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Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry

The EFFORTLESS Study

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ABSTRACT

BACKGROUND The subcutaneous implantable cardioverter-defibrillator (S-ICD) was developed to defibrillate ventricular arrhythmias, avoiding drawbacks of transvenous leads. The global EFFORTLESS S-ICD (Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD) registry is collecting outcomes in 985 patients during a 5-year follow-up.

OBJECTIVES The primary goal of the EFFORTLESS registry is to determine the safety of the S-ICD by evaluating complications and inappropriate shock rate.

METHODS This is the first report on the full patient cohort and study endpoints with follow-up ≥1 year. The predefined endpoints are 30- and 360-day complications, and shocks for atrial fibrillation or supraventricular tachycardia.

RESULTS Patients were followed for 3.1 ± 1.5 years and 82 completed the study protocol 5-year visit. Average age was 48 years, 28% were women, ejection fraction was 43 ± 18%, and 65% had a primary prevention indication. The S-ICD system and procedure complication rate was 4.1% at 30 days and 8.4% at 360 days. The 1-year complication rate trended toward improvement from the first to last quartile of enrollment (11.3% [quartile 1]) to 7.8% [quartile 2], 6.6% [quartile 3], and 7.4% [quartile 4]; quartile 1 vs. quartiles 2 to 4; $p = 0.06$). Few device extractions occurred due to need for antitachycardia ($n = 5$), or biventricular ($n = 4$) or bradycardia pacing ($n = 1$). Inappropriate shocks occurred in 8.1% at 1 year and 11.7% after 3.1 years. At implant, 99.5% of patients had a successful conversion of induced ventricular tachycardia or ventricular fibrillation. The 1- and 5-year rates of appropriate shock were 5.8% and 13.5%, respectively. Conversion success for discrete spontaneous episodes was 97.4% overall.

CONCLUSIONS This registry demonstrates that the S-ICD fulfills predefined endpoints for safety and efficacy. Midterm performance rates on complications, inappropriate shocks, and conversion efficacy were comparable to rates observed in transvenous implantable cardioverter-defibrillator studies. (Evaluation oF Factors ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD [The EFFORTLESS S-ICD Registry]; NCT01085435) (J Am Coll Cardiol 2017;70:830–41)

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The subcutaneous implantable cardioverter-defibrillator (S-ICD) was developed with the goal of providing a defibrillator system with no leads in or on the heart, thereby eliminating several important complications associated with transvenous leads, while maintaining reliable detection and defibrillation of life-threatening arrhythmias (1). Following the first human feasibility trials in 2002, S-ICD regulatory approval clinical trials began in 2008 and the S-ICD received the CE (Conformité Européene) mark in Europe in 2009 (2). Over the past 7 years, short-term follow-up data have been reported from the investigational device exemption (IDE) trial and an interim subset of less than one-half of the EFFORTLESS S-ICD (Evaluation oF Factors ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD) registry (3–5). These EFFORTLESS and IDE study patients were pooled for analysis of 889 patients (308 in the IDE trial, 568 in the EFFORTLESS registry, and 13 in both studies) followed for an average of 1.8 years and 1,571 patient-years (5).

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This paper provides the first report of the full EFFORTLESS cohort, which is the largest S-ICD database in the world with the longest follow-up so far. This includes nearly 1,000 patients followed for an average of 3.1 years (3,053 patient-years), enabling a comprehensive analysis of current important issues related to S-ICD performance. The primary goal of the EFFORTLESS registry is to demonstrate the safety of the S-ICD by evaluating complications and inappropriate shock rate (6). In addition, the following important outcomes for device performance and appropriate therapy were analyzed: 1) burden and predictors of monomorphic ventricular tachycardia (MVT); 2) incidence of recurrent MVT and impact of lack of availability of antitachycardia pacing (ATP); 3) differences in performance of the S-ICD in converting induced versus spontaneous episodes; and 4) reasons for device explant.

METHODS

The EFFORTLESS S-ICD registry is an observational, nonrandomized, standard-of-care registry enrolling up to 1,000 patients at 42 clinical centers in 10 countries. Details of the study design and endpoints were reported previously (6). Briefly, the objective of the EFFORTLESS registry is to demonstrate the early as well as mid- and long-term clinical outcomes of the S-ICD system (Cameron Health/Boston Scientific Inc., Minneapolis-St. Paul, Minnesota).

Patients eligible for implantation of an S-ICD system or with an S-ICD currently implanted at enrollment were eligible for inclusion. Exclusion criteria involved patients with spontaneous, incessant, or frequently recurring ventricular tachycardia (VT) amenable to ATP; patients with an indication for cardiac resynchronization therapy or symptomatic bradycardia, and patients with unipolar pacemakers or implanted systems that revert to unipolar pacing.

STUDY METHODS. Pre-specified endpoints were perioperative (30 days post-implantation) S-ICD complication rate, 360-day S-ICD complication rate, and the percentage of inappropriate shocks for atrial fibrillation (AF) or supraventricular tachycardia (SVT). The registry was conducted in accordance with the Declaration of Helsinki, ISO 14155:2009, and all applicable local and national regulations, and registered on ClinicalTrials.gov (NCT01085435). Patients were considered enrolled after providing written informed consent, in accordance with applicable local and national guidelines or ethics committee or internal review board requirements.

From August 2009 through December 2014, the registry enrolled 994 patients. Data were collected through the final 1-year follow-up visit for the last patient enrolled, which occurred in January 2016, thereby providing a minimum follow-up of 1 year in all eligible subjects who did not withdraw before 1 year. The database was locked in January 2016, following completion of data monitoring and resolution of data entry queries. The study protocol allowed for prospective and retrospective enrollments.

The study protocol did not require defibrillation threshold testing, but simply collected conversion testing data. Evaluable conversion tests were those

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ATP = antitachycardia pacing
CI = confidence interval
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
IDE = investigational device exemption
MVT = monomorphic ventricular tachycardia
PVT = polymorphic ventricular tachycardia
S-ICD = subcutaneous implantable cardioverter-defibrillator
SVT = supraventricular tachycardia
TV-ICD = transvenous implantable cardioverter-defibrillator
VF = ventricular fibrillation
VT = ventricular tachycardia

Dr. Hood has owned equity in Boston Scientific. Dr. Kuschyk has served as a consultant for Boston Scientific. Mr. Jones, Ms. Duffy, Mr. Husby, and Dr. Stein are employees of Boston Scientific. Dr. Lambiase has received speaker fees and research support from Boston Scientific, Medtronic, St. Jude Medical, and University College London Hospitals Biomedicine National Institute of Health Research. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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with induction of sustained VT or ventricular fibrillation (VF) that was treated by the S-ICD system. Appropriate and inappropriate spontaneous episodes were adjudicated and reported in the database by the individual investigating sites. Sites reported the pre- and post-shock rhythm for each therapy as MVT, polymorphic ventricular tachycardia (PVT), VF, sinus tachycardia, AF or flutter, or normal sinus rhythm, as well as indicating whether the rhythm was sustained or nonsustained, and if the ventricular rate was greater than the lowest programmed zone and conditional zone. In addition, a sponsor review was done to confirm the rhythm, and considered sustained shock episodes for MVT, PVT, or VF to be appropriate if the ventricular rate was above the programmed rate zone. In case of discordance, independent reviewers reclassified the episodes.

All adverse events were classified by the sponsor according to the cause of the event and resolution. Complications were defined as adverse events that resulted in invasive intervention. The EFFORTLESS registry protocol uses the same definition of complication types as the S-ICD IDE study does: type I, caused by the S-ICD system; type II, caused by the S-ICD system's user manual or labeling of the S-ICD system; type III, not caused by the S-ICD system, but would not have occurred in its absence (3).

The primary safety endpoint was predefined as the subset of complications caused by the S-ICD (type I), referred to as S-ICD complications. Additionally, all S-ICD system- and procedure-related complications (types I to III) were classified to quantify the safety of the device functionality, as well as of the S-ICD system and the implantation procedure, and are referred to simply as complications or overall complications.

All device check follow-ups for at least 360 days post-implantation date were recorded. Data collection from 360 days continued at least once annually to 60 months, with required reporting of clinical events occurring between annual follow-ups. The expected final follow-up date is December 2019.

During the course of the study, a field advisory was issued for a subset of model 1010 devices with premature battery depletion due to a battery manufacturing issue. There were no deaths reported because of this battery advisory. Device changes continued to be performed based on the regular elective replacement indicator.

STATISTICAL ANALYSIS. Descriptive statistics are reported using mean ± SD for continuous variables and frequency and percentage for categorical variables. Kaplan-Meier analyses were used to estimate the time to first event for complications, inappropriate therapy, and appropriate therapy. Multivariate analyses using the Cox proportional hazards model were performed separately for the outcomes of appropriate therapy, therapy for PVT or VF, therapy for MVT, therapy for multiple MVT episodes, and inappropriate therapy. Univariate analysis for each model was performed for inclusion in multivariate modeling. Variables with $p < 0.10$ in univariate analyses were candidates for the multivariate model. Backward selection with a $p \leq 0.05$ stay criterion was used to determine the final multivariate model. Subjects who did not experience an event and remain active in the study were censored at the date of the data snapshot for all time-to-event analyses. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

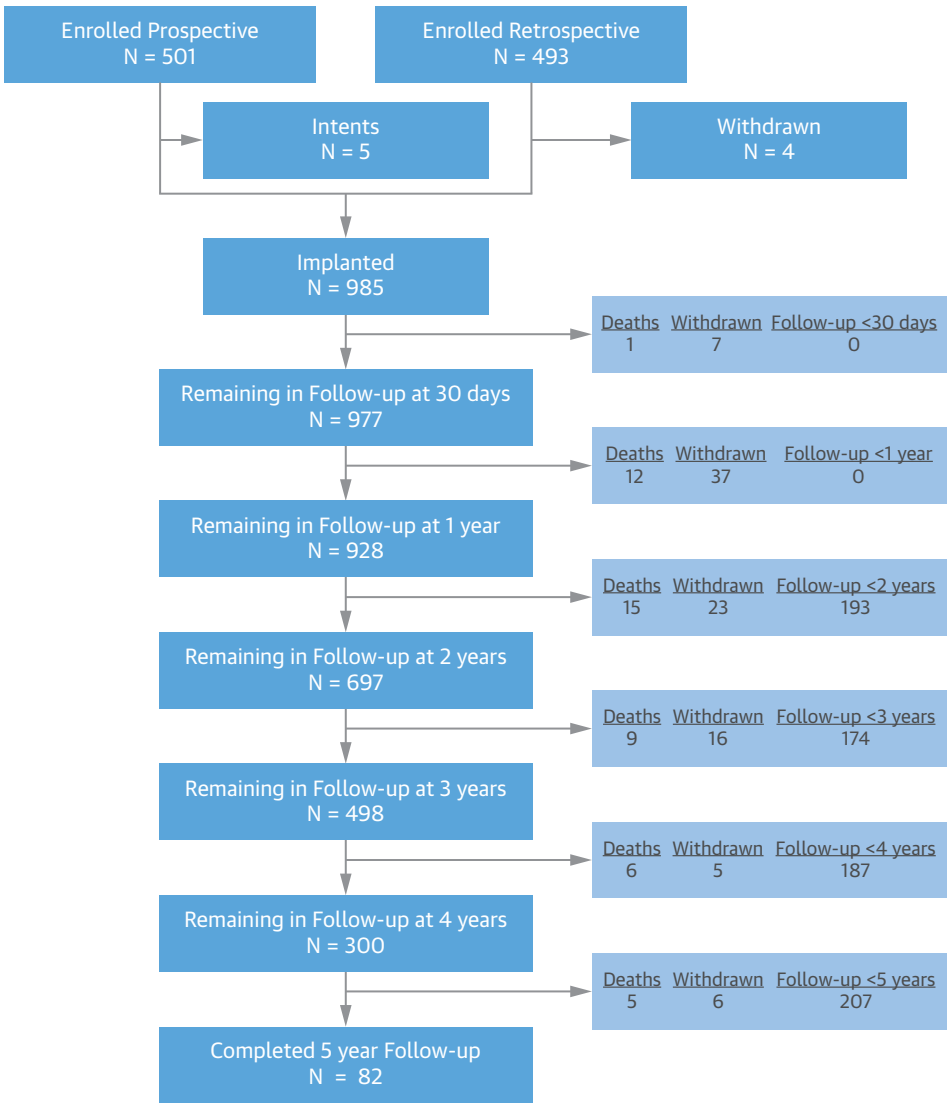
Of 994 patients enrolled, 6 were withdrawn before the implantation procedure, 3 retrospective enrollments were withdrawn before data entry due to inclusion deviation (1 participating in another study and 2 with investigational software from the CE mark approval trial). The remaining 985 patients were included in the analysis. The first-generation model 1010 S-ICD was implanted in all 985 patients. All patients were followed through the 1-year post-implantation visit (average 3.1 ± 1.5 years), and 928 patients remained in follow-up beyond 1 year (**Figure 1**).

All patient baseline demographics are shown in **Table 1**. Thirty-two percent had ischemic heart disease as an etiology, 19% had a nonischemic cardiomyopathy, 11% had hypertrophic cardiomyopathy, 20% had a channelopathy, and the remaining 19% of patients had a variety of other, less common etiologies. Statistical analysis neither revealed differences between retrospectively and prospectively enrolled patients regarding study endpoints nor differences in complications or therapies.

IMPLANTATION PROCEDURE DETAILS. Procedure time, defined as skin-to-skin time, averaged 66.8 ± 28.0 min. The mean procedure time decreased from 73.1 ± 31.9 min for successive implants 1 to 16/site, to 60.3 ± 21.8 min ($p < 0.001$), for implant number above the median of 16 implants/site.

Anesthesia use varied, with 60.4% of patients having the S-ICD implanted under general anesthesia, 33.6% having conscious sedation, and 6.0% receiving only local anesthesia. Either on the day of implantation or before discharge, 93.8% underwent a defibrillation test. The median hospitalization, from admission to discharge, was 1 day when S-ICD

FIGURE 1 Patient Flow



Patient flow chart for the EFFORTLESS (Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD) study showing the number of patients enrolled, receiving an implant, and remaining in follow-up at 30 days and at each annual follow-up through 5 years. The number of patients exiting the study for death or withdrawal at each interval is shown to the **right**, as well as the number of patients remaining in the study within the respective follow-up interval.

implantation was the sole reason for admission, and 14 days when hospitalized for other reasons, of which 2 days were from implantation to discharge.

COMPLICATIONS. For the primary pre-specified safety endpoint, the 30- and 360-day S-ICD complication rates were 0.3% (95% confidence interval [CI]: 0% to 0.6%) and 2.0% (95% CI: 1.3% to 3.1%), respectively. The most common S-ICD complications were cardiac oversensing, leading to inappropriate shocks (11 patients, 1.1%) and discomfort (n = 8, 0.8%). Complications related to product performance occurred due to premature battery depletion (n = 5), inability to communicate with the device (n = 3), or programmer error code (n = 1), with no reports of lead failure.

The overall complication rate was 4.1% at 30 days and 8.4% at 360 days (Figure 2A). All S-ICD system- or procedure-related complications are shown in Table 2. A total of 115 (11.7%) patients experienced a

TABLE 1 Baseline Demographic Data

	Overall (N = 985)	Retrospective (n = 489)	Prospective (n = 496)	p Value
Age at implantation, yrs	48 ± 17	45 ± 17	51 ± 16	<0.001
Male	709 (72.0)	338 (69.1)	371 (74.8)	0.05
BMI, kg/m^2	27 ± 6	27 ± 5	28 ± 6	0.06
Ejection fraction, %	43 ± 18	46 ± 18	41 ± 19	<0.001
QRS duration, ms	106 ± 25	104 ± 22	107 ± 27	0.07
Primary prevention	638 (64.9)	307 (62.9)	331 (66.9)	0.19
Ejection fraction ≤35%	301 (57.7)	123 (50.4)	178 (64.0)	0.002
Ischemic	221 (34.6)	87 (28.3)	134 (40.5)	0.001
Secondary prevention	345 (35.1)	181 (37.1)	164 (33.1)	0.19
Ischemic	90 (26.1)	41 (22.7)	49 (29.9)	0.13
Comorbidities				
Hypertension	279 (28.3)	121 (24.7)	158 (31.9)	0.01
MI	277 (28.1)	117 (23.9)	160 (32.3)	0.004
Cardiac arrest	275 (27.9)	144 (29.4)	131 (26.4)	0.29
Congestive heart failure	261 (26.5)	95 (19.4)	166 (33.5)	<0.001
Syncope	186 (18.9)	99 (20.2)	87 (17.5)	0.28
AF	157 (15.9)	61 (12.5)	96 (19.4)	0.003
Valve disease	120 (12.2)	72 (14.7)	48 (9.7)	0.02
Diabetes	111 (11.3)	42 (8.6)	69 (13.9)	0.008
Kidney disease	81 (8.2)	36 (7.4)	45 (9.1)	0.33
Stroke (including TIA)	51 (5.2)	21 (4.3)	30 (6.0)	0.21
COPD	49 (5.0)	18 (3.7)	31 (6.3)	0.06
Cardiac surgery				
Previous transvenous ICD	138 (14.0)	80 (16.4)	58 (11.7)	0.03
CABG	78 (7.9)	33 (6.7)	45 (9.1)	0.18
Valve surgery	62 (6.3)	30 (6.1)	32 (6.5)	0.84
Pacemaker implant	30 (3.0)	11 (2.2)	19 (3.8)	0.15
Primary cardiac disease				
Previous MI/ischemia/CAD	282 (28.6)	120 (24.5)	162 (32.7)	0.005
Channelopathy*	199 (20.2)	122 (24.9)	77 (15.5)	<0.001
Hypertrophic cardiomyopathy	106 (10.8)	50 (10.2)	56 (11.3)	0.59
Nonischemic cardiomyopathy	91 (9.2)	32 (6.5)	59 (11.9)	0.004
Dilated cardiomyopathy	84 (8.5)	53 (10.8)	31 (6.3)	0.01
Arrhythmogenic right ventricular dysplasia	32 (3.2)	13 (2.7)	19 (3.8)	0.30
Genetic	31 (3.1)	19 (3.9)	12 (2.4)	0.19
Valvular disease	21 (2.1)	15 (3.1)	6 (1.2)	0.04
Structural defect	19 (1.9)	13 (2.7)	6 (1.2)	0.10
Other†	44 (4.5)	22 (4.5)	22 (4.4)	0.96
Unknown	76 (7.7)	30 (6.1)	46 (9.3)	0.06

Values are mean ± SD or n (%). *Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, idiopathic ventricular fibrillation, torsades de pointes. †Includes variables with <1%: syncope of unknown origin, congestive heart failure, ventricular arrhythmia, myocarditis, cardiac sarcoidosis.

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; TIA = transient ischemic attack.

complication over the average 3.1-year follow-up. Infections requiring device removal occurred in 24 (2.4%) patients over the 3.1-year average follow-up. By Kaplan-Meier analysis, infections requiring device removal were most common in the first year (Figure 2B). There have been no reports of endocarditis to date. From the first to the last quartile of implants over time, the 1-year complication rate improved from 11.3% to 7.8% in quartile 2, to 6.6% in quartile 3 and 7.4% in quartile 4 (test for trend p = 0.12 for quartile 1 vs. p = 0.06 for quartiles 2 to 4).

Complications by demographic subgroups were assessed in univariate analysis (Figure 3). On multivariate analysis, nonischemic heart disease was associated with a higher rate of complications compared with ischemic heart disease (hazard ratio [HR]: 1.91; 95% CI: 1.17 to 3.10), as well as previous defibrillator (HR: 1.68; 95% CI: 1.03 to 2.75), QRS width/10-ms increase (HR: 1.11; 95% CI: 1.04 to 1.19), and body mass index per unit increase (HR: 1.03; 95% CI: 1.00 to 1.06).

Over the 3.1-year time course, the S-ICD was removed for a change in indication in 13 (1.3%) patients. This included a requirement for ATP in 5 (0.5%) patients, resynchronization therapy in 4 (0.4%) patients, and bradycardia pacing in 1 (0.1%) patient. In 2 patients, the device was removed because the indication for the implantable cardioverter-defibrillator (ICD) no longer existed due to improved left ventricular function. One patient required VT therapy for a VT rate <170 beats/min, which is below the detection or therapy limit for the S-ICD system.

INAPPROPRIATE SHOCKS. The other primary endpoint for the EFFORTLESS registry was the inappropriate shock rate for AF or SVT in the first year, which occurred in 15 (1.5%) patients. Over the 3.1-year average follow-up, 23 (2.3%) patients received a shock for AF or SVT, 3 (0.3%) patients for SVT discrimination errors. In total, 8.1% of patients received an inappropriate shock in the first year, and 11.7% received 1 over the average 3.1-year follow-up. Seventy-six (7.7%) patients received a shock for cardiac oversensing, mainly due to T-wave oversensing or low-amplitude signals (63%). Twenty-two (2.2%) patients received a shock for noncardiac oversensing, mainly electromagnetic interference.

At implantation, 850 (86%) patients had S-ICDs programmed to dual-zone detection. By programmed setting at implantation, the rate of inappropriate shocks in the first year was 7.5% for dual-zone and 11.8% for single-zone settings (p = 0.08), and 11.4% for dual-zone and 13.5% for single-zone settings at implantation (p = 0.36) over 3 years.

Univariate predictors of inappropriate therapy appear in Online Table 1. In multivariate analysis, a higher likelihood of receiving an inappropriate shock was found for subjects with a pacemaker (HR: 2.74; 95% CI: 1.29 to 5.82), prior coronary artery bypass graft (HR: 2.57; 95% CI: 1.34 to 4.89), and for each

10-ms increment in QRS width (HR: 1.11; 95% CI: 1.04 to 1.19). Patients with a prior myocardial infarction had a lower risk of inappropriate shocks (HR: 0.44; 95% CI: 0.26 to 0.75).

DEFIBRILLATION EFFICACY OF THE S-ICD SYSTEM. The large EFFORTLESS database also provides more data on the efficacy of the S-ICD over time, during both induced and spontaneous arrhythmias.

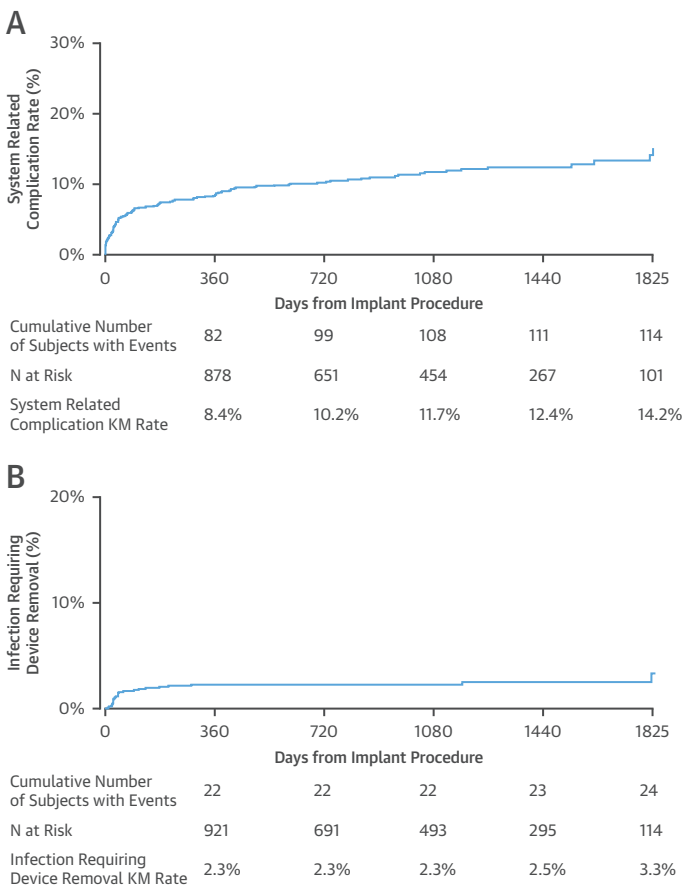
ACUTE CONVERSION TEST RESULTS. Table 3 summarizes acute conversion testing results. In the first 30 days post-implantation, 861 patients had at least 1 evaluable acute conversion test, with 857 (99.5%) patients showing at least 1 successful conversion test at ≤65 J (91.6%), 70 to 80 J (4.4%), or unrecorded energy (3.5%). Of 17 patients requiring repositioning of either the generator (n = 6) or the electrode (n = 5) or both generator and electrode (n = 6), a successful conversion test was achieved in 15 patients.

Of the 2 subjects with repositioning who did not have successful conversion testing in the acute timeframe, 1 had a successful test beyond 30 days, whereas 1 had an additional attempted conversion test, but was unable to induce VF. Both S-ICDs remained implanted. Two additional subjects failed acute conversion testing, for which the device was removed without repositioning. In total, 51 patients had conversion testing beyond 30 days after implantation (15 did not have acute testing whereas 36 had acute testing), of which 49 were successful. The 2 subjects with failed conversions had transvenous ICDs (TV-ICDs) implanted. Only 4 of 876 (0.45%) cases of acute and chronic testing failed, resulting in device removal.

APPROPRIATE THERAPY. A total of 104 patients (10.6%; annual incidence 3.4%) had 278 appropriately treated VT or VF episodes, including 86 storm episodes. Another 149 VT or VF episodes in 79 (8.0%) patients met detection criteria, but self-terminated during device charge. There were 131 MVT episodes in 58 patients and 147 PVT or VF episodes in 61 patients (Online Table 2). Twenty-two (2.2%) patients had >1 MVT treated episode over the average 3.1-year follow-up. The 1- and 5-year Kaplan-Meier rates of appropriate shock were 5.8% and 13.5% (MVT 3.8% and 7.4%; PVT or VF 3.0% and 8.4%), respectively.

Differences in time to therapy were identified between conversion testing and real-life VT or VF episodes. The mean time to therapy was 15.1 ± 3.5 s for induced versus 18.4 ± −4.3 s for spontaneous episodes ($p < 0.001$). The time to therapy for MVT episodes was 17.4 ± 3.8 s, and 19.5 ± 4.9 s for PVT or VF episodes.

FIGURE 2 Complication Rate



(A) The Kaplan-Meier (KM) estimate of the complication rate through 5 years for the subcutaneous implantable cardioverter-defibrillator system or procedure-related complications that require invasive action to correct. Complications shown in Table 2 are included. **(B)** KM estimate for infection requiring device removal.

Demographics of patients by type of appropriate therapy, as well as univariate predictors of appropriate therapy, are shown in Online Tables 1 and 3. In multivariate modeling for PVT or VF, a single MVT, or multiple MVT, secondary prevention patients were at the highest risk of receiving appropriate therapy. Patients with a prior cardiac arrest were at the highest risk for both PVT or VF and MVT (**Figure 4**). Kidney disease was an independent predictor of PVT or VF therapy, whereas wider QRS interval and chronic obstructive pulmonary disease at baseline were predictive of MVT, and channelopathy patients were less likely to receive therapy for MVT. In univariate modeling, ischemic etiology at baseline was not associated with therapy for PVT or VF ($p = 0.52$) or MVT ($p = 0.20$). A trend toward increased incidence of multiple episodes of MVT ($p = 0.090$) failed to become significant in

TABLE 2 Complications

Description	Events	Patients	% of Patients
Infection requiring device removal	27	24	2.4
Erosion	17	17	1.7
Inappropriate shock: oversensing	12	11	1.1
Other procedural complications	13	10	1.0
Hematoma	9	9	0.9
Discomfort	8	8	0.8
Suboptimal electrode position	7	7	0.7
Electrode movement	7	7	0.7
Premature battery depletion	5	5	0.5
PG movement	6	5	0.5
Unable to convert during procedure	6	5	0.5
Incision/superficial infection	5	5	0.5
Other technical complications	4	4	0.4
Suboptimal PG and electrode position	3	3	0.3
Inability to communicate with the device	3	3	0.3
Inappropriate shock: SVT above discrimination zone (normal device function)	2	2	0.2
Suboptimal pulse generator position	1	1	0.1
Total	135	115	11.7

PG = pulse generator; SVT = supraventricular tachycardia.

multivariate modeling ($p = 0.15$). AF and valve disease were associated with multiple MVT therapies. Programming zones at implantation were included in all multivariate models, and were not significant factors for appropriate or inappropriate shocks.

In discrete nonstorm VT or VF episodes, 88.5% were converted on the first shock and 97.4% (187 of 192 episodes) within 5 shocks available, whereas all patients survived their arrhythmic events. First shock conversion effectiveness was 90.5% for appropriately treated discrete episodes of MVT and 86.6% for PVT or VF. In 2 patients, VT termination occurred after the fifth shock, but was not documented in the time frame of electrogram recording. In another 2 patients, the device prematurely declared the episode ended and immediately reinitiated a new episode, with VF successfully terminated after additional shocks. One patient undergoing a myectomy procedure received multiple S-ICD and external shocks during the procedure. The subject was successfully defibrillated with an external defibrillator during S-ICD redetection.

Storm events (86 episodes in 13 VT or VF storm events) were successfully converted in 12 events. One patient with Loeffler's syndrome experienced a storm event that was not converted, as reported in a prior publication (4). There have been no reports of other deaths related to failed VT or VF conversion in the rest of the full cohort.

SURVIVAL. During the 3.1-year follow-up, 48 (4.8%) patient deaths were reported (29 among prospective enrollments and 19 in retrospective enrollments), of which the primary cause was noncardiac in 21 patients, cardiac in 21, and unknown in 6. Of the cardiac deaths, 1 was arrhythmic, as reported previously (4). Other cardiac deaths were related to pump failure (14 deaths), ischemic events (2 deaths), or other cardiac causes (4 deaths). Forty-seven (98%) deaths occurred outside the perioperative window of 30 days. No deaths were associated with the S-ICD system procedure.

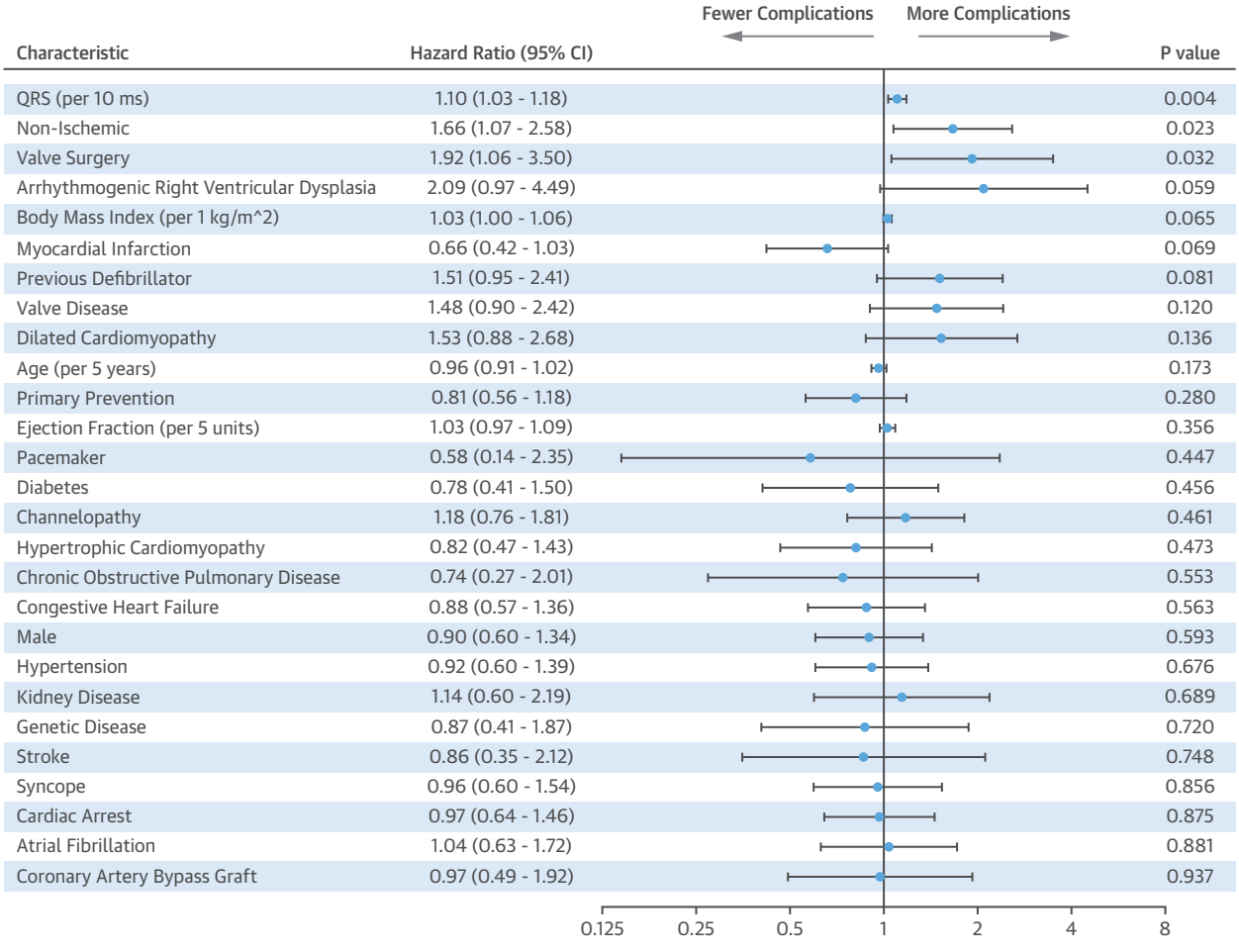
DISCUSSION

The present data provide important insights into the midterm performance of the S-ICD in the most comprehensively evaluated S-ICD cohort reported to date (**Central Illustration**). Compared with the preliminary EFFORTLESS registry publication by Lambiase et al. (4) >400 new patients were enrolled and are reported on in this analysis. Analysis of the retrospectively and prospectively enrolled cohorts showed consistency in outcomes. The larger database demonstrates consistent outcomes for efficacy and safety, in terms of successful conversion of both induced and spontaneous clinical ventricular arrhythmias, and the nature of inappropriate therapies. It also provides insights into the factors that determine the likelihood of MVT versus PVT or VF therapy in this S-ICD patient population, with implications for TV-ICD versus S-ICD device prescription.

COMPLICATIONS. The rate of complications directly caused by the S-ICD system, as well as the rate of all S-ICD system- and procedure-related complications, was low, and mirrored the IDE S-ICD rates, confirming the predictable and consistent safety of this first-generation device across geographies and patient populations. The most common reason for intervention was infection, whereas serious bloodstream infection continued to be absent in the EFFORTLESS registry population, as seen in earlier reports (5). Complication rates improved as experience grew with the S-ICD system, consistent with previous analyses (5,7). The consistent results by indication and patient demographics are also encouraging in this respect, as no patient subgroup stands out for an elevated risk of complications.

In comparison with TV-ICD complication rates, the S-ICD rates are similar, although differences in demographics, complication definitions, and follow-up time make comparisons across studies challenging (8). In 2 studies comparing matched S-ICD and TV-ICD

FIGURE 3 Univariate Analysis of Complication Risk



The complication risk is compared between patients with the characteristic present and those with the characteristic absent, or for each unit increase, as described in Table 1.

patients, complication rates were equivalent, with higher rates of lead complications in the TV-ICD patients and more nonlead complications, such as erosion, in the S-ICD patients (9,10).

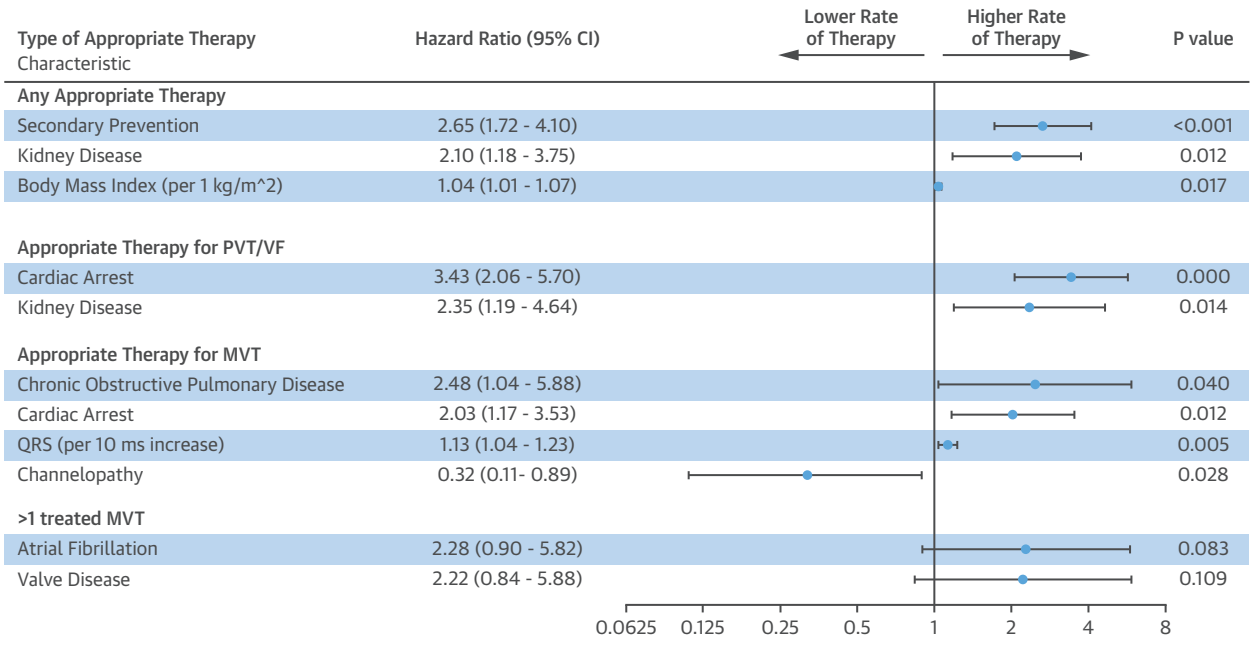
APPROPRIATE THERAPY. The study exclusion criteria mimic the device contraindications by excluding patients with a history of recurring VT who could benefit from ATP. This is likely to skew the demographics of this study in comparison with TV-ICD studies. The average age is younger than in TV-ICD studies, with a higher proportion of inherited diseases than would be expected in a TV-ICD study.

It is not surprising that secondary prevention patients and patients with prior cardiac arrest were more likely to receive appropriate therapy, whether for PVT or VF or MVT. Patients with ion channelopathy were less likely to receive therapy for MVT. Renal disease was a significant predictor of therapy for PVT or VF, which was not seen in the IDE trial that excluded patients with renal disease. Serum creatinine

TABLE 3 Acute Conversion Testing

Final Conversion Result (n = 861)	Without Repositioning	% of Total	With Repositioning	% of Total	Overall	% of Total
Success ≤65 J	777	90.2	12	1.4	789	91.6
Success >65 J	36	4.2	2	0.2	38	4.4
Success at unknown energy	29	3.4	1	0.1	30	3.5
Summary of successful conversion	842	97.8	15	1.7	857	99.5
Failed conversion testing	2	0.2	2	0.2	4	0.5

FIGURE 4 Multivariate Analysis of the Risk of Appropriate Therapy



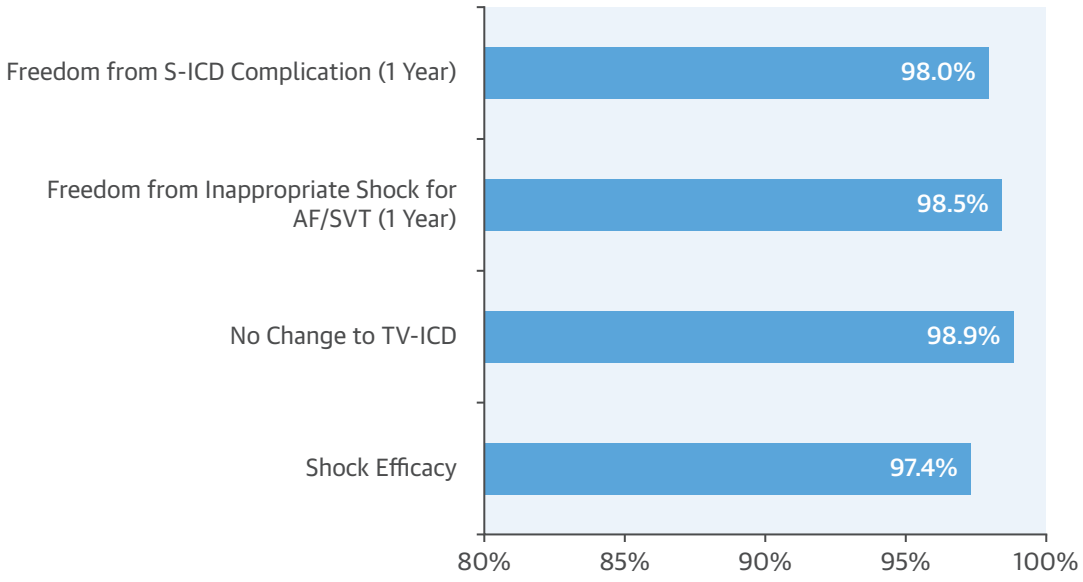
The figure shows significant prognostic factors using Cox proportional hazards models for the risk of receiving appropriate therapy. Separate models were constructed and are shown for any type of appropriate therapy received, and by type of rhythm receiving appropriate therapy: polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF), monomorphic ventricular tachycardia (MVT), or multiple treated MVTs. CI = confidence interval.

and renal dysfunction has been seen as an independent predictor of the time to first appropriate shock and sudden cardiac death in several TV-ICD studies (11-13). Patients with ischemic cardiomyopathy were not significantly more likely to receive appropriate therapy. This is consistent with MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) trial results in primary prevention patients (14,15).

A wider baseline QRS interval was an independent predictor of any appropriate therapy and treated MVT. Baseline AF was also associated with multiple treated MVT episodes. The results are consistent with SCD-HeFT trial modeling of arrhythmia risk (14), as both factors were found to be predictive, as was left bundle branch block in MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) trial (16). AF may either track with structural heart disease in its own right or promote ventricular arrhythmias through continuous cycle-length changes in the ventricle, which induce changes in ventricular refractoriness, leading to ventricular arrhythmia initiation. This reflects the finding of the PROFIT (Prospective Analysis of Risk Factor for Appropriate ICD Therapy) study, where patients with at least 2 risk factors (ejection fraction <40%, AF, QRS width ≥150 ms) had a 2-year 100% risk of VT or VF occurrence, compared with 19.3% and a 2-year risk of 25% with no or 1 risk factor (17). Furthermore, the JEWEL AF study showed that atrial tachyarrhythmias increase the risk of ventricular arrhythmias in patients with ICDs (18).

THE RELEVANCE OF MVT AND LACK OF ATP. This long-term follow-up of the entire EFFORTLESS registry cohort confirms the findings in the pooled IDE-EFFORTLESS registry analysis that the incidence of treated MVT in S-ICD recipients (5.8% in 3.1 years) is low; 36 (3.6%) patients with a single MVT episode and 22 (2.2%) patients with >1 MVT episode all successfully converted by 1 shock in the clear majority of cases. Five (0.5%) patients had the device removed for conceived need for ATP. Combining the cohorts with recurrent MVT and exchange for ATP would lead to an annualized rate of 0.9% of patients who might have benefitted from ATP. Extrapolating the PainFREE RX II (Pacing Fast Ventricular Tachycardia Reduces Shock Therapies) trial ATP efficacy of 42% for VT termination to this would yield 0.4% of patients annually that might have avoided recurrent

CENTRAL ILLUSTRATION **Outcomes After S-ICD Implantation: 1-Year EFFORTLESS Registry**



Boersma, L. et al. J Am Coll Cardiol. 2017;70(7):830–41.

Chart demonstrates freedom from subcutaneous implantable cardioverter-defibrillator (S-ICD) complication; freedom from inappropriate shock for atrial fibrillation (AF) or supraventricular tachycardia (SVT); no change to transvenous implantable cardioverter-defibrillator (TV-ICD); and shock efficacy at 1 year. EFFORTLESS S-ICD = Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD.

shocks for MVT by ATP. Future data from trials like PRAETORIAN (A PRospective, rAndomizEd Comparison of subcuTaneOous and tRansvenous ImplANtable Cardioverter Defibrillator Therapy) trial, directly comparing TV-ICD to S-ICD, may provide more data to decide if the benefit of ATP in the few, outweighs the disadvantages in the many (19). Such data will assist implanters to make an individual patient-based choice of the type of defibrillator.

High-rate programming to evaluate ATP need has been evaluated in TV-ICD studies. Clementy et al. (20) showed that programming shock-only therapy above >220 beats/min was not associated with adverse consequences, with 11.2% of patients receiving appropriate shocks and 6.6% inappropriate shocks over 3.3 years. Ventricular arrhythmias, sustained or not, were recorded in the monitoring zone (170 to 220 beats/min) in 11.8% of patients, of which only a few were symptomatic (1.9%), with no lethal consequences. In the EFFORTLESS registry cohort, the actual appropriate shock rate of 10.5% of patients (3.4%/annum) appears to be in line with TV-ICD studies with contemporary programming.

INAPPROPRIATE SHOCKS AND THE EFFECTS OF PROGRESSIVE CHANGES IN PROGRAMMING. The pre-specified primary endpoint of inappropriate therapy for AF or SVT was as low as 1.5% at 1 year in the EFFORTLESS registry. The overall inappropriate shock rate of 8.1% at 1 year appears to be similar to the overall rate in historical TV-ICD studies of 7% to 10% in the first year, rising to 18% by the fifth year (21–24). Although inappropriate shocks in MADIT-II trial of 10% were primarily due AF or SVT episodes (80%), T-wave oversensing was the main cause for the S-ICD. The second-generation S-ICD detection algorithms, available in only 7.6% of EFFORTLESS registry patients, may reduce inappropriate shocks due to cardiac oversensing by 30% to 40% (25). Modeling studies of the latest EMBLEM S-ICD (Boston Scientific, Inc., Minneapolis-St. Paul, Minnesota) algorithms using episodes from the EFFORTLESS registry showed a potential all-cause inappropriate shock incidence as low as 3.8% (70% to 80% reduction) (26).

The S-ICD inappropriate shock rate is higher than reported in the latest TV-ICD studies with more strict and controlled programming. The differences with

the latest TV-ICD shock rates may be caused by a difference in patient demographics. In the MADIT-RIT trial, each decade of age was associated with 34% reduction in the risk of inappropriate shock (27). In addition, a recent meta-analysis found TV-ICD inappropriate shock rates of 13% to 22% in patients with hypertrophic cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome (28). This demographic makes up nearly one-third of the EFFORTLESS registry cohort. In a matched comparison of S-ICD to TV-ICD, Brouwer et al. (9) observed no significant difference in rates of inappropriate shocks between S-ICD and TV-ICD patients over 5 years, with the S-ICD 1-year rate of inappropriate shocks of 8.4% being similar to the rate seen in the EFFORTLESS registry.

Programming was also uncontrolled in the EFFORTLESS registry. During the course of the study, dual-zone programming at implantation increased from 57% in 2009 to 2010, to 85% in 2011, and >90% in 2012 to 2014, whereas average rate cutoffs at implantation were raised from 208 beats/min to 224 beats/min with single-zone programming, and from 190/227 beats/min to 199/233 beats/min with dual-zone programming (Online Figure 1). In parallel to this change in implantation practice, the current longer-term multivariate analysis no longer identified dual-zone programming as lowering the rate of inappropriate therapy, whereas single-zone programming inappropriate therapy rates were lower than in previous studies (5). Alternative explanations could be reprogramming after implantation, the types of patients programmed to a single zone, or that an analysis artifact due to a low number of patients programmed to a single zone could have influenced these findings. In view of the collective data of several S-ICD studies, dual-zone programming should remain the standard for all patients.

LESSONS LEARNED FROM CONVERSION TESTING. As S-ICD technology is still novel, conversion testing during implantation is still recommended to ensure optimal sensing of induced VF and effective defibrillation (29). In the EFFORTLESS registry, there were no cases of VF under-detection preventing shock delivery, and failed acute conversion testing occurred in only a limited number of patients (<1%). Repositioning of the electrode or generator to encompass the heart may be needed to achieve successful conversion. In patients with a high body mass index, both the electrode and the generator must be positioned under the fat, in direct contact with the fascia, to ensure optimal shock impedances.

STUDY LIMITATIONS. The EFFORTLESS registry follow-up is ongoing, following patients to 5 years, and new events may be reported. A survival bias may be present in study patients who enrolled retrospectively post-implantation and had survived to the point of enrollment. The patient group selected and studied in EFFORTLESS is different from that in the classic TV-ICD trials, which hampers direct comparison.

CONCLUSIONS

This analysis of the full EFFORTLESS cohort over the first year post-implantation demonstrates that the S-ICD remains safe and effective in the treatment of lethal ventricular arrhythmias, with a low incidence of device upgrade for bradycardia, cardiac resynchronization therapy pacing, or ATP, and a low rate of implant complications. Current patient selection and device programming are efficacious, and avoid the unnecessary use of transvenous leads with their attendant complications. This cohort forms a key dataset in evaluating clinical outcomes with this new technology.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: S-ICD therapy is associated with a low incidence of device-related complications and low rate of inappropriate discharge for atrial tachyarrhythmias at 1 year, with 98% efficacy for ventricular arrhythmias during 3-year follow-up.

TRANSLATIONAL OUTLOOK: Advances in hardware and software technology and developments in leadless pacing modalities could expand the application for these less invasive therapeutic devices to a wider range of patients.

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KEY WORDS appropriate therapy, inappropriate therapy, leadless, primary prevention, secondary prevention, ventricular arrhythmias

APPENDIX For supplemental tables and a figure, please see the online version of this article.