Prospective blinded evaluation of a novel sensing methodology designed to reduce inappropriate shocks by the subcutaneous implantable cardioverter-defibrillator

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BACKGROUND Most inappropriate shocks from the subcutaneous implantable cardioverter-defibrillator (S-ICD) are caused by cardiac oversensing. A novel sensing methodology, SMART Pass (SP; Boston Scientific Corporation, Natick, MA), aims to reduce cardiac oversensing.

OBJECTIVE The purpose of this study was to evaluate the effect of SP on shocks in ambulatory patients with S-ICD.

METHODS Patients implanted in 2015–2016 and enrolled in a remote patient monitoring system were included and followed for 1 year. Shocks were adjudicated by 3 independent blinded reviewers as appropriate or inappropriate. Shock incidence was calculated for patients with SP programmed enabled or disabled at implantation, censoring patients when SP programming changed or at the last transmission. The SP setting (enabled vs disabled) was modeled as a time-dependent Cox regression variable.

RESULTS The cohort consisted of 1984 patients, and a total of 880 shocks were adjudicated. At implantation, SP was enabled in 655 patients (33%) and disabled in 1329 patients (67%). SP reduced the risk for the first inappropriate shock by 50% ($P < .001$) and the risk for all inappropriate shocks by 68% ($P < .001$) in multivariate analysis adjusted for age and device programming. The incidence of inappropriate shocks was 4.3% in the SP enabled arm vs 9.7% in the SP disabled arm. The incidence of appropriate shocks was similar (5.2% vs 6.6%; $P = .18$) along with the time to treat the first appropriate shock (17.4 seconds vs 16.7 seconds; $P = .92$) for SP enabled vs disabled, respectively.

CONCLUSION This prospective blinded evaluation of the SP filter demonstrates that enabling the SP filter results in a significant reduction of inappropriate shocks by the S-ICD without a negative effect on appropriate shocks.

KEYWORDS Arrhythmias; Appropriate shocks; Inappropriate shocks; Oversensing; Subcutaneous ICD

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Introduction

The implantable cardioverter-defibrillator (ICD) is an established therapy to prevent sudden cardiac death.[1,2] Despite the effectiveness in reducing arrhythmic mortality, conventional ICD systems have been associated with morbidity because of short- and long-term complications with endovascular leads.[3–5] To address these complications, an entirely subcutaneous implantable cardioverter-defibrillator (S-ICD) system was developed with no leads within or on the heart.[6] Several studies have demonstrated the feasibility and safety

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of the S-ICD system in detecting and terminating life-threatening ventricular arrhythmias.[7–9] Despite the safety and efficacy of the S-ICD system, the main cause of morbidity in S-ICD patients is the inappropriate shock, primarily caused by cardiac oversensing.[10,11] An initial update in the morphology-based sensing algorithm in the S-ICD reduced inappropriate charges because of T-wave oversensing by ~40%.[12] In order to reduce inappropriate shocks further, a new high-pass filter (SMART Pass [SP], Boston Scientific Corporation, Natick, MA) available within the S-ICD system was activated for cardiac sensing.

We evaluated the effect of SP on shocks in ambulatory S-ICD patients. For the purpose of this study, events in S-ICD patients enrolled in the LATITUDE remote follow-up system (Boston Scientific) were used in order to allow real-life events to be evaluated.

Methods

Study design

The LATITUDE remote patient monitoring system was market released in February 2006 for CRT-D and ICD devices. In 2015, the EMBLEM S-ICD system (Boston Scientific) was added to the LATITUDE network system. Device data are transmitted wirelessly from the implanted device to a central server via interaction with the LATITUDE communicator in the patient's home. Data are available through a secured website for review by the patient's physician. Participating centers are engaged in a data processor agreement that governs the use of LATITUDE data, and each patient signed a data authorization form that allows the use of anonymous data for research purposes. The study cohort consisted of patients who received an S-ICD between January 1, 2015 and December 31, 2016. For the purpose of the study, patients had to be enrolled in the European LATITUDE remote monitoring system. LATITUDE allows for limited demographic data, and as such, this study design focuses on events as it relates to programming.

The SP filter was approved on April 20, 2016, with CE Mark approval of the EMBLEM MRI (model A219) device, and the first implantation occurred on April 25, 2016. The SP filter was retroactively available for A209 devices through a firmware upgrade. The SP filter could be programmed active following the device setup process and selection of the optimal sensing vector.

Sensing of the S-ICD system and SP

The S-ICD system uses 3 sensing electrodes to record cardiac electrical activity: (A) superior to the sternal defibrillation coil; (B) inferior to the sternal defibrillation coil; and (C) pulse generator (CAN) implanted along the left midaxillary line at the 5th intercostal space. These electrodes represent 3 vector projections of cardiac electrical conduction, which resembles the signal characteristics of the standard surface electrocardiogram (ECG): primary, B to CAN; secondary, A to CAN; alternate, A to B. One of the 3 available vectors is selected (on the basis of the optimal QRS-to-T wave ratio) for use as a configuration for sensing. Each detected cardiac signal is sent through several noise detection and 4 double detection algorithms to determine whether oversensing is present.

Two generations of the S-ICD system—EMBLEM A209 and EMBLEM-MRI A219—can apply an additional high-pass filter to the sensing methodology, SP, in order to reduce inappropriate therapy. SP enables the high-pass filter for cardiac sensing only while continuing to use the wide-band ECG for rhythm discrimination purposes (Figure 1). The high-pass filter is activated if the sense vector signal characteristically meets the minimal QRS amplitude requirement ($\geq$0.5 mV). The activated filter is a first-order high-pass filter with corner frequency between 8 and 9 Hz and a roll-off rate of 20 dB/decade. Such a filter allows maximum reduction around the corner frequency and a gradual reduction at lower frequencies, thereby not affecting signals at higher frequencies ($>$10 Hz). Based on the fundamental frequency of T waves ($<$9 Hz) and QRS complexes ($>$10 Hz) observed on surface and subcutaneous electrocardiograms (S-ECGs), SP is more likely to reduce most T waves while allowing accurate sensing of the QRS complex owing to the improved QRS-to-T wave ratio.[13] In an effort to avoid undersensing of low-amplitude ventricular arrhythmias, SP is specifically designed to auto deactivate in the presence of low-amplitude signals (0.25 mV, SP filtered), whether cardiac or noncardiac.

Event adjudication

Before adjudication, all device-stored events were de-identified of patient data and reviewers were blinded to the SP setting (enabled vs disabled). The event adjudication committee composed of 3 investigators experienced in S-ICD and S-ECG interpretation. Two investigators (D.A.M.J.T. and T.F.B.) reviewed the events independently. In case of discordance, the third investigator (V.A.) was consulted to reclassify the event and provide a final decision.

Categories for rhythm classification were polymorphic ventricular tachycardia (PVT)/ventricular fibrillation (VF), monomorphic ventricular tachycardia (MVT), normal sinus rhythm, sinus tachycardia (ST), atrial fibrillation (AF), and supraventricular tachycardia (SVT). Shocks delivered for PVT/VF or MVT above the programmed detection rate were classified as appropriate. Shocks delivered for all other rhythms were classified as inappropriate, including PVT and MVT below the lowest programmed detection rate with oversensing. Reviewers applied standard definitions for ventricular arrhythmias: (1) *MVT* was defined as stable single QRS morphology from beat to beat; (2) *PVT* was defined as changing or multiform QRS morphology from beat to beat; and (3) *VF* was defined as a rapid irregular ventricular activity with marked variability in waveforms, usually with a ventricular rate of $>$300 betas/min. To assess the interobserver variability, the Cohen's κ statistic and percent agreement between reviewers were calculated.

Therapy characteristics were also evaluated. *Time to therapy* was defined as the interval from the onset of the arrhythmia until delivery of the first shock using the stored

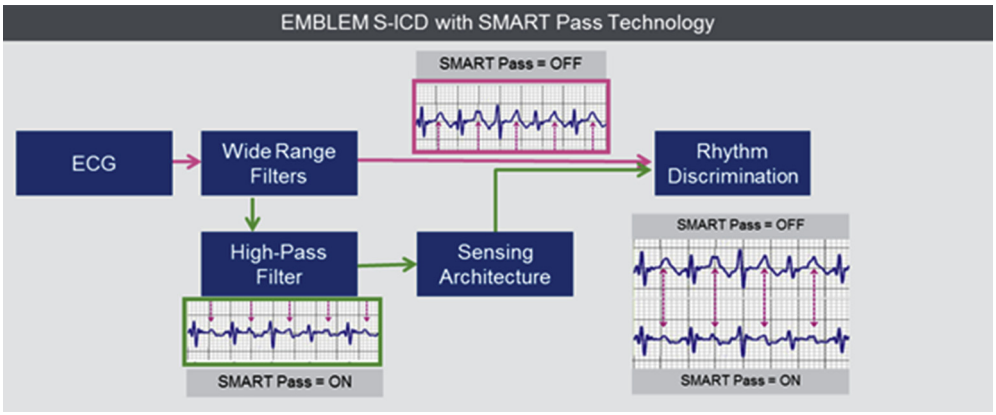


Figure 1 Signal processing in the EMBLEM S-ICD using SMART Pass technology. The ECG is sent through the high-pass filter and through several noise and double detection algorithms for accurate sensing of the QRS complex. The wide-band ECG is continuously used for rhythm discrimination. ECG = electrocardiogram; S-ICD = subcutaneous implantable cardioverter-defibrillator.

S-ECG of the device. *First shock efficacy* was defined as conversion of the ventricular arrhythmia, PVT/VF or MVT, before the start of a second charge.

Statistical analysis

All analyses were performed using R version 3.4.3 (R Development Core Team 2017). Normality of distribution was determined using the Shapiro-Wilk test. Continuous variables are presented as mean ± SD or as median (interquartile range), where appropriate. Categorical data are presented as count (percentage). A 2-sided independent Student *t* test or Mann-Whitney *U* test was used to evaluate continuous variables and Fisher exact test for categorical variables. The rhythm triggering the first shock in an episode was used for calculating the incidence of shocks. SP baseline programming was evaluated on the day of implantation. As SP can be programmed ON and OFF during follow-up, the SP setting (enabled vs disabled) was modeled as a time-dependent Cox regression variable to calculate the hazard ratio (HR) with corresponding 95% confidence interval (CI) for the incidence of both the first inappropriate shock and all inappropriate shocks (recurrent event analysis), adjusting for age and programming of detection zones. The Kaplan-Meier method was used to estimate the cumulative incidence of events at 1-year follow-up with censoring at the end of follow-up, as well as separately by censoring at programming change (as programmed). Differences between groups were compared using the log-rank test. A P value of $<.05$ was considered statistically significant.

Results

The study cohort consisted of 1984 patients; 655 patients with SP enabled (33%) and 1329 with SP disabled (67%). Patient demographic characteristics and programming of the devices are presented in Table 1. Most devices were programmed with 2 zones, which provided morphology discrimination for events with rates in the conditional zone. There was no significant difference in patients' age, but the programmed rate cutoffs were slightly different between patients with SP enabled and those with SP disabled.

Patients were followed for a mean of 1.4 ± 0.5 years after implantation. The mean follow-up period was shorter in the SP enabled group than in the SP disabled group (1.1 ± 0.3 years vs 1.6 ± 0.5 years, respectively; $P < .001$). During follow-up, 706 treated episodes with 880 shocks in 309 patients (16%) were recorded. Rhythm adjudication and appropriateness of shock therapy were available for 880 shocks. The agreement between reviewers was 94.3%, with a Cohen's κ of 0.89. The adjudication results for the first shock therapy for the 706 episodes are presented in Table 2. A total

Table 1 Patient demographic characteristics and programming of the devices

Variable	SMART Pass ON (n = 655)	SMART Pass OFF (n = 1329)	*P*
Age (y)	48 ± 16	48 ± 17	.76
Implanted model of the S-ICD			
EMBLEM A209	253 (39)	1155 (87)	<.001
EMBLEM-MRI A219	402 (61)	174 (13)	
Detection parameters (beats/min)			
Dual-zone configuration	631 (96)	1249 (94)	.04
Conditional zone	200 (200–210)	200 (200–220)	.04
Shock zone	240 (230–250)	240 (230–250)	.62
Single-zone configuration	24 (4)	78 (6)	.04
Shock zone	230 (222–250)	230 (220–240)	.20

Values are presented as mean ± SD, as median (interquartile range), or as n (%).
S-ICD = subcutaneous implantable cardioverter-defibrillator.

Table 2 Adjudication results for first shock therapy of the 706 episodes

Category	Appropriate (n = 326)	Inappropriate (n = 380)	Total (n = 706)
AF		19 (5)	19 (3)
Cardiac OS		258 (68)	258 (37)
MVT	174 (53)		174 (25)
Noncardiac OS		67 (17)	67 (9)
PVT/VF	152 (47)		152 (21)
ST		3 (1)	3 (0)
SVT		33 (9)	33 (5)

Values are presented as n (%).

AF = atrial fibrillation/flutter; MVT = monomorphic ventricular tachycardia; OS = oversensing; PVT = polymorphic ventricular tachycardia; ST = sinus tachycardia; SVT = supraventricular tachycardia; VF = ventricular fibrillation.

of 380 (54%) of treated episodes were classified as inappropriate and 326 (46%) as appropriate.

Inappropriate shocks

The Kaplan-Meier curves illustrating time to first inappropriate shock as programmed are shown in Figure 2. At 1-year follow-up, the inappropriate shock rate was lower for patients with SP enabled than for those with SP disabled (4.3% vs 9.7%; $P < .001$). The risk of the first and recurrent inappropriate shocks with SP as time-dependent variable is shown in Figure 3. Patients with SP enabled had a 50% reduction of the first inappropriately treated episode (HR 0.50; 95% CI 0.37–0.68; $P < .001$) and the overall reduction of inappropriate shocks was 68% (HR 0.32; 95% CI 0.22–0.47; $P < .001$). The cumulative incidence of recurrent inappropriate shocks per 100 patient-years is presented in Figure 4.

The causes of the 380 inappropriately treated episodes were SVT/AF above the discrimination zone (n=26; 7%), SVT/AF discrimination error (n=29; 8%), cardiac oversensing (n=241; 63%), and noncardiac oversensing (n=84; 22%). In the 241 episodes due to cardiac oversensing, the main causes were low-amplitude signals (n=118; 49%) and T-wave oversensing (n=113; 47%). The effect of SP enabled vs disabled on the different causes for the first inappropriate shock is presented in Figure 5. Inappropriate shocks due to cardiac oversensing were lower for SP enabled than for SP disabled (1.6% vs 6.4%; $P < .001$). Shocks for AF/SVT/ST without oversensing occurred in 2.3% for SP enabled vs 1.1% for SP disabled ($P = .07$). However, when cardiac oversensing was the cause of inappropriate shocks, the underlying rhythm was more often AF/SVT/ST for SP disabled vs SP enabled (4.2% vs 0.5%; $P < .001$).

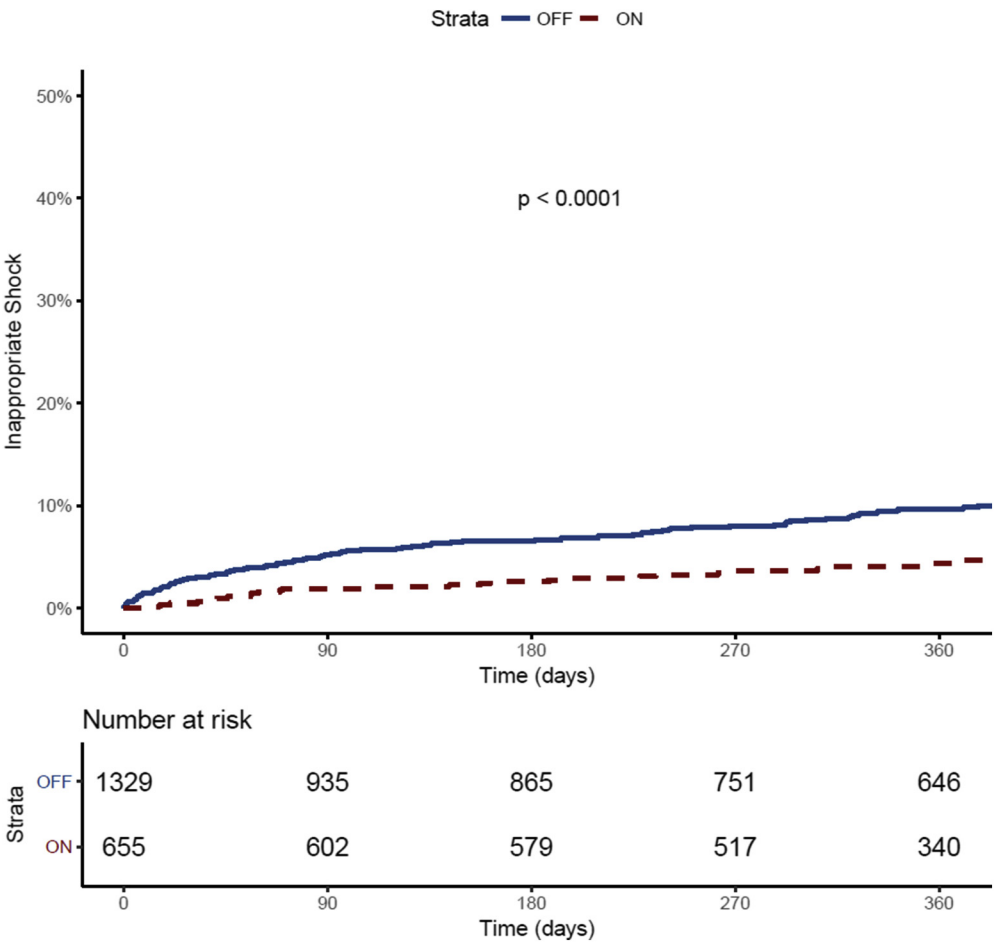


Figure 2 Incidence of the first inappropriate shock stratified by SMART Pass enabled vs disabled.

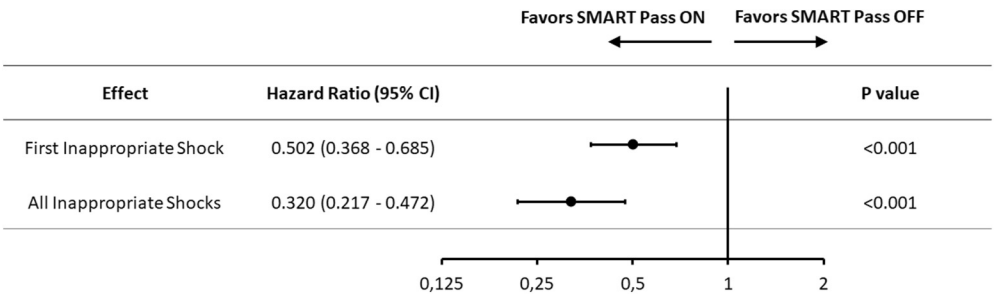


Figure 3 Forest plot illustrating the effect of SMART Pass on the risk of the first and recurrent inappropriate shocks. CI = confidence interval.

Appropriate shocks

A total of 147 patients (7.4%) had 326 appropriately treated ventricular tachyarrhythmias and were primarily discrete events in unique patients. There were 152 PVT or VF episodes (47%) in 74 patients and 174 MVT episodes (53%) in 83 patients. At 1-year follow-up, the cumulative incidence of appropriate shocks was similar for patients with SP enabled and those with SP disabled (5.2% vs 6.6%; $P = .21$). In order to assess the effect of SP on the detection of VF, PVT, and MVT, we analyzed time to therapy and conversion efficacy. No differences in time to therapy were identified: 17.4 seconds (range, 14.6–20.1 seconds) for SP enabled vs 16.7 seconds (range, 15.0–20.9 seconds) for SP disabled ($P = .92$).

During the first year of follow-up, 623 patients with SP disabled (47%) crossed over to SP enabled and 78 patients with SP enabled (12%) had at least 1 crossover programming. When no censoring is used, regardless of subsequent programming changes, the 1-year inappropriate shock incidence at baseline was 5.9% for SP enabled and 9.2% for SP disabled ($P = .03$) and the incidence of appropriate shocks was 5.2%

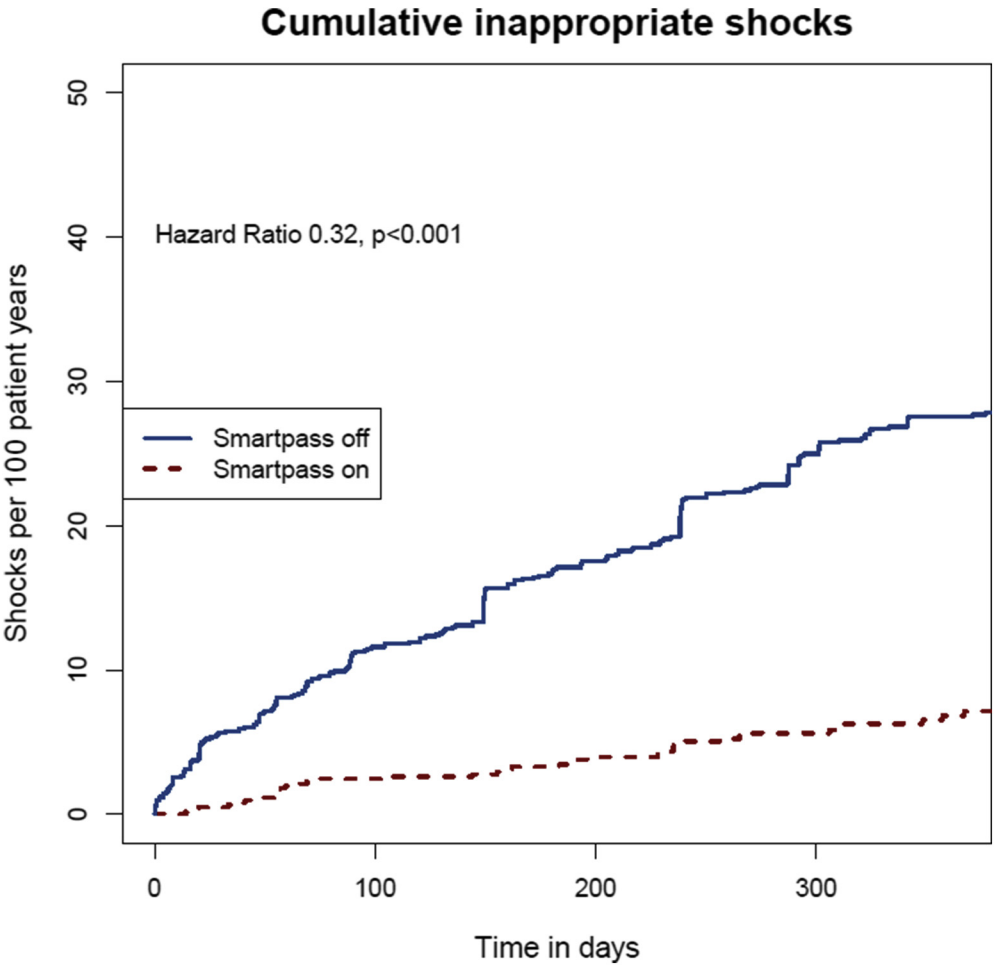
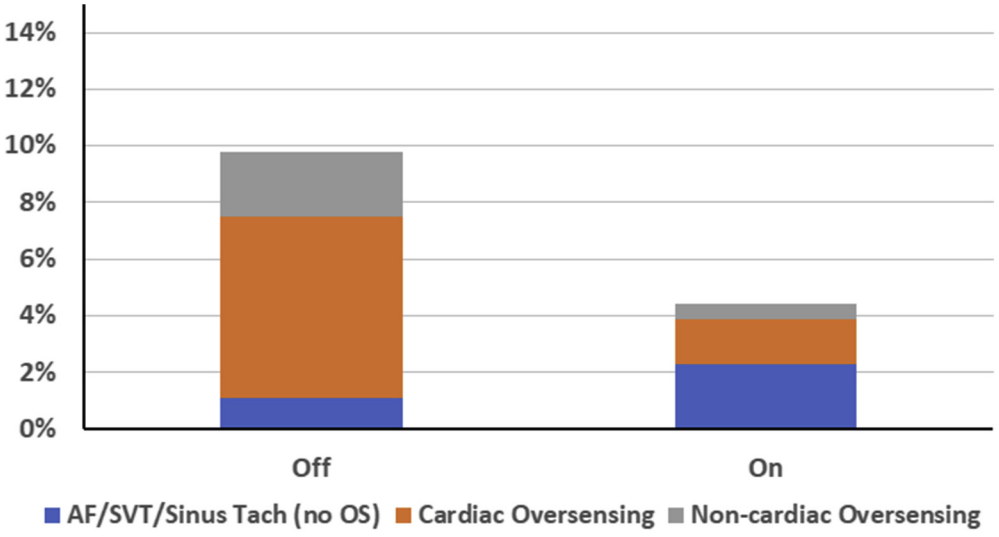


Figure 4 Cumulative incidence of recurrent inappropriate shocks per 100 patient-years stratified by SMART Pass enabled vs disabled.



IAS Reason	SP OFF	SP ON	*P*-value
AF/SVT/Sinus Tach (no OS)	1.1%	2.3%	*P*=0.07
Cardiac Oversensing	6.4%	1.6%	*P*<0.001
Non-cardiac Oversensing	2.3%	0.5%	*P*=0.003

Figure 5 Distribution of causes of the first inappropriate shock by SMART Pass enabled vs disabled. AF/SVT/Sinus Tach = atrial fibrillation/supraventricular tachycardia/sinus tachycardia; OS = oversensing.

and 7.1%, respectively ($P = .10$). In patients with SP enabled at implantation and consistently enabled during follow-up, the 1-year inappropriate shock rate was 3.7% vs 9.9% without SP consistently enabled ($P < .0001$) and the appropriate shock incidence was 5.3% vs 6.9% ($P = .12$).

Discussion

Main findings

This prospective evaluation of the effect of the high-pass filter in a real-world patient group implanted with an S-ICD yields several important findings. First, in patients in whom a high-pass filter is activated there is a large reduction of inappropriate therapy for oversensing, both in the proportion of patients with inappropriate shocks and in the total number of inappropriate shocks delivered to those patients. Second, the 1-year inappropriate shock rate is in line with rates observed in the single-chamber transvenous ICD study using therapy reduction programming strategies. Third, the rate of appropriate therapy was not different between the group with the high-pass filter enabled and the group with the high-pass filter disabled. Regarding the safety of using this filter, the time from arrhythmia onset to appropriate shock delivery did not differ between the SP groups.

Inappropriate therapies

Previous studies such as the Evaluation oF Factors ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD study and the S-ICD Investigational Device Exemption trial have reported inappropriate shock rates higher than those observed in contemporary transvenous ICD studies.[9,10] The overall inappropriate shock rate for the S-ICD system has been reported as 13% at 3-year follow-up.[9] Most of these shocks were due to oversensing of the cardiac signal, particularly oversensing of the T wave. The rates of inappropriate shocks due to cardiac oversensing are reported as 5.2%–8.1% on a per-patient basis at 11- to 12-month follow-up.[7,11] Previous improvements to the discrimination algorithm attempted to reduce this phenomenon, but were unable to address it sufficiently. With the introduction of the latest generation of the S-ICD, a new high-pass filter has become available that selectively filters the T-wave frequency. The reduction of inappropriate shocks aligns with previous benchmark testing of the filter on stored episodes, where a 74% reduction of inappropriate shocks was observed.[13]

Often the inappropriate shock rate of the S-ICD is compared against the 2% inappropriate shock rate observed in Multicenter Automatic Defibrillator Implantation Trial – Reduction in Inappropriate Therapy.[14] However, when comparing inappropriate shock rates across studies, it is important to consider both the implanted devices and the clinical characteristics of the population studied. A subanalysis of Multicenter Automatic Defibrillator Implantation Trial – Reduction in Inappropriate Therapy demonstrated that cardiac resynchronization patients and older patients, who accounted for 50% of the trial population, experienced half as many inappropriate shocks as ICD patients and younger patients.[15] The S-ICD is often selected in young and active patients, as is also the case in the present cohort with a mean age of 48 years. A recent meta-analysis of matched studies of transvenous vs S-ICD therapy with balanced baseline

characteristics such as age and diagnosis did not find a significantly higher inappropriate shock rate in S-ICD patients.[16] However, it did demonstrate that the etiology of inappropriate shocks is different between the devices, as in transvenous ICDs most were caused by SVT discrimination errors whereas oversensing was the main cause in S-ICDs.

The recently published subanalysis of the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III trial in single-chamber ICD patients demonstrated that in the therapy reduction programming intervention arm (30/40 NID), the inappropriate shock rate was 4.8% at 1-year follow-up.[17] The 1-year inappropriate shock rate of 4.3% in the SP enabled group observed in our study is in line with the rate observed in the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III trial. In addition, a subanalysis of the Pain Free Smart Shock Technology study of single-chamber devices found a 2.5% inappropriate shock rate at 1-year follow-up.[18] The low inappropriate shock rate observed in this study could not be explained in a recent meta-analysis comparing 16 studies of single-chamber transvenous ICDs and S-ICDs reporting on inappropriate shocks.[19] This comprehensive review of studies found an annual inappropriate shock rate of 6.4% in patients with a single-chamber device, with a tendency toward a lower rate in the most recent years. The tendency toward a lower inappropriate shock rate is confirmed by our study, as continuous improvement of technology reduced the annual inappropriate shock rate from 8.1% as observed in the Evaluation oF Factors ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD study to 4.3% in the present study in patients with SP enabled.[11]

Appropriate therapies

The appropriate shock rate in patients with SP enabled was numerically lower, but did not reach statistical significance. Also, the time from the onset of ventricular arrhythmia until delivery of the appropriate shock did not differ. Both these findings suggest that the filter does not compromise the detection of ventricular arrhythmias or time to therapy. Importantly, the appropriate shock rate was similar to the rate recently reported by Auricchio et al[19] in a systematic review and meta-analysis. Within a subgroup of the 16 studies that reported appropriate shocks, 7 studies with 31,336 patients followed for 6631 patient-years were included. Three of these studies were of S-ICDs. The annualized appropriate shock rate was estimated at 5.8% (95% CI 5.3%–6.3%), which is similar to the rate observed in our study.

Study limitations

This study has several limitations. The study was not a randomized trial comparing 2 treatment strategies and relies on physician-directed programming. As programming could change during follow-up, patients were evaluated as programmed in order to determine programming associated with inappropriate shocks and sensitivity to VT/VF. All shock episodes were systematically collected using the remote monitoring system, which essentially eliminates the chance of underreporting. LATITUDE allows for limited demographic data; therefore, limited baseline characteristics and no mortality data are available.

Conclusion

This prospective blinded evaluation of the SP filter demonstrates that enabling the SP filter results in a significant reduction of inappropriate shocks by the S-ICD without a negative effect on appropriate shocks.

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