First introduced to clinical practice in 1980,1 the implantable cardioverter-defibrillator (ICD) improves survival in patients at high risk for sudden cardiac death.2–5 Randomized, multicenter studies have shown a relative risk reduction in total mortality of up to 54% and an arrhythmic mortality reduction of 50% to 70%. Offsetting this mortality benefit, however, are significant acute and chronic morbidities associated with the use of transvenous leads.6–9 Procedure-related transvenous lead complications include major events such as lead dislodgement, pneumothorax, cardiac perforation, pericardial effusion, and cardiac tamponade. Chronic transvenous lead complications include systemic infections as well as insulation breaches and conductor coil breaks, which can cause inappropriate shocks and physical trauma to the heart and may render ICD therapy unavailable. The lead is the most common failure mechanism for a transvenous ICD system, and patients often outlive the useful life of the lead.9–11

Background—The most frequent complications associated with implantable cardioverter-defibrillators (ICDs) involve the transvenous leads. A subcutaneous implantable cardioverter-defibrillator (S-ICD) has been developed as an alternative system. This study evaluated the safety and effectiveness of the S-ICD System (Cameron Health/Boston Scientific) for the treatment of life-threatening ventricular arrhythmias (ventricular tachycardia/ventricular fibrillation).

Methods and Results—This prospective, nonrandomized, multicenter trial included adult patients with a standard indication for an ICD, who neither required pacing nor had documented pace-terminable ventricular tachycardia. The primary safety end point was the 180-day S-ICD System complication-free rate compared with a prespecified performance goal of 79%. The primary effectiveness end point was the induced ventricular fibrillation conversion rate compared with a prespecified performance goal of 88%, with success defined as 2 consecutive ventricular fibrillation conversions of 4 attempts. Detection and conversion of spontaneous episodes were also evaluated. Device implantation was attempted in 321 of 330 enrolled patients, and 314 patients underwent successful implantation. The cohort was followed for a mean duration of 11 months. The study population was 74% male with a mean age of 52±16 years and mean left ventricular ejection fraction of 36±16%. A previous transvenous ICD had been implanted in 13%. Both primary end points were met: the 180-day system complication-free rate was 99%, and sensitivity analysis of the acute ventricular fibrillation conversion rate was >90% in the entire cohort. There were 38 discrete spontaneous episodes of ventricular tachycardia/ventricular fibrillation recorded in 21 patients (6.7%), all of which successfully converted. Forty-one patients (13.1%) received an inappropriate shock.

Conclusions—The findings support the efficacy and safety of the S-ICD System for the treatment of life-threatening ventricular arrhythmias.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01064076.
(Circulation. 2013;128:944-953.)

Key Words: defibrillators, implantable ■ heart arrest ■ tachycardia

The long-term complications associated with the transvenous ICD leads have been a rationale to develop a totally subcutaneous ICD (S-ICD). The S-ICD System (Cameron Health/Boston Scientific) senses, detects, and treats malignant ventricular tachycardia (VT)/ventricular fibrillation (VF) but leaves the heart and vasculature untouched. The subcutaneous pulse generator and electrode are placed extrathoracically, and no part of the system is exposed to most of the risks associated with the use of transvenous leads.6–9 Procedure-related transvenous lead complications include major events such as lead dislodgement, pneumothorax, cardiac perforation, pericardial effusion, and cardiac tamponade. Chronic transvenous lead complications include systemic infections as well as insulation breaches and conductor coil breaks, which can cause inappropriate shocks and physical trauma to the heart and may render ICD therapy unavailable. The lead is the most common failure mechanism for a transvenous ICD system, and patients often outlive the useful life of the lead.9–11

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with an intravascular location or mechanical stresses caused by cardiac contractions. Avoiding the intravascular space has its own limitations because the first-generation S-ICD lacks the ability to provide antitachycardia pacing, advanced diagnostics, or radiofrequency interrogation with remote monitoring and as such is meant to be an addition to the tools available to combat sudden death. The initial feasibility, safety, and effectiveness of subcutaneous defibrillation were established in earlier human studies of the S-ICD System.12,13 The present study sought to establish the safety and effectiveness of the S-ICD System for the treatment of life-threatening VT/VF in a larger patient cohort.

Methods

This was a prospective, nonrandomized, multicenter, observational study that used objective performance criteria sanctioned and conducted in cooperation with the US Food and Drug Administration.

Patient Selection

Patients were enrolled if they were aged ≥18 years and had a guide-line indication for ICD implantation.14 Patients then were required to pass a preoperative surface ECG screening test. The screening ECG is a modified trichannel surface ECG that mimics the sensing vectors of the S-ICD System.15 The device uses 1 of 3 nearly orthogonal and unique sensing vectors, selected noninvasively.16 The electrodes combine to encompass the majority of the left ventricle to provide the largest proportion of R wave to T wave.16,17 Once the 3 vector ECG tracings were obtained, a template tool was then used to assess the ratio of R wave to T wave for appropriate signal characteristics and relationships across the 3 sensing vectors used by the S-ICD System.

Patients were excluded from enrollment if the subject’s circumstances limited his or her ability to comply with the study requirements. Pregnant or lactating as well as premenopausal women who were unwilling to use adequate birth control for the duration of the study were excluded. Participation in any other investigational study was discouraged. Patients with a life expectancy of <1 year were not enrolled. Patients with documented spontaneous and frequently recurring VT reliably terminated with antitachycardia pacing were excluded unless the patient was not a candidate for a transvenous ICD system. Patients with existing epicardial patches or subcutaneous electrodes in the left thoracic space were also excluded. Patients with unipolar pacemakers or pacing devices that revert to unipolar pacing could not participate in the study. Patients with an estimated glomerular filtration rate ≤29 mL/min per 1.73 m² were excluded.

Study Design and Coprimary End Points

The study was designed to enroll 330 patients at multiple centers with 33 sites in the United States, New Zealand, the Netherlands, and the United Kingdom. It was performed under an investigational device exemption (G090013) granted by the US Food and Drug Administration and is registered on http://www.clinicaltrials.gov. The protocol and consent forms were approved by the local institutional review boards. All patients gave written consent for participation. The primary safety end point was the 180-day S-ICD System (type I) complication-free rate, which was compared with a prespecified performance goal of 79%. All reported complications (adverse clinical events that required an invasive intervention) were categorized by a clinical events committee into 4 categories on the basis of the follow-up definition: type I, caused by the S-ICD System; type II, caused by the S-ICD System user’s manual or labeling of the S-ICD System; type III, not caused by the S-ICD System but would not have occurred in the absence of the implanted S-ICD System; and type IV, caused by a change in the patient’s condition.

Although the safety end point included only type I complications, an additional analysis of all complications related to any aspect of the S-ICD System, labeling, or implantation procedures (type I through III complications) was performed. To assess the impact of missing safety end point observations, a sensitivity analysis was performed by imputing as complications all study exits that occurred before 180 days after implantation and recalculating the primary safety end point.

The primary effectiveness end point was the acute induced VF conversion rate at the time of device implantation compared with a performance goal of 88%. Defibrillation testing induced VF with the use of 50-Hz transthoracic pacing under moderate to deep sedation or general anesthesia. Detection was performed automatically by the device, in which a successful conversion test required 2 consecutive VF conversions at 65 J in either shock vector, within a maximum of 4 VF conversion attempts with the use of the same polarity. A sensitivity analysis was performed in which incomplete effectiveness protocol testing attempts at acute implantation were imputed as failures to assess the potential impact of missing end point observations. These incomplete effectiveness data resulted from failure to complete the full testing protocol because of clinical concerns or inability to induce VF.

Secondary Study Objectives

Predetermined secondary objectives were part of this study and included procedural implantation of the S-ICD System without medical imaging, time to therapy for induced episodes during acute conversion testing, incidence and appropriateness of postshock pacing, postconversion creatinine and creatine phosphokinase levels, spontaneous arrhythmia episodes, and chronic conversion of induced VF.

Spontaneous Episode Categories

For analysis, spontaneous VT/VF episodes were subdivided into 2 classes: (1) discrete episodes and (2) VT/VF storm episodes that comprised ≥3 treated VT/VF episodes within 24 hours in the same patient.18 Analyzing these groups separately prevents the device conversion efficacy rates from being disproportionately affected by a small number of patients who experienced multiple, temporally clustered events.

Chronic Conversion Testing

Chronic conversion testing (≥150 days after implantation) was part of the secondary end points that were included in the analysis to examine postimplantation effectiveness. This substudy was conducted in 78 patients enrolled at 18 centers. A separate informed consent form was signed by eligible patients before testing. Induction was the same as described previously, and a single 65-J shock was delivered in the chronically programmed vector. If this shock failed, then the investigators could allow the device to deliver its normal maximum shock strength of 80 J or instigate rescue with external defibrillation at their discretion. In the case of failure to achieve conversion with 65 J in the chronic polarity, the protocol required that the polarity be reversed and induction testing be repeated in the opposite polarity. A chronic conversion test episode was deemed to be nonevaluable when testing was stopped before the exhaustion of all conversion attempts in either polarity.

Patient Follow-Up

Enrolled patients who were implanted with an S-ICD System were followed up until hospital discharge and at 30, 90, and 180 days after implantation. After the 180-day follow-up visit, patients were followed semiannually until study closure. Device interrogations were performed at each scheduled visit, and chest x-rays were performed after implantation, at each follow-up visit through 1 year, and annually thereafter. The S-ICD System was also interrogated if a patient received shocks or if the clinical status of the patient changed. Patients who participated in the chronic conversion substudy also had their device interrogated at the time of their VF/VT induction.

A field advisory was issued during the study after a single premature battery depletion identified a battery manufacturing issue.
Devices potentially affected by the field advisory were identified by batch, and monitoring was undertaken by implanting centers. There were no morbidity or mortal clinical outcomes as a result of this battery manufacturing field advisory. Pulse generator changes occurred as clinically indicated on the basis of the elective replacement indicator and are included in the safety analysis. This manufacturing issue was resolved before US Food and Drug Administration approval of the device system.

Statistical Analysis
The target sample size was 330 patients based on the number of patients needed to provide 80% power for each coprimary end point and assumed 10% patient attrition. The coprimary end points for safety and effectiveness were tested in hierarchical sequence to maintain a familywise significance level of 0.025 (1-sided) with 80% power. The safety end point was tested first for superiority to the safety performance goal (79%). The primary safety end point was also analyzed with the use of Kaplan–Meier estimates calculated as a function of time from implantation with corresponding 95% confidence intervals based on the Peto estimate of the standard error. The effectiveness end point was tested for superiority to the effectiveness performance goal (88%), for which superiority was assessed with the use of the definition of conversion success described previously. Descriptive statistics are reported as mean±SD unless indicated otherwise. All statistical analyses were performed and independently validated with the use of the SAS Enterprise Guide, version 4.3 (SAS 9.3).

Results
Enrollment Cohort
Of the 330 enrollments, 321 underwent an implantation procedure, and 9 were withdrawn before the implantation procedure. Of 321 implantation attempts, 314 patients were discharged with the device, and 293 remained active in the study at the time of end point analysis. A total of 276 patients (87.9%) had a follow-up duration of ≥180 days. There were 38 patients with follow-up duration <180 days: 28 (8.9%) had their last visit before 180 days, 7 (2.2%) withdrew from the study, and 3 (1.0%) died. During the entire follow-up, 21 patients had undergone successful device implantation but discontinued participation: 11 patients were withdrawn subsequent to S-ICD System explantation, 8 patients died, 1 patient with limited life expectancy withdrew consent and requested that the S-ICD System be turned off, and 1 patient with congenital heart disease was withdrawn because of a heart transplant (Figure 1).

Baseline patient characteristics, medications, and indications for the 321 patients with an attempted implantation of the S-ICD System are summarized in Table 1. The mean age of the patients was 52±16 years (range, 18–85 years). The majority (74%) were male. Comorbid conditions included congestive heart failure, hypertension, ischemic heart disease, diabetes mellitus, and atrial fibrillation. Notably, 13% of patients had a previous transvenous ICD system that was extracted because of infection, vascular injury/clot, or device/lead failure. The majority of study patients (79%) had a primary prevention indication, similar to the proportion of patients with a primary prevention indication in the American College of Cardiology National Cardiovascular Data Registry ICD Registry.18 Moderate to severe left ventricular dysfunction was well represented, and the mean

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**Figure 1.** Patient flow chart for S-ICD System Investigational Device Exemption Clinical Trial. S-ICD indicates subcutaneous implantable cardioverter-defibrillator; and VF, ventricular fibrillation.
The mean follow-up duration of implanted patients was 330 days, with a range of 17 to 715 days (median=330 days), for a cumulative duration of 3456 months.

**Implantation Procedure**

Medical imaging was used in 17 cases to assess the position of the system after difficulty in either inducing VF or defibrillating the patient during acute conversion testing. In only 3 (0.9%) of the cases was fluoroscopy used for >1 minute. Creatinine and creatine phosphokinase were collected from the first 50 patients 36 hours before and 24±4 hours after acute conversion testing. Preconversion and postconversion testing creatinine values were in the normal range, and no increase in the mean postconversion testing creatinine level was observed (1.1±0.3 mg/dL before and 1.1±0.4 mg/dL after testing; P=0.11). A mild and expected increase in creatine phosphokinase was observed after conversion testing (135±148 U/L before and 400±422 U/L after testing; P<0.0001) without clinical consequence.

**Primary Safety End Point**

The primary safety objective was achieved successfully. The 180-day type I complication-free rate was 99.0% with a 95% lower confidence limit (2-sided) of 97.9%, well above the performance goal of 79%. A sensitivity analysis was performed in the safety cohort and included all device-related (type I), labeling-related (type II), and procedure-related (type III) complications. The 180-day type I through III complication-free rate was 92.1% with a lower confidence limit of 88.9%, once again above the performance goal (Figure 2). There were no cases of lead failures, endocarditis or bacteremia, tamponade, cardiac perforation, pneumothorax, hemothorax, or subclavian vein occlusion associated with the S-ICD System. There was no electrode or pulse generator movement in 99% of implanted patients throughout the follow-up period. An additional sensitivity analysis showed that the safety performance objective was achieved even when all study exits before 180 days were imputed as complications.

**Primary Effectiveness End Point**

The primary effectiveness objective was also achieved successfully. The primary effectiveness cohort consisted of 304 patients who completed the full testing protocol, providing evaluable conversion tests according to the protocol definitions. As shown in Table 2, the conversion rate in the evaluable conversion tests demonstrated 100% acute conversion with a 95% lower confidence limit of 98.8%, far exceeding the prespecified objective performance goal of ≥88%. In a total of 265 patients (82.8%), acute conversion of VF was

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**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.9±15.5</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>74.1</td>
</tr>
<tr>
<td>White, %</td>
<td>64.8</td>
</tr>
<tr>
<td>Black, %</td>
<td>23.7</td>
</tr>
<tr>
<td>Primary prevention indication, %</td>
<td>79.4</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.7±7.2</td>
</tr>
<tr>
<td>Ejection fraction, % (n=299)</td>
<td>36.1±15.9</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>61.4</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>15.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>58.3</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>41.4</td>
</tr>
<tr>
<td>Previous (transvenous) ICD, %</td>
<td>13.4</td>
</tr>
<tr>
<td>Previous pacemaker, %</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Values are mean±SD or percentage; n=321 patients with an implantation attempt unless indicated otherwise. ICD indicates implantable cardioverter-defibrillator.

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**Figure 2.** Kaplan–Meier (K-M) analysis and lower confidence bound (LCB) for freedom from device-, labeling-, and procedure-related complications (n=321). The 92.1% estimated 180-day complication-free rate for the study compares favorably with the 79% objective performance goal.
successful on consecutive shocks 1 and 2 in the first polarity tested after the final position was achieved. Not included in the primary analysis are 16 patients deemed nonevaluable and 1 patient who did not undergo any testing because of persistent left ventricular thrombus. In most of the 16 nonevaluable tests, the testing protocol was stopped short of completion because of clinical circumstances precluding continued testing (eg, hemodynamic instability, sudden change in respiratory status, and inability to induce or reliably convert VF). Ten of the 16 nonevaluable patients, including 1 patient not tested because of left ventricular thrombus, remained with the device and were followed up for the safety end point, whereas 7 patients were not implanted with the S-ICD System and were withdrawn from the study. A sensitivity analysis was performed to assess the impact of excluding all 17 patients who did not complete VF conversion testing. When all 17 excluded tests were imputed as failures, the acute VF conversion rate had a success rate of 94.7% with a 95% lower confidence limit of 91.7%, which demonstrates that the missing patients do not affect the conclusions that can be drawn when compared with the performance goal of 88%.

Deaths
There were a total of 8 deaths (2.5%) during the study. Five were noncardiac, nonsudden, and unrelated to the implantation procedure. One patient died unwitnessed at home; interrogation of the device showed a successfully treated episode of a single ventricular arrhythmia episode. One unwitnessed, presumed sudden death did not have a final device interrogation because the center was not notified until 2 months after the patient’s death. This patient was diagnosed with atypical pneumonia and hypoxia before his death. The last death occurred outside the United States, and repeated attempts to contact the family were unsuccessful. The cause of death remains unknown.

Spontaneous Episodes Treated
A total of 119 spontaneous VT/VF episodes in 21 patients were treated by the S-ICD System (38 discrete VT/VF episodes and 81 occurring during VT/VF storms). The 38 discrete VT/VF episodes comprise 22 episodes of monomorphic VT (13 patients) and 16 episodes of polymorphic VT or VF (11 patients). A total of 43 appropriate shocks were delivered in these 38 discrete VT/VF episodes, all of which terminated the arrhythmia. The S-ICD System converted 35 of 38 episodes (92.1%) on the first shock and 37 of 38 (97.4%) with 1 or more shocks. The single episode not converted by the S-ICD System was an episode of monomorphic VT that terminated spontaneously while the device was charging to deliver a second shock; of note, this patient had another episode ≈1 month later that was successfully terminated by the initial S-ICD System shock.

There were 81 device episodes associated with 4 VT/VF storm events in 2 patients. Forty stored VT/VF storm episodes were documented to have successful conversion by the S-ICD System. Forty-one episodes exceeded the episode storage capacity of the S-ICD, in which an investigator of the clinical trial witnessed the events in the emergency department and reported normal function and defibrillation of the 41 unstored episodes by the S-ICD System. Three of the 4 VT/VF storms were ultimately terminated by the S-ICD System, and 1 storm terminated after the emergency department team shocked the patient externally while the S-ICD was charging to deliver the first shock. There were no known arrhythmic deaths in the study.

Chronic Conversion Substudy
Of the 78 patients who underwent induced chronic conversion testing, 75 results were evaluable, and 3 results were not evaluable because the second polarity was not tested after a failed 65-J shock, as required by the protocol. In all 3 nonevaluable tests, a failed 65-J shock was followed by a successful 80-J S-ICD System shock, and the investigator elected not to test the opposite polarity at 65 J. Of the 75 evaluable results, 72 (96%) were successful, and 3 (4%) were unsuccessful at 65 J. In the 3 unsuccessful 65-J tests, the S-ICD System was successful in detecting and converting VF with a subsequent 80-J shock, which is the only energy level delivered in an out-of-hospital setting.

Induced VT/VF Detection Sensitivity
Of the 899 episodes of induced VT or VF during acute or chronic VF conversion testing, 897 (99.8%) resulted in accurate VT/VF detection and defibrillation (Table 3). In 2 cases (0.2%) involving 2 patients, the investigator delivered an external rescue shock. In both cases, subsequent testing demonstrated acceptable VF detection.

In the first patient, during 1 induced VF episode, an external shock was applied after 30 seconds with no shock from the S-ICD System. Subsequently, the sense vector was changed, and VF induction testing was repeated. Appropriate detection and treatment of VF were noted, with a time to therapy of 16.5 seconds. Analysis of diagnostic log files indicated the presence of noise immediately after induction, which caused a delay in VF detection. The source of noise is unknown; however, the log file analysis supports that, although delayed, therapy delivery was imminent before the delivery of the external shock. The S-ICD System has remained implanted in this patient.
In the second case, after induction of VF, an external shock was delivered after 30 seconds with no shock from the S-ICD System. VF induction testing continued, and 5 subsequent induced VF episodes were treated by the S-ICD System with an average time to therapy of 19.3 seconds. Of note, VF conversion by the S-ICD System was unsuccessful, and the system was ultimately removed before hospital discharge. Analysis of diagnostic log files for the first induced event confirmed that the device detected VF and initiated charging at 9.8 seconds after induction; however, cyclic amplitude variations of the VF caused undersensing that resulted in the delay to deliver therapy.

Infections
There were 18 total suspected or confirmed infections reported by principal investigators and adjudicated by the clinical events committee. Four infections required device explantation in the first third of implantations. None of these 4 patients who had a device explanted for infection had been previously implanted with a transvenous ICD. There were no infections requiring explantation in the final two thirds of the patients enrolled in the study.

Superficial or incisional infections were managed without system explantation in 14 patients (4.4%). Thirteen of the superficial/incisional-related infection patients were managed with antibiotics, and 1 patient underwent sternal wound revision. The majority of these conservatively treated patients with superficial/incisional-related infections continued with their S-ICD Systems through the follow-up period. One patient had the S-ICD electively explanted after study exit and against medical advice, and 1 patient withdrew consent and elected do-not-resuscitate status at the end of life for reasons unrelated to the infection.

Inappropriate Shocks
The overall incidence of inappropriate therapy was 13.1% (41 patients) over the 11-month average follow-up, as detailed in Table 4. Supraventricular tachycardia in the high-rate zone (no discriminators), in which rate alone determines whether a shock is delivered, was the cause in 16 patients (5.1%); these inappropriate shocks were representative of normal sensing behavior by the S-ICD System at rates above the high-rate zone. No patient experienced an inappropriate shock in the conditional zone as a result of a discrimination error. Oversensing caused inappropriate shocks in 25 patients (8.0%); 22 patients experienced oversensing of T waves or, more rarely, broad QRS complexes, whereas 3 patients experienced oversensing as a result of external noise while working with electric equipment.

The use of a conditional zone (rate plus discriminators) was associated with significantly lower risk of inappropriate shocks for oversensing (56% relative reduction) and supraventricular tachycardia (70% relative reduction), as detailed in Figure 3. Inappropriate shocks were addressed during the study after it was noted that the discrimination zone was effective at preventing inappropriate shocks, and use of dual-zone programming (conditional and high-rate zones) was more common in the latter two thirds of implantations in the study. Thirty-two of the 41 patients who experienced an inappropriate shock were managed noninvasively with system reprogramming or medication changes. Resolution of inappropriate shocks was associated with an invasive procedure in 9 patients: 2 devices were explanted because of QRS morphology changes that affected detection, 2 devices were turned off for reasons unrelated to inappropriate shocks, 1 electrode was repositioned, 1 pulse generator was repositioned, a MAZE surgery was performed, a radiofrequency ablation was performed, and an electrophysiology study was performed without ablation.

Time to Therapy
Time to therapy was measured in 839 inductions in which sustained VT or VF was induced by the S-ICD System and resulted in a 65-J shock being delivered by the S-ICD System during acute and chronic testing. Time to therapy was defined as the interval starting 2000 milliseconds after the last induction artifact and ending at the onset of the shock deflection on a standard ECG recording. The mean time to therapy for all inductions was 14.6±2.9 seconds, with a range of 9.6 to 29.7 seconds. A time to therapy of >18 seconds was noted in 13% of episodes. There were no clinical events reported

Table 4. Adverse Clinical Events for Inappropriate Shocks by Cause

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical Events</th>
<th>Patients (%) of 314</th>
<th>Patients Managed Noninvasively</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVT above discrimination zone (normal device function)</td>
<td>21</td>
<td>16 (5.1)</td>
<td>12/16</td>
</tr>
<tr>
<td>Inappropriate sensing</td>
<td>30</td>
<td>25 (8.0)</td>
<td>20/25</td>
</tr>
<tr>
<td>Oversensing, cardiac</td>
<td>27</td>
<td>22 (7.0)</td>
<td>17/22</td>
</tr>
<tr>
<td>Oversensing, noncardiac</td>
<td>3</td>
<td>3 (1.0)</td>
<td>3/3</td>
</tr>
<tr>
<td>Discrimination errors</td>
<td>0</td>
<td>0 (0.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>41 (13.1)</td>
<td>32/41</td>
</tr>
</tbody>
</table>

N/A indicates not applicable; and SVT, supraventricular tachyarrhythmias.
in association with the maximum time to therapy. A slightly longer time to therapy has the benefit of allowing spontaneous self-termination of many VT/VFs (Figure 4). In the study, untreated spontaneously self-terminating VT episodes ranged from 170 to >250 bpm, with most episodes occurring at <200 bpm. There was no instance of syncope associated with nonsustained spontaneous episodes.

**Postshock Pacing**
The S-ICD System is capable of delivering postshock pacing in a demand mode at 50 ppm for up to 30 seconds after shock. Postshock pacing was appropriately delivered in all 184 instances in which the intrinsic heart rate was <50 bpm and was appropriately inhibited in 543 of 544 instances in which the intrinsic heart rate was >50 bpm. In 1 instance, a single ectopic beat was undersensed after shock. In response, 1 postshock pacing pulse was delivered that should have been inhibited. No clinical event was associated with this instance. ECG-verified capture was achieved in all instances in which pacing was delivered appropriately.

**Discussion**
The results of this study demonstrate that the S-ICD System is safe and well tolerated as a chronically implanted ICD and is effective in terminating both induced and spontaneous VT/VF. The results corroborate results reported by Bardy et al in which induced VF was converted consecutively with two 65-J shocks in 58 of 59 patients (98%). Our study had similar results and had more spontaneous events along with the chronic conversion study for induced VF that is additive to the literature of S-ICD System experience. A recent article from Germany evaluating 40 patients with the S-ICD System demonstrated a lower first shock efficacy for spontaneous episodes. However, this was in only 4 patients (10%) with idiopathic VF and may represent an outlier population of patients compared with the ≈83% first shock efficacy in this larger, more diverse cohort of primary prevention patients with well-monitored prospective follow-up. The device can be implanted in the majority of patients with current ICD indications without the need for fluoroscopy and is associated with a low complication rate. In this study, there were no instances of acute complications associated with the use of transvenous lead insertion, such as pericardial effusion, cardiac tamponade, cardiac perforation, hemothorax, or pneumothorax. There was no instance of ICD-related endocarditis. The S-ICD System complications and adverse events were most often managed with noninvasive interventions.

**Patient Selection**
The patients enrolled in this study were representative of a typical patient population meeting guideline indications for an ICD. Approximately 80% of the patients had a primary prevention indication, which is reflective of the American College of Cardiology National Cardiovascular Data Registry Database for current ICD usage. Typical comorbidities, low ejection fraction, sex, and minority demographic groups were all well represented. However, the mean age of 52 years in the S-ICD implantation group was considerably younger than that reported in recent ICD implantation trials and registries. Epstein et al reported a mean age of 69 years in the Advancements in ICD Therapy registry of both primary and secondary implantation indications. That article suggested a trend toward an increased age of the average primary prevention ICD recipient, with many having pacing indications. Younger patients without resynchronization or antitachycardia pacing indications, with an adequate sensing ECG, were safely enrolled in the study. The resulting implantation group included a larger cohort of cardiomyopathy or channelopathy patients than in recently reported ICD usage studies.

**Infections**
All 4 infections that required extraction occurred early in the trial. The decrease in infection rate has been attributed

**Figure 4.** Histogram showing incidence of untreated self-terminating monomorphic ventricular tachycardia (MVT) episodes of sufficient duration to cause the S-ICD System to charge but not to deliver a shock. Note that the majority of these events fall in rates <200 bpm. S-ICD indicates subcutaneous implantable cardioverter-defibrillator.
to standardizing and emphasizing unique aspects of patient preparation through physician training materials and education. None of the 13 patients with a reported superficial/incisional infection required chronic antibiotic use. It is unlikely that a true pocket infection would resolve with the use of oral antibiotics without extraction. The rate of transvenous ICD–related infection has been on the rise. The total number of infections in this study compares favorably with currently published data on ICD infections, which range from 0.13% to 19.9%.22,23 Interestingly, during this study, 33 patients whose transvenous ICD was explanted because of infection underwent implantation with the S-ICD System and remained free of infection throughout the follow-up period. Most notably in this study, there were no reports of S-ICD–related endocarditis, a complication reported in 22% to 54% of cardiac device infections and associated with a 2-fold increase in mortality.23,24

Inappropriate Shocks
Regardless of the type of ICD (transvenous or entirely subcutaneous), inappropriate ICD shocks remain too common and are a cause for clinical concern, with a frequency in some series as high as 40%.25 Such shocks contribute to poor acceptance of ICDs,26 decrease in quality of life,27 and even possibly an increase in mortality, as shown in a Sudden Cardiac Death in Heart Failure Trial substudy.28 This study demonstrated that the S-ICD System did not perform any better than the transvenous ICD when compared historically, with an overall similar rate of inappropriate shocks for supraventricular tachyarrhythmias or oversensing. A preclinical study by Gold et al29 demonstrated that the sensing algorithm of the S-ICD System was as sensitive and as specific as currently available transvenous ICD sensing algorithms at discriminating atrial arrhythmias and sensing VT/VF. Investigator adoption of dual-zone programming resulted in lower risk of inappropriate shocks for oversensing and atrial arrhythmias. The number of inappropriate shocks for nonventricular arrhythmias in this study appears to be lower than in previous transvenous ICD reports, whereas the number of inappropriate shocks for T-wave oversensing was higher in this study than in transvenous ICD systems without lead failure.30 Knowledge gained from using the preoperative ECG screening tool may decrease oversensing as more implantation experience improves the sensing algorithm.

Time to Therapy and Antitachycardia Pacing
The mean duration from arrhythmia detection to treatment in this study was consistent with recent trends in ICD programming in which trials have demonstrated safety and decreased treatment rates for asymptomatic self-limiting VT episodes.31–33 No reports of syncope were associated with the detection and treatment algorithms of S-ICD during this study. The Primary Prevention Parameters Evaluation (PREPARE) study31 and, more recently, the Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy (MADIT-RIT) study32 increased detection times and fixed programming rates and essentially extended time to therapy. PREPARE, which fixed the cutoff zone at 170 bpm, added in longer time to therapy and programmed fixed antitachycardia pacing protocols. PREPARE reported fewer treated episodes and more syncope compared with their historical control group. An exclusion criterion in this S-ICD study was reliably terminable VT with overdrive pacing. No patient in the study had the device removed because of a perceived need for antitachycardia pacing. Moreover, no patient experienced a clinically untoward event because of prolonged time to clinical therapy. On the contrary, the deliberate programming of the sensing algorithm to discriminate and classify rhythm, then charge, allowed many ventricular arrhythmias to self-terminate, thus avoiding the need for therapy from the device and risks of acceleration.

Limitations
The major limitation of this study is the lack of a control group. This study, however, was not intended to prove the concept of defibrillation in the prevention of sudden cardiac death, which has already been firmly established.2–5 This study was designed to determine the safety and effectiveness of a new ICD implantation system that uses only the subcutaneous space, and data from multiple previous ICD trials were used to derive objective performance criteria. The short duration of the follow-up in the patient cohort does not take into total account the possibility of dynamic progression of conduction disease, which could happen in unknown degrees over time depending on the patient and the substrate. The follow-up time was relatively short. However, with average follow-up of nearly 1 year, safety and effectiveness goals with objective performance criteria were achieved, and a wide array of spontaneous episodes was successfully treated.

Conclusions
The S-ICD System is safe and well tolerated in a broad range of patients requiring ICD therapy. The S-ICD System is effective at detecting and treating both induced and spontaneous VT/VF. Chronic conversion testing results were consistent with acute conversion testing. Significant clinical complications were infrequent. Those that did occur were manageable without invasive intervention in the majority of cases. The S-ICD System represents a viable alternative to conventional ICD therapy in patients at risk of death from VT/VF.

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References


**CLINICAL PERSPECTIVE**

The implantable cardioverter-defibrillator decreases mortality in selected populations at increased risk of sudden cardiac death. This benefit is mitigated in part by both short- and long-term complications of the defibrillator implant or system, most commonly associated with transvenous leads. In an effort to minimize lead complications, a totally subcutaneous implantable cardioverter-defibrillator system was developed to avoid the need for transvenous lead placement. The present study is the first large prospective trial of this system, and it was designed to evaluate the effectiveness and safety of the subcutaneous implantable cardioverter-defibrillator. The primary effectiveness and safety end points were met, demonstrating a very high termination rate of induced ventricular tachyarrhythmias and an acceptably low complication rate. Moreover, the defibrillation efficacy is stable over time for both spontaneous and induced arrhythmias. The device effectively withholds shocks for most supraventricular arrhythmias, particularly if the conditional zone is activated for discrimination. To achieve reliable defibrillation and arrhythmia discrimination, the device delivers only high-energy shocks (80 J), and the time to therapy is typically \( \approx 20 \) seconds. This is consistent with the longer time to therapy now recommended to improve patient outcomes on the basis of the Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy study. The results of the present study indicate that the subcutaneous implantable cardioverter-defibrillator is a viable alternative to transvenous systems among patients who do not require pacing therapy for heart failure, bradycardia, or ventricular tachycardia.
Safety and Efficacy of a Totally Subcutaneous Implantable-Cardioverter Defibrillator

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