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Friedman, Paul; Murgatroyd, Francis; Boersma, Lucas V.A.; Manlucu, Jaimie; O'Donnell, David; Knight, Bradley P.; Clémenty, Nicolas; Leclercq, Christophe; Amin, Anish; Merkely, Béla P.; Birgersdotter-Green, Ulrika M.; Chan, Joseph Y.S.; Biffi, Mauro; Knops, Reinoud E.; Engel, Greg; Muñoz Carvajal, Ignacio; Epstein, Laurence M.; Sagi, Venkata; Johansen, Jens B.; Sterliński, Maciej; Steinwender, Clemens; Hounshell, Troy; Abben, Richard; Thompson, Amy E.; Wiggenhorn, Christopher; Willey, Sarah; Crozier, Ian; Extravascular ICD Pivotal Study Investigators

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ORIGINAL ARTICLE

Efficacy and Safety of an Extravascular Implantable Cardioverter–Defibrillator

P. Friedman, F. Murgatroyd, L.V.A. Boersma, J. Manlucu, D. O'Donnell, B.P. Knight, N. Clémenty, C. Leclercq, A. Amin, B.P. Merkely, U.M. Birgersdotter-Green, J.Y.S. Chan, M. Biffi, R.E. Knops, G. Engel, I. Muñoz Carvajal, L.M. Epstein, V. Sagi, J.B. Johansen, M. Sterliński, C. Steinwender, T. Hounshell, R. Abben, A.E. Thompson, C. Wiggenhorn, S. Willey, and I. Crozier, for the Extravascular ICD Pivotal Study Investigators*

ABSTRACT

BACKGROUND

The extravascular implantable cardioverter–defibrillator (ICD) has a single lead implanted substernally to enable pause-prevention pacing, antitachycardia pacing, and defibrillation energy similar to that of transvenous ICDs. The safety and efficacy of extravascular ICDs are not yet known.

METHODS

We conducted a prospective, single-group, nonrandomized, premarket global clinical study involving patients with a class I or IIa indication for an ICD, all of whom received an extravascular ICD system. The primary efficacy end point was successful defibrillation at implantation. The efficacy objective would be met if the lower boundary of the one-sided 97.5% confidence interval for the percentage of patients with successful defibrillation was greater than 88%. The primary safety end point was freedom from major system- or procedure-related complications at 6 months. The safety objective would be met if the lower boundary of the one-sided 97.5% confidence interval for the percentage of patients free from such complications was greater than 79%.

RESULTS

A total of 356 patients were enrolled, 316 of whom had an implantation attempt. Among the 302 patients in whom ventricular arrhythmia could be induced and who completed the defibrillation testing protocol, the percentage of patients with successful defibrillation was 98.7% (lower boundary of the one-sided 97.5% confidence interval [CI], 96.6%; P<0.001 for the comparison with the performance goal of 88%); 299 of 316 patients (94.6%) were discharged with a working ICD system. The Kaplan–Meier estimate of the percentage of patients free from major system- or procedure-related complications at 6 months was 92.6% (lower boundary of the one-sided 97.5% CI, 89.0%; P<0.001 for the comparison with the performance goal of 79%). No major intraprocedural complications were reported. At 6 months, 25 major complications were observed, in 23 of 316 patients (7.3%). The success rate of antitachycardia pacing, as assessed with generalized estimating equations, was 50.8% (95% CI, 23.3 to 77.8). A total of 29 patients received 118 inappropriate shocks for 81 arrhythmic episodes. Eight systems were explanted without extravascular ICD replacement over the 10.6-month mean follow-up period.

CONCLUSIONS

In this prospective global study, we found that extravascular ICDs were implanted safely and were able to detect and terminate induced ventricular arrhythmias at the time of implantation. (Funded by Medtronic; ClinicalTrials.gov number, NCT04060680.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Friedman can be contacted at friedman.paul@mayo.edu or at the Department of Cardiovascular Medicine, Mayo Clinic, 200 First Ave. SW, Rochester, MN 55905.

*A full list of the investigators in the Extravascular ICD Pivotal Study is provided in the Supplementary Appendix, available at NEJM.org.

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The implantable cardioverter–defibrillator (ICD) reduces cardiac mortality among patients at risk for ventricular arrhythmias.[1,2] Transvenous ICD implantation may be complicated by vascular injury, cardiac perforation, pneumothorax, hemothorax, and venous obstruction.[3-5] Transvenous leads are also subject to mechanical failure and serious infection resulting in lead extraction.[3,4] The subcutaneous ICD was developed to avoid the vascular risks of transvenous ICDs.[6,7] In a recent comparison with transvenous ICDs, the subcutaneous ICD effectively prevented sudden arrhythmic death with fewer complications; however, it was associated with shocks for ventricular tachycardia that might have been avoided if antitachycardia pacing were available.[8,9] The subcutaneous ICD lead is placed between the skin and sternum, leaving bone between electrodes and the myocardium. Consequently, a high current is required to pace, resulting in extracardiac stimulation, and to defibrillate, necessitating a larger device. Antitachycardia pacing is not available, and bradycardia pacing is limited to the immediate period after a shock and is uncomfortable owing to skeletal muscle stimulation.[10] In addition, higher defibrillation energy requirements necessitate a larger generator than transvenous ICDs (60 cm^3 vs. 30 cm^3), with compromised longevity (projected life span, 7.3 years vs. 13.6 years).[6,11,12]

We hypothesized that substernal electrodes would retain the benefits of an extravascular ICD while providing pause-prevention and antitachycardia pacing with lower-energy defibrillation owing to their juxtaposition to the heart.[13] Short-term and long-term studies in animals and short-term studies involving humans supported this concept.[14-17] Subsequently, the Extravascular ICD Pilot Study showed device safety and efficacy at 3 months with no major intraprocedural complications.[18] To confirm longer-term safety and efficacy, the global Extravascular ICD Pivotal Study was performed.

METHODS

STUDY DESIGN

The Extravascular ICD Pivotal Study was a prospective, global, multicenter, single-group, nonrandomized, premarket approval study designed to enroll up to 400 patients at up to 60 sites. Ethics committees at the participating sites approved the study protocol (available with the full text of this article at NEJM.org), and all the patients provided written informed consent. After implantation, patients were followed up at 2 weeks, 3 months, 6 months, and every 6 months until study closure. Details of the full study design, population, and statistical methods have been reported previously.[13]

A Quick Take is available at NEJM.org

PATIENT POPULATION

Patients with a class I or IIa indication for an ICD for primary or secondary prevention according to international guidelines were recruited. Patients who required bradycardia pacing or cardiac resynchronization therapy or who had undergone sternotomy were excluded. (Full inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.)

OVERSIGHT

The study was sponsored by Medtronic, with design and conduct oversight provided by a global steering committee of physicians (Table S2). An independent data monitoring committee reviewed accumulating data and interim analyses to protect the interests of patients and monitor the overall conduct of the study. Major complications (defined in Table S3) were adjudicated by an independent clinical-events committee, and sustained arrhythmic episodes were adjudicated by an episode-review committee (see the Methods section in the Supplementary Appendix). The original manuscript was written by the first author with critical review, revision, and agreement to submit from all the authors, including those employed by the study sponsor. Final review and approval were the responsibility of the first author. Data were collected by investigators and site personnel, analyzed by statisticians employed by the sponsor, and interpreted by the authors. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

END POINTS

The primary efficacy end point was successful defibrillation at implantation, defined as termination of an induced sustained shockable ventricular arrhythmia either with one 20-J shock or with 30 J on two consecutive episodes. The efficacy objective would be met if the lower bound-

ary of the one-sided 97.5% confidence interval for the percentage of patients with successful defibrillation was greater than 88% when testing was performed with a safety margin of 10 J or more. The primary safety end point was freedom from major system- or procedure-related complications at 6 months. The safety objective would be met if the lower boundary of the one-sided 97.5% confidence interval for the percentage of patients free from such complications was greater than 79%.[13] Ancillary end points are outlined in the Methods section in the Supplementary Appendix. Analyses of ancillary end points and additional analyses other than the 6-month primary safety analysis used the full follow-up cohort (mean [±SD], 10.6±6.0 months), unless otherwise specified.

A video showing the implantation procedure is available at NEJM.org

SYSTEM DESCRIPTION AND IMPLANTATION

The extravascular ICD system and implantation procedure have been described in detail elsewhere.[13,19] In brief, the pulse generator, implanted along the patient's left midaxillary line, has a volume of 33 cm^3 and delivers shocks of up to 40 J (Fig. 1). Leads were implanted substernally with the use of anteroposterior and lateral fluoroscopic guidance. Pacing features include pause prevention, antitachycardia pacing, and pacing after a shock has been delivered. Implantations were performed in cardiac catheterization laboratories or hybrid operating rooms by cardiologists who underwent a structured hands-on training program emphasizing anatomy (Video 1; also see the study protocol and the Methods section in the Supplementary Appendix).

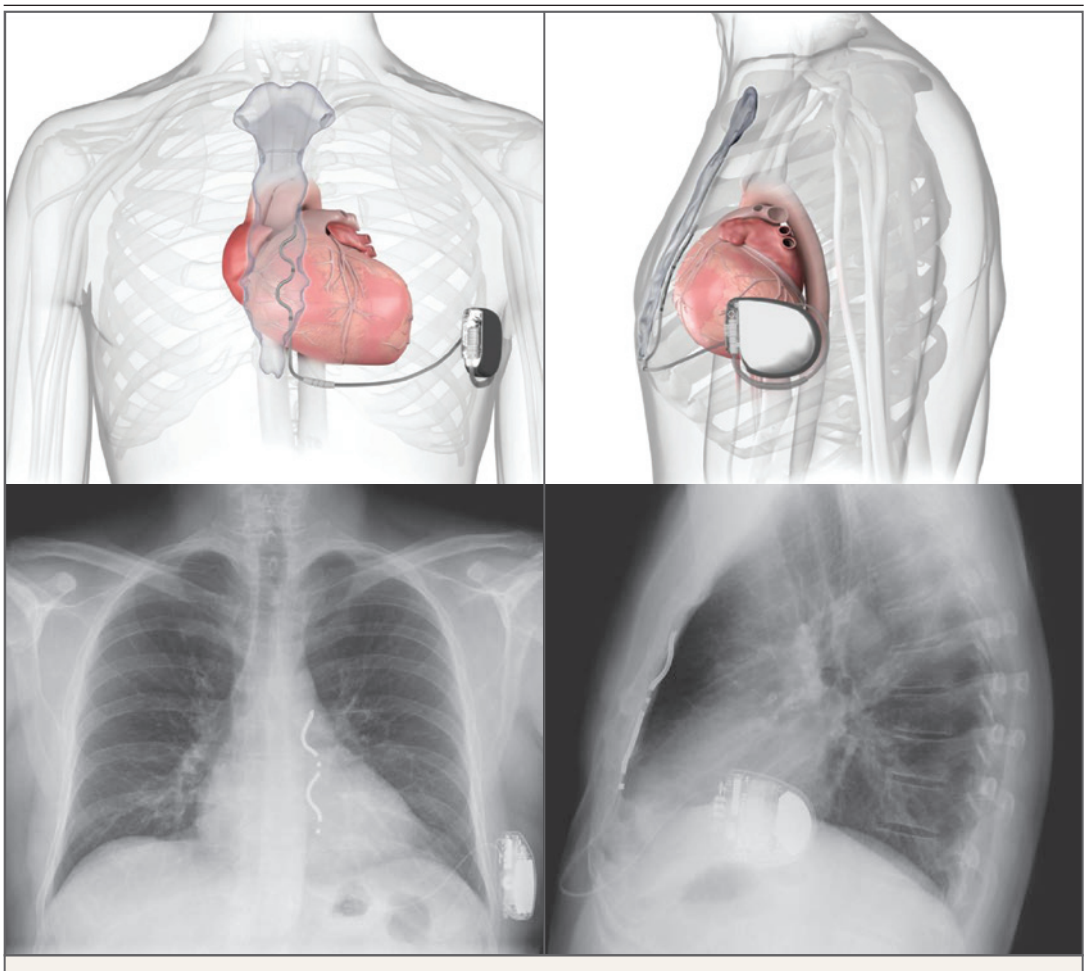

Figure 1. Implanted Extravascular ICD System.

The extravascular implantable cardioverter–defibrillator (ICD) system is shown in anteroposterior (left) and lateral (right) views. Reproduced with permission from Medtronic.

STATISTICAL ANALYSIS

To calculate the sample size for the primary efficacy end point, it was assumed that the true probability of successful defibrillation at implantation was 93.5%. The statistical software package PASS 2008 (NCSS) was used to determine that in order to achieve 90% power, 292 patients would need to complete the defibrillation protocol. To estimate the statistical power for the primary safety end point, a Weibull distribution was used to model the occurrence of major complications, under the assumption that the percentage of patients free of such complications would be 90% at 1 month and 86% at 6 months. A Weibull distribution was also used to model attrition due to study exit or death, with an incidence of 9% at 1 month and 16% through the first year of follow-up after implantation. Under these assumptions, the study results were simulated 10,000 times, with each simulated sample including 292 patients. For each simulated sample, a 182-day Kaplan–Meier estimate of the percentage of patients free from major complications and a confidence interval were calculated; the results of the simulation showed that a sample of 292 patients was sufficient to provide 90% power for this objective. For the primary efficacy end point, there were no missing data; however, the analysis was restricted to patients who completed the defibrillation protocol. For the primary safety end point, data from patients were censored at the time of study exit or last study contact. There was no adjustment for multiple comparisons; therefore, the confidence intervals should not be used to infer definitive treatment effects.

The estimated percentage of patients free from major complications was generated with the use of the Kaplan–Meier method; the associated one-sided 97.5% confidence interval was calculated with the use of a log–log transformation. Defibrillation success was evaluated with an exact binomial test and Clopper–Pearson confidence interval. The success rate of antitachycardia pacing was assessed with generalized estimating equations. (Additional information on statistical analyses are provided in the Methods section in the Supplementary Appendix.)

RESULTS

PATIENTS

From September 2019 through October 2021, a total of 356 patients were enrolled at 46 centers in 17 countries across North America, Europe, Asia, and Oceania. Of these, 316 underwent an implantation attempt (25.3% female; mean [±SD] age, 53.8±13.1 years); 40 patients exited the study before an implantation attempt (reasons are detailed in Fig. S1). Recipients of an extravascular ICD had a mean body-mass index (the weight in kilograms divided by the square of the height in meters) of 28.0±5.6 and a mean left ventricular ejection fraction of 38.9±15.4%. The clinical characteristics of the patients enrolled in the study are shown in Tables 1 and S4.

IMPLANTATION PROCEDURE

A total of 45 physicians performed implantation procedures in 316 patients. Among 316 patients with an implantation attempt, the lead was placed in 315 (99.7%). Sensing function was acceptable in 307 patients, who underwent defibrillation testing. Reasons for patient discharge without implantation included failed or incomplete defibrillation testing and inadequate R-wave sensing (Fig. S2). The median time from first incision to final lead position was 35.5 minutes (interquartile range, 25 to 50), and the median time from first incision to final suture, inclusive of defibrillation testing, was 66 minutes (interquartile range, 50 to 93). Additional details of implantation procedures are provided in the Results section in the Supplementary Appendix and in Table S5.

PRIMARY EFFICACY END POINT

Defibrillation testing was initiated in 307 patients, completed in 302, and successful in 298 (Fig. S2). One device remained implanted at the physician's discretion despite incomplete electrical testing. Thus, in 316 implantation attempts, 299 patients (94.6%) underwent complete implantation and proceeded to long-term follow up. The percentage of patients with successful defibrillation was 98.7% (one-sided 97.5% confidence interval [CI], 96.6%; $P<0.001$ for the comparison with the efficacy performance goal of 88%), with 72.5% successful at 20 J and 27.5% successful at 30 J (Fig. 2A; also see the Results section in the Supplementary Appendix). A total of 29 patients underwent generator repositioning (20 patients), lead repositioning (5 patients), or other maneuvers (20 patients) to complete the defibrillation protocol (Table S6). All but 10 patients had defibrillation testing completed on the date of implantation. Ventricular tachycardia

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Patients with Implantation Attempted (N=316)
Age — yr	53.8±13.1
Female sex — no. (%)	80 (25.3)
Indication for ICD — no. (%)	
Primary prevention	258 (81.6)
Secondary prevention	57 (18.0)
Unclassified	1 (0.3)
NYHA functional class — no. (%)	
I	75 (23.7)
II	184 (58.2)
III	23 (7.3)
IV	0
Not available	34 (10.8)
Body-mass index	28.0±5.6
Left ventricular ejection fraction — %	38.9±15.4
Cardiomyopathy — no. (%)	265 (83.9)
Primary or idiopathic electrical disease — no. (%)	24 (7.6)
Stroke or stroke-related event — no. (%)	24 (7.6)
Spontaneous arrhythmia — no. (%)	
Atrial fibrillation	44 (13.9)
Ventricular arrhythmia	135 (42.7)
Other medical history — no. (%)	
Diabetes	66 (20.9)
Renal dysfunction	30 (9.5)
Medication type — no. (%)	
Beta-blocking agent, excluding sotalol	238 (75.3)
Antiarrhythmic drug: class I or III, including sotalol	19 (6.0)
ACE inhibitor, ARB, or ARNI	200 (63.3)
Mineralocorticoid receptor antagonist	124 (39.2)
Race or ethnic group — no. (%)†	
Asian	7 (2.2)
Black	16 (5.1)
Hispanic or Latino	7 (2.2)
White	87 (27.5)
Not reported owing to local requirements in non-U.S. countries	197 (62.3)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.

† Data on race and ethnic group were collected from medical records, the physician, or the patient. Full information on race and ethnic group is provided in Table S9 in the Supplementary Appendix.

or ventricular fibrillation was detected with the use of a programmed sensitivity of 0.2 mV or more (approximately 3 times the maximum sensitivity of 0.075 mV) in all 307 patients in whom defibrillation testing was initiated (see the Methods section in the Supplementary Appendix).

PRIMARY SAFETY END POINT

The Kaplan–Meier estimate of the percentage of patients free from major system- or procedure-related complications through 182 days was 92.6% (lower boundary of the one-sided 97.5% CI, 89.0%; P<0.001 for the comparison with the safety performance goal of 79%) (Fig. 2B). No major intraprocedural complications were reported, and a single minor complication of muscle injury (inadvertent blunt dissection of the rectus fascia) resolved without sequelae. Through 6 months, 25 major complications were observed in 23 patients, most commonly lead dislodgment (10 events in 9 patients) (Table 2). No major complications had further clinical sequelae. No deaths from arrhythmia related to ineffective device therapy were reported (Table S7). Through 6 months, the Kaplan–Meier estimates of the percentage of patients with major procedure-related and major system-related complications were 5.4% and 4.9%, respectively. There was one report of a device lockup at implantation related to a software–hardware interaction that resulted in device replacement. Programming guidance was provided to prevent this interaction in other devices, and a software revision that was released during the study eliminated the problem.

Two lead fractures occurred, both after more than 6 months (see the Results section in the Supplementary Appendix). The lead fractures resulted from implantation below the xiphisternum and substantial unanticipated bending conditions; these events led to updates in implantation guidance. The lead fractures did not result in harm to patients other than the need to undergo repeat interventions.

LONG-TERM DEFIBRILLATION TESTING

A total of 37 patients were enrolled in a prespecified 6-month defibrillation protocol distinct from the implantation protocol (see the Methods section in the Supplementary Appendix). Ventricular arrhythmia could not be induced in 1 patient. Among the 36 patients who

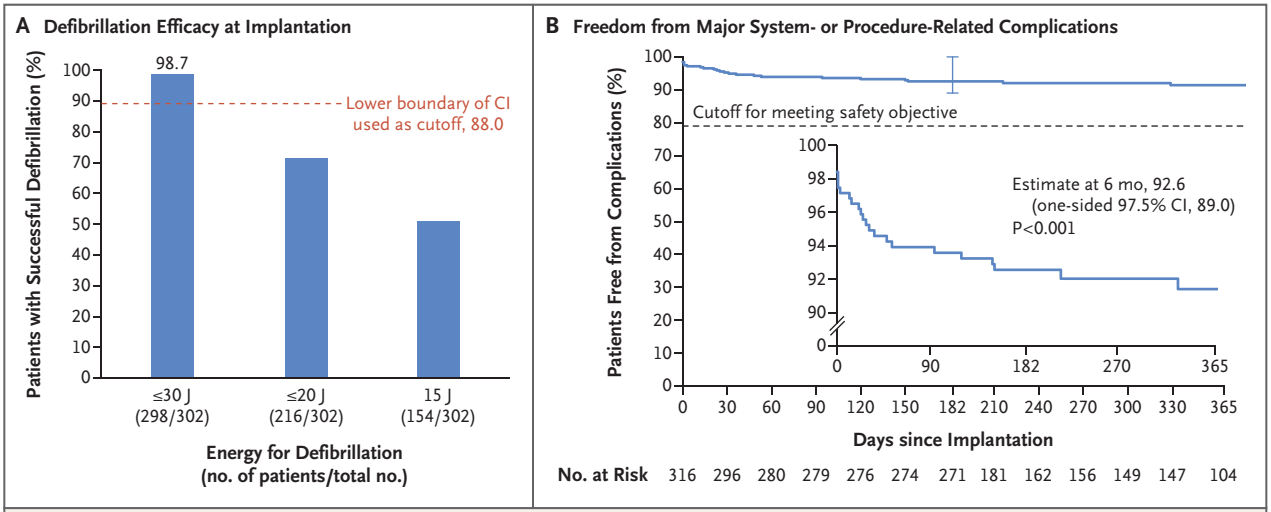

Figure 2. Defibrillation Efficacy at Implantation and Freedom from Major Complications at 6 Months.

In Panel A, defibrillation efficacy is shown at 30 J or less, 20 J or less, and 15 J. The lower boundary of the one-sided 97.5% confidence interval that was used as the cutoff for meeting the prespecified efficacy objective is shown in red. Panel B shows a Kaplan–Meier plot and one-sided 97.5% confidence interval of freedom from major system- or procedure-related complications. The estimated percentage of patients free from such complications at 6 months is shown with inset text (92.6%; lower boundary of the one-sided 97.5% CI, 89.0% at 182 days after implantation). The cutoff for meeting the prespecified safety objective (79%) is shown as a dashed black line. The I bar represents the confidence interval. The inset shows the same data on an expanded y axis.

completed testing, the testing was successful in all 36: 30 patients underwent defibrillation with 30 J, and 6 patients underwent defibrillation with 40 J. Additional defibrillation testing was conducted at the physician's discretion from 1 to 405 days after implantation in 18 patients, all of whom underwent defibrillation successfully with 40 J or less.

PACING THERAPY PROGRAMMING AND PACING SENSATION

A total of 17 of 299 patients (5.7%) had the pause-prevention pacing therapy feature programmed as "on" through at least one follow-up visit, with 4.6% of the patients having therapy turned off owing to the pacing sensation not being acceptable at 6-month follow-up. Antitachycardia pacing was not programmed or was turned off in 72 of 284 patients (25.4%) at 6 months, with 14 of 72 being due to the pacing sensation not being acceptable. A total of 249 of 299 patients (83.3%) had postshock pacing turned on at any point from prehospital discharge; no episodes resulted in treatment. At the 6-month follow-up, 5 of 284 patients (1.8%) had postshock pacing turned off owing to the pacing sensation not being acceptable.

APPROPRIATE THERAPIES

A total of 66 spontaneous arrhythmic episodes occurred in 16 patients who received appropriate therapies through the 10.6-month mean follow-up. Among discrete spontaneous events treated with shock, 18 of 18 episodes (100%) were successfully converted to sinus rhythm. The first-shock conversion efficacy with respect to discrete episodes was 14 of 18 (78%). In addition, 3 patients with arrhythmia storm (≥3 events within 24 hours) had 15 combined episodes, 12 of which were successfully converted to sinus rhythm by the device; for 3 episodes in a single patient, the outcome could not be determined owing to device storage limitations. The patient was treated in the hospital, and the arrhythmia was resolved.

Antitachycardia pacing was delivered in 10 patients and successfully terminated 32 of 46 episodes (70%) (Fig. S3), including 3 episodes in which immediate spontaneous arrhythmia reinitiation resulted in shock delivery. After adjustment for multiple episodes per patient with the use of generalized estimating equations, the success rate of antitachycardia pacing was 50.8% (95% CI, 23.3 to 77.8). Of 14 episodes not terminated by antitachycardia pacing, 4 were terminated

Table 2. Summary of Major Complications in Patients with an Implantation Attempt through 6 Months.

Event Type	Death	Permanent Loss of Defibrillation Function*	Hospitalization	Hospitalization Prolonged by ≥48 Hours	System Revision	Total	
			no. of events†			*no. of events*	*no. of patients with event (%)*‡
Procedure-related only	0	0	7	1	6	9	9 (2.8)
Hemorrhage at implantation site	0	0	0	0	1	1	1 (0.3)
Infection at implantation site	0	0	2	0	2	2	2 (0.6)
Pain at implantation site	0	0	0	1	0	1	1 (0.3)
Impaired healing at incision site	0	0	1	0	0	1	1 (0.3)
Postoperative wound infection	0	0	4	0	3	4	4 (1.3)
System-related only	0	0	6	0	4	7	7 (2.2)
Inappropriate shock delivery	0	0	3	0	0	3	3 (0.9)
Lead dislodgement	0	0	3	0	4	4	4 (1.3)
System- and procedure-related	0	1	1	2	8	9	8 (2.5)
Device software–hardware interaction	0	1	0	0	1	1	1 (0.3)
Device placement issue	0	0	0	0	1	1	1 (0.3)
Lead dislodgement	0	0	1	2	5	6	5 (1.6)
Discomfort at medical device site	0	0	0	0	1	1	1 (0.3)
Total major complications§	0	1	14	3	18	25	23 (7.3)

* Shown are events involving permanent loss of defibrillation function (specifically shock) due to mechanical or electrical dysfunction of the device.
† Events are not mutually exclusive; an event could meet more than one major-complication criterion.
‡ Percentages were computed as the number of patients with an event divided by 316.
§ The number and percentage of patients with an event for each major-complication criterion are as follows: for death, no patients; for permanent loss of defibrillation function, 1 patient (0.3%); for hospitalization, 13 patients (4.1%); for hospitalization prolonged by at least 48 hours, 3 patients (0.9%); and for system revision, 17 patients (5.4%).

without shock. Through the programming of antitachycardia pacing, shock was avoided in 33 episodes. Among the patients with pause-prevention pacing therapy enabled, 2 had a total of 7 episodes of asystole that were detected and treated with 19 or fewer paces delivered.

INAPPROPRIATE THERAPIES

Of 299 patients who underwent implantation, 29 (9.7%) received 118 inappropriate shocks for 81 arrhythmic episodes during the 10.6-month mean follow-up. The median number of inappropriate shocks per patient was 2. The Kaplan–Meier estimated frequency of inappropriate shock was 8.5% at 6 months. Causes of inappropriate shocks were P-wave oversensing (34 episodes), lead noise (19), T-wave oversensing (11), atrial fibrillation or atrial flutter (10), electromagnetic interference (4), other supraventricular tachycardia or sinus tachycardia (2), and nonsustained ventricular tachycardia (1).

SYSTEM REVISIONS

Through a 10.6-month mean follow-up, 22 extravascular ICD system modifications were reported in 22 patients. Eight system modifications resulted in full system explantation without replacement (see the Results section in the Supplementary Appendix). The most common reason for system revision was lead dislodgement; 6 of 9 such events were associated with the anchoring sleeve. Four lead dislodgements were identified periprocedurally (≤3 days after implantation), 3 during routine postoperative chest radiography, and 1 after detection of lead noise. Five dislodgements were identified between 23 and 120 days after implantation (4 manifesting with inappropriate shock and 1 with high impedance alert). Among 15 patients who underwent extravascular ICD lead explantation (14 to 392 days after implantation), all leads were removed with manual traction in their entirety without complication.

INFECTION

A total of 13 system- or procedure-related infections were reported in 13 patients (4.1%) through the 10.6-month mean follow-up, 9 of which were addressed through medication with or without wound care. Four infections resulted in system removal (1.3%; 26 to 188 days after implantation); all 4 infections were related to the lateral device pocket, with 2 also involving the xiphoid incision site.

DISCUSSION

In this prospective, multicenter, nonrandomized study, we found that extravascular ICDs were implanted safely and that they effectively terminated acute ventricular arrhythmias, exceeding the prespecified safety and effectiveness criteria; they also terminated chronic ventricular arrhythmias in a subgroup of patients. Because the lead is placed substernally, in proximity to the myocardium, antibradycardia and antitachycardia pacing could be delivered successfully despite the absence of an intravascular electrode. In addition, the median energy for defibrillation was 15 J at implantation, similar to that of transvenous ICDs and approximately half of that reported with the subcutaneous ICD.[6]

Implantation of the extravascular ICD requires accessing the substernal space, an anatomical location not traditionally approached by cardiologists. In our study, which involved a dedicated training program and initial collaboration with a cardiac surgeon, implantation procedures were performed safely in electrophysiology laboratories, which supports both the importance of a comprehensive training program and the generalizability of the practice. We observed no major intraprocedural complications or unique major complications related to the extravascular ICD procedure or system that have not been observed in subcutaneous and transvenous devices previously.[8,9,20,21]

The 92.6% freedom from system- and procedure-related complications reported for the extravascular ICD matches that reported in the subcutaneous ICD investigational device exemption trial (92.1%)[7] and a range of transvenous ICD studies (85.4 to 93.8%) (Fig. S4).[1,22-26] The mean (±SD) procedure time (skin-to-skin) of the extravascular ICD implantation procedure (74.6±33.2 minutes) (Table S5) was similar to early experience with the subcutaneous ICD (69±27 minutes).[27] The frequency of revision of the extravascular system was less than or similar to the frequencies reported previously for transvenous and subcutaneous ICD systems.[8,28]

Defibrillation efficacy was high at implantation (98.7%), at 6 months (100% in 36 patients), and for discrete spontaneous events (100% in 18

events). These results reflect a greater defibrillation efficacy at implantation than observed in historical transvenous ICD studies (90.5 to 93.0%),[29-32] and efficacy similar to that of the subcutaneous ICD (100%)[7] despite a smaller generator (Fig. S5). The first-shock efficacy for the extravascular ICD (78%; 14 of 18 events) was lower than current efficacies for transvenous and subcutaneous systems[33] but similar to or better than those reported for early subcutaneous systems.[34] Extravascular sensing and detection also functioned well, with induced ventricular tachycardia or ventricular fibrillation detected in all patients with a safety margin during implant testing (307 patients; ventricular fibrillation detected at ≥0.2 mV sensitivity). Antitachycardia pacing delivered endocardially or from coronary veins interrupts reentrant circuits painlessly and is associated with a 52 to 58%[35,36] rate of termination of ventricular arrhythmia. We found that 32 of 46 monomorphic ventricular tachyarrhythmia events (70%) were treated successfully by pacing from the extravascular space over the right ventricle.

The most common reason for inappropriate shocks in the extravascular ICD was P-wave oversensing (34 of 81 arrhythmic episodes; 42%), a function of lead location relative to the right atrial appendage. Inappropriate shocks due to P-wave oversensing decreased with experience over the study duration (28 episodes in 6 patients in the first half of study implants vs. 6 episodes in 4 patients in the second half of study implants). The frequency of inappropriate shock of 8.5% at 6 months exceeds that of current ICDs[9] but is similar to that of early-generation transvenous and subcutaneous systems.[37] Algorithms to mitigate inappropriate shocks in the extravascular ICD have been developed and deployed but have not yet been well studied clinically.[38]

Eight extravascular ICDs were removed without replacement during the study, and four of these removals were due to infection (1.3%). It is notable that no cases of mediastinitis, sepsis, or endocarditis related to the extravascular ICD were reported. The overall incidence of extravascular ICD infection resulting in system removal was similar to that seen with subcutaneous ICDs; in the investigational device exemption trial of the subcutaneous ICD, infections leading to device removal occurred in 1.3% of the patients,[7] and 1.1 to 2.4% of patients had infection leading to device removal over the long term.[8,20,39] One instance of pocket hematoma (0.3%) was observed in our study, which did not progress to pocket infection; by contrast, the subcutaneous ICD resulted in a higher incidence of hematoma (1.9%) than a smaller transvenous ICD (0.5%) in a direct comparison.[9] A larger patient cohort will be required in order to determine whether the smaller size of the extravascular ICD generator relative to the subcutaneous ICD contributes to a reduction in hematoma and pocket infection.

Our study is best interpreted in the context of its limitations. There was no transvenous or subcutaneous ICD control group for comparison. Implantation procedures were performed at expert centers within the context of a clinical study, with a prespecified follow-up and testing plan. The number of episodes of spontaneous arrhythmia remains modest, and defibrillation testing may not be a good surrogate for clinical shock efficacy. The study population was younger than typical ICD recipients and had a high frequency of hypertrophic cardiomyopathy, so extrapolation to an older, sicker population should be performed with caution. The representativeness of the study patients is outlined in Table S8. Testing at 6 months was performed in a subgroup of patients and was designed to assess maintained shock efficacy for ventricular arrhythmia and not the defibrillation threshold. Therefore, these data do not provide information on threshold changes over time. Observations regarding pause-prevention pacing are limited.

In this prospective global study, an extravascular ICD with a substernal lead safely and effectively detected and terminated induced and spontaneous ventricular arrhythmias. The results from this study support the hypothesis that substernal placement of electrodes retains the benefit of extravascular placement while providing pause-prevention pacing, antitachycardia pacing, and low-energy defibrillation.

Supported by Medtronic.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Paul Friedman, M.D., Francis Murgatroyd, F.R.C.P., Lucas V.A. Boersma, M.D., Ph.D., Jaimie Manlucu, M.D., David O'Donnell, M.B., B.S., Bradley P. Knight, M.D., Nicolas Clémenty, M.D., Ph.D., Christophe Leclercq, M.D., Ph.D., Anish Amin, M.D., Béla P. Merkely, M.D., Ph.D., D.Sc., Ulrika M. Birgersdotter-Green, M.D., Joseph Y.S. Chan, M.B., B.S., Mauro Biffi, M.D., Reinoud E. Knops, M.D., Ph.D., Greg Engel, M.D., Ignacio Muñoz Carvajal, M.D., Laurence M. Epstein, M.D., Venkata Sagi, M.D., Jens B. Johansen, M.D., Ph.D., Maciej Sterliński, M.D., Ph.D., Clemens Steinwender, M.D., Troy Hounshell, M.D., Richard Abben, M.D., Amy E. Thompson, M.S., Christopher Wiggenhorn, Ph.D., Sarah Willey, M.P.H., and Ian Crozier, M.B., Ch.B.

The authors' affiliations are as follows: Mayo Clinic, Rochester (P.F.), and Medtronic, Mounds View (A.E.T., C.W., S.W.) — both in Minnesota; King's College Hospital, London (F.M.); the Cardiology Department, St. Antonius Hospital, Nieuwegein (L.V.A.B.), and Amsterdam University Medical Centers, Amsterdam (L.V.A.B., R.E.K.) — both in the Netherlands; London Health Sciences Centre, London, ON, Canada (J.M.); Austin Hospital, Heidelberg, VIC, Australia (D.O.); Northwestern University, Evanston, IL (B.P.K.); Centre Hospitalier Régional Universitaire de Tours–Hôpital Trousseau, Tours (N.C.), and Centre Hospitalier Universitaire de Rennes–Hôpital Pontchaillou, Rennes (C.L.) — both in France; Riverside Methodist Hospital, Columbus, OH (A.A.); Heart and Vascular Center, Semmelweis University, Budapest, Hungary (B.P.M.); the University of California, San Diego, La Jolla (U.M.B.-G.), and Sequoia Hospital, Redwood City (G.E.) — both in California; Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China (J.Y.S.C.); the Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero–Universitaria di Bologna, Bologna, Italy (M.B.); Hospital Universitario Reina Sofía, Cordoba, Spain (I.M.C.); Northwell Health, Manhasset, NY (L.M.E.); Baptist Health, Jacksonville, FL (V.S.); Odense Universitetshospital, Odense, Denmark (J.B.J.); Klinika Zaburzeń Rytmu Serca/Narodowy Instytut Kardiologii–Stefana Kardynała Wyszyńskiego, Warsaw, Poland (M.S.); Kepler University Hospital, Linz, Austria (C.S.); the Iowa Heart Center, West Des Moines (T.H.); the Cardiovascular Institute of the South, Houma, LA (R.A.); and Christchurch Hospital, Christchurch, New Zealand (I.C.).

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