corresponding to a percentage free from IS of 98.1% (95% confidence interval [CI] 96.8%–98.9%). Annual incidence rates (per 100 person-years) of patients with IS were 1.0 (95% CI 0.59–1.69) and 2.1 (95% CI 1.46–3.02) in the primary and worst-case analyses, respectively. In ICD patients, rates were 1.2 (95% CI 0.68–2.23) and 2.3 (95% CI 1.47–3.53), and in CRT-D patients 0.59 (95% CI 0.19–1.83) and 1.8 (95% CI 0.93–3.44) per 100 person-years.

CONCLUSION The annual rate of defibrillator patients with IS using the enhanced PARAD+ discrimination algorithm alone ranged from 1.0 to 2.1 per 100 person-years in a general population implanted for primary or secondary prevention.

KEYWORDS Defibrillation; Discrimination algorithm; Shock; Ventricular fibrillation; Ventricular tachyarrhythmia

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Introduction

The primary aim of implantable cardioverter-defibrillators (ICDs) is to preserve life by terminating life-threatening ventricular arrhythmias.^{1–5} Although ICD shocks are lifesaving for sustained ventricular tachyarrhythmias, shocks also can be delivered unnecessarily for nonsustained episodes or inappropriately for supraventricular arrhythmias, nonarrhythmic noise, or artifacts,⁶ resulting in unnecessary hospital admissions with a negative impact on quality of life⁷ as well as on morbidity and mortality.^{8,9} Furthermore, unnecessary shocks lead to earlier battery depletion and increased health care costs.¹⁰

Inappropriate shocks (IS) are consistently received by many patients after ICD implantation. IS rates are as high as 10%.^{9,11–13} By far the leading cause of IS is device misclassification of supraventricular arrhythmia (most commonly atrial fibrillation [AF]) as ventricular tachycardia (VT). Consequently, the role of arrhythmia discrimination algorithms is determinant.

The PARAD+ algorithm (MicroPort CRM, Clamart, France) is able to discriminate supraventricular from ventricular arrhythmias. A meta-analysis of 10,000 tachycardia episodes treated by PARAD+ showed specificity of 94% in a conventional ICD population, with an IS rate of 5% overall.¹⁴ However, many factors may have influenced these results, such as population, follow-up duration, and device programming. The aim of ISIS-ICD (Inappropriate Shock Reduction with PARAD+ Rhythm Discrimination–Implantable Cardioverter Defibrillator) was to further assess the performance of the PARAD+ algorithm in reducing IS in a general population implanted for primary or secondary prevention.

Methods

Trial design

The ISIS-ICD study was an interventional, multicenter, prospective clinical investigation. Eligible subjects were patients indicated for an ICD or cardiac resynchronization therapy–defibrillator (CRT-D) for primary or secondary prevention according to applicable guidelines^{15,16} in sinus rhythm or with paroxysmal atrial tachyarrhythmia and cardioversion planned within 3 months. Major exclusion criteria were absence of an atrial lead and permanent atrial tachyarrhythmia.

The investigational plan was approved by institutional review boards and/or ethics committees. All patients provided written informed consent. Subjects were evaluated at months 0, 6, and 12, although investigators were encouraged to continue evaluation for up to 24 months.

Data collection

Data were collected using paper case report forms and electronic files from the ICDs at each follow-up. Adverse events and hospitalizations were documented and classified by the sponsor's safety officer.

All shocks recorded in the electronic files were independently adjudicated by a Clinical Event Committee (CEC), consisting of a board of 3 independent, experienced electrophysiologists. Final adjudication was obtained by the agreement of 2 electrophysiologists. The CEC was responsible for classifying all shocks as VT, ventricular fibrillation (VF), AF, supraventricular tachycardia (SVT), junctional tachycardia, noise (signal unrelated to cardiac activity), or undetermined. The CEC also determined whether the shock was appropriate (Yes, No, or Not Known). A shock was considered appropriate when it delivered on a VT or VF, and inappropriate for any other reason. In cases for which an electrogram was missing, shocks were not adjudicated. An exception was

made when an adjudicated shock occurred within the same episode as a shock for which an electrogram was missing. These shocks were indirectly adjudicated based on the adjudication of the previous shock(s) in the episode.

Study endpoints

The primary endpoint was the proportion of patients free from IS among patients implanted with a PARAD+ algorithm–enabled CRT-D or dual-chamber (DR)-ICD at 24 months.

Secondary endpoints were the proportions of IS and appropriately delivered shocks. Ancillary endpoints included the reasons for IS and appropriate shocks (AS), and the incidence rate of IS. Analysis of time to first IS or AS was also performed.

Devices and programming

All patients received an ICD device (PARADYM DR and CRT-D models; Sorin Group Italia S.r.l., Saluggia, Italy) featuring the discrimination algorithm PARAD+ (Figure 1).^{17,18} PARAD+ allows the differentiation of supraventricular from ventricular arrhythmias based on ventricular rate stability, AV association analysis, long cycle search, rate onset analysis, and chamber of origin in the case of 1:1 tachycardia (Supplementary Figures S1 and S2).

The protocol required an enabled PARAD+ algorithm, along with programming of the slow VT zone >150 bpm, VT zone >185 bpm, and fast VT, and VF zone >230 and >255 bpm, respectively. The corresponding mandatory and recommended therapies are detailed in Table 1.

Sample size and statistical analysis

The primary objective was to show that at least 92.5% of subjects implanted with a PARAD+ algorithm–enabled CRT-D or DR-ICD were free from IS. This target percentage was derived from previous studies with other algorithms estimating the percentage of a general ICD population that received IS.^{11,12} With a 1-sided alpha of 0.025 and a desired power of 80%, 800 patients were required. Assuming a 20% dropout rate, the required sample size was 1000 patients.

The primary endpoint was the proportion of patients free from IS at 24 months based on Kaplan-Meier analysis. A sensitivity analysis was performed based on the patient incidence rate per 100 person-years. The reasons for IS and AS were reported, as well as the incidence rate of IS events. Kaplan-Meier plots were also used to present survival from IS and AS over time, along with 95% confidence intervals (CI), overall and per device model (DR and CRT-D). Hazard ratio (HR) with 95% CI were calculated to compare HRs of IS and AS in patients with CRT-D or DR-ICD using a Cox model. Analyses were carried out in implanted patients with PARAD+ activated. Patients with missing outcome data were considered as follows: assuming none experienced the outcome of interest for dichotomous variables; or

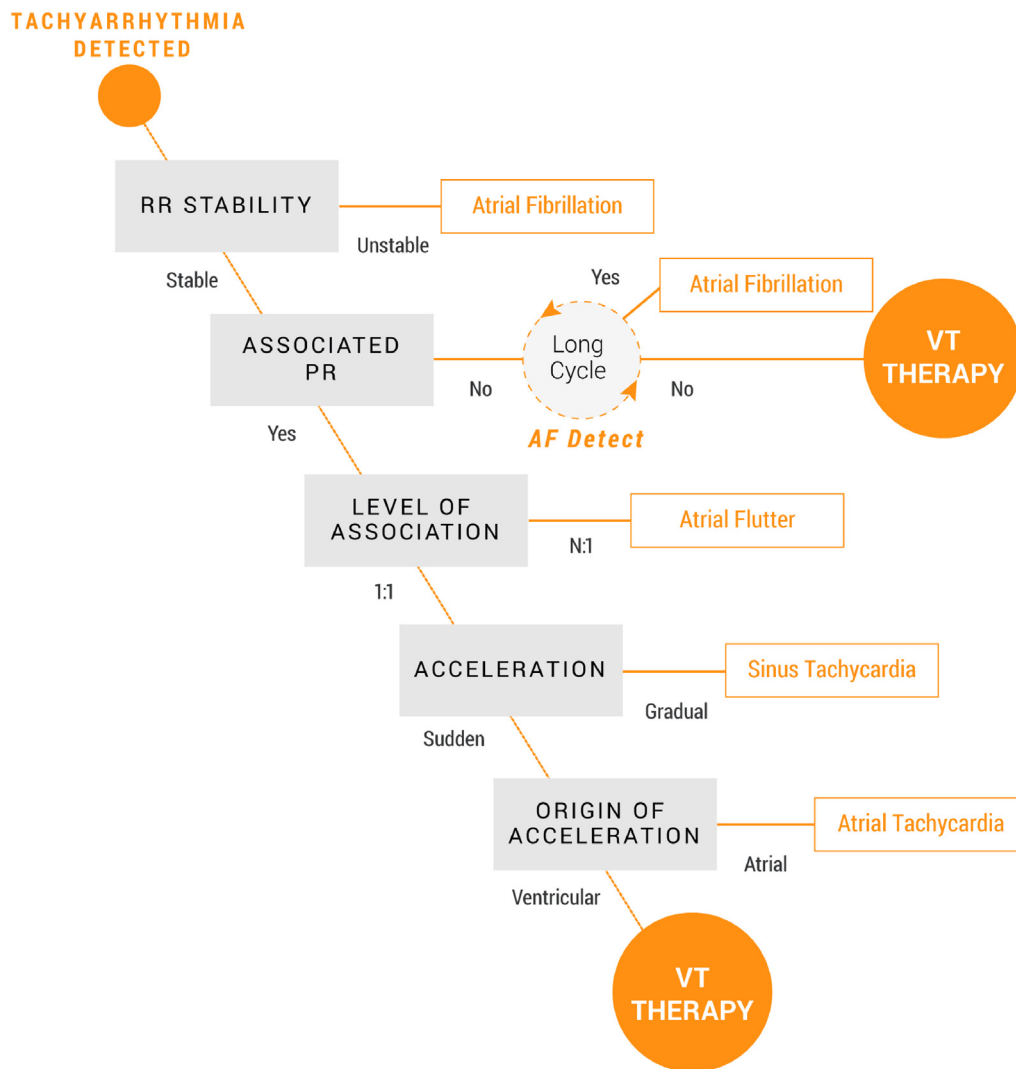


Figure 1 PARAD+ rhythm discrimination algorithm. The rhythm discrimination algorithm PARAD+ distinguishes supraventricular from ventricular arrhythmias based on analysis of several criteria, including ventricular rate stability, PR association (including long cycle detection), AV association, rate of onset, and chamber of origin (in the case of 1:1 tachycardia). AF = atrial fibrillation; VT = ventricular tachyarrhythmia.

censored at the time of last follow-up for survival analysis. A worst-case analysis considered all patients with missing data or nonadjudicated shocks as presenting the event, that is, as having had an IS.

Summary results were presented as follows: (1) for continuous variables, summary statistics were reported using

median and interquartile range (Q1; Q3) or mean ± SD; and (2) for categorical variables, frequency and percentage with 95% CI. Number of missing data was presented. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used for statistical analyses.

Results

A total of 1013 patients were included in the ISIS-ICD trial at 112 sites in 7 countries worldwide, including Europe and the United States, between October 2011 and March 2014. The PARAD+ algorithm was enabled in implanted devices in 993 subjects, 639 with an ICD and 354 with a CRT-D, who were thus considered for the primary analysis. The clinical characteristics of the population are listed in [Supplementary Table S1](#). In brief, most patients (80.6%) were male, median age was 68.0 years (60.0; 76.0), median left ventricular ejection fraction was 30.0% (25.0%; 35.0%), and more patients were implanted for primary (66.5%) than secondary (30.1%) prevention.

Table 1 Mandatory programming of devices

	Slow VT ON	VT ON	Fast VT+VF ON	
Rate ranges	150	185	230	255
Persistence ranges	30	16	8	
Detection criteria	PARAD+		Rate + stability	Rate
Therapies	ATP1 ATP2 <u>Shocks</u>	ATP1 Shocks	ATP Shocks	
Autoswitch ATP	<u>Yes (not in USA)</u>			

Mandatory in bold/recommended in underline.
ATP = antitachycardia pacing; VF = ventricular fibrillation; VT = ventricular tachycardia.

Primary, secondary, and ancillary endpoints

Over median follow-up of 552 days (354.0; 725.0), there were 188 shocks in 64 patients (6.4%). Of these 64 patients, 42 had all their shocks adjudicated, 6 had some shocks adjudicated, and 16 had no shocks adjudicated, giving a total of 129 adjudicated shocks in 48 patients and 59 nonadjudicated shocks (due to missing electrograms) in 22 patients (Table 2).

Fourteen patients received at least 1 IS. Therefore, the percentage of patients free from IS at 24 months was 98.1% (95% CI 96.8%–98.9%) overall (Figure 2A), so the primary endpoint of at least 92.5% of subjects implanted with a PARAD+ algorithm-enabled CRT-D or DR-ICD being free from IS was met. In ICD patients and CRT-D patients, the percentage of patients free from IS at 24 months was 97.6% (95% CI 95.5%–98.7%) and 99.1% (95% CI 97.2%–99.7%), respectively. These results were confirmed by a sensitivity analysis showing annual patient incidence rates of IS of 1.0 (95% CI 0.59–1.69) per 100 person-years overall, 1.2 (95% CI 0.68–2.23) per 100 person-years in ICD patients, and 0.59 (95% CI 0.19–1.83) per 100 person-years in CRT-D patients. The worst-case analysis produced annual patient incidence rates of IS of 2.1 (95% CI 1.46–3.02) per 100 person-years overall, 2.3 (95% CI 1.47–3.53) per 100 person-years in ICD patients, and 1.8 (95% CI 0.93–3.44) per 100 person-years in CRT-D patients.

Of the 129 adjudicated shocks, 88 (68%) were appropriate and 41 (32%) were inappropriate (Table 2). The majority of the 41 IS were due to noise, with 23 IS (56%) in 7 patients. Of these 7 patients, 2 presented with lead fracture, which accounted for 18 IS; in 2 other patients external noise was reported; and in 3 patients external noise was suspected but not demonstrated. Eight IS were due to misclassification of supraventricular arrhythmias by the PARAD+ algorithm in 7 patients, which represents 20% of all IS. Six of these 7 patients were taking beta-blockers and/or amiodarone or sotalol. Finally, 10 indirectly adjudicated IS in 1 patient could not be classified due to a missing electrogram (Table 2). The

Table 2 Reasons for appropriate and inappropriate shocks

Classification	Patients (N = 64)*	Shocks (N = 188)
Adjudicated shocks	48	129
Inappropriate		
AF	2	2 (5)
SVT	5	6 (15)
Noise	7	23 (56)
Other†	1	10 (24)
All‡	14	41 (100)
Appropriate		
VF	12	33 (38)
VT	28	54 (61)
Other†	1	1 (1)
All‡	36	88 (100)
Nonadjudicated shocks	22	59

Values are given as N or N (%).

AF = atrial fibrillation; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Some patients had both adjudicated and nonadjudicated shocks.

†Shock was indirectly adjudicated and therefore classified as "Other."

‡A single patient may have several appropriate and/or inappropriate shocks.

annual IS incidence rate was 2.9 per 100 patient-years (5% CI 2.14–3.94) (Table 3).

Time-to-event analyses

Kaplan-Meier survival free from first IS and AS during the 2-year follow-up is shown in Figures 2A and 2B, respectively.

Overall, the percentage of patients free from IS was 99.1% (95% CI 98.3–99.6) at 6 months, 98.9% (95% CI 98.0–99.4) at 12 months, and 98.4% (95% CI 97.2–99.1) at 18 months. CRT-D patients had a 43% lower risk of IS compared to ICD patients (HR 0.57; 95% CI 0.2–2.1).

Similarly, the percentage of patients free from AS was 97.7% (95% CI 96.5–98.6) at 6 months, 96.6% (95% CI 95.2–97.6) at 12 months, 96.3% (95% CI 94.8–97.3) at 18 months, and 95.6% (95% CI 93.8–96.8) at 2 years. CRT-D patients had a 49% lower risk of AS compared to ICD patients (HR 0.51; 95% CI 0.2–1.1).

Adverse events

The safety analysis was based on the 1013 enrolled subjects (Supplementary Table S2). During the whole clinical investigation, 71 deaths were reported, none related to the device. Furthermore, 2 cases of sudden cardiac death (SCD) were reported that may have been related to a failure to treat life-threatening VT/VF. A total of 491 serious emergent adverse events were reported in 282 patients. Of these, 240 were cardiovascular, 175 noncardiovascular, and 76 device-related. None of the device-related issues were unexpected adverse events. Of the 25 lead-related events, there were 17 cases of lead dislodgment (9 atrial, 8 ventricular), 4 cases of lead fracture (2 atrial, 2 ventricular), and 4 other cases.

Discussion

ISIS-ICD enrolled 1013 patients implanted with a defibrillator for primary or secondary prevention of SCD. Our study showed that the annual rate of patients experiencing IS with defibrillators (ICD and CRT-D) using the enhanced PARAD+ discrimination algorithm alone ranged from 1.0 (primary analysis) to 2.1 (worst-case analysis) per 100 person-years. Observed mortality was in line with that seen in similar studies of patients implanted with a defibrillator (ICD or CRT-D) for primary or secondary prevention of SCD.^{19–24}

ICDs are indicated for patients at high risk for VT or VF, for both primary and secondary prevention of SCD.²⁵ In order to accurately detect life-threatening arrhythmias, ICD detection algorithms have always been designed to focus on sensitivity rather than specificity. This has inevitably led to inappropriate ICD therapies,^{6,26} which are associated with multiple adverse effects including impaired quality of life, worse prognosis, and increased mortality.²⁷ Today, the percentage of patients with IS at \approx 1.5 years in clinical trials ranges from 3% to 11%, which outlines the need to further improve strategies to reduce IS.

Over the past 10 years, strategies to reduce IS have mainly focused on device programming adjustment and/or

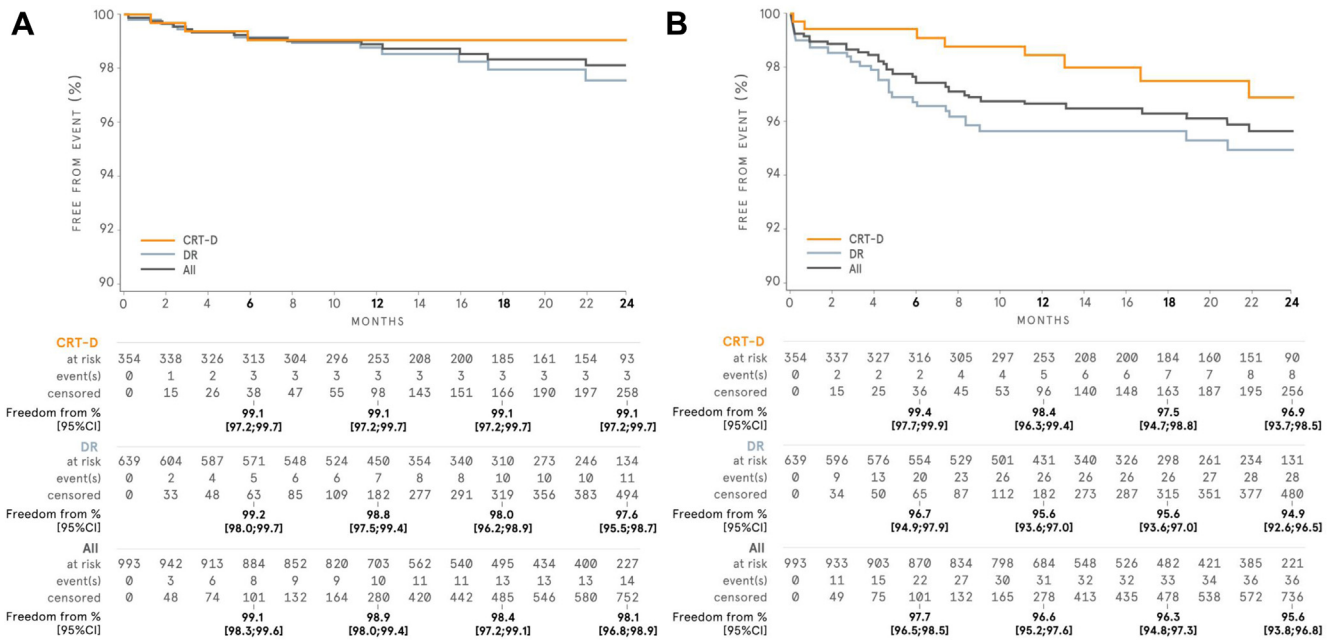


Figure 2 Kaplan-Meier curves of time to first event of inappropriate (A) and appropriate (B) shocks, overall and per device model. CRT-D = cardiac resynchronization therapy–defibrillator; CI = confidence interval; DR = dual chamber (implantable cardioverter-defibrillator).

discrimination algorithm enhancement (Table 3). Device programming adjustment reduced IS in the MADIT-RIT (Multi-center Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy), ADVANCE (Avoid Delivering TherApies for Non-sustained Arrhythmias in ICD PatiEnts) III, and PROVIDE (Programming Implantable Cardioverter-Defibrillators in Patients With Primary Prevention Indication to Prolong Time to First Shock) studies.^{19–23} IS can be further reduced by combining device programming adjustment with enhanced algorithm discrimination, for example, in the PainFREE SST (Pacing Fast Ventricular Tachycardia Reduces Shock Therapies-SmartShock Technology) observational study, which reported a rate of IS of 1.5% at 1 year.²⁴ The use of high cutoff rates and/or long detection time in these studies meant, however, that the sensitivity of VF detection was compromised. With PARAD+ it was not; the sensitivities of slow VT detection and VT/VF detection are 94% and 99.3%, respectively.¹⁴ The specificity of sinus rhythm/SVT recognition is 94%, positive predictive value 79.3%, and negative predictive value 99.2%. In ISIS, using an enhanced discrimination strategy (PARAD+) alone in a wide spectrum of frequencies without the programming of a high cut-off rate and/or extended persistence, the annual patient incidence rate of IS ranged from 1.0 (primary analysis) to 2.1 (worst-case analysis) per 100 person-years, which to our knowledge is one of the lowest rates reported in the literature. Similarly, the annual IS incidence rate observed in ISIS (2.9 IS per 100 person-years), which takes into account event multiplicity, was lower than most of those observed in other studies (Table 3).^{19–24}

Underlying causes of inappropriate ICD interventions include SVTs (especially AF with rapid ventricular response), noise oversensing, T-wave oversensing, and lead

or connector malfunction.⁶ In contrast to prior trials,¹⁹ no T-wave oversensing was reported in our study, and noise was the main reason for IS (23/41 [56.1%]). It should be noted that most of these IS (n = 18) were received by 2 patients due to ventricular lead fracture. SVT/AF was the cause of only 8 IS, which represents 6% of total adjudicated shocks (and 20% of IS). Although this figure may be an underestimate because no adjudication could be performed in 59 of the 188 shocks, this result suggests the importance of applying enhanced discrimination algorithms to prevent inappropriate ICD interventions at high rates, especially in primary prevention patients.

At the other end of the rate spectrum, one of the biggest differences between PARAD+ and other SVT-VT discrimination algorithms is that long-cycle AF rejection is effective with relatively slow detection intervals found in the slowest treated VTs. PARAD+ with a slow VT detection interval of 400 ms (Table 1) rejected SVTs at least as well as other SVT-VT discrimination algorithms with detection intervals of 330–300 ms. The inability of ICDs to treat life-threatening VT/VF with recommended generic programming thresholds²⁸ (primary prevention ICDs 185–200 bpm; secondary prevention ICDs ≈ 10 bpm slower than the slowest VT) may well be harmful.²⁹ Our results suggest that the current programming tradeoff may not be the only solution.

Of note, a trend toward a lower rate of IS was observed in CRT-D devices compared to DR devices in the ISIS-ICD study. This result may be explained by the higher proportion of primary indication patients in the CRT-D group, although more patients presented with a history of AF in the CRT-D group. A small minority of patients still remained subject to IS due to AF, so there remains a role for both pharmacologic and nonpharmacologic treatment measures in these

Table 3 Strategies for shock reduction and associated rates of inappropriate shocks

Study	MADIT-RIT (2012) ^{19,23}	ADVANCE III (2013) ^{20,21,23}	PROVIDE (2013) ^{22,23}	PainFREE SST (2015) ²⁴	ISIS (2017)
Devices	ICD and CRT-D	Primary Conventional	Primary Conventional	Primary and secondary Conventional	Primary and secondary Conventional
Indication	Primary	Primary and secondary	Primary	Primary and secondary	Primary and secondary
Arm	Conventional	Conventional	Conventional	Conventional	Conventional
Strategy for shock reduction	TX reduction	TX reduction	TX reduction	TX reduction	TX reduction
Device programming	↘	↘	↘	↘	↘
Discrimination algorithm	↘	↘	↘	↘	↘
Rate of inappropriate shocks	6% at 1.4 y	—	10.9% at 515 d	1.5%-2.5% at 1 y* 2.8%-3.7% at 2 y*	1.9% at 2 y
Percent of patients	15	10	10	—	1.0-2.1
Patients per 100 person-years	15	4 to 7	4	8	—

CRT-D = cardiac resynchronization therapy-defibrillator; TX = therapy.

*Lower percentage in range for dual-/triple-chamber implantable cardioverter-defibrillators (ICDs), higher percentage for single-chamber ICDs.

patients. Lastly, our results add further evidence in favor of dual-chamber ICDs to the debate on the benefit of dual-chamber ICDs with SVT discrimination vs single-chamber devices with generic programming in terms of IS reduction.³⁰

Study limitations

The main limitation of our study is the large number of censored patients at 24 months. The Kaplan-Meier method takes into account the risk of IS in censored patients. Thus, it was used for the primary endpoint analysis rather than incidence proportion, which would have underestimated the rate of IS. The Kaplan-Meier method used ignored the competitive risk of death, but values obtained with it nevertheless closely approximate those of a competitive risk method. Another limitation was the lack of electrogram information for 16 patients and incomplete information for 6 patients, which prevented shock adjudication in these 22 patients. The sensitivity analysis, nevertheless, confirms the results as does the worst-case analysis, which considers all nonadjudicated shocks as inappropriate. Information on the use of mandatory programming was not collected, so noncompliance may have occurred. The number of untreated, sustained episodes of VT/VF is difficult to obtain; in our study 2 sudden deaths could have been due to untreated VT/VF. ICD and CRT-D patients had different clinical characteristics at baseline, and neither ICD nor CRT-D treatment was randomized. No single-chamber ICDs were studied; analysis was restricted to a dual-chamber SVT-VT discrimination algorithm. Finally, the rate of inappropriate therapy for other tachyarrhythmia therapies (eg, antitachycardia pacing) was not assessed, which could have led to a bias toward IS.

Conclusion

Current strategies to reduce IS based on programming adjustment (long detection delays and/or high cutoff) have been shown to be highly effective. In the ISIS-ICD study, use of the enhanced discrimination algorithm PARAD+ also led to a very low rate of patients with IS (range 1.0–2.1 per 100 person-years) in a general population implanted for primary or secondary prevention.

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Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2019.03.016>.

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