# Performance of the subcutaneous implantable cardioverter-defibrillator in patients with a primary prevention indication with and without a reduced ejection fraction versus patients with a secondary prevention indication

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**BACKGROUND** The subcutaneous implantable defibrillator (S-ICD) provides an alternative to the transvenous ICD for the prevention of sudden cardiac death, but has not been well studied in the most commonly treated transvenous ICD patient population, namely, primary prevention (PP) patients with left ventricular dysfunction.

**OBJECTIVE** The analyses in the present study were designed to compare clinical outcomes for PP patients with and without a reduced ejection fraction (EF) and secondary prevention (SP) patients implanted with the S-ICD.

**METHODS** All patients 18 years and older from the S-ICD IDE study and the EFFORTLESS Registry with available data as of November 18, 2013, were included (n = 856; mean follow-up duration 644 days). Outcomes were evaluated in 2 analyses: (1) comparing all PP patients (n = 603, 70.4%) with all SP patients (n = 253, 29.6%) and (2) comparing all PP patients with an EF ≤35% (n = 379) with those with an EF >35% (n = 149, 17.4%).

**RESULTS** No differences were observed in mortality, complications, inappropriate therapy, or ability to convert ventricular tachyarrhythmias between SP and PP patients. However, SP patients had a higher incidence of appropriate therapy than did PP patients (11.9% vs 5.0%; $P = .0004$). In the PP subanalysis, the cohort with an EF ≤35% had significantly older patients with more comorbidities and higher mortality (3.0% annually vs 0.0%). Despite these differences, device-related complications, conversion efficacy, and incidence of inappropriate shock therapies were not significantly different between PP subgroups.

**CONCLUSION** The S-ICD performs well in protecting patients with either PP or SP implant indications from sudden cardiac death. Within PP patients, device performance was independent of EF.

**KEYWORDS** Subcutaneous ICD; Primary prevention; Secondary prevention; Ejection fraction; Appropriate shock

(Heart Rhythm 2016;0:1–9) 

## Introduction

The benefit of implantable defibrillator (ICD) therapy in reducing arrhythmic death in patients with either a secondary

The S-ICD IDE study and the EFFORTLESS S-ICD Registry are sponsored in its entirety by Cameron Health, Inc., a subsidiary of Boston Scientific Corporation. Dr Boersma has received consulting fees from Medtronic and Boston Scientific. Dr Burke has received consulting fees, research grants, and honoraria from Boston Scientific; research grants from Medtronic and St. Jude Medical; and consulting fees from AtCor Medical; he also owns an equity in AtCor Medical. Dr Theuns has received research grants from Biotronik and Boston Scientific and consulting fees from Boston Scientific. Dr Herre has received consulting fees from Medtronic and research support from Medtronic, Boston Scientific, and St. Jude Medical. Dr Weiss has received consulting fees, speaker fees, and research grants from Biosense Webster, Biotronik, Boston Scientific, Medtronic, and St. Jude Medical. Dr Kremers is a consultant to Medtronic, is a speaker for Boston Scientific, and owns an equity (<$20,000) in Boston Scientific. Mr Husby, Mr Carter, and Mr Stivland are employees of Boston Scientific. **Address reprint requests and correspondence:** Dr Lucas Boersma, Cardiology Department, St. Antonius Hospital, PO 2500, 3430M Nieuwegein, The Netherlands. E-mail address: l.boersma@antoniusziekenhuis.nl.

1547-5271/$-see front matter  http://dx.doi.org/10.1016/j.hrthm.2016.11.025

prevention (SP)[1,2] or a primary prevention (PP) indication[3,4] has been established through a number of studies over the past 2 decades. As these studies have resulted in an increased number of patients receiving a transvenous ICD (TV-ICD), the incidence of device- and lead-related complications requiring reoperation or explantation has also increased concomitantly.[5,6]

The subcutaneous implantable defibrillator (S-ICD) was developed as an alternative to the TV-ICD, without the need to implant transvenous or epicardial leads. The safety and effectiveness of the S-ICD has been established,[7,8] and the largest S-ICD studies include a wide variety of ICD-indicated patients.[9] The S-ICD is often selected for younger patients with inherited diseases and normal ventricular function,[10] yet patients with the more common indication of a reduced left ventricular (LV) ejection fraction (EF) remain the largest major subgroup implanted. We sought to understand the device performance and patient outcomes in patients with a PP indication, and specifically those with a reduced EF. We retrospectively evaluated the long-term clinical outcomes of patients implanted with the S-ICD for both primary and secondary indications. A second analysis was performed to compare outcomes for PP patients with an EF cutoff of ≤35% ("PP EF ≤35%") with those for PP patients with an EF >35% ("PP EF >35%").

## Methods

### Patient population

The patients included in the analysis were those implanted as part of the pivotal S-ICD System Clinical Investigation ("IDE study") and the initial cohort of the EFFORTLESS S-ICD Registry ("EFFORTLESS Registry") as previously described.[11] In brief, the IDE study was designed to demonstrate the safety and efficacy of the S-ICD system for Food and Drug Administration approval while the EFFORTLESS Registry is an ongoing standard-of-care postmarket evaluation of long-term clinical outcomes in 1000 patients commercially implanted with the S-ICD in countries outside the United States. For the IDE study, the data presented reflect information from all implanted patients (implanted between January 27, 2010, and May 20, 2011), while for the ongoing EFFORTLESS Registry, the data reflect information available as of November 18, 2013 (first implantation on August 20, 2009). Ethical approval was obtained in all centers for the purpose of each study, and all patients provided informed consent according to national and institutional regulations.

For the present analysis, the initial pooled data set consists of 889 enrolled patients: 308 from the IDE study, 568 from the EFFORTLESS Registry, and 13 patients common to the 2 studies. The analysis included patients from 58 clinical centers in 8 countries. Twenty-nine patients were subsequently excluded from the analysis because they were younger than 18 years at the time of implantation, and an additional 4 patients were excluded because of insufficient baseline data to characterize the indication for implantation. The remaining 856 patients are included in the analysis of SP and PP patients for all-cause mortality and device- and procedure-related complications. Only patients successfully implanted with the S-ICD system (853) are included in the analysis of shock therapy (appropriate and inappropriate). The analysis of PP patients by EF level included all PP patients with sufficient EF data. EF measurements were recorded as available for patients in the IDE study and EFFORTLESS Registry. Device programming was left to the discretion of the implanting physician in both studies.

### Statistical and data analysis

All outcomes were evaluated through the latest available follow-up. Two separate analyses were completed. First, clinical outcomes for all patients implanted for SP were compared with patients implanted for PP. Second, a subsequent analysis further subdivided the PP patients on the basis of EF into PP EF >35% or PP EF ≤35%. The appropriateness of pooling study data, event definitions, and event adjudications have been previously described.[8,10]

Baseline demographic and clinical characteristics, including medical history, risk factors, comorbidities, and New York Heart Association functional class for heart failure, are presented as available. Continuous variables are summarized as means ± SDs or as medians and ranges, where appropriate. Continuous data were compared using the Student *t* test. Categorical variables are summarized as frequencies and percentages and compared using the $\chi^2$ test. Freedom from complications, mortality, and appropriate shock and inappropriate shock rates are analyzed using the Kaplan-Meier method. All statistical analyses were performed using SAS Enterprise Guide, version 5.1 (SAS 9.3, SAS Institute Inc. NC USA).

## Results

Of the 856 patients in the primary analysis cohort, 29.6% were SP patients (n = 253) and 70.4% were PP patients (n = 603). Of the 603 PP patients, 379 had an EF ≤35% (62.9%), 149 had an EF >35% (24.7%), and 75 (12.4%) lacked sufficient data to determine baseline LVEF. Missing LVEF values were observed primarily in the EFFORTLESS Registry, predominantly in patients with etiologies that are not characterized by low EF. The mean follow-up duration for all patients was 644 days, with a range of 2–1542 days (median 633 days). There were no significant differences in follow-up duration between any of the groups evaluated (663, 636, 621, and 658 days for SP, PP, PP EF ≤35%, and PP EF >35%, respectively).

### Baseline demographic characteristics

Patient characteristics and baseline demographic characteristics are summarized in Tables 1 and 2. In general, SP patients had a lower incidence of comorbidities than did PP patients (Table 1). The mean LVEF was significantly higher in SP patients (48%) than in PP patients (36%) ($P < .0001$). PP patients had a significantly higher incidence of congestive

**Table 1** Baseline demographic and clinical characteristics of secondary prevention and primary prevention patients

| Demographic | Statistic/Category | Secondary Prevention Patients | Primary Prevention Patients | P-Value |
|---|---|---|---|---|
| Gender | Male | 180 (71.1) | 442 (73.3) | 0.5188 |
| Medical History | NYHA Classification II-IV (n, %) | 49 (19.4) | 278 (46.3) | <.0001 |
| | Atrial Fibrillation | 47 (18.7) | 94 (15.6) | 0.2802 |
| | COPD | 12 (4.8) | 44 (7.3) | 0.1669 |
| | Diabetes | 24 (9.5) | 132 (22.0) | <.0001 |
| | Hypertension | 81 (32.1) | 250 (41.7) | 0.0092 |
| | Myocardial Infarction | 70 (27.8) | 232 (38.7) | 0.0024 |
| | Stroke | 9 (3.6) | 36 (6.0) | 0.1481 |
| | Valve Disease | 35 (13.9) | 79 (13.2) | 0.7775 |
| | Ablation | 17 (6.7) | 23 (3.8) | 0.0666 |
| | CABG | 32 (12.7) | 69 (11.5) | 0.6214 |
| | Percutaneous Revascularization | 45 (17.9) | 150 (25.0) | 0.0242 |
| | Valve Surgery | 25 (9.9) | 27 (4.5) | 0.0026 |
| | Prior Pacemaker | 7 (2.8) | 15 (2.5) | 0.8127 |
| | Prior Defibrillator | 70 (27.8) | 49 (8.2) | <.0001 |
| | Explant Due to Infection | 43 (17.1) | 33 (5.5) | <.0001 |
| | Explant Due to Lead Failure | 21 (8.3) | 9 (1.5) | <.0001 |

Values are presented as mean ± SD, mean ± SD (range), or n (%).
BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association.

heart failure (New York Heart Association class II–IV), diabetes, hypertension, and prior myocardial infarction than did SP patients and were more likely to have previously undergone a percutaneous revascularization procedure, but not coronary artery bypass. Nearly 30% of SP patients had previously undergone an implantation of a TV-ICD, the majority of which (61.4%) had been explanted because of infection. This compares to only 8.2% of PP patients, who had received a TV-ICD. Primary underlying disease can be seen in Figure 1A: 41% of the PP patients had ischemic cardiomyopathy and 28% nonischemic cardiomyopathy as compared to the SP population composed of 33% ischemic and 12% nonischemic cardiomyopathy patients.

Within the PP group, there were significant differences between subgroups with respect to medical history, comorbidities, and underlying disease (Table 2). Patients in the PP EF ≤35% cohort were the oldest group (mean age 57 years) and were significantly older than those in the PP EF >35% cohort (mean age 40 years). The mean LVEF in the PP EF ≤35% group measured 26% ± 6% vs 60% ± 10% in the PP EF >35% group, suggesting overall a relatively preserved EF cohort. Patients with an EF ≤35% had more overall comorbidities. For example, 68.8% had a history of congestive heart failure vs 9.4% of patients with an EF >35% ($P < .0001$). Likewise, the incidence of a history of diabetes, hypertension, and myocardial infarction was 31.0%, 57.3%, and 57.8% for those in the PP EF ≤35% cohort vs 7.4%, 17.4%, and 7.4%, respectively, for those with an EF >35%. Among patients whose EF was >35%, the majority had either hypertrophic cardiomyopathy (40%)

**Table 2** Baseline demographic and clinical characteristics of primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%) and ≥35% (PP EF >35%)

| Demographic | Statistic/Category | Primary Prevention Low EF Patients | Primary Prevention High EF Patients | P-Value |
|---|---|---|---|---|
| Gender | Male | 299 (78.9) | 98 (65.3) | 0.0012 |
| Medical History | NYHA Classification II-IV (n, %) | 260 (68.8) | 14 (9.4) | <.0001 |
| | Atrial Fibrillation | 81 (21.4) | 9 (6.0) | <.0001 |
| | COPD | 36 (9.5) | 6 (4.0) | 0.0353 |
| | Diabetes | 117 (31.0) | 11 (7.4) | <.0001 |
| | Hypertension | 216 (57.3) | 26 (17.4) | <.0001 |
| | Myocardial Infarction | 218 (57.8) | 11 (7.4) | <.0001 |
| | Stroke | 31 (8.2) | 3 (2.0) | 0.0091 |
| | Valve Disease | 65 (17.2) | 9 (6.0) | 0.0009 |
| | Ablation | 13 (3.4) | 7 (4.7) | 0.4995 |
| | CABG | 67 (17.8) | 2 (1.3) | <.0001 |
| | Percutaneous Revascularization | 142 (37.6) | 6 (4.0) | <.0001 |
| | Value Surgery | 21 (5.6) | 4 (2.7) | 0.1610 |
| | Prior Pacemaker | 9 (2.4) | 2 (1.3) | 0.4526 |
| | Prior Defibrillator | 26 (6.9) | 16 (10.7) | 0.1406 |
| | Explant Due to Infection | 21 (5.6) | 9 (6.0) | 0.8288 |
| | Explant Due to Lead Failure | 2 (0.5) | 4 (2.7) | 0.0357 |

Values are presented as mean ± SD, mean ± SD (range), or percentage.
BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association.

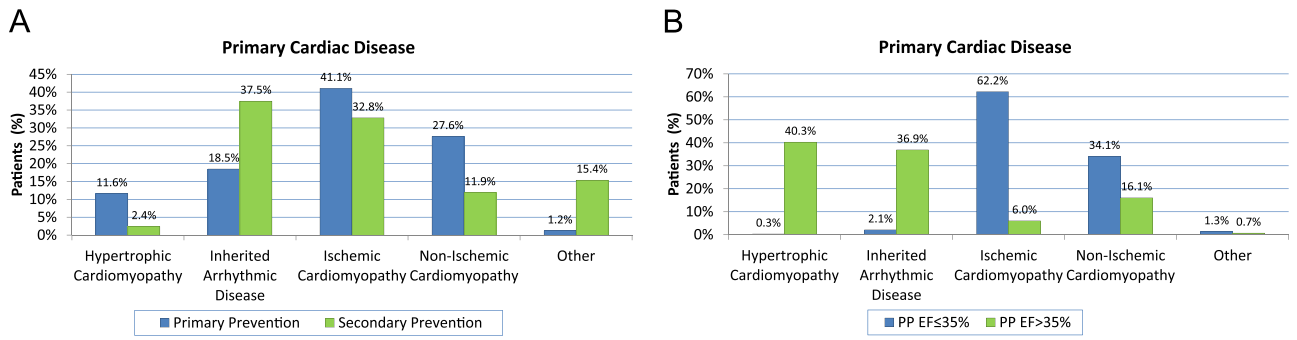



**Figure 1** **A:** Differences in clinical etiology of secondary prevention and primary prevention patients. **B:** Differences in clinical etiology of primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%) and with an ejection fraction >35% (PP EF ≥35%).

or an inherited arrhythmic disease (34%) and only 6% had ischemic disease, whereas those with a reduced EF had mostly ischemic (62%) or nonischemic (34%) cardiomyopathy (Figure 1B).

## Procedure- and device-related complications

Despite the differences in clinical characteristics, comorbidities, and underlying substrate, the incidence of device- and procedure-related complications was not significantly different for any of the groups, and the risk of clinical complications was generally low. The majority of clinical complications were documented within the first 90 days of the procedure in all groups. The most commonly reported clinical complication was due to device system infection (n = 17 total events in 15 patients [1.8%]).

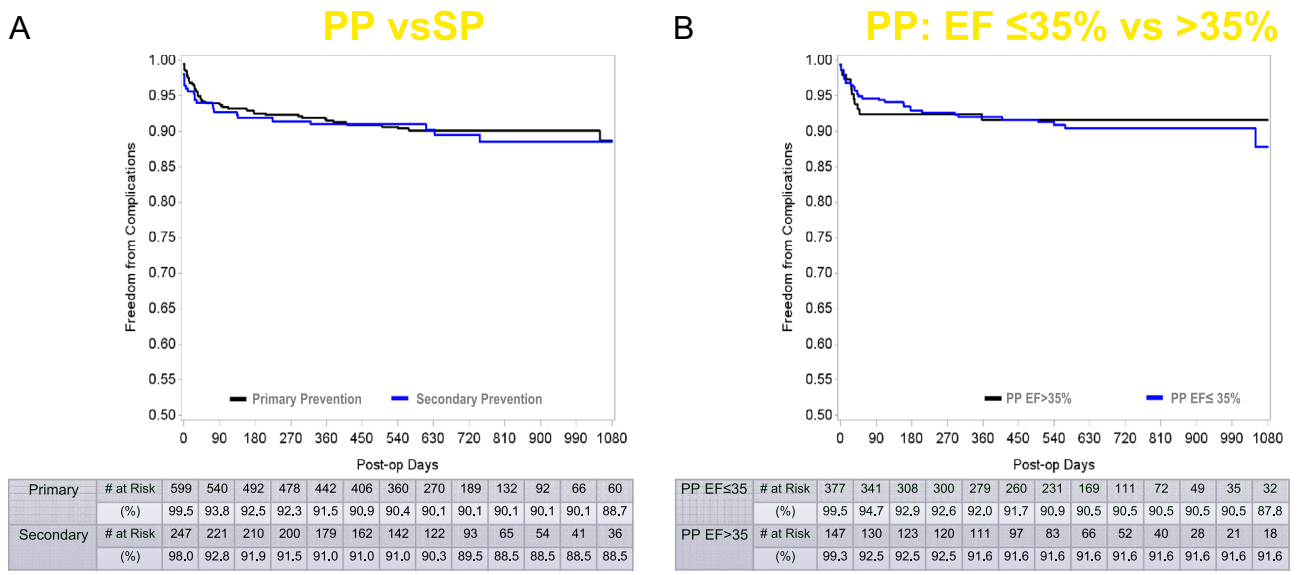
A total of 25 of 253 SP patients experienced a clinical complication during follow-up (9.9%) vs 57 of 603 (9.4%) PP patients (see Kaplan-Meier curves for freedom from complications in Figure 2). After 3 years of follow-up, the complication-free rate was 88.5% in SP patients vs 88.7% in PP patients (0.77; Figure 2A). PP EF ≤35% and PP EF >35% cohorts were also similar, with 3-year complication-free rates of 87.8% and 91.6%, respectively ($P$ = .76; Figure 2B).

## All-cause mortality

There was no significant difference in mortality between the 2 groups (Figure 3A). There were 26 total deaths (3.1%) documented over the duration of follow-up, with a rate of 2.3% (n = 6) in the SP group vs 3.3% (n = 20) in the PP group. There was a significant difference in mortality risk within the PP group; all 19 deaths occurred in the PP EF ≤35% cohort of patients (5.0% total mortality). The overall risk of death was also highest (3% annually) within this cohort compared to all others (Figure 3B). Only 1 death is reported to be arrhythmic, after a storm event, in a Loffler syndrome patient implanted for SP.[8,9]

## Delivery of appropriate therapy

Device programming did not differ significantly between SP and PP patients with respect to the use of the

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary | # at Risk | 599 | 540 | 492 | 478 | 442 | 406 | 360 | 270 | 189 | 132 | 92 | 66 | 60 |
| | (%) | 99.5 | 93.8 | 92.5 | 92.3 | 91.5 | 90.9 | 90.4 | 90.1 | 90.1 | 90.1 | 90.1 | 90.1 | 88.7 |
| Secondary | # at Risk | 247 | 221 | 210 | 200 | 179 | 162 | 142 | 122 | 93 | 65 | 54 | 41 | 36 |
| | (%) | 98.0 | 92.8 | 91.9 | 91.5 | 91.0 | 91.0 | 91.0 | 90.3 | 89.5 | 88.5 | 88.5 | 88.5 | 88.5 |

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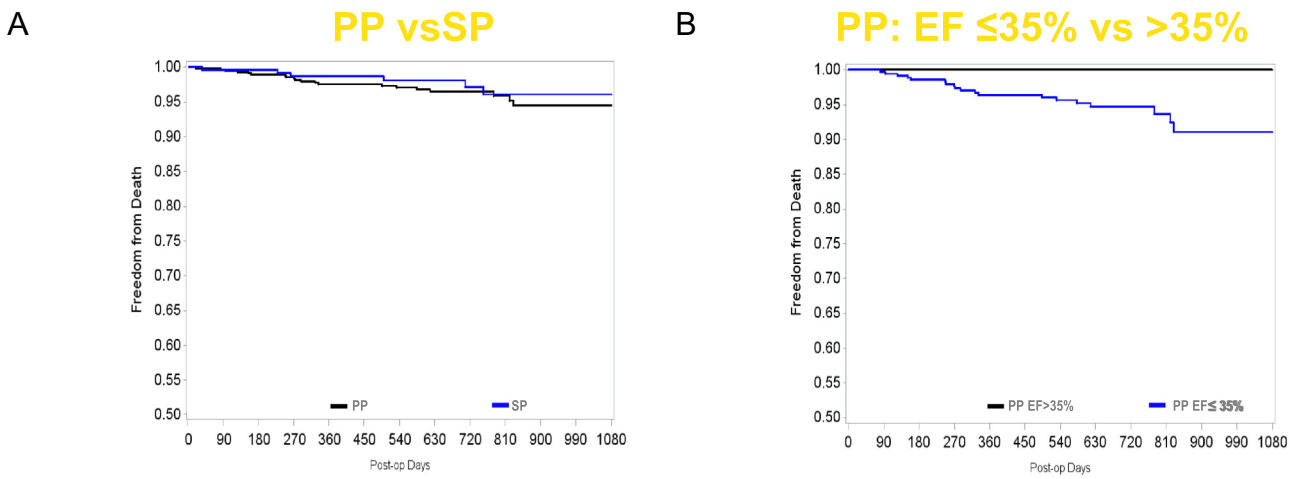
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PP EF≤35 | # at Risk | 377 | 341 | 308 | 300 | 279 | 260 | 231 | 169 | 111 | 72 | 49 | 35 | 32 |
| | (%) | 99.5 | 94.7 | 92.9 | 92.6 | 92.0 | 91.7 | 90.9 | 90.5 | 90.5 | 90.5 | 90.5 | 90.5 | 87.8 |
| PP EF>35 | # at Risk | 147 | 130 | 123 | 120 | 111 | 97 | 83 | 66 | 52 | 40 | 28 | 21 | 18 |
| | (%) | 99.3 | 92.5 | 92.5 | 92.5 | 91.6 | 91.6 | 91.6 | 91.6 | 91.6 | 91.6 | 91.6 | 91.6 | 91.6 |

**Figure 2** **A:** Kaplan-Meier curves demonstrating freedom from device- and procedure-related complications between primary and secondary prevention subcutaneous implantable defibrillator patients. **B:** Kaplan-Meier curves demonstrating freedom from device- and procedure-related complications between primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%) and with an ejection fraction >35% (PP EF >35%).

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary | # at Risk | 602 | 569 | 525 | 507 | 474 | 438 | 393 | 296 | 206 | 144 | 102 | 74 | 66 |
| | (%) | 100 | 99.7 | 98.9 | 98.2 | 97.6 | 97.6 | 97.1 | 96.5 | 96.5 | 95.9 | 94.5 | 94.5 | 94.5 |
| Secondary | # at Risk | 252 | 237 | 225 | 216 | 195 | 178 | 155 | 134 | 102 | 74 | 61 | 46 | 41 |
| | (%) | 100 | 99.6 | 99.6 | 98.7 | 98.7 | 98.7 | 98.1 | 98.1 | 97.2 | 96.1 | 96.1 | 96.1 | 96.1 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PP EF≤35 | # at Risk | 379 | 357 | 328 | 317 | 298 | 279 | 251 | 184 | 118 | 76 | 53 | 38 | 35 |
| | (%) | 100 | 99.7 | 98.6 | 97.4 | 96.4 | 96.4 | 95.7 | 94.8 | 94.8 | 93.7 | 91.0 | 91.0 | 91.0 |
| PP EF>35 | # at Risk | 148 | 139 | 131 | 128 | 119 | 103 | 89 | 71 | 56 | 44 | 31 | 23 | 19 |
| | (%) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Figure 3** **A:** Kaplan-Meier curves demonstrating freedom from mortality between primary and secondary prevention subcutaneous implantable defibrillator patients. **B:** Kaplan-Meier curves demonstrating freedom from mortality between primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%) and with an ejection fraction >35% (PP EF >35%).

conditional zone (dual-zone programming) or the programmed cutoff rates. However, far fewer devices were programmed with a shock zone higher than 220 beats/min (30.6%) in the PP EF ≤35% cohort than in the PP EF >35% cohort (56% for >220 beats/min). Also, a higher proportion of devices in the PP EF ≤35% cohort had cutoff rates programmed lower for both shock and conditional zones than in the PP EF >35% cohort (30.6% vs 18.6% for <220 beats/min and 77.5% vs 62.1% for <200 beats/min, respectively) (see Online Supplement Table 1).

There were no differences between any of the groups in the ability of the S-ICD to convert an induced ventricular arrhythmia (ventricular tachycardia/ventricular fibrillation [VT/VF]) at the time of implantation. Conversion success at 80 J was achieved in 98%–99% in all groups. Ninety-five percent of SP patients vs 94% of PP patients had at least 1 successful shock conversion at ≤65 J at the time of implantation. There was also no difference in conversion rate at ≤65 J within the 2 PP groups (94% for both EF cohorts). The overall conversion efficacy of the S-ICD for spontaneous episodes VT/VF did not differ in the cohorts. All (100%) discrete (defined as episodes not part of a storm event) spontaneous VT/VF arrhythmias were successfully converted to sinus rhythm, with ~90% converting on the first shock in both SP and PP patients (42 of 47 [89%] and 55 of 61 [90%], respectively). More details by type of arrhythmia are provided in Online Supplement Table 2. Only a single event of polymorphic ventricular tachycardia/VT in each group failed to convert within the defined episode; one of these terminated beyond the time limit of electrogram recording, while the other was prematurely declared by the device as having terminated. The device then immediately redetected and terminated the episode.

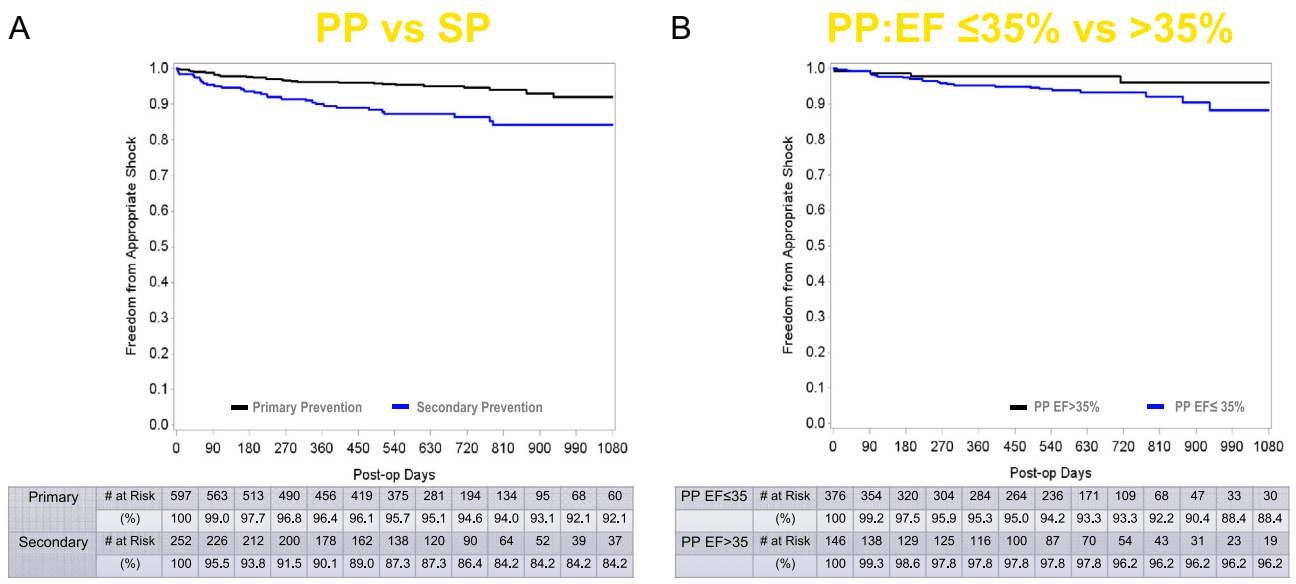
## Incidence of treated and untreated VT/VF

All rhythms meeting device-defined detection criteria for VT/VF that were logged in the device were included in the analysis of treated (appropriate therapy) vs untreated (self-terminating) episodes for the respective patient cohorts. There were significant differences in the need for appropriate therapy between the cohorts. The freedom from any appropriate VT/VF therapy was 84.2% in the SP group and 92.1% in the PP group (Kaplan-Meier estimate over 3 years; $P = .0001$; Figure 4A). In the PP subanalysis, freedom from appropriate therapy was 88.4% in the PP EF ≤35% cohort vs 96.2% in the PP EF >35% cohort (Kaplan-Meier estimate over 3 years; $P = .0724$; Figure 4B).

In PP patients, almost half of the VT/VF episodes recorded (48%) spontaneously terminated without the need for treatment, while this proportion was lower in the SP group (31%). In SP patients, VT/VF episodes were recorded in 16.3% of patients; 12.3% of patients received at least 1 appropriate therapy, 9.1% experienced at least 1 self-terminating VT/VF episode, and 5.2% had both types of episodes. In contrast, only 10.1% of PP patients had a VT/VF episode; 4.9% received at least 1 appropriate therapy, 7.5% had at least 1 self-terminating VT/VF episode, and 2.3% had both types of episodes. Within the PP group, both EF cohorts had a proportionately high rate of patients experiencing spontaneous episodes of VT/VF that self-terminated. In PP EF ≤35% patients, 6.4% received at least 1 appropriate therapy and 9.8% had at least 1 self-terminating VT/VF episode as compared with 2.1% and 2.7%, respectively, in PP EF >35% patients (Figure 5).

## Incidence of inappropriate therapy

In contrast to the need for appropriate therapy, there was no relationship between the incidence of inappropriate therapy and SP or PP indication (Figure 6A). There was also no

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary | # at Risk | 597 | 563 | 513 | 490 | 456 | 419 | 375 | 281 | 194 | 134 | 95 | 68 | 60 |
| | (%) | 100 | 99.0 | 97.7 | 96.8 | 96.4 | 96.1 | 95.7 | 95.1 | 94.6 | 94.0 | 93.1 | 92.1 | 92.1 |
| Secondary | # at Risk | 252 | 226 | 212 | 200 | 178 | 162 | 138 | 120 | 90 | 64 | 52 | 39 | 37 |
| | (%) | 100 | 95.5 | 93.8 | 91.5 | 90.1 | 89.0 | 87.3 | 87.3 | 86.4 | 84.2 | 84.2 | 84.2 | 84.2 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PP EF≤35 | # at Risk | 376 | 354 | 320 | 304 | 284 | 264 | 236 | 171 | 109 | 68 | 47 | 33 | 30 |
| | (%) | 100 | 99.2 | 97.5 | 95.9 | 95.3 | 95.0 | 94.2 | 93.3 | 93.3 | 92.2 | 90.4 | 88.4 | 88.4 |
| PP EF>35 | # at Risk | 146 | 138 | 129 | 125 | 116 | 100 | 87 | 70 | 54 | 43 | 31 | 23 | 19 |
| | (%) | 100 | 99.3 | 98.6 | 97.8 | 97.8 | 97.8 | 97.8 | 97.8 | 96.2 | 96.2 | 96.2 | 96.2 | 96.2 |

**Figure 4** **A:** Kaplan-Meier curves demonstrating freedom from appropriate shock therapy between primary and secondary prevention subcutaneous implantable defibrillator patients. **B:** Kaplan-Meier curves demonstrating freedom from appropriate shock between primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%) and with an ejection fraction >35% (PP EF >35%).

difference in inappropriate therapy based on EF in the PP cohort (Figure 6B). Overall, 12.3% of SP patients received at least 1 inappropriate shock over the duration of follow-up compared with 10.2% of PP patients. The groups were similar regardless of single- or dual-zone programming, as the incidence of inappropriate therapy occurring with single-zone programming (SP 18.0%; PP 18.0%; $P = 1.00$) was reduced in both groups by the presence of a second zone (SP 10.8%; PP 8.2%; $P = .27$). There was no significant difference in the incidence of inappropriate therapy between the 2 PP EF cohorts (10.1% for PP EF ≤35% vs 11.6% for PP EF >35%), nor in the respective patient subsets with devices programmed with dual zones (8.2% and 7.9%, respectively).

## Discussion

### Overview

The S-ICD has emerged as a viable alternative to the TV-ICD in varied patient populations.[7–10] In addition, the S-ICD may provide benefits to specific patient groups such as younger patients or TV-ICD patients requiring reimplantation after infection.[11,12] Whether the S-ICD performs comparably to the TV-ICD in the population traditionally referred for a PP indication remains to be determined. The population selected for S-ICD implantation to date has been younger, with a lower incidence of ischemic heart disease and a lower overall cardiovascular risk than does the traditional TV-ICD population. In the present analysis, the PP EF ≤35% cohort better resembles the patients included in historical TV-ICD trials, with a mean age of ~60 years, a mean EF of 26%, and a higher incidence of cardiac comorbidities. This analysis demonstrates consistent device-related outcomes, including procedural complications, shock efficacy, and frequency of inappropriate shock across all the groups evaluated. We did observe differences in rates of VT/VF and overall mortality, likely related to age and underlying etiology.

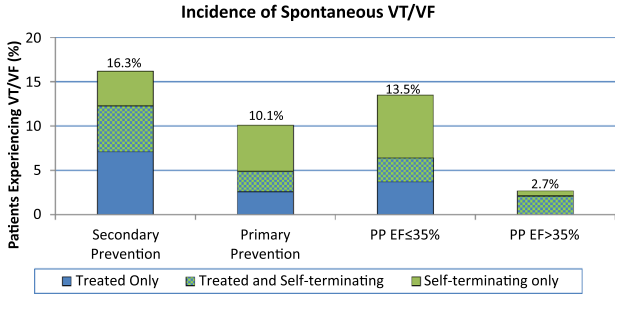
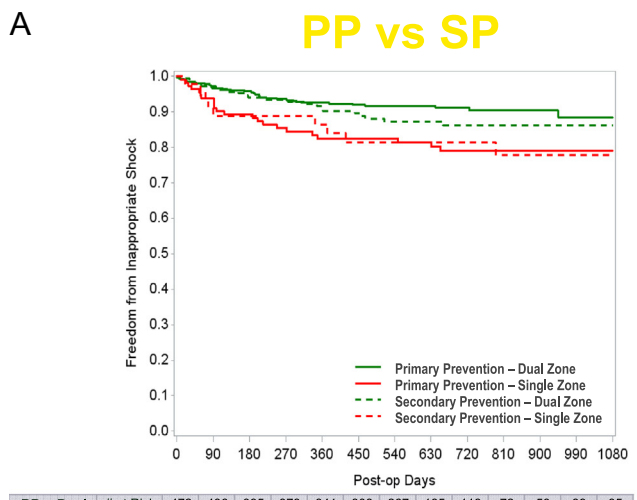


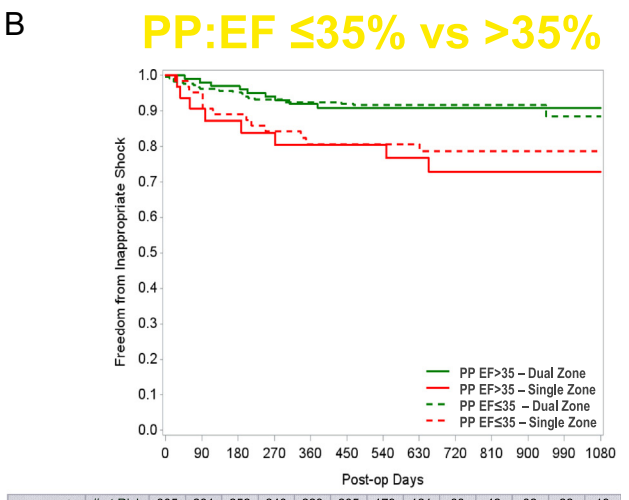

**Figure 5** Incidence of patients experiencing treated ventricular tachycardia/ventricular fibrillation (VT/VF) episodes, self-terminating VT/VF episodes, or both types of episodes in secondary prevention patients, primary prevention patients, primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%), and primary prevention patients with an ejection fraction >35% (PP EF >35%).

### Device- and procedure-related outcomes

Despite the significant demographic differences observed between the SP and PP patient populations (and within the PP population), there were no differences in complication rates between any of the evaluated cohorts. While SP patients had a prior TV-ICD explanted for reasons of infection 3 times more often than PP patients, we saw no difference in the proportion of patients that developed a postimplantation infection between the 2 groups. The consistency of complication rates between the 2 PP EF cohorts is also remarkable, considering that long-term complication rates in TV-ICD studies are generally higher in younger patients as well as in those patients with a lower EF.[13–16] The low rates observed in the younger PP EF >35% cohort provide support for S-ICD use in these patients.

The ability of the S-ICD to convert induced and spontaneous episodes of VT/VF did not differ between SP and PP

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PP – Dual Zone | # at Risk | 472 | 436 | 395 | 373 | 341 | 308 | 267 | 185 | 113 | 72 | 53 | 39 | 35 |
| | (%) | 99.8 | 96.7 | 95.8 | 93.6 | 92.6 | 92.0 | 91.7 | 91.7 | 91.2 | 90.4 | 90.4 | 88.5 | 88.5 |
| PP – Single Zone | # at Risk | 114 | 104 | 94 | 87 | 82 | 82 | 78 | 70 | 60 | 47 | 30 | 23 | 20 |
| | (%) | 100 | 93.8 | 89.3 | 85.5 | 82.5 | 82.5 | 82.5 | 81.4 | 79.1 | 79.1 | 79.1 | 79.1 | 79.1 |
| SP – Dual Zone | # at Risk | 198 | 181 | 165 | 157 | 137 | 124 | 102 | 85 | 59 | 40 | 32 | 23 | 20 |
| | (%) | 100 | 97.4 | 94.1 | 93.5 | 91.0 | 89.6 | 87.3 | 87.3 | 86.2 | 86.2 | 86.2 | 86.2 | 86.2 |
| SP- Single Zone | # at Risk | 46 | 40 | 38 | 38 | 35 | 31 | 30 | 29 | 27 | 19 | 14 | 11 | 9 |
| | (%) | 100 | 88.9 | 88.9 | 88.9 | 86.5 | 81.5 | 81.5 | 81.5 | 81.5 | 77.8 | 77.8 | 77.8 | 77.8 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PP EF≤ 35 Dual | # at Risk | 305 | 281 | 252 | 240 | 223 | 205 | 179 | 121 | 68 | 42 | 32 | 22 | 19 |
| | (%) | 99.7 | 96.3 | 95.3 | 93.4 | 92.6 | 92.1 | 91.7 | 91.7 | 91.7 | 91.7 | 91.7 | 88.5 | 88.5 |
| PP EF≤ 35 Single | # at Risk | 66 | 61 | 55 | 50 | 46 | 46 | 43 | 39 | 33 | 25 | 15 | 12 | 12 |
| | (%) | 100 | 95.4 | 89.1 | 84.2 | 80.7 | 80.7 | 80.7 | 80.7 | 78.7 | 78.7 | 78.7 | 78.7 | 78.7 |
| PP EF>35 Dual | # at Risk | 112 | 104 | 96 | 91 | 81 | 67 | 55 | 39 | 27 | 18 | 12 | 9 | 8 |
| | (%) | 100 | 98.1 | 97.2 | 94.1 | 92.0 | 90.9 | 90.9 | 90.9 | 90.9 | 90.9 | 90.9 | 90.9 | 90.9 |
| PP EF>35 Single | # at Risk | 32 | 28 | 26 | 24 | 23 | 23 | 22 | 20 | 18 | 16 | 11 | 9 | 7 |
| | (%) | 100 | 90.6 | 87.3 | 83.9 | 80.4 | 80.4 | 80.4 | 76.8 | 72.9 | 72.9 | 72.9 | 72.9 | 72.9 |

**Figure 6** **A**: Kaplan-Meier curves demonstrating freedom from inappropriate shocks between secondary and primary prevention subcutaneous implantable defibrillator patients. **B:** Kaplan-Meier curves demonstrating freedom from inappropriate shocks between primary prevention patients with an ejection fraction ≤35% (PP EF ≤35%) and with an ejection fraction >35% (PP EF >35%).

groups, nor within each of the 2 PP subgroups. Almost 99% of patients in all groups had a successfully converted induced arrhythmia at the time of implantation. Likewise, conversion of discrete spontaneous episodes of VT/VF was consistently 100%, and conversion upon first shock was approximately 90% in each group. These findings are consistent with data from large TV-ICD PP trials such as Sudden Cardiac Death in Heart Failure Trial,[4] which documented an 86% first shock conversion rate, and more recent broad inclusion studies of both PP and SP patients, such as the Shockless IMPLant Evaluation trial,[17] where first shock efficacy was 89% in the defibrillation threshold testing arm and 92% in the no–defibrillation threshold testing arm.

Higher risk of inappropriate therapy has been documented in younger patients[18,19] and those with congenital arrhythmic disorders[20] and hypertrophic cardiomyopathies.[21,22] In this study of S-ICD patients, the incidence of inappropriate therapy was not linked to indication or EF level. There were no differences in overall rates seen between SP and PP cohorts or within the PP subanalysis cohorts, even in the younger high-risk PP EF >35% cohort. A clear impact of device programming was, however, demonstrated with patients programmed to a dual-zone configuration, having a substantially lower incidence of inappropriate therapy as previously described.[8,23]

## Treatment of VT/VF and mortality

It is known that PP patients, in general, have a lower risk of receiving an appropriate therapy than do SP patients.[24,25] The present analysis demonstrates similar findings, with PP patients overall experiencing lower numbers of VT/VF episodes and being half as likely to receive an appropriate therapy, despite a lower use of antiarrhythmic drugs (4.7% vs 21.2% in the IDE study). Since the S-ICD does not provide antitachycardia pacing (ATP), the rates of treated vs untreated VT/VF episodes are of particular interest. This analysis is the first to examine the incidence of VT/VF at an episode level. It shows that as a result of the S-ICD detection and treatment algorithms, there are substantial numbers of episodes that are allowed to self-terminate, avoiding delivery of unnecessary therapy. Interestingly, approximately half of the appropriately sensed VT/VF episodes in the PP group were self-terminating as compared with only 30% in the SP group. Over the mean follow-up duration of 22 months, 9.8% of PP EF ≤35% patients had at least 1 episode of VT/VF that was allowed to self-terminate, with no indication of an associated increase in arrhythmic mortality.

The resulting incidence of delivered appropriate shock in this cohort was 3.9% annually, similar to the incidence rate of shock in the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy trial[26] despite its use of ATP and modern programming (conventional programming arm 4%; high rate programming arm 4%; delayed therapy arm 3%), although not matched for etiologies.

The present study provides further insight into the low mortality rates previously reported from these S-ICD studies, given that the younger age and varied etiology have made comparisons to other ICD studies difficult. In the present analysis, the overall mortality rate during follow-up was low (a total of 26 deaths or 3.0% of the total population over a median follow-up duration of 644 days), and despite the higher incidence of appropriate therapy in the SP group, there was no indication of an increased risk of death in that group. The highest mortality rate

(3.0% annual risk) was in fact documented within the PP EF ≤35% patient cohort, which is most likely related to the fact that these patients were significantly older and sicker than patients in other cohorts. An important observation from our analysis of mortality demonstrated that in the PP EF >35% group no deaths were reported during follow-up in 147 patients. With low complications and high conversion rates, these data support S-ICD use, particularly in these patients, and indeed this has been a population commonly associated with the S-ICD. Even so, the higher mortality rate of the older, sicker PP patients with an EF ≤35% was similar to that documented in the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy trial (annual Kaplan-Meier estimate per arm 5%, 2%, and 4%)[26]. Further insight into mortality rates in these more standard PP ICD patients can be gained from the Défibrillateur Automatique Implantable en Prévention Primaire registry,[14] wherein the researchers reported PP outcomes by age: mortality of 3.1% in patients aged 18–59 years (mean 51 years), 5.7% in patients aged 60–74 years (mean 67.6 years), and 7.6% in patients aged ≥74 years (mean 77.8 years). In our study, PP EF ≤35% patients implanted with an S-ICD had a mean age of 57 years and did well in comparison to a low annual mortality of 3.0%. The controlled pivotal studies of ICD therapy for PP show a similar age affect, although slightly higher overall rates. A recent meta-analysis[27] of mortality rates from pivotal PP trials reported that patients with a reduced EF and younger than 55 years died at a rate of 8.1% over 2.6 years of follow-up (3.2% annually) and patients aged 55–64 years died at a rate of 18.4% over 2.6 years (7.1% annually). Given these studies are not matched for etiologies and other important factors, randomized trials designed to study morbidity and mortality will be needed to determine whether S-ICD use has a potential survival benefit in comparison to TV-ICD use.

### Study limitations

The retrospective nature of the data leads to certain limitations in this analysis, and the differences in the study design and follow-up between the US IDE study and EFFORTLESS Registry are acknowledged. The patients included in these S-ICD studies do not represent the total ICD population because of S-ICD exclusion criteria and other selection bias. Reduced vs preserved EF group analyses do not include the 12% of PP patients with missing EF measures, primarily comprising younger patients with inherited diseases and fewer comorbidities, which may limit the understanding of the preserved EF cohort in this analysis. As expected, demographic characteristics and medical history vary significantly between groups, including a significantly higher percentage of SP patients with a history of ICD device implantation than of PP patients. Antiarrhythmic drug use was higher for SP in the IDE study and unknown in the EFFORTLESS study, and differences in the incidence of treated and untreated VT/VF between groups may be caused, in part, by differences in antiarrhythmic drug use. Mortality comparisons are limited because the mode of death was not available, nor was the mortality rate of patients withdrawn from the study. Conclusions about TV-ICD comparisons discussed are limited, as the overall patient population varies from TV-ICD trials referenced, and it cannot be assumed that longer-term outcomes will follow a similar trajectory as in TV-ICD patients. Furthermore, longer follow-up beyond the current 2 years is needed to understand long-term benefits and drawbacks of S-ICD therapy.

## Conclusion

The S-ICD performs well in protecting both PP and SP patients from sudden cardiac death, including PP patients with EF values of >35% or ≤35%. In the S-ICD implanted population studied, there were no significant differences in device performance between groups relative to device- and procedure-related complication rates, inappropriate shock rates, or conversion efficacy. Mortality rates were low and well aligned with age and comorbidity differences observed between the studied groups. In PP patients, the incidence of VT/VF episodes was markedly lower than that in SP patients, and episodes were more often self-terminating than requiring a shock. This study supports S-ICD consideration in SP patients without a history of bradycardia or ATP-terminable monomorphic VT events and in all PP patients not requiring pacing.

## Acknowledgments

We acknowledge the large contribution of investigators and institutions participating in the EFFORTLESS S-ICD Registry and S-ICD IDE study. We also thank Helen Reeve, PhD, for writing assistance.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.11.025.

## References

1. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576–1583.
2. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Sakensa S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933–1940.
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML, Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
4. Bardy GH, Lee KL, Mark DB, et al. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
5. Kleeman T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation 2007;115:2474–2480.
6. Maytin M, Wilkoff BL, Brunner M, et al. Multicenter experience with extraction of the Riata/Riata ST ICD lead. Heart Rhythm 2014;11:S1547–S1577.

7. Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W, Burke MC. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation 2013; 128:944–953.
8. Burke MC, Gold MR, Knight BP, et al. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol 2015;65: 1605–1615.
9. Lambiase PD, Barr C, Theuns DA, et al. EFFORTLESS Investigators. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J 2014;35:1657–1665.
10. Pedersen SS, Lambiase P, Boersma LV, Murgatroyd F, Johansen JB, Reeve H, Stuart AG, Adragao P, Theuns DA. Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD: design and rationale of the EFFORTLESS S-ICD Registry. Pacing Clin Electrophysiol 2012;35:574–579.
11. Lambiase PD, Gold MR, Hood M, Boersma L, Theuns DA, Burke MC, Weiss R, Russo AM, Kääb S, Knight BP. Evaluation of subcutaneous ICD early performance in hypertrophic cardiomyopathy from the pooled EFFORTLESS and IDE cohorts. Heart Rhythm 2016;13:1066–1074.
12. Boersma L, Burke Mc, Neuzil P, Lambiase P, Friehling T, Theuns DA, Garcia F, Carter N, Stivland T, Weiss R. Infection and mortality after implantation of the subcutaneous ICD follwoing transvenous ICD extraction. Heart Rhythm 2016;13:157–164.
13. Morrison TB, Rea RF, Hodge DO, Crusan D, Koestler C, Asirvatham SJ, Bradley D, Shen WK, Munger TM, Hammill SC, Friedman PA. Risk factors for implantable defibrillator lead fracture in a recalled and a nonrecalled lead. J Cardiovasc Electrophysiol 2010;2:671–677.
14. Fauchier L, Marijon E, Defaye P, et al. DAI-PP Investigators. Effect of age on survival and causes of death after primary prevention implantable cardioverter-defibrillator implantation. Am J Cardiol 2015;115:1415–1422.
15. Cohen TJ, Asheld WJ, Germano J, Islam S, Patel D. A comparative study of defibrillator leads at a large-volume implanting hospital: results from the Pacemaker and Implantable Defibrillator Leads Survival Study ("PAIDLESS"). J Invasive Cardiol 2015;27:292–300.
16. Ranasinghe I, Parzynski CS, Freeman JV, et al. Long-term risk for device-related complications and reoperations after implantable cardioverter-defibrillator implantation: an observational cohort study [published online ahead of print May 3, 2016]. Ann Intern Med. ⟨http://dx.doi.org/10.7326/M15-2732⟩.
17. Healey JS, Hohnloser SH, Glikson M, et al. Shockless IMPLant Evaluation (SIMPLE) Investigators. Cardioverter defibrillator implantation without induction of ventricular fibrillation: a single-blind, non-inferiority, randomised controlled trial (SIMPLE). Lancet 2015;385:785–791.
18. Biton Y, Huang DT, Goldenberg I, Rosero S, Moss AJ, Kutyifa V, McNitt S, Strasberg B, Zareba W, Barsheshet A. Relationship between age and inappropriate implantable cardioverter-defibrillator therapy in MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy). Heart Rhythm 2015;19:S1547–S5271.
19. van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ, Schalij MJ. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. J Am Coll Cardiol 2011;57:556–562.
20. Olde Nordkamp LR, Postema PG, Knops RE, van Dijk N, Limpens J, Wilde AA, de Groot JR. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: a systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm 2016;13: 443–454.
21. Magnusson P, Gadler F, Liv P, Mörner S. Hypertrophic cardiomyopathy and implantable defibrillators in Sweden: inappropriate shocks and complications requiring surgery. J Cardiovasc Electrophysiol 2015;26:1088–1094.
22. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405–412.
23. Gold MR, Weiss R, Theuns DA, Smith W, Leon A, Knight BP, Carter N, Husby M, Burke MC. Use of a discrimination algorithm to reduce inappropriate shocks with a subcutaneous implantable cardioverter-defibrillator. Heart Rhythm 2014;11:1352–1358.
24. Yung D, Birnie D, Dorian P, Healey JS, Simpson CS, Crystal E, Krahn AD, Khaykin Y, Cameron D, Chen Z, Lee DS. Survival after implantable cardioverter-defibrillator implantation in the elderly. Circulation 2013;127: 2383–2392.
25. Sabbag A, Suleiman M, Laish-Farkash A, Samania N, Kazatsker M, Goldenberg I, Glikson M, Beinart R, Israeli Working Group of Pacing and Electrophysiology. Contemporary rates of appropriate shock therapy in patients who receive implantable device therapy in a real-world setting: from the Israeli ICD Registry. Heart Rhythm 2015;12:2426–2433.
26. Moss AJ, Schuger C, Beck CA, et al. MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275–2283.
27. Hess PL, Al-Khatib SM, Han JY, et al. Survival benefit of the primary prevention implantable cardioverter-defibrillator among older patients: does age matter? An analysis of pooled data from 5 clinical trials. Circ Cardiovasc Qual Outcomes 2015;8:179–186.