A Modular Communicative Leadless Pacing-Defibrillator System

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ABSTRACT

Background

The subcutaneous-implantable cardioverter-defibrillator (ICD) has fewer lead-related complications than a transvenous-ICD; however, the subcutaneous-ICD cannot provide bradycardia and antitachycardia pacing therapy. Whether a modular pacing-defibrillator system comprised of a leadless pacemaker in wireless communication with a subcutaneous-ICD to provide anti-tachycardia and bradycardia pacing is safe remains unknown.

Methods

We conducted a multicenter, single arm, international trial that enrolled 293 patients at risk for sudden cardiac death with 162 patients completing the 6-month follow-up period. The primary safety end point was freedom from major leadless pacemaker-related complications compared to an 86% performance goal. The primary performance end points were successful communication between the leadless pacemaker and subcutaneous-ICD compared to an 88% performance goal and the percentage of patients with pacing threshold measurements ≤ 2.0 volts at a 0.4 millisecond pulse-width compared to a performance goal of 80%.

Results

The mean age of patients was 60 years, 16.7% were female and the mean (±SD) left ventricular ejection fraction was 33.1±12.6%. The major leadless pacemaker-related complication-free rate was 97.5%, exceeding the prespecified performance criterion. The wireless device communication success rate was 98.8%, exceeding the prespecified performance criterion. Of 151 patients, 147 (97.4%) had pacing thresholds ≤ 2.0 volts, exceeding the prespecified performance criterion. The antitachycardia pacing success rate to terminate arrhythmia was 61.3% and there were no episodes where antitachycardia pacing was not delivered due to communication failure. There were 8 deaths (4.9%), none of which were related to arrhythmias or the implant procedure.

Conclusion

The leadless pacemaker in wireless communication with a subcutaneous-ICD exceeded performance goals for freedom from major leadless pacemaker-related complications, communication between the leadless pacemaker and subcutaneous-ICD, and the percentage of patients with a pacing threshold ≤ 2.0 volts at a 0.4 millisecond pulse-width at 6 months.

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Introduction

The transvenous implantable cardioverter-defibrillator (transvenous-ICD) is the established method for treating life-threatening ventricular arrhythmias in patients at risk of sudden cardiac death.[1] However, patients are at risk of lead-related complications due to conductor failure, breakdown of insulation, and infection, which increases over time.[2] The subcutaneous-ICD was developed to circumvent transvenous lead-related complications. Subcutaneous-ICD safety and performance have been well established.[3,4] Lead-related complications are less frequent and overall device-related complications, including infections, are less serious for patients with subcutaneous-ICD devices vs. transvenous-ICD devices.[5,6] However, the subcutaneous-ICD can neither provide prolonged bradycardia nor antitachycardia pacing therapy. Antitachycardia pacing can terminate ventricular arrhythmias, particularly ventricular tachycardia, thereby potentially allowing avoidance[7] of painful shock delivery.[8] Without antitachycardia pacing capability, the subcutaneous-ICD is contraindicated for patients who require antitachycardia pacing for arrhythmia termination.[9] The MODULAR ATP trial[10] investigated the safety and performance of a modular pacing-defibrillator system—the subcutaneous-ICD in wireless communication with a leadless pacemaker—in patients with an ICD indication who are at risk of sudden cardiac death due to ventricular arrhythmias that may potentially be terminated by antitachycardia pacing.[10-16]

Methods

TRIAL DESIGN AND OVERSIGHT

The MODULAR ATP trial is an ongoing, prospective, multicenter, non-randomized, single arm, global trial whose study design has been described previously.[10] The trial was designed to demonstrate the safety and performance of an investigational modular pacing-defibrillator system comprised of a subcutaneous-ICD coupled with a leadless pacemaker (Boston Scientific). The trial was sponsored by Boston Scientific and approved by each center's institutional review board. Informed consent was obtained from patients and documented in accordance with the principles of the Declaration of Helsinki, ISO 14155, and all pertinent individual country governance. An independent Data Monitoring Committee oversaw safety data and trial conduct. An independent Clinical Events Committee reviewed adverse

events and episodes of arrhythmia that were treated. The sponsor collected and monitored trial data and performed outcome analyses per the statistical analysis plan and protocol that are available online with the full text of this article at NEJM.org. All manuscript drafts were written by the primary co-authors (who had final authority of content) and an employee of the sponsor Amy Brisben; and were reviewed and edited by the other authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

PATIENTS

Patients age 18 years or older with an indication for ICD implantation[17,18], who had a pre-existing subcutaneous-ICD, or transvenous-ICD that was to be extracted, and were considered to be at high risk for monomorphic ventricular tachycardia (VT) [17] were eligible for enrollment if they did not require pacing at baseline, had chronotropic incompetence, or required pacing for ventricular dyssynchrony. Risk for monomorphic VT was defined as a history of nonsustained monomorphic VT with a left ventricular ejection fraction of up to 50% or substantial cardiac scar; history of sustained VT or ventricular fibrillation with a left ventricular ejection fraction of up to 50%; history of syncope that is arrhythmic in origin; history of ischemic cardiomyopathy with a left ventricular ejection fraction of up to 35%; or a history of nonischemic cardiomyopathy with a left ventricular ejection of up to 35% and a substantial cardiac scar. A full description of the inclusion and exclusion criteria is provided in the Supplementary Appendix (available online at NEJM.org).

TRIAL PROCEDURES

The investigational leadless pacemaker (EMPOWER; Boston Scientific) when co-implanted with a subcutaneous-ICD delivers antitachycardia pacing and bradycardia pacing (Fig. S1).[11-16] The leadless pacemaker is implanted in the right ventricle via a dedicated delivery catheter and introducer sheath and can be retrieved by a dedicated retrieval catheter. The pacemaker is enabled to verify the rate of a ventricular arrhythmia after subcutaneous-ICD detection and deliver antitachycardia pacing if the sensed

rate is 158 to 261 beats per minute.[19,20] The leadless pacemaker can also function as an independent, single-chamber, rate-responsive bradycardia pacemaker.

Trial investigators underwent a prespecified training program and competence assessment prior to trial participation.[21] The leadless pacemaker was delivered and deployed under fluoroscopy. Fixation and electrical testing were performed. Device recapture and redeployment were allowed as needed to achieve acceptable electrical parameters and position as determined by the implanter. If the pacemaker location and performance were acceptable, the pacemaker was released from the tether. Patients who received a de novo subcutaneous-ICD underwent subcutaneous-ICD and pacemaker implantation simultaneously or within 30 days of pacemaker implantation, per the trial site's standard-of-care methods and subcutaneous-ICD user manual instructions.[22] The remainder of patients had a previously-implanted subcutaneous-ICD and underwent pacemaker implantation alone. Procedure medications, venous closure, and hemostasis methods were at the implanter's discretion. Antitachycardia pacing requests were programmed on for all therapy zones.

After system implantation (Fig. S2), patients underwent system testing prior to discharge and during follow-up visits at 1, 6, and 12 months and semi-annual visits thereafter. System testing was performed from induced arrythmias and resting heart rates. This included defibrillation testing during induced ventricular fibrillation and termination with a subcutaneous-ICD-shock that was performed during asynchronous pacing at maximum pacing output to test interaction between pacing stimuli and subcutaneous-ICD arrhythmia detection; and subcutaneous-ICD sensing during overdrive pacing to detect oversensing of paced artifacts. Additional visits were required for reportable adverse events, arrhythmia episodes, or device deficiencies.

TRIAL END POINTS

The safety end point was the major leadless pacemaker-related complication-free rate through 6 months post-implantation compared to an 86% performance goal (see Supplementary Appendix for additional information). A major leadless pacemaker-related complication was defined as any complication related to the pacemaker, its implantation procedure, or its therapy delivery that resulted in system revision, permanent loss of pacemaker function, hospitalization, or death. All adverse events were adjudicated by the Clinical Events Committee.

The first performance end point was wireless communication testing during which the subcutaneous-ICD requested the pacemaker to deliver pacing at a rate faster than the patient's intrinsic rhythm. Since device communication can be affected by the relative orientation of the devices, the end point was assessed at four different body postures. The second performance end point was the percentage of patients with pacing threshold measurements ≤2.0 volts at 0.4 milliseconds pulse width. All end points and objectives are summarized in Table S1.

STATISTICAL ANALYSIS

The study end points and statistical analyses are summarized in Table S2 and all are based on one-sided hypotheses. A pre-specified hierarchical testing procedure was developed such that the performance end points are evaluated after the safety end point was met, and ancillary objectives were evaluated if the performance end points were met. The study design included a group sequential design with a pre-specified early analysis of the safety end point after at least 134 patients underwent system implantation and were followed for at least 6 months, with 90% power and a one-sided 1.2% significance level. The safety end point assumes that the binomial rate approximating the survival analysis rate of freedom from major pacemaker-related complications would be 93%, with an 86% performance goal, similar to other

leadless pacemakers (see the Supplementary Appendix)[23,24] If the safety end point was met at this early analysis, then the 6-month end points will not be evaluated with the full study cohort.

The first performance end point was evaluated using the adjusted communication success rate calculated from a repeated measure logistic regression model, across the four tested postures during the 6-month visit (Fig. S3). The expected communication success rate was assumed to be 95% with a performance goal of 88%. Assuming an 80% power level and a one-sided 2.5% significance level, 152 tests were needed from 38 patients. Data usability criteria are detailed in Table S3 and additional information regarding derivation of the performance goal are provided in the Supplementary Appendix.

The second performance end point was the percentage of patients with adequate pacing threshold (≤2 volts at 0.4 millisecond pulse width) measured at the 6-month visit. Assuming a 90% power level and a one-sided 2.5% significance level, 57 patients were needed. The end point's performance goal is 80%, similar to that used for other leadless pacemakers.[23,24]

The overall type I error rate for study end points was controlled using the Intersection-Union Test methodology. Tipping point analyses were conducted to assess the impact of missing data for each end point. Other study results, such as mortality rate, overall system-related complications, and therapy performance to arrhythmia episodes, are observational in nature. The widths of confidence intervals reported have not been adjusted for multiplicity and the intervals should not be used in place of hypothesis testing. Missing data was assumed to be missing at random and death was treated as a competing risk (see the Supplementary Appendix). Additional statistical analysis methods are available in the Supplementary Appendix. Statistical analyses were performed using SAS version 9.4 (SAS Institute). The database snapshot date was January 24, 2024.

Results

PATIENTS

From July 2021 through January 2024, 293 patients were enrolled at 38 centers (Fig. 1). Due to variable timing of follow up visits, the 6-month end point cohort is made up of 162 patients who underwent implantation on or before the implantation date of the 134th patient to complete the 6-month follow-up visit (Fig. S4). The mean age of patients was 60 years, 16.7% were female, 61.1% had ischemic cardiomyopathy, and the mean (±SD) left ventricular ejection fraction was 33.1±12.6%. A total of 87 patients (53.7%) received a subcutaneous-ICD for primary prevention (Table 1 and Table S4). The representativeness of patients compared to the population is shown in Table S5. The median follow-up duration was 12.4 months, and 151 patients completed the 6-month follow-up visit. The sample size was 162, 147, and 151 patients for the safety end point, the first performance end point, and the second performance end point, respectively (Table S6).

DEVICE IMPLANTATION AND TESTING

All leadless pacemaker and ICD devices were successfully implanted, with 66 patients (40.7%) undergoing isolated pacemaker implantation procedures and 96 patients (59.3%) underwent both pacemaker and ICD implantation (Table S4). The median procedure and fluoroscopy times were 35.0 and 6.7 minutes, respectively, for isolated pacemaker implantation procedures and 77.0 and 6.8 minutes, respectively, for dual pacemaker and ICD implantation procedures. In five patients, multiple attempts at implanting the pacemaker were required (see the Supplementary Appendix); 3 of these patients underwent intraprocedural retrieval of the pacemaker; in these patients the median procedure and fluoroscopy times were 134.0 and 36.9 minutes, respectively. Intraprocedural pacemaker repositioning was required in 43 patients (26.5%), with 21 (12.9%) needing more than one repositioning during the implantation procedure. There were no full dislodgments from the myocardium (indicated by worsening electrical parameters or imaging) requiring re-intervention.

A total of 153 of 162 patients had at least one evaluable ventricular defibrillation test and 1 patient had tests that could not be evaluated. In an additional 3 patients, induction testing was attempted but a sustained arrhythmia could not be induced. Testing was not attempted in 5 patients. A total of 14 patients received more than one defibrillation test (see Supplementary Appendix). During ventricular fibrillation induced in 153 patients there were no instances where pacing delayed or inhibited subcutaneous-ICD therapy. Among 145 of 162 patients, during resting heart rate testing there was no evidence of oversensing the paced QRS complexes in the selected subcutaneous-ICD sense vector. For the remaining 17 patients, intermittent oversensing took place during testing, which was mitigated by reprogramming the pacemaker (see the Supplementary Appendix).

FOLLOW-UP

Overall system-related complications are shown in Table 2. The risk of complications related to the overall system was 8.6% (Fig. S5). There were no adverse events attributed to the pacemaker or therapy delivery after the implantation procedure and no patient requested inactivation of pacemaker therapy for any reason (Table S7). One patient withdrew from the trial after receiving a heart transplantation. Eight deaths occurred during the 6-month follow-up period (Fig. S6). Three deaths were related to cardiac pump failure, two were non-cardiac, and the cause of death was unknown for 3 patients. No deaths were adjudicated to be device- or procedure-related (Table S8). During follow-up, 2 patients (0.7%) underwent successful pacemaker retrieval procedures without complication: one patient where the initial implant was determined to be in the left ventricle and one patient who developed complete heart block, unrelated to the pacing-defibrillator system, and received a dual chamber leadless pacemaker.

END POINTS

The safety end point of major leadless pacemaker-related complication-free rate was evaluated on 162 patients with a result of 97.5%, the one-sided 95% lower confidence limit was 94.2%, which exceeded the

performance goal of 86% (Fig. 2). When analysis was performed without factoring mortality as a competing risk, end point results prevailed (Fig. S7). There were 4 major complications related to the leadless pacemaker that occurred in 4 patients (Table 2). One patient experienced a sudden drop in heart rate and blood pressure during extubation, immediately after subcutaneous-ICD implantation, required cardiopulmonary resuscitation and return of spontaneous circulation was achieved. Two patients experienced myocardial perforation with cardiac tamponade during the pacemaker implantation procedure; both recovered without sequelae after pericardiocentesis. The fourth patient was discovered to have the pacemaker implanted in the left ventricle during a routine echocardiogram 126 days after implantation; this was believed to have occurred due to inadvertent crossing of a patent foramen ovale. The pacemaker was extracted without complication and a second pacemaker was successfully implanted in the right ventricle.

For the first performance end point, a total of 147 of 162 patients had communication testing data at the 6-month visit. The communication success rate between the subcutaneous-ICD and the pacemaker was 98.8% with a one-sided 97.5% lower confidence limit of 97.0%, meeting the 88% performance goal (Fig. 3A). Communication success is shown in Fig 3B for each posture and in Table S9.

For the second performance end point, 151 of 162 patients had threshold testing at the 6-month follow-up. Among these patients, 147 (97.4%) patients had pacing thresholds ≤2.0 volts (at 0.4 millisecond pulse width) with a 97.5% one-sided lower confidence limit of 93.4%, exceeding the 80% performance goal (Fig. 3C). The mean pacing threshold was 0.70 volts at implant and 0.56 volts at 6 months (Fig. 3D). The mean R-wave amplitude was 11.1 millivolts at implantation and 14.6 millivolts at the 6-month visit (Fig. S8A. The mean pacing impedance was 812 ohms at implantation and 713 ohms at the 6-month visit (Fig. S8B). Tipping point analyses are shown in Table S10. Baseline characteristics do not appear to differ between patients with and without missing data for each end point (Tables S11, S12, and S13).

SPONTANEOUS ARRHYTHMIA EPISODES AND THERAPY

Antitachycardia pacing was delivered for 31 episodes of arrhythmia in 13 patients and successfully terminated 61.3% of episodes (Fig. S9). Antitachycardia pacing accelerated the arrhythmia in 3 episodes. All episodes that were not terminated by antitachycardia pacing were terminated by ICD shock, self-terminated, or the arrhythmia stabilized to a rate below the conditional defibrillation zone. Overall, appropriate therapy and shock risk were 9.3% and 6.2%, respectively (Fig. S10). No patient experienced a failure of therapy delivery due to device communication failure. Inappropriate therapy was recorded in 36 episodes that occurred in 14 patients, with a majority due to cardiac oversensing of slow ventricular arrhythmias (Tables S14-S20). The risks of inappropriate therapy and shock were 6.2% and 4.9%, respectively (Fig. S11-S17). No inappropriate episodes were due to the oversensing of pacing (see the Supplementary Appendix).

Discussion

In this prospective, international, multicenter, single-arm trial, a modular pacing-defibrillator system comprised of a leadless pacemaker receiving wireless communication from a subcutaneous-ICD exceeded the prespecified safety end point of major leadless pacemaker-related complication-free rate and performance requirements defined as communication success between the pacemaker and the ICD and pacing thresholds ≤2.0 volts (0.4 millisecond pulse width). System implantation was successful in all patients with 97.5% of patients being free of major leadless pacemaker-related complications at 6 months and 91.4% free of overall system-related complications. Ventricular perforation occurred in 1.2% of patients and was resolved with pericardiocentesis, a percentage similar to what has been reported for implantation of other single-chamber leadless pacemakers.[24,25] There were no pacemaker dislodgments up to 6 months after implantation, in contrast to what has been reported for other leadless pacemakers.[25,26] In two patients, device retrieval at a time remote from implantation was performed successfully.

Although the pacing-defibrillator system requires implantation of two separate devices, the major pacemaker-related complication rate of 2.5% appears comparable to the 4.0 and 6.7% complication rates associated with single-chamber leadless pacemakers.[24,25] The lower complication rate in our study might be explained by selecting investigators with ample experience implanting leadless pacemakers and subcutaneous-ICDs. Despite the generally high comorbidity of patients requiring ICD implantation, there were no device- or procedural-related deaths in our study.

Pacing thresholds appeared consistently low through follow-up with 97.4% of patients having 6-month pacing thresholds ≤2.0 volts, exceeding the 80% performance goal. There were no pacemaker revisions required for inadequate pacing thresholds. R-wave amplitude and pacing impedance were within the acceptable boundaries and seemed similar to other leadless pacemakers.[24,25]

This pacing-defibrillation system relies on unidirectional communication from the subcutaneous-ICD to the leadless pacemaker for antitachycardia pacing delivery. In our study, the in-office communication rate was 98.8% at 6 months, which exceeded the 88% performance goal. Modular communication was demonstrated across 4 different patient postures and appeared stable during follow-up. There were no instances where pacing resulted in subcutaneous-ICD arrhythmia undersensing during defibrillation testing and during clinical follow-up. The concept of modular communicating pacemaker-defibrillators enables individual component upgrades or revisions without complete replacement of the hardware, eliminates single points of failure, and allows multi-chamber and multidevice interaction by intrabody communication without transvenous leads, which are a source of long-term transvenous device morbidity.[2]

Antitachycardia pacing-mediated termination of ventricular arrhythmias occurred in 61.3%, which appears similar to the 46% to 72% success rates reported from large ICD trials[27,28] and the 70% success rate reported in an extravascular-ICD study.[29] However, patients with an extravascular-ICD have

experienced pain or discomfort with antitachycardia pacing or pause-prevention pacing, resulting in requests for providers to disable the pacing feature [29] and device extraction[30]. Inappropriate shocks were delivered in 4.9% patients, which is higher than the 2.1% that was reported by a recent subcutaneous-ICD trial at 6-months.[31] As most inappropriate shocks were delivered to slower ventricular arrhythmias, this finding may be attributable to patient selection and device programming.

At present, the subcutaneous-ICD has received a class IIa indication for patients who require an ICD and do not require pacing and a class III indication (contraindicated) for those patients that require an ICD with antitachycardia pacing for arrhythmia termination.[17] The inability of the subcutaneous-ICD to deliver antitachycardia pacing has been a barrier to subcutaneous-ICD therapy adoption in patients that may otherwise benefit from avoiding transvenous lead implantation. The reported percentage of successful communication between the pacemaker and the ICD and antitachycardia pacing termination of arrhythmias with the pacing-defibrillator system may potentially expand patient eligibility for a subcutaneous-ICD.

Our study has limitations. The study is limited by the inherent disadvantages of a prospective longitudinal, non-randomized design with no comparator group. We compared patient outcomes to pre-specified performance criteria for safety and performance based on benchmarks from prior published literature. Therefore, we can only report on performance and not efficacy. Our study enrolled patients with a high risk of ventricular tachycardia that were intentionally selected and our findings may not be generalizable to other patients who require ICDs or with ICDs already implanted.

In conclusion, the Modular ATP clinical trial prospectively demonstrated that the leadless pacemaker in wireless communication with a subcutaneous-ICD exceeded performance goals for freedom from major leadless pacemaker-related complications, communication between the leadless pacemaker and

subcutaneous-ICD, and the percentage of patients with a pacing threshold ≤ 2.0 volts at a 0.4 millisecond pulse-width at 6 months.

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Figure Legends

Figure 1 **Disposition of Patients.** The figure provides the disposition of the 293 patients who enrolled in the MODULAR ATP study and detailed disposition of the 162 patients available for the 6-month end point analysis.

Figure 2 **Freedom from Major Complications Related to the Leadless Pacemaker or Implantation Procedure.** The complication-free rate at 6 months and the one-sided 97.5% lower confidence limit is shown along with its prespecified performance goal of 86%.

Figure 3 **Wireless Communication Between the Subcutaneous-ICD and Leadless Pacemaker and Electrical Performance of the Leadless Pacemaker.** Panel A shows communication between the leadless pacemaker and ICD evaluated at the 6-month follow-up visit, across 4 patient postures (lying on left side, right side, supine, and upright). The success rate and the 97.5% one-sided lower confidence limit are presented with the pre-specified performance goal. Panel B shows the communication success of patients' individual postures and the 97.5% one-sided lower confidence limit for each posture in comparison with the performance goal. The widths of the confidence limits have not been adjusted for multiplicity; hence these should not be used in place of a hypothesis test. Panel C shows the results of the percentage of patients' pacing thresholds ≤2.0 volts (0.4 millisecond pulse width). The end point and its 97.5% one-sided lower confidence limit are presented with the pre-specified performance goal. Panel D shows the patients' pacing thresholds at implant, pre-discharge, and subsequent follow-up visits. Vertical bars represent standard errors. The widths of which have not been adjusted for multiplicity; hence these should not be used in place of a hypothesis test.

Tables

Table 1 Patient Characteristics at Baseline*

Patient Characteristics	**N=162**
Age–yr	60±12
Sex—no (%)	
Female	27 (16.7)
Male	135 (83.3)
Body-mass index†	29.8±5.9
Race or ethnic group—no. (%) ‡	
White	110 (67.9)
Black or African heritage	12 (7.4)
Other	10 (6.2)
Not Disclosed	31 (19.1)
Indication for ICD	
Primary prevention—no. (%)	87 (53.7)
Secondary prevention—no. (%)	75 (46.3)
NYHA classification—no. (%)	
Class I	40 (24.7)
Class II	82 (50.6)
Class III	38 (23.5)
Class IV	2 (1.2)
LVEF—%	33.1±12.6
Diabetes—no. (%)	57 (35.2)
Hyperlipidemia—no. (%)	103 (63.6)
Renal dysfunction—no. (%)	32 (19.8)
Cardiac Disease History—no. (%)§	
Ischemic cardiomyopathy	99 (61.1)

Non-ischemic cardiomyopathy	59 (36.4)
Other cardiac diseases	52 (32.1)
No Cardiac Disease History	**9 (5.6)**
Ventricular Arrhythmias—no. (%)⁋	
VT	86 (53.1)
Sustained VT and non-sustained VT	19 (11.7)
Monomorphic VT – non-sustained	35 (21.6)
Monomorphic VT – sustained	31 (19.1)
Stable VT	24 (14.8)
VF	28 (17.3)
Sustained VF and non-sustained VF	2 (1.2)
Non-sustained VF	3 (1.9)
Sustained VF	23 (14.2)
No Ventricular Arrhythmias	**67 (41.4)**
Prior cardiovascular implantable electronic device —no. (%)	
Transvenous pacemaker	0 (0.0)
Transvenous defibrillator	16 (9.9)
Subcutaneous defibrillator	69 (42.6)

*Plus-minus values are mean±SD. NYHA denotes New York Heart Association, LVEF denotes left ventricular ejection fraction, VF denotes ventricular fibrillation, and VT denotes ventricular tachycardia. Percentages may not total 100 because of rounding.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Data on race and ethnic group were voluntarily reported by the patients. Patients could select more than one category, and the sum of the numbers may exceed the total number of patients.

§Patients could have more than one category of cardiac disease history.

‖Patients could have multiple ventricular arrhythmia substrates.
**A total of 8 patients reported having a prior transvenous-ICD as well as subcutaneous-ICD

Comentado [JW1]: Should this be “or” rather than “as well as”?

Comentado [AB2R1]: 8 had both !!! [probably t then s

Table 2: Complications Related to the Pacing-defibrillator System, Implantation procedure

	Complication	
Classification	**Events**	**No. patients (%)**
Total	**18**	**16 (9.9)**
Related to LP or Procedure – During Procedure	**6**	**5 (3.1)**
Myocardial perforation with tamponade*	2*	2 (1.2) *
LP inadvertently implanted in the left ventricle via interatrial communication*	1*	1 (0.4) *
Adverse reaction - respiratory	1	1 (0.6%)
Venous access site bleeding	1	1 (0.6)
Atrial Fibrillation	1	1 (0.6)
Related to S-ICD System or Procedure—During Procedure	**3**	**3 (1.9)**
Adverse reaction - vasovagal syncope *†	1*†	1 (0.6) *†
Adverse reaction - respiratory	1	1 (0.6)
Hypotension attributed to IV antibiotic	1	1 (0.6)
Hematoma – S-ICD pocket (≤ 30d post-implant)	1	1 (0.6)
Related to S-ICD Programmable Generator	**2**	**2 (1.2)**
Premature cell battery depletion	1	1 (0.6)
S-ICD migration/revision	1	1 (0.6)
Related to S-ICD Electrode	**2**	**2 (1.2)**

	Complication	
Classification	**Events**	**No. patients (%)**
Invasive intervention to address inappropriate tachycardia therapy - noise (non-cardiac) - electrode	1	1 (0.6)
Electrode migration/revision	1	1 (0.6)
Related to S-ICD System Therapy	**1**	**1 (0.6)**
Invasive intervention to address VT below rate cut-off with oversensing	1	1 (0.6)
Related to S-ICD System Diagnosis	**1**	**1 (0.6)**
Random component failure - memory corruption	1	1 (0.6)
Related to S-ICD System; Patient Related	**1**	**1 (0.6)**
Incisional/superficial infection (>30d post-implant without explant)	1	1 (0.6)
Cardiovascular	**0**	**0 (0.0)**
Non-cardiovascular	**2**	**2 (1.2)**
Unclassified	**0**	**0 (0.0)**

*Adjudicated as major complications and, thus, contributed to the safety end point

†Adverse event classifications as presented in this table were adjudicated by the CEC.

Note that this adverse event was classified by the trial site as an observation (see Table S7) but this was adjudicated as a complication.

GA denotes general anesthesia, IV intravenous, LP leadless pacemaker, NSR normal sinus rhythm, RBBB right bundle branch block, SVT supraventricular tachycardia, S-ICD subcutaneous implantable cardioverter-defibrillator, and VT ventricular tachycardia.