The Subcutaneous Implantable Cardioverter-Defibrillator: New Insights and Expanding Populations

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Abstract
Implantable cardioverter defibrillators (ICDs) have become a mainstay of treatment in patients at risk for sudden cardiac death. The majority of contemporary ICDs are implanted transvenously; however, this approach carries acute procedural and long-term risks. The subcutaneous ICD (S-ICD) was developed, in part, to circumvent some of these adverse events or as an alternative option in patients unable to undergo transvenous implantation. Early promising trials evaluating the S-ICD were small and focused on niche populations. More recently, larger trials included broader populations with worse heart failure and co-morbidities that may be more representative of typical ICD recipients. These studies have consistently demonstrated positive results. This review describes the S-ICD system, implantation, and the safety and efficacy of the device.

Keywords
Subcutaneous ICD, implantation, safety, efficacy, sudden cardiac death

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Subcutaneous Implantable Cardioverter-Defibrillator System, Screening, and Implantation

The subcutaneous ICD system consists of a pulse generator that is connected to a lead containing a single high-voltage, low-impedance shock coil and two sensing electrodes. The device senses from one of three different vectors: proximal ring to generator (primary); distal tip electrode to generator (secondary); and distal tip to proximal ring electrode (alternate). The volume of the first generation of the device is 69 ml, with a mass of 145 g.10 The second generation is slightly smaller, with a volume of 59.5 ml and mass of 130 g.11

Preliminary short-term trials beginning in 2001 sought to identify the most effective electrode position for the subcutaneous ICD (S-ICD) on the basis of anatomical landmarks. Four different electrode positions were tested and the most effective location was a left lateral pulse generator with an 8-cm coil electrode positioned to the left of the sternum.12 Patients under consideration for S-ICD implantation should undergo a preimplant ECG to assess for QRS-T wave morphology to reduce double counting of T-waves resulting in inappropriate defibrillations.13 ECG screening is necessary to ensure patient compatibility with one of the three vectors utilized with the S-ICD device. In the largest registry to date, patients were required to pass the screening in at least one vector in the supine and standing position. Of the 1637 patients evaluated, full data on all three vectors were available for review in 1622 patients. ECG vector screening was acceptable in two and all three vectors in 93.8% and 51.4% of patients, respectively. Lower BMI or higher left ventricular...
ejection fraction (LVEF) were predictive characteristics of patients only passing one vector.\textsuperscript{14}

The generator is implanted between the mid-axillary and anterior axillary lines connected to the electrode, which is tunneled typically 1 to 2 cm to the left of and parallel to the sternum.\textsuperscript{15} Figure 1 illustrates the anatomic location as well as the sensing vectors of the S-ICD system. In early implantations, the lead was tunneled via an inferior and superior parasternal incision (three-incision technique). In a recent trial, however, the majority of implantations were via the two-incision technique, requiring only an inferior sternal incision.\textsuperscript{14} A study of 69 patients implanted with an S-ICD at three German centers demonstrated a mean implantation time of 70.8 ± 27.9 min, which did not differ significantly from conventional ICD implantation times.\textsuperscript{16} Sedation strategies have varied widely across trials, with the rates of general anesthesia use ranging from 47 \% to 100 \%.\textsuperscript{17} In the recently published US S-ICD post-market approval study (S-ICD PAS), general anesthesia was utilized in 64.1 \% of implantations.\textsuperscript{18} Arrhythmia termination is typically tested using 65 J shocks at the conclusion of the procedure. Once implanted, the device output is a non-programmable 80 J shock. The device automatically reverses the polarity of the shock if the initial attempt is unsuccessful. Maximum therapy consists of five defibrillations.\textsuperscript{14} Aside from 30 sec of post-shock asystole demand pacing, the device has no anti-bradycardic or anti-tachycardia (ATP) functions.\textsuperscript{15}

The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend S-ICD implantation in patients meeting criteria for ICD whom:

- have inadequate vascular access or an unacceptable risk of infection (Class I, level of evidence [LOE] B- non-randomized [NR]); or
- pacing for bradycardia, termination of ventricular tachycardia, or CRT is neither needed nor anticipated (Class III, LOE B-NR).

S-ICD implantation is not recommended in patients in whom pacing for bradycardia, ATP, or CRT is necessary or envisioned (Class III, LOE B-NR).\textsuperscript{16}

**Populations Studied**

Evaluation of the clinical trials investigating the S-ICD system requires knowledge of the population analyzed. Early studies commonly included a high proportion of niche populations who were younger with little or no structural heart disease and fewer co-morbidities than most series of patients receiving transvenous ICDs. Mean age ranged from 42 to 53 years.\textsuperscript{16–22} Two publications reported median ages of 20 and 33 years.\textsuperscript{23,24} The majority of early cohorts consisted of fewer than 120 patients.\textsuperscript{16–19,23,24} Subsequently, the results from the EFFORTLESS (Evaluation of FactOrs Impacting Clinical Outcome and Cost EffectiveNESS of the S-ICD) registry were reported on a population of 985 S-ICD recipients.\textsuperscript{25} Within these studies, the prevalence of primary electrical heart disease ranged from 20 \% to 75 \%.\textsuperscript{23} When reported, mean LVEF was greater than 35 \% in all cases\textsuperscript{14–22,25} and greater than 40 \% in five studies.\textsuperscript{14–21,25} Primary prevention was the initial indication for implantation in 42 \% to 79 \% of cases. Men represented at least 70 \% of each cohort\textsuperscript{16–22,25} in all but one trial, where men accounted for 9 out of 16 patients.\textsuperscript{23} Although these studies provided valuable information regarding the S-ICD system, as noted above the cohorts studied are not entirely representative of typical ICD patients. Accordingly, these differences should be considered when extrapolating the results to broader populations.

Two recent publications have analyzed S-ICD implantation in larger populations with higher prevalence of concomitant co-morbidities. Friedman et al retrospectively analyzed NCDF ICD data from 2012 to 2015 and performed a propensity matched analysis of 5760 patients in a 1:1 fashion to compare outcomes among patients implanted with S-ICD, single-chamber, and dual chamber ICD. Patients implanted with S-ICD were found to be more often younger, female, African American, and dialysis dependent, and were more likely to have experienced prior cardiac arrest when compared with more traditional ICD counterparts. Mean LVEF was 32 \% and the prevalence of dialysis dependence was 20 \% in the S-ICD cohort.\textsuperscript{26} A second study, mandated following FDA approval (PAS study), prospectively enrolled and followed patients who received an S-ICD. This population consisted of 1637 S-ICD recipients, 13.4 \% of whom were on dialysis. Mean LVEF (32 \%) was also lower than other prior S-ICD studies and patients within this study had more co-morbidities than prior publications. The majority of patients had both heart failure and hypertension and over one-third had diabetes. Patients with an LVEF < 35 \% and heart disease constituted approximately 75 \% of all patients. Additionally, a lower number of patients with inherited channelopathies were enrolled.\textsuperscript{14} The PAS study demonstrated that in contemporary clinical practice, the S-ICD population has shifted more from selected niche population to typical ICD cohorts. Table 1 compares the populations studied from the S-ICD Clinical Investigation (IDE), EFFORTLESS, and S-ICD PAS trials.

**Safety**

As with any medical procedure, there are risks inherent in the implantation of ICDs. However, these risks differ among the types of ICDs implanted. Complications associated with the implantation of transvenous ICDs include pneumothorax, hemothorax, nerve or vascular damage, hematoma, infection, lead dislodgment or malfunction, cardiac perforation, and tamponade. A meta-analysis of traditional ICD
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randomized controlled trials demonstrated a complication rate of 9.1%, though a few studies included devices implanted via a thoracotomy. This was compared with a ‘real-world’ complication rate of 3.08% for ICD implantation derived from NCDR between 2006 to 2010. Discrepancy between the two rates may be, at least somewhat, accounted for by the intrinsic nature of a comparison between randomized controlled trials and registry data. It is likely that the NCDR registry underestimates long-term complications given the nature of the data collection post implant. It is also possible that the discrepancy observed between the rates may be, at least in part, accounted for by the nature of the data collection in registry studies. It is also possible that the discrepancy observed between the rates may be, at least in part, accounted for by the nature of the data collection post implant.

Table 1: Baseline Patient Characteristics: S-ICD IDE, EFFORTLESS, and S-ICD PAS

|                      | S-ICD IDE | EFFORTLESS | S-ICD PAS |
|----------------------|-----------|------------|-----------|
| Patients             | 314       | 985        | 1637      |
| Age (years)          | 51.9 ± 15.5 | 48.0 ± 17.0 | 52.0 ± 15.0 |
| Male                 | 74.1%     | 72.0%      | 68.6%     |
| Mean LVEF            | 36.1 ± 15.9 % | 43.0 ± 18.0 % | 32.0 ± 14.6 % |
| LVEF ≥ 35 %          | NR        | 57.7%      | 75.4%     |
| Primary prevention   | 79.0%     | 64.9%      | 76.7%     |
| CHF                  | 61.4%     | 26.5%      | 74.0%     |
| HTN                  | 15.3%     | 28.3%      | 61.6%     |
| Diabetes             | NR        | 11.3%      | 33.6%     |
| Kidney disease       | NR        | 8.2%       | 25.6%     |

Baseline patient characteristics in three large trials. CHF = congestive heart failure; HTN = hypertension; LVEF = left ventricular ejection fraction; NR = not reported.

Inappropriate shocks are associated with worsened quality of life, increased healthcare costs, so minimizing such events has been an area of intense study for ICDs. The cause of inappropriate shocks with S-ICD have been inappropriate sensing of myopotentials, T-wave oversensing, changes in QRS morphology, or failure to discriminate supraventricular tachycardia (SVT). In one study, no further inappropriate shocks were observed following a software update specifically addressing myopotential oversensing. Other software updates addressing T-wave oversensing, changes in sensing vectors during exercise, or the addition of new templates have led to reductions in inappropriate therapy.

For transvenous ICDs, conservative programming of tachycardia treatment zones by prolonging detection duration or increasing threshold rates for therapy has been shown to not only reduce inappropriate shocks, but also improve mortality. The Subcutaneous versus Transvenous Arrhythmia Recognition Testing (START) study demonstrated that the S-ICD discriminated SVT more effectively than transvenous ICD systems. Thus, the use of dual zone programming employing a conditional zone (rate plus discriminators) markedly reduces inappropriate shocks. Continued reductions in inappropriate shocks as well as improvements in device implantation and technique with new generations of the S-ICD device will likely lead to an even more acceptable safety profile. These differences in the types of lead complications and inappropriate shocks between transvenous and subcutaneous ICDs has been further supported by a recent meta-analysis.

The safety profiles of a device are also affected by longevity. A device with a shorter battery life or time to the elective replacement interval (ERI) exposes the patient to more procedures with their intrinsic risks.
Conventional ICDs implanted after 2002 were found to have a mean battery life of 5.6 years.\textsuperscript{24} Although device longevity varies somewhat with manufacturer and programmed mode, overall longevity of devices continues to improve with more recently implanted devices.\textsuperscript{27} The manufacturer of the S-ICD initially projected device longevity of 5 years.\textsuperscript{30} A nearly 6-year follow-up of 55 patients enrolled in the European Regulatory Trial demonstrated a device replacement rate of 47 %. The majority of devices were replaced on ERI (81 %) and the median time for device replacement was 5 years. Premature battery depletion occurred in 9 % of the initial S-ICD cohort leading to a field safety notification regarding a battery manufacturing issue. Following correction, premature battery depletion was observed in 0.6 % in the IDE trial and 0.2 % in the EFFORTLESS registry.\textsuperscript{32} Published rates of premature battery depletion in transvenous ICDs are 8–9 %.\textsuperscript{32,35} The second generation S-ICD system has manufacturer projected longevity of over 7 years,\textsuperscript{11} though this will need to be validated with subsequent analyses.

Efficacy
Conversion testing is typically performed following implantation with induction of VT/VF and a 65 J shock providing an adequate (15 J) safety margin.\textsuperscript{12,14,16,18} An early trial comparing temporary S-ICD systems with transvenous ICDs found that conversion efficacy was similar, though S-ICD were successfully converted at 80 J.\textsuperscript{20} Mean time to therapy has been ≥ 150 days after implantation. Of the 75 patients with evaluable results, detected, successful defibrillation was obtained in 100 % of patients.\textsuperscript{20} In those instances where VT/VF was successfully induced VT/VF established a 99.8 % rate of successful VT/VF detection and defibrillation. In those instances where VT/VF was successfully detected, successful defibrillation was obtained in 100 % of patients.\textsuperscript{20} An early study of 40 consecutive S-ICD patients did demonstrate a low conversion efficacy with the initial shock; however, 96.4 % had successful conversion within the five allotted shocks.\textsuperscript{25} Recent large trials further corroborate the ability of the S-ICD system to successfully defibrillate induced VT/VF.\textsuperscript{12} Failure of conversion with the first shock is predicted by patient height and BMI.\textsuperscript{14} Conversion testing has also been performed ≥ 150 days after implantation. Of the 75 patients with evaluable results, 72 (96 %) were successfully converted at 65 J. The third paradigm for programming of defibrillation therapy for transvenous systems.\textsuperscript{30}

Limitations
Despite evidence establishing the safety and efficacy of the S-ICD, the device does have limitations. The system does not have the ability to provide chronic anti-bradytic, anti-tachycardic pacing, or CRT. It is able to provide up to 30 sec of post-shock asystole pacing at a rate of 50 bpm.\textsuperscript{33} The inability to provide pacing chronically emphasizes the importance of appropriate patient screening to exclude those patients with, or who may develop, bradycardic indications. In the 3-year follow-up of the EFFORTLESS registry, the S-ICD was explanted for the indication of bradycardia in 0.1 %, ATP in 0.5 %, and CRT in 0.4 % of patients.\textsuperscript{34} Low rates of S-ICD explantation and transition to transvenous devices for bradycardia, CRT, or ATP likely reflect the importance of proper patient selection.

Conclusion
The S-ICD device is a safe and effective alternative to contemporary transvenous ICDs in selected patients. Additionally, new studies have demonstrated both safety and efficacy in broader, sicker populations.\textsuperscript{12,24} This is being studied in even more detail in the UNTOUCHED trial of primary prevention patients with a reduced ejection fraction.\textsuperscript{41} Though direct randomized comparisons between the two systems are currently unavailable, the Prospective, Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter-Defibrillator Therapy (PRAETORIAN) trial is ongoing.\textsuperscript{42} In selected patients, and arguably most, who qualify for ICD therapy without an indication for pacing, CRT, or ATP, the subcutaneous ICD system should be considered.\textsuperscript{30}
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