

The Rational and Design of the Understanding Outcomes with the S-ICD in Primary Prevention Patients with Low Ejection Fraction Study (UNTOUCHED)

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Abstract:

Aims: The UNTOUCHED study will assess the safety and efficacy of the subcutaneous implantable cardioverter defibrillator (S-ICD) in the most common cohort of patients receiving ICDs. The primary goal is to evaluate the inappropriate shock (IAS) free rate in primary prevention patients with a reduced ejection fraction and compare with a historical control of transvenous ICD patients with similar programming.

Methods and Results: The UNTOUCHED Study is a global, multi-site, prospective, non-randomized study with a primary endpoint of freedom from IAS at 18 months. The lower 95% confidence bound of the observed incidence will be compared to a performance goal of 91.6%, which was derived from the IAS rate in MADIT-RIT. The secondary endpoints are, all-cause shock free rate at 18 months, and system and procedure related complication free rate at one and six months. Enrollment of a minimum of 1100 subjects from up to 200 centers worldwide is planned based on power calculations of the primary and principal secondary endpoints.

Conclusions: This trial will provide valuable information regarding shock therapy with the S-ICD in the most common group of patients receiving ICDs and will help determine the option of this device in a much larger cohort of patient than is presently used.

Key words: Subcutaneous ICD, primary prevention, reduced ejection fraction, inappropriate shock rate, safety, efficacy

Introduction

The implantable cardioverter-defibrillator (ICD) is well established for either primary or secondary prevention of sudden cardiac death (SCD). ICDs reduce mortality and are cost-effective in specific patient populations at increased risk of SCD (1-5). Despite the proven efficacy and relative safety of traditional ICDs, there are significant risks of complications associated with these devices, including infection, pneumothorax, venous thrombosis, lead dislodgement, lead malfunction, and myocardial perforation (6, 7). In addition, inappropriate shocks are associated with reduced quality of life, hospitalization and possibly mortality (8, 9). Long term, transvenous lead failure rate at 10 years are about 20% (10). These short- and long-term complications with transvenous ICDs contribute to the morbidity and mortality associated with these devices and may reduce utilization of this important therapy.

In response to complications associated with transvenous ICDs an entirely subcutaneous ICD (S-ICD) was developed (11). This system consists of a pulse generator and single lead with a shock coil. The pulse generator is implanted in the left lateral position between the anterior and mid-axillary lines near the apex of the heart. A single lead for sensing and defibrillation is tunneled from the lateral pocket medially to the xiphoid process, with the distal tip near the manubriosternal junction(11). The S-ICD lacks functionality for bradycardia or antitachycardia pacing, but has novel arrhythmia discrimination algorithms (12-15). The functional limitations as well as the novelty of this device likely contribute to the atypical patient populations receiving this device. Compared with contemporary transvenous ICD use, S-ICD trials typically had younger patients with less advanced heart disease and often “niche” indications, including channelopathies, hypertrophic cardiomyopathy, previous ICD infection, or congenital heart

disease (16-23). Although, these types of patients benefit from ICD therapy, they do not represent the cohorts most commonly receiving such devices. Specifically, primary prevention patients with left ventricular systolic dysfunction usually with heart failure represent the majority of patients who receive ICDs, including more than 70% of new ICD implants in the US (7). This is based on guidelines largely derived from the results of the MADIT II and SCD HeFT trials (3,4). To assess the safety and efficacy the S-ICD in the more traditional cohort of patients receiving ICDs, the Understanding Outcomes with the S-ICD in Primary Prevention Patients with Low Ejection Fraction Study (UNTOUCHED) study is being undertaken.

Study Hypotheses

The primary hypothesis of UNTOUCHED is that among primary prevention patients with a reduced ejection fraction, the inappropriate shock free rate will not be lower than in an historical control of transvenous ICDs with similar programming (9).

Study design

The UNTOUCHED Study is a global, multi-centre, prospective, non-randomized study that will enroll subjects who intend to undergo de novo implantation of an EMBLEM™ or later generation S-ICD System (Boston Scientific, St Paul, MN) and have an indication for primary prevention of sudden cardiac death with a left ventricular ejection fraction $\leq 35\%$. The key inclusion criteria are summarized in Table 1 and require that passing a screening electrocardiogram be achieved, which is standard for this device. Programming of the device will be mandated with zone cut-offs at 200 bpm (Conditional Shock Zone) and 250 bpm (Shock Zone). The key exclusion criteria are summarized in Table 2. Patients with a pacing indication or previous history of sustained ventricular arrhythmias (secondary prevention) are excluded as are patients with NYHA IV CHF or end stage renal disease. Subjects will be followed semi-annually for a minimum of 540 days (i.e., 18 months) post implant. Occurrence of shocks from the ICD and occurrence of reportable events will be evaluated at each follow-up. Figure 1 is a flow chart which describes the proposed study plan from first enrollment to study closure.

Study Population

The study population consists of patients:

- with an ICD indication for primary prevention of sudden cardiac death and a reduced ejection fraction; and
- who are at risk for life-threatening ventricular tachyarrhythmias and who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing.

The inclusion and exclusion criteria are further described in detail within Tables 1 and 2.

Study Endpoints

The primary endpoint of UNTOUCHED is freedom from inappropriate shocks at 18 months. The lower 95% confidence bound of the observed incidence will be compared to a performance goal of 91.6%. This performance goal was derived from the 18 month inappropriate shock free rate of 94.6% observed in ICD subjects in MADIT RIT (9, 24) treatment Arms B and C (N= 484) plus a delta of approximately 3% to account for clinical equivalence ($\approx 1\%$) and calculation of the lower confidence bound ($\approx 2\%$).

The secondary hypotheses include: 1) freedom from all-cause shocks at 18 months compared to a performance goal is 85.8% (derived in a similar way to the primary endpoint), and 2) freedom from system and procedure related complications at 30 days, compared to a performance goal of 93.8%. An additional endpoint will be analyzed specifically to meet the Post Market Clinical Follow-up (PMCF) requirements for CE marking: freedom from system and procedure related

complications at 6 months, compared to a performance goal of 85.0%. All study endpoints are listed in Table 3.

In addition to the formal endpoint hypotheses, summary statistics will be calculated for pre-specified analyses that include, but are not limited to:

- Freedom from Appropriate Shocks at 18 months
- All-cause mortality
- Syncope related to VT/VF episodes
- Implantation of a concomitant pacemaker
- Explants and causes

Trial Oversight

The local ethics committees of all participating sites are required to approve the study protocol. Central and onsite monitoring, data review and safety oversight is provided by the sponsor, Boston Scientific (St Paul, MN, USA). All shock episodes (primary endpoint related events) will be reviewed by an independent clinical event committee. All device related adverse events regardless whether they are considered serious or not and all serious adverse events regardless whether device related will be reviewed. Quarterly safety review meetings will be held to ensure patient safety throughout the trial.

Power Calculations

For the primary outcome of freedom from inappropriate shock, the sample size is powered to get a 90% confidence level with a one-sided alpha of 5%. The expected shock free rate is 94.6% with a performance goal of 91.6% as noted previously. Total attrition is expected to be 15%. Under those assumptions a minimum of 786 subjects will be enrolled to achieve 668 patients in the analysis cohort.

The secondary effectiveness outcome, freedom from all cause shocks will be compared to a performance goal of 85.8% with an expected shock free rate of 89.2%. The sample size is powered to get a 90% confidence level with a one-sided alpha of 5%. Total attrition is expected to be 15%. Under those assumptions a minimum of 1013 subjects will be enrolled to achieve 861 patients in the analysis cohort.

The primary safety outcome is freedom from perioperative system and procedure related complications (at 30 days). This will be compared to a performance goal of 93.8% with an expected complication free rate of 96.6%. The sample size is powered to get an 80% confidence level with a one-sided alpha of 5%. Total attrition is expected to be 15%. Under those assumptions a minimum of 471 subjects are needed in the analysis cohort. At least 427 de novo S-ICD subjects who have completed the 30 day follow up at the time of the data lock will be included in the analysis.

The secondary safety outcome is freedom from system and procedure related complications after 6 months will be compared to a performance goal of 85% with an expected complication free rate of 92.9%. The sample size is powered to get an 80% confidence level with a one-sided alpha of 5%. Total attrition is expected to be 15%. Under those assumptions a minimum of 118

subjects are needed in the analysis cohort. Analysis of the PMCF endpoint will be done when 200 de novo S-ICD subjects have a follow up visit recorded at least 180 days after implant.

Statistical Analyses

Kaplan-Meier analysis will be performed for all endpoints. The analysis will take into account the time from implant until the occurrence of the event. Data from any subjects who are event-free will be right censored on the date of study exit. A pooling analysis will be performed for patients with atrial fibrillation, who were excluded in MADIT RIT. It is expected that results may differ for subjects with permanent atrial fibrillation compared to those without atrial fibrillation or with non-permanent atrial fibrillation. Specifically, a likelihood ratio test from a logistic regression model will be conducted.

The logistic regression model will include additional baseline covariates to attempt to adjust for any imbalances between baseline data. The following baseline covariates will be considered: age, gender, etiology of cardiomyopathy (ischemic vs nonischemic), race, left ventricular ejection fraction, NYHA classification, medications, arrhythmia history, associated diseases/risk factors, height, weight and geography. To determine which covariates are significantly associated with an endpoint, a backwards selection process will be employed, using a significance level equal to 10%.

If poolability is confirmed for permanent atrial fibrillation subjects, then the study results will be reported combining all subjects.

Prespecified analysis

Summary statistics will be provided for the following secondary endpoints:

- Freedom from Appropriate Shocks at 18 months
- All-cause mortality
- Syncope related to VT/VF episodes
- Implantation of a concomitant pacemaker
- Explants and causes (e.g., infection, need for pacing therapy, inappropriate shocks)

Discussion

The role of ICDs to prevent sudden cardiac death is well established (25, 26). The populations implanted with the S-ICD to date have largely been skewed towards younger patients with less structural heart disease and fewer co-morbidities. Although the device has performed well in these groups, suitability in the larger groups of eligible patients still remains incompletely understood. For this reason, UNTOUCHED was designed to understand better the safety and efficacy of the S-ICD in the most common cohort undergoing ICD implantation in North America and Europe, namely primary prevention patients with a reduced ejection fraction

The S-ICD is a newer device that has both advantages and disadvantages compared with transvenous devices (27, 28). Specifically, implantation of this system avoids many of the complications associated with transvenous leads, such as pneumothorax, cardiac tamponade and bacteremia. Early and mid-term results suggest a very low incidence of lead failure (15, 19). In general, ICD procedural outcomes improve with number of implants performed by physicians (29). This has also been observed for the S-ICD (30), so only centers that have experience with this device will be included. The potential limitations of the S-ICD include the lack of antitachycardia pacing and it has only very short duration post-shock bradycardia pacing. Given these features, the S-ICD has clearly filled important voids where transvenous leads are relatively or absolutely contraindicated, such as patients with a lack of venous access or those with systemic infection (22, 31, 32).

The S-ICD has a unique discrimination algorithm that uses a number of features including template matching, rate, electrogram width and waveform stability to classify arrhythmias. A

head to head comparison of this algorithm with conventional ICD algorithms for a series of induced supraventricular arrhythmias showed superiority of the S-ICD system (13). However, early clinical experience showed higher rates of inappropriate shocks, although this was rarely due to errors in discrimination of supraventricular arrhythmias (19). Rather, such shocks are most commonly due to T-wave oversensing and the failure to activate the conditional zone of the device, where the discrimination algorithms are used (33). More recently, the algorithm has been modified to reduce further the risk of oversensing (14, 34). UNTOUCHED will be the first study of the S-ICD to have prescriptive programming requiring activation of the conditional zone with no therapies delivered for rates < 200 bpm. This is consistent with the high rate arm of MADIT RIT which is the study used to establish the performance goal for all shock endpoints.

The most rigorous scientific approach to assess the role of the S-ICD among patients with primary prevention indications and a reduced left ventricular ejection fraction is to perform a randomized trial. PRAETORIAN is such a randomized trial comparing the S-ICD and transvenous systems and is currently recruiting patients (35). However, that study does not restrict subjects by ejection fraction or indication, but simply requires that patients be appropriate for either device. This will likely result in an atypical cohort of patients as with other S-ICD trials, despite the importance of this trial as a randomized study. To repeat such a study in the low ejection fraction, primary prevention population would require a very large study and many years to complete. Therefore, it was decided best to compare the results with an historical control.

MADIT RIT was chosen as the control group for several reasons. First, the programming is similar to that used in the S-ICD. Specifically, high rates and relatively long detection durations were used in MADIT RIT (9, 24). The marked reduction in inappropriate therapies established

such programming as optimal and is now recommended in consensus documents for primary prevention patients (36). Thus, UNTOUCHED will compare S-ICD outcomes with a very aggressive programming strategy from clinical trials which resulted in a marked reduction in shocks. This will serve to minimize the risk that if the performance measures are met that this will still be considered inadequate results to justify the use of the S-ICD in contemporary populations.

In summary, UNTOUCHED is a prospective open labeled study that will be the first trial of the S-ICD to study the device in the primary prevention population with a reduced ejection fraction. Moreover, it is also the first S-ICD trial with prescriptive programming aimed to demonstrate the safety of using the discrimination algorithm at rates as up to 250 bpm. The results of this trial will provide an accurate estimate of shock therapy with this device in the most common group of patients receiving ICDs and will help determine the option of this device in a much larger cohort of patient then is presently used in clinical practice.

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Tables

Table 1: Inclusion Criteria

- Patient with ischemic or non-ischemic heart disease who meets current guidelines for ICD therapy and intends to undergo a de novo implant procedure for an EMBLEM™ S-ICD (or newer generation BSC S-ICD)
- Left ventricular ejection fraction $\leq 35\%$
- A passing EMBLEM™ S-ICD (or newer generation BSC S-ICD) screening ECG
- Patient ≥ 21 years of age willing and capable of giving informed consent
- Patient willing and capable of complying with follow-up visits

ICD, implantable cardioverter defibrillator, BSC, Boston Scientific Corporation, S-ICD, subcutaneous implantable cardioverter defibrillator, ECG, electrocardiogram.

Table 2: Exclusion Criteria

- Patient with a history of spontaneous sustained VT or VF
- Patient with bradycardia pacing indication
- Patient eligible and planned for cardiac resynchronization therapy
- Patient with a previous S-ICD or a previous transvenous pulse generator (pacemaker or defibrillator)
- Patient in NYHA Class IV within 90 days before enrolment
- Patient with life expectancy shorter than 18 months due to any concomitant medical condition
- Patient receiving hemodialysis within 180 days of enrolment
- Patient unwilling or unable to cooperate with the protocol

VT/VF, ventricular tachyarrhythmia/ ventricular fibrillation, S-ICD, subcutaneous implantable cardioverter defibrillator, NYHA, New York Heart Association classification.

| | Table 3: UNTOUCHED Study Endpoint Hypotheses |
|---------------------------|--|
| Primary Endpoint | The Inappropriate Shock Free Rate at 18 months exceeds the performance goal of 91.6%. |
| Secondary Endpoint | The All-Cause Shock Free Rate at 18 months exceeds the performance goal of 85.8% |
| Secondary Endpoint | The System and Procedure Related Complication Free Rate at 1 month exceeds the performance goal of 93.8%. |
| PMCF Endpoint | The System and Procedure Related Complication Free Rate at 6 months exceeds the performance goal of 85.0%. |

Figures

Figure 1: UNTOUCHED Study Design

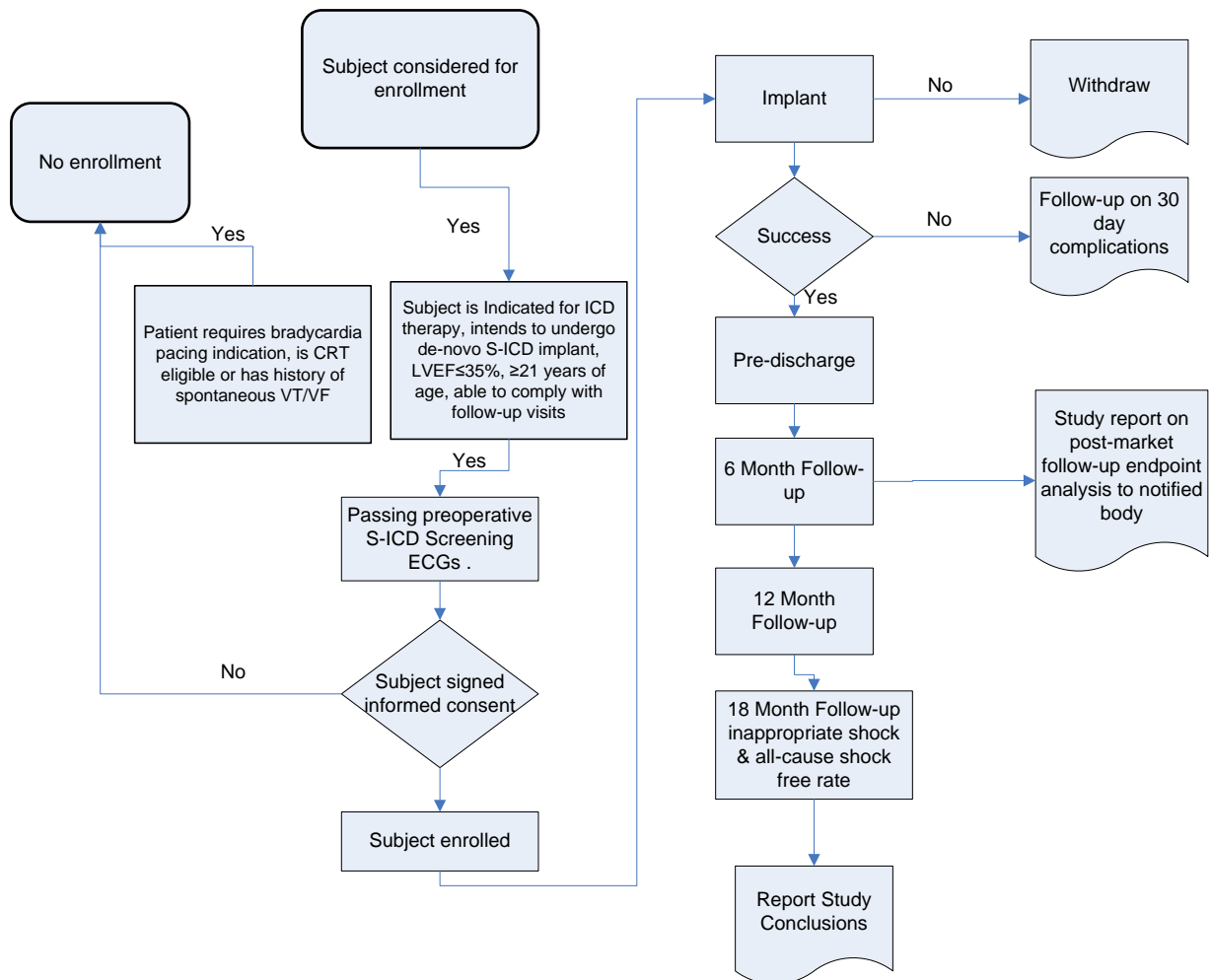


Figure Legends

Figure 1: Flow chart of the UNTOUCHED study design from enrollment of first patient to study closure. The duration of the study is expected to be approximately 58 months. PMCF: Post Market Clinical Follow-up Endpoint, CRT: Cardiac Re-synchronization Therapy, VT/VF: Ventricular Tachycardia/Ventricular Fibrillation, LVEF: Left Ventricular Ejection Fraction, S-ICD: Subcutaneous Implantable Cardioverter Defibrillator, ECG: Electrocardiogram.