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ORIGINAL ARTICLE

Inappropriate Therapy and Shock Rates Between the Subcutaneous and Transvenous Implantable Cardiac Defibrillator: A Secondary Analysis of the PRAETORIAN Trial

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BACKGROUND: Inappropriate therapy (IAT) is an undesirable side effect of implantable cardiac defibrillator (ICD) therapy. Early studies with the subcutaneous ICD (S-ICD) showed relatively high inappropriate shock (IAS) rates. The PRAETORIAN trial demonstrated that the S-ICD is noninferior to the transvenous ICD (TV-ICD) with regard to the combined end point of IAS and complications. This secondary analyses evaluates all IAT in the PRAETORIAN trial.

METHODS: This international, multicenter trial randomized 849 patients with an indication for ICD therapy between S-ICD (n=426) and TV-ICD therapy (n=423). ICD programming was mandated by protocol. All analysis were performed in the modified intention-to-treat population.

RESULTS: In both groups 42 patients experienced IAT (48-month Kaplan-Meier estimated cumulative incidence, 9.9% and 10.1%, respectively; hazard ratio (HR), 0.99 [95% CI, 0.65–1.52]; *P*=0.97). There was no significant difference in patients experiencing IAS between both groups (*P*=0.14). In the S-ICD group, 81 IAT episodes with 124 IAS and 1 inappropriate antitachycardia pacing occurred versus 89 IAT episodes with 130 IAS and 124 inappropriate antitachycardia pacing in the TV-ICD group. IAT episodes were most frequently caused by supraventricular tachycardias in the TV-ICD group (n=83/89) versus cardiac oversensing in the S-ICD group (n=40/81). In the TV-ICD group, a baseline heart rate >80 bpm (HR, 1.99 [95% CI, 1.05–3.76]; *P*=0.03), a history of atrial fibrillation (HR, 2.66 [95% CI, 1.41–5.02]; *P*=0.003), and smoking (HR, 2.46 [95% CI, 1.31–4.09]; *P*=0.005) were independent predictors for IAT. A QRS duration >120 ms was an independent predictor for IAT caused by cardiac oversensing in the S-ICD group (HR, 3.13 [95% CI, 1.34–7.31]; *P*=0.008). Post-IAS interventions significantly reduced IAS recurrence in both groups (*P*=0.046).

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CONCLUSIONS: There was no significant difference in IAT and IAS rates between the S-ICD and TV-ICD in a conventional ICD population, but causes and predictors for IAT differed between the devices. After the first IAS, an intervention significantly reduced the recurrence rate of IAS.

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Key Words: atrial fibrillation ■ deibrillators ■ heart rate ■ incidence ■ smoking

WHAT IS KNOWN?

- The main cause of inappropriate therapy in patients with subcutaneous implantable cardiac defibrillator (ICD) is T-wave oversensing.
- The main cause of inappropriate therapy in patients with transvenous ICD is an supraventricular tachycardia in the therapy zone.
- Previous studies comparing both devices are hampered by differences in programming, nonrandomized design, and were often performed in relatively young ICD recipients.

WHAT THE STUDY ADDS

- In a randomized conventional ICD population, the total inappropriate shock rate and inappropriate therapy rate were not significantly different between the subcutaneous ICD and transvenous ICD.
- An intervention after an inappropriate shock significantly reduced the recurrence rate of inappropriate shocks in both the transvenous ICD and the subcutaneous ICD.
- Proactive interventions, encompassing changes in medication, changes in programming, or invasive interventions, should be consistently pursued to mitigate the recurrence of inappropriate shocks.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ATP	antitachycardia pacing
HR	hazard ratio
ICD	implantable cardiac defibrillator
IAS	inappropriate shock
S-ICD	subcutaneous implantable cardiac defibrillator
SVT	supraventricular tachycardia
TV-ICD	transvenous implantable cardiac defibrillator
VT	ventricular tachycardia

Implantable cardioverter defibrillator (ICD) therapy is an effective treatment for life-threatening ventricular arrhythmias.[1–3] Different types of ICDs are currently available: transvenous ICDs (TV-ICDs), which have an endocardial lead, and subcutaneous ICDs (S-ICDs), which are completely extrathoracic. Due to the different lead positions, these devices have different sensing mechanisms. Unfortunately, ICD therapy is associated with the risk of inappropriate therapy. Inappropriate therapy rates are reported in a wide range between 3% and 10% per year for both device types, depending on patient selection, available software and programming.[4–7] Inappropriate therapy can have a significant impact on a patient's quality of life, may provoke ventricular arrhythmia and reduce battery longevity.[7–10]

Over the years, various approaches have been introduced to reduce the risk of inappropriate therapy. In the TV-ICD, programming higher rate cutoff zones and longer duration criteria before therapy delivery have shown to be effective in reducing inappropriate shocks (IASs).[6,11] For S-ICDs, IAS rates were reduced over time by dual-zone programming, exercise-optimized programming, and improved morphology algorithms including SMART Pass, a software feature reducing the risk of T-wave oversensing.[12–14] Over the years, the annual IAS rate decreased from 13.1% in the initial reports to 2.4% in patients with the latest-generation S-ICD.[4,5]

Previous studies comparing inappropriate therapy in the S-ICD and TV-ICD were hampered by differences in programming, nonrandomized design and were often performed in relatively young ICD recipients.[15,16] The PRAETORIAN trial is the first randomized controlled trial comparing the effectiveness and safety of the S-ICD and TV-ICD in a conventional ICD population, with prespecified ICD programming, and showed noninferiority of the S-ICD with regard to the combined primary end point of IAS and complications.[17] The current secondary analysis will provide additional insights into the occurrence, underlying cause, predictors, and safety of all inappropriate therapy—both antitachycardia pacing and shocks—in both groups, as well as the effect of interventions after IAS.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design and Population of the PRAETORIAN Trial

The PRAETORIAN trial is an international, multicenter comparative trial in which 849 patients were randomized 1:1 to receive an S-ICD or TV-ICD. The rationale and design of the PRAETORIAN trial are described in detail elsewhere.[18] In brief, patients with a Class I or IIa indication for ICD therapy and without the need for bradycardia pacing or cardiac resynchronization therapy were included from March 2011 until January 2017 and randomized to S-ICD or TV-ICD therapy. Key exclusion criteria were a history of ventricular tachycardia (VT) below 170 bpm or therapy-refractory monomorphic VT. The primary end point was the composite of IAS and device-related complications. An analysis of the difference in inappropriate shock therapy between devices was a prespecified secondary analysis of the PRAETORIAN trial. ICD programming was mandated by protocol and was based on the PREPARE trial.[6] In the TV-ICD group, the advised rate cutoff settings were set at or as close as possible to 182 bpm for the fast VT zone and at or as close as possible to 250 bpm for the ventricular fibrillation zone. In the S-ICD group, the advised rate cutoff settings were programmed at 180 bpm for the conditional zone and 250 bpm for the unconditional zone. One burst of antitachycardia pacing (ATP), which consists of 8 intervals with a pacing cycle length of 88% of the tachycardia cycle length, when technically possible, was programmed in the TV-ICD. When clinically necessary, adaptations in programming were allowed per physician's discretion. The PRAETORIAN study protocol was approved by the institutional medical ethical committees, and all patients provided written informed consent.

Data Collection and Definitions

For all device episodes with ICD therapy, the electrogram was collected. The underlying rhythm and appropriateness of the therapy were adjudicated by an independent clinical events committee. If no electrogram was present, the clinical events committee could decide to adjudicate based on other source documents or to not adjudicate. Per protocol, inappropriate therapy was defined as any therapy, shock, or ATP for any rhythm other than VT or ventricular fibrillation. By this definition, therapy was also considered to be appropriate on a VT with a rate under the programmed therapy zone, where cardiac oversensing led to a higher detected rate. For the current analysis, all episodes with inappropriate therapy per clinical events committee adjudication were analyzed. An inappropriate therapy episode was defined as an episode during which >1 inappropriate therapy was given. Inappropriate therapy device episodes within 5 minutes of each other were combined into 1 episode as they were considered to be related to the same underlying cause.[7] Cardiac oversensing was defined as oversensing of the cardiac signals. Noncardiac oversensing was defined as the oversensing of any signal originating outside the heart, such as myopotentials and noise. Noise can among others be caused by electromagnetic interference, air entrapment after implantation, or lead and device malfunction. An intervention was defined as a change in programming, a change in medication, or an invasive intervention to reduce the recurrence of IAS. Invasive interventions included any surgical procedure, such as repositioning, replacement, or removal of the lead and pulse generator, or an ablation.

Statistical Analysis

Data were analyzed using a modified intention-to-treat analysis. Descriptive statistics are reported as mean±SD or median with interquartile range for continuous variables and numbers and percentages for categorical variables. Baseline variables were compared using the Fisher exact test, χ^2 test, Student *t* test, or Mann-Whitney *U* test, as appropriate. For time-to-event variables, Kaplan-Meier curves displaying the pattern of events were constructed, and 48-month Kaplan-Meier estimates of the event rate are reported for both study groups and compared using log-rank tests. Participants without events were censored at their last known event-free time point. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazard models, and Cox assumptions were assessed using Schoenfeld residuals. Univariable and multivariable Cox proportional hazard models were performed to identify predictors for inappropriate therapy. Two-sided $P<0.05$ were considered statistically significant. All statistical analyses were performed using R software, version 4.2.1 (RStudio PBC).

RESULTS

Patients were randomized to receive an S-ICD (n=426) or TV-ICD (n=423; 21). During a median follow-up of 49.1 (interquartile range, 40.2–63.6) months, 42 patients in the S-ICD group and 42 patients in the TV-ICD group received at least 1 inappropriate therapy (48-month Kaplan-Meier estimated cumulative incidence, 9.9% [95% CI, 6.8%–12.9%] and 10.1% [95% CI, 7.0%–13.1%], respectively; HR, 0.99 [95% CI, 0.65–1.52]; *P*=0.97, Figure 1A). The median time-to-first inappropriate therapy was 13.8 (interquartile range, 2.7–28.9) months in the S-ICD group and 9.6 (interquartile range, 2.3–17.7) months in the TV-ICD group.

Baseline characteristics of patients receiving inappropriate therapy were comparable between both groups, except for the mean QRS duration, which was significantly longer in the S-ICD group (109±17 versus 100±17, Table 1). QRS duration was not an independent predictor for inappropriate therapy in the S-ICD group, but it was an independent predictor for inappropriate therapy caused by cardiac oversensing (HR, 3.13 [95% CI, 1.34–7.31]; *P*=0.008). In the TV-ICD group, a baseline heart rate >80 bpm (HR, 1.99 [95% CI, 1.05–3.76]; *P*=0.03), a history of atrial fibrillation (AF) (HR, 2.66 [95% CI, 1.41–5.02]; *P*=0.003), and a history of smoking (HR, 2.46 [95% CI, 1.31–4.09]; *P*=0.005) were independent predictors for IAT (Table S1).

Inappropriate Therapy: Shocks and ATP

In the S-ICD group, 42 patients had a total of 81 episodes of inappropriate therapy, in which there were 124 IAS and 1 inappropriate ATP; the latter occurred in 1 patient who crossed over to a TV-ICD. In the TV-ICD group, 42 patients had a total of 89 inappropriate therapy episodes, in which there were 130 IAS and 124

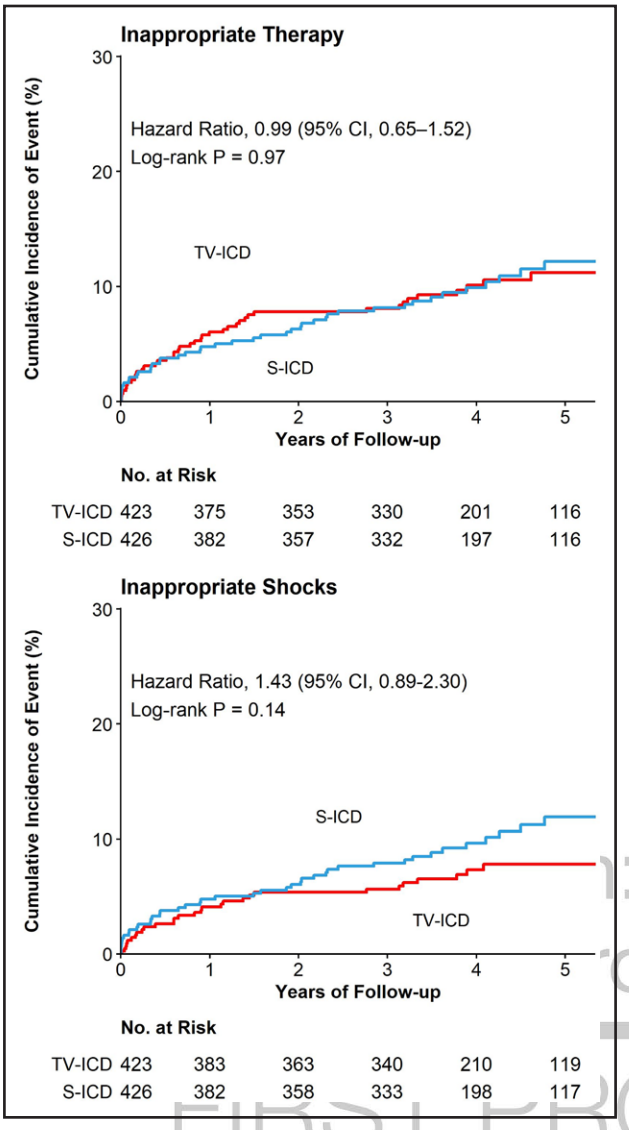

Figure 1. Time-to-first-event curves for (A) total inappropriate therapy and (B) inappropriate shocks.
S-ICD indicates subcutaneous implantable cardioverter defibrillator; and; TV-ICD, transvenous implantable cardioverter defibrillator.

inappropriate ATP (Figure 2). Of the patients with a TV-ICD with inappropriate therapy, 1 patient crossed over to an S-ICD and received 1 IAS.

In the S-ICD group, 41 patients received an IAS versus 29 patients in the TV-ICD group (48-month Kaplan-Meier estimated cumulative incidence, 9.7% [95% CI, 6.6%–12.6%] and 7.3% [95% CI, 4.6%–10.0%], respectively; HR, 1.43 [95% CI, 0.89–2.3], *P*=0.14; Figure 1B). The cumulative incidence of IAS was highest in the first year after implantation (4.8% in the S-ICD and 4.1% in the TV-ICD). Approximately half of the patients with IAS experienced recurrent IAS (19/41 in the S-ICD group; 16/29 in the TV-ICD group), of which half occurred within 6 months. Five or more IAS episodes were observed in 6 of 41 (14.6%) patients in the S-ICD group and 5/29 (17.2%) patients in the TV-ICD group (Table S2). One

Table 1. Patient Characteristics

	Patients with inappropriate therapy (n=84)		
	S-ICD (n=42)	TV-ICD (n=42)	*P* value
Median age, y (IQR)	65 (57–71)	63 (54–68)	0.17
Women, n (%)	4 (9.5)	6 (14.3)	0.74
Diagnosis, n (%)			0.70
Ischemic cardiomyopathy	27 (64.3)	23 (54.8)	
Nonischemic cardiomyopathy	11 (26.2)	14 (33.3)	
Genetic arrhythmia syndrome	3 (7.1)	4 (9.5)	
HCM	2	1	
HCM and Brugada	1	0	
DPP6	0	2	
DCMP	0	1	
Idiopathic VF	0 (0.0)	1 (2.4)	
Congenital heart disease	1 (2.4)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	
Secondary prevention, n (%)	7 (16.7)	7 (16.7)	1.00
Median ejection fraction, % (IQR)	28 (23–38)	27 (20–35)	0.55
Mean QRS duration, ms ±SD	109±17	100±17	0.01
Mean heart rate, bpm ±SD	76±18	79±13	0.39
Heart rate >80 bpm	14/42 (33.3)	16/41 (39.0)	0.76
QRS >120, ms	11 (26.2)	6 (14.3)	0.28
NYHA class, n (%)			0.99
I	12/42 (37.2)	11/42 (26.2)	
II	22/42 (44.2)	22/42 (52.4)	
III/IV	8/42 (18.6)	9/42 (21.4)	
Median BMI, IQR	27.1 (24.9–29.7)	29.1 (25.3–31.2)	0.34
History of atrial fibrillation, n (%)	14 (33.3)	17 (40.5)	0.65
Use of β blockers, n (%)	35 (83.3)	35 (83.3)	1.00
Smoking, n (%)	9 (21.4)	21 (50.0)	0.01
Dual chamber ICD	NA	5 (11.9)	NA
Sensing vector S-ICD			
Primary	29/41 (70.7)	NA	NA
Secondary	9/41 (22.0)	NA	NA
Alternate	3/41 (7.3)	NA	NA

BMI indicates body mass index; DCMP, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IQR, inter quartile range; NA, not applicable; NYHA, New York Heart Association; S-ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator; and VF, ventricular fibrillation.

patient with an S-ICD experienced 18 IAS, and 1 patient with a TV-ICD experienced 54 IAS. At the time of IAS, most devices were programmed in agreement with the prespecified therapy zones (Table S3). SMART Pass was

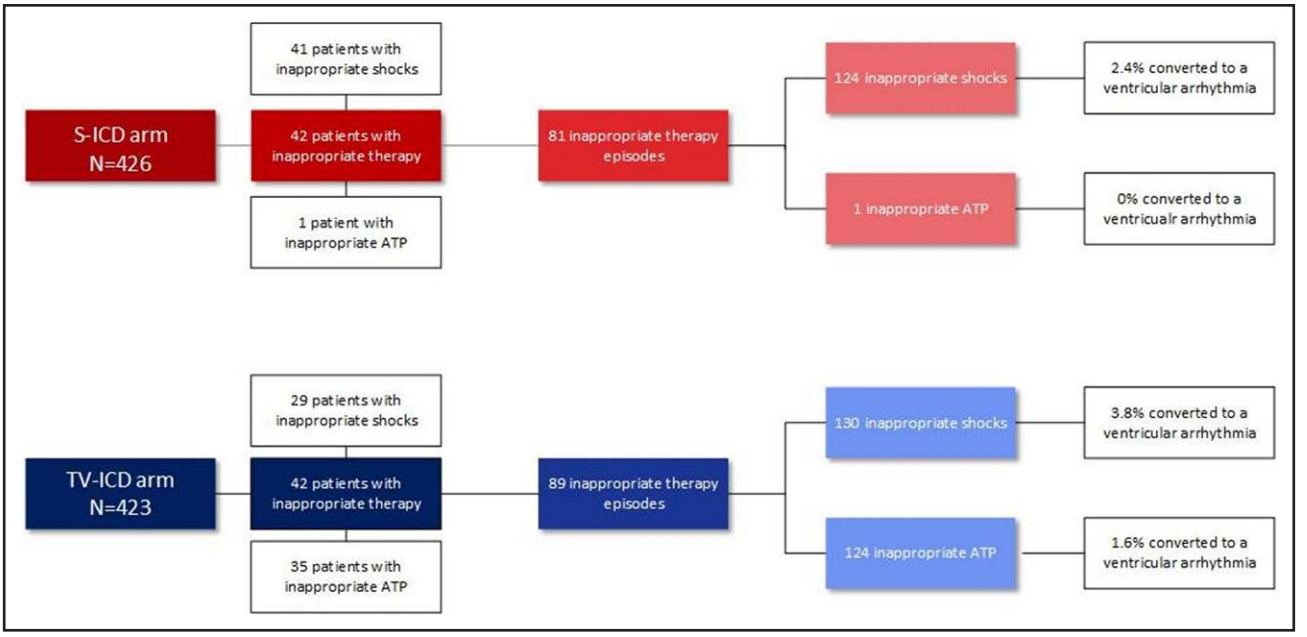

Figure 2. Overview of total patients receiving inappropriate therapy, total inappropriate therapy episodes, total inappropriate shocks, antitachycardia pacing (ATP), and pro-arrhythmia to ventricular arrhythmia.
S-ICD indicates subcutaneous implantable cardioverter defibrillator; and; TV-ICD, transvenous implantable cardioverter defibrillator.

not available in 29/41 (70.7%) patients at the time of IAS in the S-ICD group, of whom 17/29 (58.6%) received an IAS due to T-wave oversensing. In 1 patient, SMART Pass was deactivated at the time of the IAS (Table S4).

Pro-arrhythmia of Inappropriate Therapy

In 6 patients, there were 10 pro-arrhythmic events resulting from inappropriate therapy. In the TV-ICD group, 5 IAS (3.8%) and 2 inappropriate ATP (1.6%) deteriorated the rhythm to a ventricular arrhythmia in 3 patients, compared with 3 IAS (2.4%) in 3 patients in the S-ICD group. In 7 of 10 pro-arrhythmic inappropriate therapies, the ventricular arrhythmia terminated spontaneously. In almost all cases (9/10), the initially inappropriately sensed underlying rhythm was a supraventricular tachycardia (SVT). Postshock bradycardia pacing was observed after 9 of 124 (7.3%) IAS in the S-ICD group, and after 2 of 130 (1.5%) IAS in the TV-ICD group.

Causes of Inappropriate Therapy and Heart Rate and Heart Rhythm During Inappropriate Therapy

The primary cause of inappropriate therapy episodes in the S-ICD group was cardiac oversensing (n=40/81, 49.4%), followed by SVT with heart rates in the programmed therapy zone (n=25/81, 30.9%), and noncardiac oversensing (n=17/81, 21%; Table 2). One episode contained both cardiac and noncardiac oversensing. T-wave oversensing was the most prevalent cause of cardiac oversensing, and noise was the most prevalent cause of noncardiac oversensing (Table 2). Two patients experienced inappropriate therapy in a new episode with a different cause compared with the first episode. In the TV-ICD group, inappropriate therapy episodes were mostly caused by SVTs in the programmed therapy zone (n=83/89, 93.3%; Table 2).

In both groups, the majority of the inappropriate therapies were given for AF or other SVTs, as this was the initial heart rhythm in 60.8% and 73.2% of the inappropriate therapies in the S-ICD and TV-ICD groups, respectively. Inappropriate therapy converted 16.4% (43/262) of the supraventricular arrhythmias into sinus rhythm (26 in the S-ICD and 17 in the TV-ICD groups). No pro-arrhythmia from sinus rhythm into supraventricular arrhythmia was observed.

In both the TV-ICD and S-ICD groups the majority of inappropriate therapies were delivered in the conditional/VT discrimination zone (96.6% and 84.7%, respectively). Patients receiving inappropriate therapy in the S-ICD group had a lower initial heart rate compared with patients in the TV-ICD group (147±59 versus 189±25 bpm, $P<0.001$; Figure S1). In the S-ICD group, 31.7% of the patients had an inappropriate shock episode with a detected rate below 200 bpm, while in the TV-ICD group, 55.2% of the patients had an IAS episode with a detected rate below 200 bpm.

Interventions After Inappropriate Shocks

An intervention was performed in 28 of 41 (68.3%) patients experiencing IAS in the S-ICD group and in 19 of 29 (65.5%) patients in the TV-ICD group. An

Table 2. Causes of Inappropriate Therapy Episodes in the S-ICD and TV-ICD

Inappropriate therapy episodes with:	S-ICD* (n=81)	TV-ICD (n=89)
SVT in the programmed therapy zone	25 (31%)	83 (93%)
Noncardiac oversensing	17 (21%)	0
Myopotentials	4	0
Wandering baseline	2	0
EMI	1	0
Air entrapment	5	0
Noise	7	0
Cardiac oversensing	40 (49%)	6 (6.7%)
T-wave oversensing	39	4†
P-wave oversensing	8	0
Low-amplitude signal	8	0
Other‡	1	2

EMI indicates electromagnetic interference; S-ICD, subcutaneous implantable cardioverter defibrillator; SVT, supraventricular tachycardia; and TV-ICD, transvenous implantable cardioverter defibrillator.

*One patient in the S-ICD group experienced an inappropriate therapy episode with both cardiac and noncardiac oversensing.

†One patient experienced 4 inappropriate therapy episodes due to T-wave oversensing in the TV-ICD group while having an S-ICD (crossover).

‡One patient in the S-ICD group experienced an episode of cardiac oversensing due to a dying heart, 1 patient in the TV-ICD group experienced 2 episodes of cardiac oversensing due to lead dislocation.

intervention significantly reduced the recurrence rate of IAS with the same underlying cause (P=0.046; Figure S2). In the S-ICD group, the most common intervention was a change in programming (18/28), and 1 patient had a concomitant change in medication. Five patients had a change in medication only. In the TV-ICD group, a change in medication (12/19) was the most common intervention, and 3 patients had a concomitant change in programming (Figure 3). Solely reprogramming the device as an intervention resulted in a recurrence rate of 23.5% (4/17) in the S-ICD and 16.7% (1/6) in the TV-ICD group, while a change in medication resulted in a recurrence rate of 40% (2/5) in patients with S-ICD and 44% (4/9) in patients with TV-ICD. In 5 of the 28 patients with IAS in the S-ICD group, an invasive intervention was performed: 2 crossovers from S-ICD to TV-ICD because of IAS caused by cardiac oversensing, 1 revision of the subcutaneous lead due to IAS on myopotentials, 1 revision of the lateral pocket due to air in the pocket resulting in IAS and 1 electrophysiological procedure due to IAS caused by T-wave oversensing during an SVT. In the TV-ICD group, 1 patient underwent an invasive intervention: a revision of the transvenous lead after lead dislocation resulting in IAS due to cardiac oversensing. After all invasive interventions, no recurrence of IAS was observed.

DISCUSSION

This study is a secondary analysis of the PRAETORIAN trial and showed no significant differences in the rates of inappropriate therapy and inappropriate shocks between the S-ICD and TV-ICD. In addition, the number of inappropriate shocks was comparable. Predictors for inappropriate therapy in the TV-ICD group included AF, HR >80 bpm, and smoking, while no predictors were observed in the S-ICD group, although longer QRS duration was an independent predictor for inappropriate therapy caused by cardiac oversensing. A small percentage of inappropriate therapy episodes was pro-arrhythmic, mainly when delivered during an SVT. The causes of inappropriate therapy differed between the S-ICD and TV-ICD resulting in different interventions needed to prevent recurrence. Nonetheless, in both groups an intervention reduced the risk of IAS recurrence compared with a conservative approach.

The 1-year cumulative incidence of IAS in patients with S-ICD in our study is lower compared with the EFFORTLESS registry (4.8% versus 8.7%).[5] This lower IAS rate could be the result of availability of contemporary software algorithms and dual-zone programming in which a second shock zone is added with an active discrimination algorithm. In addition, the availability of remote monitoring in our study may have resulted in earlier detection of preventable oversensing and SVTs. Finally, patients included in EFFORTLESS were younger and more often had inherited cardiac diseases, which are both associated with IAS.[19–21] The more recent UNTOUCHED S-ICD registry, which included patients with a reduced ejection fraction, demonstrated a lower 1-year cumulative incidence of IAS compared with our study (3.1% versus 4.8%).[4] In that study, the SMART Pass algorithm, which was specifically designed to reduce T-wave oversensing, was available for the majority of patients, whereas in this current study, only 11.3% of patients were implanted with S-ICD devices with SMART Pass availability. Indeed, SMART Pass was not available in 70.7% of patients at the time of IAS in the S-ICD group, of whom 58.6% received an IAS due to T-wave oversensing. These IAS might have been prevented with this filter. The SMART Pass algorithm has been shown to reduce 1-year IAS rates by 50%,[14] mainly by preventing T-wave oversensing. However, SMART Pass can also automatically deactivate in specific circumstances such as low-amplitude signals. Deactivation is reported to occur in 9% of patients and is significantly associated with an increased risk of inappropriate therapy.[22] The effect of the SMART Pass filter may have had on the IAS rate in this study is therefore difficult to calculate. Another explanation that the IAS rate in the UNTOUCHED S-ICD registry was lower, is because of the higher rate cutoff zones of 200 bpm mandated by their protocol. As in the current study, one-third of IAS episodes had a detected rate <200 bpm; these may have been prevented with higher therapy zones.

In patients with TV-ICD, early landmark trials such as the MADIT-II reported a much higher 1-year cumulative incidence of IAS compared with our study (10%

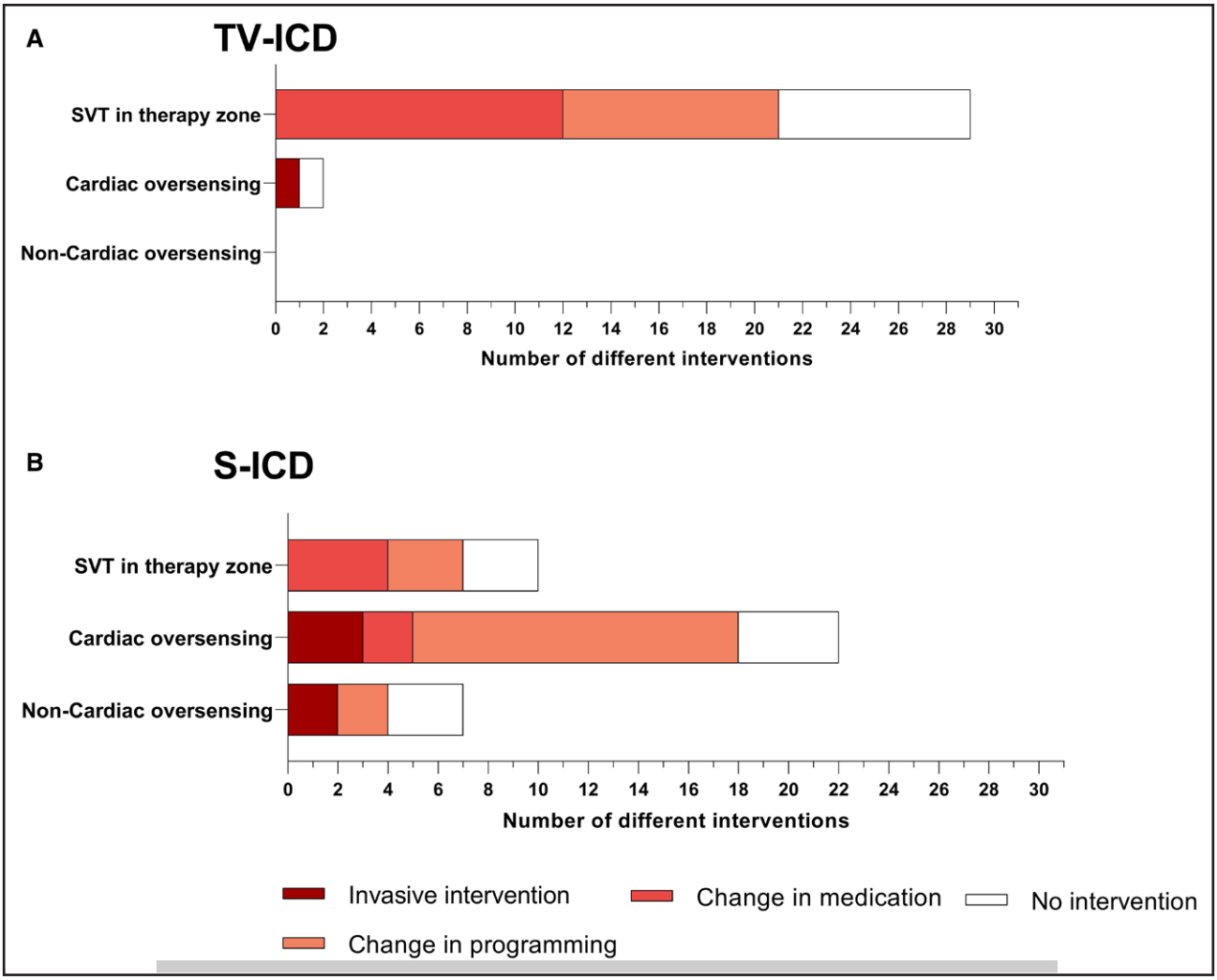

Figure 3. Interventions undertaken after first IAS classified by causes of the IAS.
S-ICD indicates subcutaneous implantable cardioverter defibrillator; SVT, supraventricular tachycardia; and TV-ICD, transvenous implantable cardioverter defibrillator.

versus 4.1% respectively). This disparity could mainly be attributed to the programming, which was up to the discretion of the investigator in that study.[7] Later trails like PREPARE and MADIT-RIT, which used similar programming strategies to our study, demonstrated comparable rates of inappropriate shocks of 3% to 5% in the first year after implantation, which is in line with the findings in our study.[6,11]

Difference in Causes and Predictors of Inappropriate Therapy

Cardiac oversensing was the most frequent cause of inappropriate therapy in the S-ICD group. This is likely due to the extrathoracic electrode position and morphology-based sensing.[19] Morphology-based sensing is more vulnerable to oversensing of P-waves and T-waves or double counting of QRS complexes. Especially during exercise, QRS and T-wave morphology can change, resulting in cardiac oversensing. No independent predictors for inappropriate therapy in the S-ICD arm were found in this study, but QRS duration was an independent predictor for inappropriate therapy caused by cardiac oversensing. Hypertrophic cardiomyopathy was not found to be predictive for inappropriate therapy by cardiac oversensing, but the number of patients with hypertrophic cardiomyopathy in this study may have been too low to demonstrate this. ECG screening to analyze the morphology-based sensing before implantation was performed per local routine, but data were not collected. The predictive value of low-amplitude signals or low R- to T-wave ratio during screening could therefore not be calculated. Earlier studies showed that a morphology template acquired during exercise may prevent inappropriate shocks.[12] Although another study could not confirm these results probably due to a low number of events,[23] exercise-optimized S-ICD programming after implantation might be recommended, especially in patients at

higher risk of inappropriate shocks, such as patients with widened QRS complexes or hypertrophic cardiomyopathy patients.[24]

SVTs in the therapy zone were the most frequent cause of inappropriate therapy in the TV-ICD group. In TV-ICDs sensing is based on near-field morphology discrimination reducing the risk of cardiac oversensing. Moreover, as at the time of this study, there is more experience with this technology compared with the S-ICD, software algorithms are more advanced. However, algorithms using near-field morphology work less effectively during high heart rates, such as during SVT, resulting in a risk of inappropriate shocks on SVTs. Moreover, in the TV-ICD group a baseline heart rate >80 bpm, a history of AF and smoking were predictors for inappropriate therapy. All these predictors increase the risk of SVTs.[7] In earlier S-ICD studies, AF was also shown to be a predictor of inappropriate therapy in S-ICD patients.[19] This was however not confirmed in our traditional ICD population, which had a higher prevalence of patients with AF. Therefore, S-ICD therapy might be the preferred choice in patients with AF. Recognizing the differences in underlying cause between both devices is important when discussing the risk of IAS for individual patient in need of ICD therapy.

A small fraction of S-ICD patients received inappropriate therapy due to noncardiac oversensing due to air entrapment and myopotentials, which is also reported previously.[25] Although noncardiac oversensing was not seen in the TV-ICD group, this has been reported to be a cause for inappropriate therapy in TV-ICDs as well.[26]

Pro-Arrhythmic Effect and Postshock Pacing

In some patients inappropriate therapy induced ventricular arrhythmias. Remarkably, in 9 of the 10 cases of pro-arrhythmic inappropriate therapy, the therapy was given for SVT. SVTs may be more pro-arrhythmic than sinus rhythm due to higher heart rates, which is accompanied with an increased activation of the sympathetic nervous system and shorter ventricular refractory period and may aggravate myocardial ischemia. These factors may increase the pro-arrhythmic excitability of the ventricles. During sinus rhythm without increased sympathetic activation or cardiac ischemia, the upper limit of vulnerability is higher, such that shocks on this underlying rhythm are less arrhythmogenic.[27]

The need for postshock pacing after inappropriate therapy, which can be painful in the S-ICD due to its extrathoracic position and subsequent higher electrical output, was higher in the S-ICD group compared with the TV-ICD group. Brady-arrhythmias can occur after cardioversion due to the simultaneous reset of atrial myocardium and sinus node.[28] The higher incidence of postshock pacing in the S-ICD group, may be attributed to the higher shock output of the S-ICD, as a higher shock output is associated with a longer postshock asystole.[29] Whereas it is not determined whether the higher shock output indeed results in higher energy delivered to the heart, a previous study has indicated that the shock output of the S-ICD can potentially be reduced, which might reduce the need for postshock pacing.[30]

IAS Risk Reduction

Intervention after IAS effectively reduced the risk of recurrence of IAS with similar causes in both groups. In the S-ICD group the intervention was most frequently a change in programming, whereas in the TV-ICD group the most common intervention was a change in medication.

For TV-ICDs, where SVTs in the programmed therapy zone were the most frequent cause of IAS, programming higher rate cutoff zones is most effective to prevent recurrence.[11] In the MADIT-RIT trial, the majority of inappropriate therapy occurred at rates below 200 bpm,[31] which aligns with findings in our study for patients with TV-ICDs. However, in patients with S-ICDs, the majority of inappropriate therapy was delivered at detected rates above 200 bpm, indicating a lesser impact of high-rate cutoff programming in reducing inappropriate therapy in patients with S-ICD. To reduce cardiac oversensing in the S-ICD, a vector change or new template has proven to be effective.[12] Whereas in this analysis only changes in programming after occurrence of IAS were considered, reprogramming following untreated inappropriate episodes, for both TV-ICD and S-ICD, may be helpful to prevent occurrence of IAS.

In the S-ICD group, an invasive intervention was performed more frequently than in the TV-ICD group. Less implant experience with the S-ICD may have resulted in air entrapment around the lead or generator, suboptimal implant positioning or crossover. With increased implanters' experience and early evaluation of the electrogram and x-ray after implantation, the risk of IAS and the need for subsequent invasive interventions may be reduced.[32]

Inappropriate shocks are related to adverse outcome. Multiple studies showed that IAS are related to an increased mortality, although it is not clear whether this is due to the detrimental effects of inappropriate shocks per se or due to the baseline characteristics or interim events, such as AF, causing both inappropriate shocks and an increased risk of mortality.[7,33] In addition, several studies showed a reduction in quality of life after receiving both appropriate and inappropriate shocks with a larger reduction in quality of life when receiving multiple shocks.[9,34–36] Moreover, the results of the European Heart Rhythm Association survey showed that 80.1% of patients with ICD were afraid of unexpected shocks and patients who experienced an IAS felt less safe with their ICD.[36] These findings highlight that IAS can have a major impact on patient's quality of life, underlining the importance to undertake action after a first IAS to avoid recurrence of IAS.

Limitations

This study has several limitation. First, the PRAETORIAN trial started in 2011 and cutoff rates were set at 182 bpm, based on best available data at the start of this trial, whereas current programming is mostly set at 200 bpm, based on evidence from the MADIT-RIT trial.[11] Use of these higher cutoff values could have led to lower inappropriate therapy rates in both arms of this trial.

Second, due to the unavailability of some electrograms, particularly in the TV-ICD group and mostly as a result of storage constraints arising from frequent episodes, causes of IAS and rhythm and rate could not be determined for these episodes. Therefore, there might be an underreporting of total amount of inappropriate therapy, especially in the TV-ICD group. Furthermore, due to the timing of the study, most patients in the S-ICD arm received first generation S-ICDs which could not be updated with the SMART Pass filter. The total IAS rate in the S-ICD group might have been lower if this study had been performed with more contemporary devices which all have SMART Pass available. The combination of a potential lower IAT rate with current S-ICD devices with SMART Pass availability and a probable underreporting of IAT in the TV-ICD group needs to be taken into account when interpreting the results of this study in the current era of device therapy.

Next, the S-ICD screenings ECGs which are made before implantation were not collected in this study and therefore an analysis whether certain characteristics on these screening ECGs were predictive for cardiac oversensing in the S-ICD arm could not be performed.

Finally, only 19.7% of the patients in the PRAETORIAN trial were women, and rates of women with inappropriate therapy in this subanalysis were even lower. Although, there is no single explanation, patients did not have influence on the choice of device type and women might find this more difficult to accept, in particular since the type of device has esthetical consequences. Moreover, in some regions women are not the predominant decision-makers in matters concerning their health.[37] Low inclusion rates of women in clinical ICD trials might create a lack of crucial knowledge of the benefit and risk of different types of ICDs in both males and females.

Conclusions

This multicenter randomized study found no significant difference in inappropriate therapy rates and IAS rates between the S-ICD and TV-ICD in a conventional ICD population. Differences were observed in underlying cause and predictors for inappropriate therapy. In addition, whereas type of intervention after inappropriate shock therapy differs between the S-ICD and TV-ICD, interventions similarly reduced recurrence compared with a conservative approach. These results are valuable in helping clinicians make an informed decisions on selection of device type for individual patients.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5
Figures S1 and S2

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