ORIGINAL ARTICLE

An Entirely Subcutaneous Implantable Cardioverter–Defibrillator

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ABSTRACT

BACKGROUND

Implantable cardioverter–defibrillators (ICDs) prevent sudden death from cardiac causes in selected patients but require the use of transvenous lead systems. To eliminate the need for venous access, we designed and tested an entirely subcutaneous ICD system.

METHODS

First, we conducted two short-term clinical trials to identify a suitable device configuration and assess energy requirements. We evaluated four subcutaneous ICD configurations in 78 patients who were candidates for ICD implantation and subsequently tested the best configuration in 49 additional patients to determine the subcutaneous defibrillation threshold in comparison with that of the standard transvenous ICD. Then we evaluated the long-term use of subcutaneous ICDs in a pilot study, involving 6 patients, which was followed by a trial involving 55 patients.

RESULTS

The best device configuration consisted of a parasternal electrode and a left lateral thoracic pulse generator. This configuration was as effective as a transvenous ICD for terminating induced ventricular fibrillation, albeit with a significantly higher mean (±SD) energy requirement (36.6±19.8 J vs. 11.1±8.5 J). Among patients who received a permanent subcutaneous ICD, ventricular fibrillation was successfully detected in 100% of 137 induced episodes. Induced ventricular fibrillation was converted twice in 58 of 59 patients (98%) with the delivery of 65-J shocks in two consecutive tests. Clinically significant adverse events included two pocket infections and four lead revisions. After a mean of 10±1 months, the device had successfully detected and treated all 12 episodes of spontaneous, sustained ventricular tachyarrhythmia.

CONCLUSIONS

In small, nonrandomized studies, an entirely subcutaneous ICD consistently detected and converted ventricular fibrillation induced during electrophysiological testing. The device also successfully detected and treated all 12 episodes of spontaneous, sustained ventricular tachyarrhythmia. (ClinicalTrials.gov numbers, NCT00399217 and NCT00853645.)

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The use of implantable cardioverter–defibrillators (ICDs) is an established therapy for the prevention of death from ventricular arrhythmia.[1-5] However, conventional ICDs rely on transvenous leads for cardiac sensing and defibrillation. Complications of defibrillator implantation have been associated mainly with transvenous lead insertion and have included pneumothorax, hemothorax, and cardiac tamponade.[6-10] Difficulties in achieving venous access can prolong the procedure and occasionally result in failed ICD implantation.[11-13] In the long term, lead failure remains a major limitation in the use of ICDs, despite decades of innovations in lead design.[12-22] Lead failure either generates inappropriate shocks or impedes appropriate therapy.[20-23] Moreover, failed leads often require removal, a procedure that is associated with substantial morbidity and mortality.[24-36] If cardiac pacing is not necessary, there may be a clinical advantage in avoiding the use of transvenous electrodes. In this report, we describe the initial evaluation of an entirely subcutaneous ICD system designed to avoid the need for the placement of sensing and therapy electrodes within or on the heart.

Methods

Study Design

We report the results of two short-term trials of a temporarily inserted subcutaneous ICD electrode system, followed by two trials of long-term subcutaneous ICD implantation of a fully functional system. All the studies were sponsored by the manufacturer of the subcutaneous ICD, Cameron Health, and were designed by six of the academic investigators. The protocols were approved by the ethics committee at each participating institution and associated national and local regulatory agencies. All study participants satisfied standard criteria for ICD implantation[37] and provided written informed consent. Study data were collected by all the authors; device data were provided by engineers employed by the sponsor. The original manuscript was written by the first author with review and revision by all coauthors. All authors vouch for the accuracy and completeness of the data and the analyses.

Evaluation of Lead Configuration

From September 2001 through February 2004, we conducted the first short-term defibrillation trial to identify the best electrode configuration among those tested for the subcutaneous ICD. Four electrode configurations were selected on the basis of the use of specific anatomical landmarks: a left lateral pulse generator with an 8-cm coil electrode positioned at the left parasternal margin, a left pectoral pulse generator with a 4-cm coil electrode at the left inferior sternum, a left pectoral pulse generator with an 8-cm coil electrode curving from the left inferior sternum across to the inferior margin of the left sixth rib, and a left lateral pulse generator with a left parasternal 5-cm^2 oval disk (Fig. 1).

A total of 78 patients participated in this trial. Each patient underwent temporary subcutaneous implantation of one or more of the four device configurations evaluated and testing of the defibrillation threshold. The details of the protocol for defibrillation-threshold testing are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. Testing was conducted in an interleaved fashion with the use of a Latin square design; the data were evaluated by means of analysis of variance.[38,39] After completion of the study, all temporary subcutaneous devices were explanted, and each patient underwent implantation of a conventional transvenous ICD.

Comparison of Temporary Subcutaneous ICD with Transvenous ICD

From April 2004 through June 2005, in a second short-term trial involving 49 patients, we compared the best of the tested subcutaneous ICD systems in the first short-term trial (Fig. 1A) with a transvenous ICD system. For each patient, both the subcutaneous and transvenous devices were implanted during the same procedure. Defibrillation thresholds were compared after both systems were in position and both surgical pockets had been closed. The system that was tested first was selected randomly. The protocol for defibrillation-threshold testing of the subcutaneous ICD was identical to that used in the first short-term trial, as described in the Supplementary Appendix. The statistical comparison of the defibrillation thresholds for the devices was performed with the use of a paired t-test. After completion of the study, the subcutaneous device was explanted.

Permanent Implantation

After the two short-term trials, we performed two trials of permanent subcutaneous ICD implantation: a pilot trial involving 6 patients who underwent implantation in July 2008 in New Zealand,

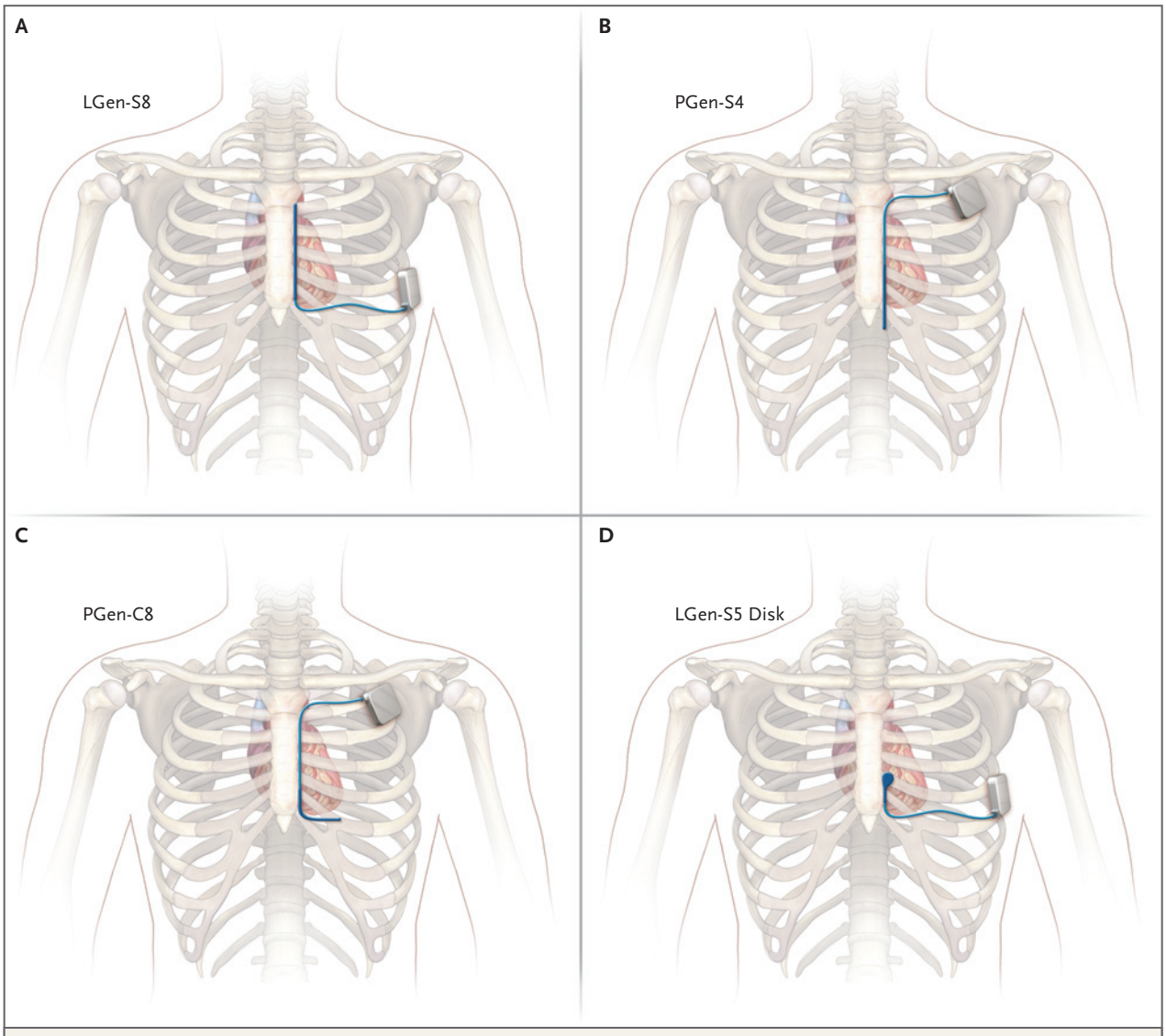

Figure 1. Four Configurations of a Subcutaneous Implantable Cardioverter–Defibrillator.

The four lead systems that were tested to select the best of these candidates were a left lateral pulse generator with an 8-cm coil electrode positioned at the left parasternal margin, designated LGen-S8 (Panel A); a left pectoral pulse generator with a left parasternal 4-cm coil electrode at the inferior sternum, designated PGen-S4 (Panel B); a left pectoral pulse generator with an 8-cm coil electrode curving from the left inferior parasternal line across to the inferior margin of the left sixth rib, designated PGen-C8 (Panel C); and a left lateral pulse generator with a left parasternal 5-cm^2 oval disk, designated LGen-S5 (Panel D).

followed by a trial involving 55 patients who underwent implantation in New Zealand and Europe between December 2008 and February 2009. We identified candidates for subcutaneous ICD implantation among the patients who were referred for ICD implantation at each participating center. The inclusion criterion was a class I, IIa, or IIb indication for ICD therapy.[37] Exclusion criteria were an estimated glomerular filtration rate of less than 30 ml per minute, a requirement for antibradycardia pacing, a history of ventricular tachycardia at rates slower than 170 beats per minute, and documented ventricular tachycardia known to be reliably terminated with antitachycardia pacing. The primary end point was successful immediate conversion of two consecutive episodes of induced ventricular fibrillation, each with a single 65-J shock.

SUBCUTANEOUS ICD SYSTEM

The subcutaneous ICD system that we tested in these studies consists of a 3-mm tripolar parasternal electrode (polycarbonate urethane 55D), which is connected to an electrically active pulse generator. The electrode is positioned parallel to and 1 to 2 cm to the left of the sternal midline, and the pulse generator is positioned over the sixth rib between the midaxillary line and the anterior axillary line (Fig. 2). The electrode has an 8-cm shocking coil, flanked by two sensing electrodes. The distal sensing electrode is positioned adjacent to the manubriosternal junction, and the proximal sensing electrode is positioned adjacent to the xiphoid process. The insertion of the subcutaneous ICD is guided exclusively by anatomical landmarks; no fluoroscopy is required. The surgical procedure and the device-testing protocol during implantation are described in the Supplementary Appendix.

During device operation, the cardiac rhythm is detected by the two sensing electrodes or by either of the sensing electrodes and the pulse generator. The subcutaneous ICD system automatically selects an appropriate vector for rhythm detection and for avoiding double QRS counting and T-wave oversensing. Once signals have been validated as free of noise and double detection, feature analysis and rate detection are used to sort rhythm type and determine the need for therapy. A conditional discrimination zone incorporating a feature-extraction technique can be programmed between rates of 170 and 240 beats per minute to distinguish supraventricular tachycardia from ventricular tachycardia and avoid inappropriate treatment of the former. Reconfirmation of ventricular tachyarrhythmia follows capacitor charging to avoid the delivery of shocks for nonsustained ventricular tachyarrhythmias. Testing of the device during implantation is done with the use of 65-J shocks to ensure a margin of safety. However, after the device has been implanted, it delivers only 80-J shocks. It can also reverse shock polarity automatically if the initial shock is not successful. In addition, demand pacing at 50 beats per minute is available for 30 seconds after a shock, with the use of a 200-mA biphasic transthoracic pulse. Pacing is activated only after more than 3.5 seconds of post-shock asystole.

All device settings are automated except for shock therapy (on/off), pacing after a shock (on/off), conditional discrimination of supraventricular tachycardia (on/off), and the upper-rate cutoff for the conditional shock zone (between 170 and 240 beats per minute). Data storage includes pre-event electrograms and rhythm markers through event termination. Up to 24 treated episodes can be stored, with up to 120 seconds of data per episode.

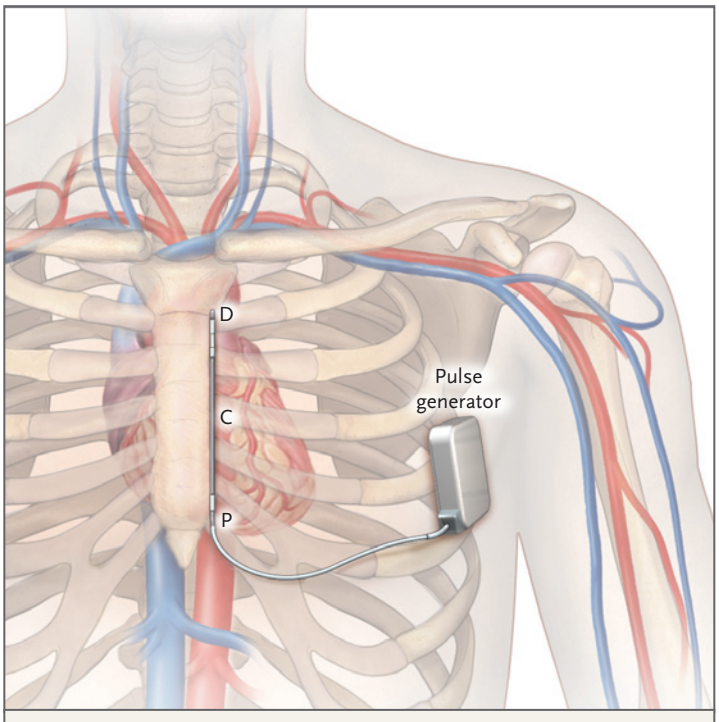

Figure 2. Locations of the Components of a Subcutaneous Implantable Cardioverter–Defibrillator In Situ.

The distal and proximal sensing electrodes (D and P, respectively) of the LGen-S8 device are shown, with the left lateral pulse generator and an 8-cm parasternal coil electrode (C).

RESULTS

EVALUATION OF LEAD CONFIGURATION

In the study comparing four lead configurations, the mean (±SD) age of the 78 patients was 61±11 years (range, 31 to 80), and 72 of the patients were men. The average weight was 82.4±15.2 kg (range, 53.0 to 143.5 [182±34 lb; range, 117 to 316]). The mean ejection fraction was 0.35±0.14 (range, 0.10 to 0.69). The mean defibrillation thresholds were 32.5±17.0 J (95% confidence interval [CI], 27.8 to 37.3) for configuration 1, 40.4±13.7 J (95% CI, 35.4 to 45.4) for configuration 2, 40.1±14.9 J (95% CI, 33.7 to 46.5) for configuration 3, and 34.3±12.1 J (95% CI, 28.8 to 39.8) for configuration 4 (Fig. 3A).

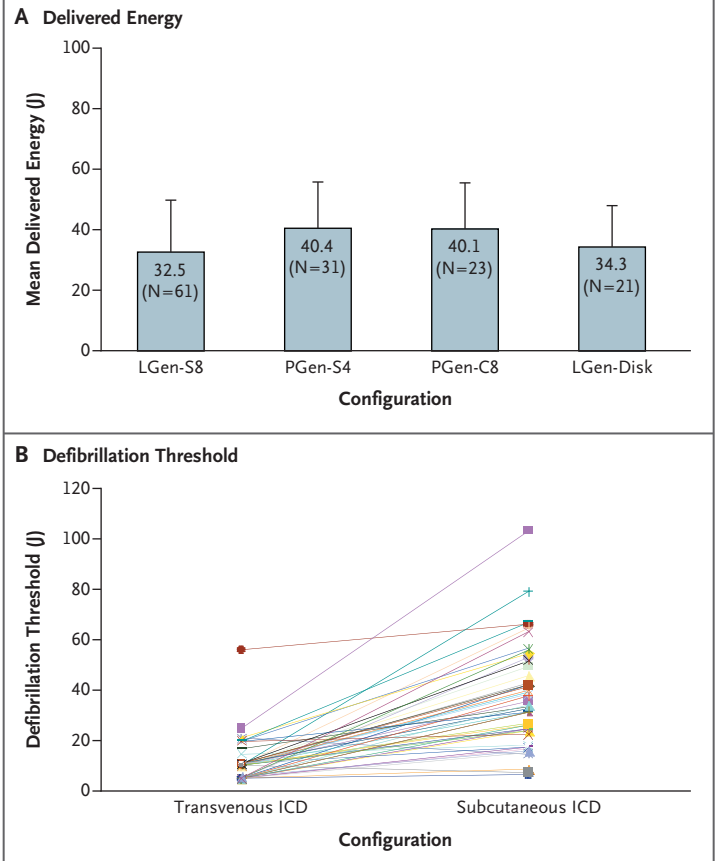

Figure 3. Energy Delivered with the Subcutaneous Implantable Cardioverter–Defibrillator (ICD), According to Lead Configuration, and a Comparison of Defibrillation Thresholds in Transvenous and Subcutaneous ICDs.

Panel A shows delivered defibrillation-threshold energies (measured in joules) in the four practical lead configurations that are described in Figure 1, as tested during trials of acute defibrillation ranges involving 78 patients. The T bars indicate standard deviations. Panel B shows a comparison of paired defibrillation-threshold data for transvenous ICDs and subcutaneous ICDs in 49 consecutive patients during randomized testing. The subcutaneous ICD was as effective as a transvenous ICD for terminating induced ventricular fibrillation, although with a significantly higher mean (±SD) energy requirement (36.6±19.8 J vs. 11.1±8.5 J, P<0.001). In these tests, the transvenous ICD in one patient and the subcutaneous ICD in another patient failed to defibrillate induced ventricular fibrillation at maximum device output. In each of these two cases, 20 J was arbitrarily added to the highest energy tested to assign a defibrillation-threshold value. In the patient whose subcutaneous device failed defibrillation testing, the parasternal electrode had been incorrectly placed 6 cm lateral to the sternum.

The left lateral pulse generator with the 8-cm parasternal coil electrode (Fig. 1A) had the lowest mean defibrillation threshold, although the differences among the configurations were not significant (P=0.07 for all comparisons by analysis of variance).

TEMPORARY SUBCUTANEOUS ICD VERSUS TRANSVENOUS ICD

In the study comparing the subcutaneous ICD with the transvenous ICD, the mean age of the 49 patients was 64±11 years (range, 42 to 79), and 47 of the patients were men. The average weight was 85.3±12.8 kg (range, 61.0 to 114.0 [188±28 lb; range, 134 to 251]). The mean ejection fraction was 0.37±0.13 (range, 0.19 to 0.70). The mean defibrillation threshold was 11.1±8.5 J (95% CI, 8.6 to 13.5) with the transvenous ICD and 36.6±19.8 J (95% CI, 31.1 to 42.5) with the subcutaneous ICD (P<0.001) (Fig. 3B). The transvenous device in one patient and the subcutaneous device in another patient failed to terminate induced ventricular fibrillation at maximum device output. In the patient whose subcutaneous ICD failed defibrillation testing, the parasternal electrode had been incorrectly positioned approximately 6 cm to the left of the sternum, beyond the left lateral margin of the heart.

PERMANENT SUBCUTANEOUS ICD PILOT STUDY

Six patients requiring ICD therapy underwent permanent subcutaneous device implantation in the pilot study. The mean age of the patients was 60±11 years (range, 46 to 72), with a mean weight of 99.0±12.0 kg (range, 87.0 to 114.0 [218±26 lb; range, 192 to 251]). All the patients were men. The mean ejection fraction was 0.23±0.07 (range, 0.15 to 0.35). Five of the patients had coronary disease, and one had nonischemic cardiomyopathy. Two had undergone previous cardiac surgery. One patient had a secondary-prevention indication, and five had a primary-prevention indication.

All six patients underwent successful implantation of the subcutaneous ICD, and in all the patients, defibrillation with 65-J submaximal shocks was successful during two consecutive episodes of induced ventricular fibrillation. A total of 18 episodes of ventricular fibrillation were induced (with one patient having multiple episodes of nonsustained ventricular fibrillation terminating before shock delivery); all the episodes were appropriately detected. After 488±2 days of follow-up (95 patient-months of subcutaneous ICD therapy), no spontaneous episodes of ventricular tachycardia or ventricular fibrillation had occurred in the six patients, and all were well, with no device-related complications or inappropriate shocks. Figure 4 shows data from one patient, with postoperative chest radiographs and an elec-

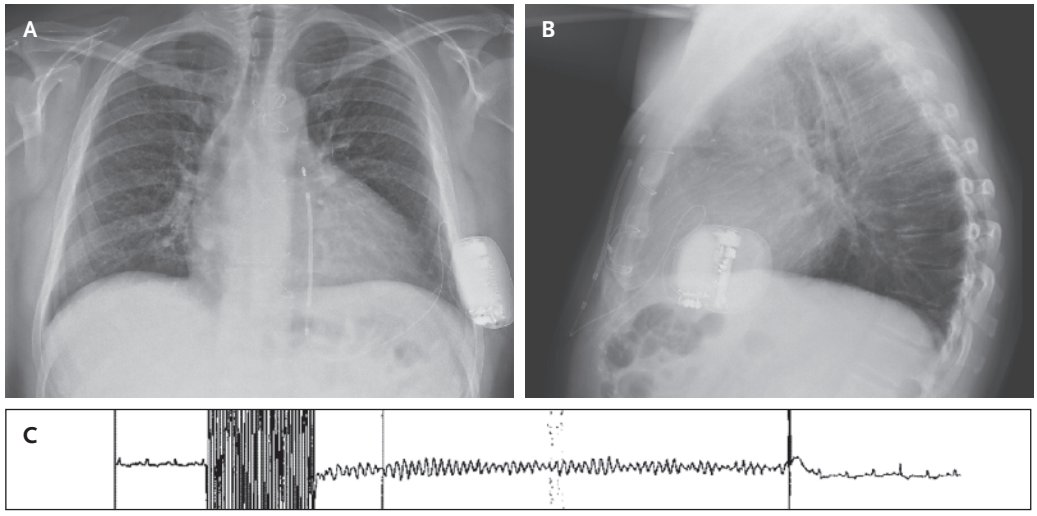

Figure 4. Chest Radiographs and an Electrocardiogram in a Patient Who Underwent Placement and Testing of a Subcutaneous Implantable Cardioverter–Defibrillator (ICD).

The radiographs in Panels A and B show the locations of the electrode and pulse generator of a subcutaneous ICD in a 54-year-old man who was evaluated in the pilot study. Panel C shows an electrocardiogram of an episode of induced ventricular fibrillation and its termination in the patient. The subcutaneous ICD was being evaluated for primary prevention in the patient, who had coronary disease, New York Heart Association class II heart failure with an ejection fraction of 15%, and obstructive lung disease; the patient's weight was 92 kg (203 lb).

trogram from one episode of induction and termination of ventricular fibrillation.

EUROPEAN CLINICAL TRIAL

For the European single-group clinical trial, 65 patients who presented for ICD implantation satisfied the enrollment criteria. Eight patients declined to participate in the study, and in two cases, the patient's physician opted for implantation of a transvenous ICD. Thus, 55 patients were enrolled in the trial, and all received a subcutaneous ICD. The clinical characteristics of the patients are shown in Table 1.

Defibrillation testing was not possible in two patients because of intraoperative hemodynamic instability in one patient and failure to induce ventricular fibrillation in the other. Therefore, 53 patients were evaluated for sensing and defibrillation during implantation. Of 137 episodes of induced ventricular fibrillation, 100% were detected by the subcutaneous ICD. In 52 of the 53 patients who were tested (98%), two consecutive episodes of induced arrhythmia were successfully converted at 65 J. Among these 52 patients, conversion was achieved with standard polarity in 50 patients and with reverse polarity in 2 patients. In the 53rd patient, defibrillation at 65 J was achieved during the first induction but not during the second induction. As specified by the protocol, this patient received a transvenous ICD. In another patient, it was necessary to reposition the electrode, which was initially inserted in an inappropriate location 6 cm from the midline. The mean time to delivery of a shock was 14.0±2.5 seconds. The mean duration of the procedure, which was performed for the first time by most of the practitioners, including device insertion and at least two induction and termination tests, was 67±33 minutes. The procedure time was reduced to 55±23 minutes for practitioners who completed at least three implantations.

After 10±1 months and 46 patient-years of follow-up, 54 of 55 patients (98%) were alive. One death from renal failure occurred 6 months after device implantation in an 84-year-old patient. Eighteen days before he died, the patient requested that his subcutaneous ICD be turned off. A pocket infection developed in two patients; pocket revision was performed in one patient, and the other elected to discontinue defibrillator therapy. There were no cases of pocket erosion. No lead fractures developed in any patient, and no generator migration occurred. Minor lead migration was noted during follow-up in two patients.

Table 1. Clinical Characteristics of 55 Patients in the European Clinical Trial of a Subcutaneous Implantable Cardioverter–Defibrillator (ICD).*

Characteristic	Value
Age — yr	
Mean	56±13
Range	22–84
Male sex — no. (%)	44 (80)
Body-mass index†	
Mean	28±5
Range	17–40
Left ventricular ejection fraction	
Mean	0.34±0.13
Range	0.14–0.73
Cause of cardiac disease — no. (%)	
Coronary artery disease	37 (67)
Nonischemic cardiomyopathy	10 (18)
Congenital heart disease	2 (4)
Other condition	6 (11)
Previous cardiac surgery — no. (%)	17 (31)
Indication for ICD — no. (%)	
Primary prevention	43 (78)
Secondary prevention	12 (22)

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Another three patients had parasternal lead dislodgment due to inadequate anchoring of the distal tip of the electrode. In each of these patients, lead repositioning was required within a week after surgery. In another patient, lead dislodgment occurred at 6 months, during vigorous physical activity.

In one patient, oversensing occurred because of inadequate placement of the electrode in the header block, resulting in inadequate contact with one of the sensing electrodes. This problem was addressed the day after surgery with reprogramming of the detection vector rather than reoperation. Inappropriate sensing due to muscle noise occurred in three patients; the problem was addressed with device reprogramming in all three cases. One patient who had received a new drug therapy had inappropriate sensing (double detection) after the narrow QRS complex in sinus rhythm changed to a right bundle-branch block during sinus tachycardia (150 beats per minute). During 3 months of further follow-up after the detection algorithm was revised, no inappropriate shocks occurred. No shocks were delivered inappropriately for atrial fibrillation, sinus tachycardia, or supraventricular tachycardia at any time during the study when such episodes occurred at rates of more than 170 beats per minute.

A total of 12 episodes of spontaneous ventricular tachycardia were detected and successfully treated in three patients, including 1 episode after the above-mentioned software revisions (see the figure in the Supplementary Appendix). All patients were treated before the onset of syncope, and there were no adverse events. One of these patients was successfully treated for repetitive ventricular tachycardia ("VT storm"), including seven successive episodes of ventricular tachycardia.

DISCUSSION

In the studies reported here, we describe the initial evaluation of an entirely subcutaneous ICD system. We identified a suitable device configuration, assessed the defibrillation threshold of the device in comparison to that of the standard transvenous ICD, and conducted two small, single-group trials of permanent device implantation. In the permanent-implantation studies, the subcutaneous ICD successfully and consistently detected and converted ventricular fibrillation that was induced during electrophysiological testing. The device also successfully detected and treated 12 episodes of spontaneous ventricular tachyarrhythmia that occurred in patients who were enrolled in the European clinical trial.

The goal of developing a subcutaneous ICD was to overcome some of the problems that are associated with transvenous leads in conventional ICDs.[3,6-11,14,15,40] Such a device could potentially reduce or eliminate problems such as failure to achieve vascular access, intravascular injury, and lead failure requiring difficult procedures for extraction and replacement. Additional potential benefits of such a device include the preservation of venous access for other uses and the avoidance of radiation exposure during fluoroscopy, which is required for transvenous ICD implantation. These benefits would be especially important for young patients, in whom leads may fail during the decades that therapy is needed.[41]

The need for ICD systems that avoid the use of transvenous leads has been recognized previously,[42-49] and some earlier exploratory efforts led to the present work.[50,51] Some physicians have adapted existing technology to treat children with

limited venous access. Leads have been inserted in unusual locations, and epicardial and subcutaneous leads have been used.[44-46] Other subcutaneous defibrillation systems have been shown to work with an approximate tripling of the energy that is required by a transvenous system, findings that are consistent with the results of our study.[47,48] However, such systems have not incorporated subcutaneous rhythm detection but instead have used transvenous or epicardial sensing electrodes for detection.

Our studies are preliminary, early-phase trials that were primarily intended to show the feasibility of an entirely subcutaneous ICD. They provide limited information regarding the detection and conversion of ventricular tachyarrhythmia in the clinical setting, despite the demonstration of consistent detection and termination of ventricular fibrillation at the time of implantation. These studies cannot show whether subcutaneous ICDs are superior to conventional transvenous ICDs with respect to such characteristics as lead stability or failure. Indeed, the initial experience includes several cases of problems such as lead migration, lead dislodgment, and inappropriate sensing. With respect to each of these issues, the subcutaneous ICD system was adjusted shortly after implantation in an effort to improve the system's reliability. Problems with lead dislodgment have led to the introduction of an anchoring sleeve and a new surgical technique. Inappropriate sensing has been addressed through software revision, with no incidents in the 3 months after revision. However, these modifications will require further testing in additional groups of patients. Ultimately, the relative benefit of subcutaneous ICDs, as compared with transvenous ICDs, will need to be shown in large, long-term, randomized, prospective, multicenter clinical trials.

In addition, there are inherent limitations of this device design. Although transient post-shock pacing is available, the subcutaneous ICD cannot provide long-term pacing. It is therefore not an alternative to transvenous ICDs when antibradycardia pacing is required. Also, the subcutaneous ICD is not designed to treat patients with ventricular tachycardia at rates slower than 170 beats per minute. The lack of capability to provide antitachycardia pacing may be a limitation in patients with frequent, recurrent, monomorphic ventricular tachycardia.

In conclusion, we found that in small, nonrandomized studies, an entirely subcutaneous ICD system successfully and consistently detected and converted episodes of ventricular fibrillation that were induced during electrophysiological testing. It also successfully detected and treated all 12 episodes of spontaneous, sustained ventricular tachyarrhythmia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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