

## FEATURED ARTICLE

# The development of the extravascular defibrillator with substernal lead placement: A new Frontier for device-based treatment of sudden cardiac arrest

Amy E. Thompson MS, MBA<sup>1</sup>  | Brett Atwater MD<sup>2</sup> | Lucas Boersma MD, PhD<sup>3</sup> | Ian Crozier MD, CHB<sup>4</sup>  | Gregory Engel MD<sup>5</sup> | Paul Friedman MD, FHRS<sup>6</sup>  | J. Rod Gimbel MD<sup>7</sup> | Bradley P. Knight MD<sup>8</sup> | Jaimie Manlucu MD<sup>9</sup> | Francis Murgatroyd FRCP<sup>10</sup> | David O'Donnell MBBS<sup>11</sup> | Juergen Kuschyk MD<sup>12</sup>  | Paul DeGroot MS<sup>13</sup>

<sup>1</sup>Medtronic Clinical Research, Medtronic plc, Mounds View, Minnesota, USA

<sup>2</sup>Cardiology/Electrophysiology, Inova Medical Group, Mclean, Virginia, USA

<sup>3</sup>Cardiology/Electrophysiology, St. Antonius Hospital Nieuwegein and Amsterdam UMC, Nieuwegein, Netherlands

<sup>4</sup>Cardiology/Electrophysiology, Christchurch Hospital, Christchurch, New Zealand

<sup>5</sup>Cardiology/Electrophysiology, Palo Alto Medical Foundation, Mountain View, California, USA

<sup>6</sup>Cardiology/Electrophysiology, Mayo Clinic, Rochester, Minnesota, USA

<sup>7</sup>Cardiology/Electrophysiology, Lutheran Medical Group, Fort Wayne, Indiana, USA

<sup>8</sup>Cardiology/Electrophysiology, Northwestern University, Chicago, Indiana, USA

<sup>9</sup>Cardiology/Electrophysiology, London Health Sciences Centre, London, Ontario, Canada

<sup>10</sup>Cardiology/Electrophysiology, King's College Hospital, London, United Kingdom

<sup>11</sup>Cardiology/Electrophysiology, GenesisCare, Heidelberg, Victoria, Australia

<sup>12</sup>Cardiology/Electrophysiology, University of Mannheim, Mannheim, Germany

<sup>13</sup>Research & Technology, Medtronic plc, Mounds View, Minnesota, USA

## Correspondence

Amy E. Thompson MS, MBA, Medtronic plc, Mounds View, MN, USA.

Email: amy.thompson@medtronic.com

## Abstract

**Introduction:** The extravascular implantable cardioverter-defibrillator (EV ICD) system with substernal lead placement is a novel nontransvenous alternative to current commercially available ICD systems. The EV ICD provides defibrillation and pacing therapies without the potential long-term complications of endovascular lead placement but requires a new procedure for implantation with a safety profile under evaluation.

**Methods:** This paper summarizes the development of the EV ICD, including the preclinical and clinical evaluations that have contributed to the system and procedural refinements to date.

**Results:** Extensive preclinical research evaluations and four human clinical studies with >140 combined acute and chronic implants have enabled the

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Journal of Cardiovascular Electrophysiology* published by Wiley Periodicals LLC.

**Disclosure:** Dr. Atwater is a consultant for Medtronic plc, Abbott, Biosense Webster, and Biotronik and receives research funding from Abbott and Medtronic plc. Prof. Boersma is a consultant for Medtronic, Boston Scientific Corp., Philips, Acutus, and Adagio and his institution receives grant support from Medtronic and Boston Scientific. Dr. Crozier is a consultant for and receives research support and fellow support from Medtronic plc and grants from Boston Scientific Corp. Dr. Engel is a consultant for Medtronic plc. Dr. Friedman has received research support and/or served as consultant to Abbott, Medtronic, Boston Scientific, and Leadex, with all proceeds going to Mayo Clinic. He has licensed intellectual property to NeoChord, Preventice, AliveCor, Anumana, Champion Medical, Marani Health, and MediCool. Dr. Gimbel is a consultant for Medtronic plc and Zoll Medical. Dr. Knight is a consultant for and receives research support and fellowship support from Medtronic plc. He also has received research support from and/or served as consultant to Abbott, Boston Scientific Corp., Biotronik, CVRx, Baylis, and Philips. Dr. Manlucu is a consultant for and receives research and fellowship support from Medtronic plc. She also has received research support from and/or served as consultant to Abbott, Boston Scientific Corp. and Baylis Medical. Dr. Murgatroyd is a consultant for Medtronic plc. In the last 3 years, he has also consulted for Abbott Inc, and Boston Scientific Corp., and his department has received research support from AbbottInc, Boston ScientificCorp. and Medtronic plc. Dr. O'Donnell has received research support and/or served as consultant to Abbott and Medtronic plc. Dr. Kuschyk is a consultant for Medtronic plc. Ms. Thompson and Mr. DeGroot are employees of Medtronic plc.

#### Funding information

Medtronic plc

development and refinement of the EV ICD system, currently in worldwide pivotal study.

**Conclusion:** The EV ICD may represent a clinically valuable solution in protecting patients from sudden cardiac death while avoiding the long-term consequences of transvenous hardware. The EV ICD offers advantages over transvenous and subcutaneous systems by avoiding placement in the heart and vasculature; relative to subcutaneous systems, EV ICD requires less energy for defibrillation, enabling a smaller device, and provides pacing features such as antitachycardia and asystole pacing in a single system.

#### KEYWORDS

anterior mediastinum, arrhythmia, extravascular, ICD, substernal

## 1 | INTRODUCTION

Sudden cardiac death (SCD) affects as many as 300 000 people annually in the United States and accounts for 15%–20% of all deaths worldwide each year.<sup>1</sup> Malignant ventricular tachyarrhythmia termination via an automated implantable defibrillator was first described in 1970, and since the advent of the transvenous implantable cardioverter-defibrillator (TV-ICD) in the 1990s, it has served as the device-based standard of care for protection against SCD.<sup>2–4</sup>

One important advancement in modern TV-ICD technology was the introduction of antitachycardia pacing (ATP) for ventricular tachycardia (VT) to reduce appropriate but painful and often unnecessary shocks.<sup>5</sup> Clinical evidence has demonstrated that ATP is effective in terminating sustained ventricular arrhythmias, even those with short cycle lengths, and that ATP may reduce shocked arrhythmia episodes by 52% in selected populations when partnered with long detection intervals.<sup>6</sup>

Despite widespread utilization of TV-ICD technology and important feature advances through decades of use, the TV-ICD utilizes defibrillation leads delivered into the endocardial aspect of the heart via vascular access, which are associated with short- and long-term complications. Pneumothorax, venous thrombosis, lead dislodgment or malfunction, lead-related perforation and bleeding, infection, and concerns with chronic system extraction persist as impediments to TV-ICD usage.<sup>7,8</sup>

## 2 | ALTERNATIVES TO TV-ICD

In situations where TV-ICD implantation is either not possible or desired, clinicians have sought alternative solutions. Epicardial patches and coils, subcutaneous arrays, and lead implantation through surgical means or via novel implant locations such as within the pericardial sac, the parietal pleura, transatrially, and through

alternate vascular access points have all been described, all with their own merits and limitations.<sup>9–12</sup>

The subcutaneous ICD (S-ICD; Boston Scientific), with lead and device placement entirely within the subcutaneous plane, was designed to provide defibrillation therapy without entry into the heart or vasculature, circumventing some of the clinical disadvantages of TV-ICD systems.<sup>13</sup> Longer-term results for S-ICD have shown acceptable short- and long-term safety as well as defibrillation efficacy rates similar to those observed in transvenous systems.<sup>14,15</sup> However, a subcutaneous lead arrangement is not well suited for termination of ventricular arrhythmias with ATP, since pacing stimuli would need to pass through the thoracic wall to electrically capture the heart and would thus require high voltage outputs, though future embodiments of the S-ICD (or other extravascular systems) could include communication with a leadless pacemaker to help enable pacing capabilities. For the same reasons, the S-ICD system requires higher energy for defibrillation, resulting in a larger device size with attendant longevity and device comfort concerns relative to TV-ICDs.<sup>13,14,16,17</sup> And while the inappropriate shock rate with S-ICD has approached that of TV-ICD in its most recent evaluation,<sup>15</sup> the cause of inappropriate shock in S-ICD systems is frequently T-wave or extracardiac oversensing, whereas in TV-ICDs the common cause is supraventricular tachycardia.<sup>18</sup> Modern inappropriate shock rates for S-ICD are in part benefitted by pre-implant screening to assess R- and T-wave amplitudes, whereby 13% of patients are considered to be less eligible for S-ICD due to unfavorable R/T-wave metrics.<sup>15</sup> Thus, while the S-ICD provides an alternative to TV-ICD, it is not without limitations caused by ICD lead distance from the heart.

### 3 | SUBSTERNAL ICD LEAD PLACEMENT

To address the limitations of existing commercially available TV-ICD and S-ICD systems, an alternative extravascular approach was developed that provides the benefits of a single-chamber TV-ICD system and, like transvenous and subcutaneous systems, is intended to be implanted by practicing electrophysiologists (EPs) in an EP lab (Table 1).

The first human experience of defibrillation lead placement in the substernal extracardiac space was reported by Tung et al. in 2007 using a minimally invasive approach.<sup>19</sup> In three patients (two with ipsilateral venous occlusion and one wishing to avoid additional transvenous hardware placement), either a Model 6996SQ lead or Model 6937 Transvene-SVC lead (both Medtronic plc) was tunneled to the substernal space anterior to the right ventricle (RV) from the superior sternal aspect near the manubrium. A second defibrillation coil (Model 6996SQ) was positioned on the patient's back to form an appropriate defibrillation vector, and a TV-ICD was positioned in a pectoral pocket. All implants were successful without complication. Ventricular fibrillation (VF) was induced with T-wave shock, and in each patient, the safety margin for defibrillation was determined to be  $\geq 10$  Joules (J) by two successful VF terminations.<sup>19</sup>

More recently, case reports of commercial S-ICD and TV-ICD leads using substernal placement have been described to meet various patient needs and overcome the challenges of TV- and S-ICD systems. Guenther et al. reported the results of failed S-ICD implantation in one patient with superior vena cava occlusion syndrome for whom defibrillation threshold (DFT) testing at 65 and 80 J (the maximum energy of the S-ICD system) failed to terminate VF six times.<sup>20</sup> As a result of failed DFT testing, the S-ICD lead was

**TABLE 1** Overview of transvenous, subcutaneous, and extravascular ICD systems.

	Transvenous ICD <sup>a</sup>	Subcutaneous ICD <sup>b</sup>	Extravascular ICD <sup>c</sup>
Lead location	Endovascular/endocardial	Parasternal (subcutaneous)	Anterior mediastinum (substernal)
Potential for cardiac injury/perforation	Present	Absent	Present
ICD generator location	Pectoral	Left midaxillary region	Left midaxillary region
Maximum delivered energy	40 J	80 J	40 J
ATP	Available	Not available	Available
Chronic pacing therapy	Available as chronic pacing therapy	Not available	Available as short-duration pause prevention pacing
Postshock pacing	Available	Available	Available
Generator volume	33 cc	60 cc	33 cc
Generator mass	79 g	130 g	77 g

Abbreviations: ATP, antitachycardia pacing; EV ICD, extravascular implantable cardioverter-defibrillator; MRI, magnetic resonance imaging; S-ICD, subcutaneous ICD.

<sup>a</sup>Cobalt™ XT single-chamber ICD (Medtronic plc).

<sup>b</sup>Emblem™ MRI S-ICD (Boston Scientific).

<sup>c</sup>EV ICD is not approved and Pivotal data are not available.

instead positioned substernally; thereafter, DFT testing was successful, and sensing quality was acceptable. There were no complications, and the patient reported no chronic pain.<sup>20</sup>

Boyle et al. described a patient with a Hemodialysis Reliable Outflow (HeRO) graft (Merit Medical Systems) who was not a candidate for S-ICD or TV-ICD due to the location of the graft and bilateral subclavian occlusion.<sup>21</sup> An S-ICD lead was placed substernally and there were no observed T-wave or artificial potentials; DFT testing was successful at 70 J on two episodes.<sup>21</sup>

Bhagwandien et al. described a patient with no venous access due to superior vena cava syndrome and a high risk of thrombosis from the femoral approach.<sup>22</sup> The patient was not a suitable candidate for S-ICD due to the unfavorable R/T-wave ratio observed on preimplant surface electrogram screening as well as documented episodes of VT. An epicardial pace/sense electrode (Myodex 1084 T; St Jude Medical) was positioned via thoracotomy and a defibrillation coil (Transvene-SVC) was placed substernally, both of which were connected to a TV-ICD (Evera MRI XT Surescan DVMB2D4; Medtronic) on the left midaxillary line. DFT testing was successful at 40 J.<sup>22</sup>

To overcome challenges associated with younger patients still in their growth, Hata et al. described implantation of a TV-ICD lead (Model 0184; Boston Scientific) in the substernal space of a 2-year-old along with an epi-myocardial bipolar lead (Model 4968, Medtronic), both of which were connected to a TV-ICD (Fortify ST VR 1235-40; St. Jude Medical) in the abdominis muscle. Subsequently, the system successfully treated VT with the first shock.<sup>23</sup>

Do et al. presented a case study of a patient with venous anomalies who required an ICD for primary prevention.<sup>18</sup> S-ICD preimplant screening with surface electrocardiograms demonstrated favorable signals, but only in a secondary vector. The patient was initially implanted with the S-ICD system with the lead in the subcutaneous plane, but 3 months postimplant, the patient presented with inappropriate shock due to T-wave oversensing. Despite reprogramming and the use of a sensing filtering algorithm, inappropriate shocks recurred. To overcome these issues, the S-ICD lead was moved to the substernal location, where the R/T-wave ratio improved significantly and there was no evidence of T-wave oversensing.<sup>18</sup>

## 4 | EARLY DEVELOPMENT OF THE EXTRAVASCULAR ICD

The aforementioned reports of TV- or S-ICD lead placement within the substernal space emerged alongside the commercial development of an extravascular ICD (EV ICD; Medtronic) system designed specifically for substernal lead placement and therapy delivery.

Research and development of the EV ICD system began in 2012 after preclinical research evaluations demonstrated the feasibility of achieving pacing capture from leads placed within the substernal space using a minimally invasive subxiphoid approach and fluoroscopic guidance. Thereafter, preclinical evaluations began in earnest

to begin to optimize substernal pacing, evaluate substernal sensing signals, assess energy requirements for defibrillation, and characterize the surrounding anatomy to help develop the implant procedure.

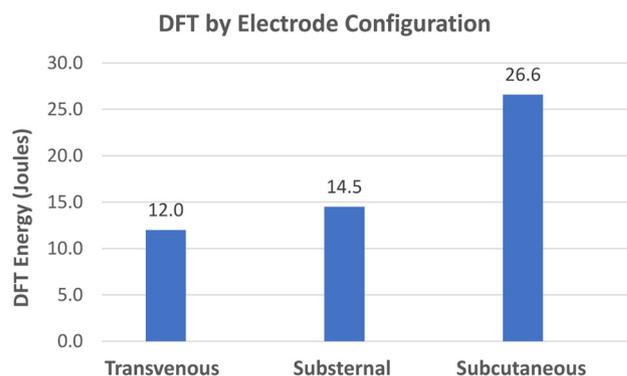
### 4.1 | Early pacing and sensing evaluations

To begin to optimize a dedicated substernal lead design, nine different lead concepts with different electrode spacings, coil positions, and lead shapes were evaluated in swine. Average R-wave amplitudes across all designs ranged from approximately 2.0–4.5 mV and included various distances from the cardiac silhouette. Using a maximum pacing output of 10 V and 1.5 ms pulse width, pacing capture was achieved for 84/108 (78%) electrode sites within 1 cm of the epicardial surface, including all sites located between 10 and 45 mm from the apex.<sup>24</sup>

The ability to pace at high rates is an important determinant that ATP can successfully terminate a re-entrant rhythm. However, to more fully assess substernal ATP capability, preclinical *in silico* and animal evaluations were completed.<sup>25,26</sup>

Six unique biofidelic *in silico* heart models were generated from magnetic resonance imaging with three different VT circuits, and sustained VTs were initiated within the numerical models. Various ATP protocols were tested using different pairs of electrodes from within the substernal space and compared to transvenous pacing electrodes. Across 114 ATP trials, >80% of VTs were terminated with burst and ramp protocols, both for substernal and endocardial electrodes, indicating that ATP from the substernal space should be as effective as from endocardial electrodes while the rate of acceleration was <1%. The model also demonstrated potential optimizations for substernal ATP through electrode selection and timing sequence adjustments.<sup>25</sup>

Subsequent animal studies corroborated the ATP modeling results. Five pigs and one sheep were implanted with a left ventricular (LV) pacing lead and a substernal lead. The pacing was delivered from the LV lead at 180 paces per minute (ppm) to simulate VT, and ATP was delivered from the substernal lead at 185–240 ppm.



**FIGURE 1** Modeling-predicted defibrillation threshold. Modeling predictions of defibrillation threshold for transvenous, substernal, and subcutaneous leads.

The pace-simulated VT was entrained successfully by the substernal ATP sequences, with an average of  $3 \pm 2$  ATP pulses required at an average cycle length of  $306 \pm 16$  ms ( $91 \pm 6\%$  of VT cycle length).<sup>26</sup>

## 4.2 | Energy requirements for defibrillation

The ability to pace the heart from the substernal space suggested that defibrillation energies from a substernal arrangement could be significantly lower than those required for S-ICD. To corroborate this assumption, finite element analysis (FEA) was conducted. A human thorax model was created based on computed tomography (CT) to calculate and compare DFTs for coils placed in transvenous, subcutaneous (SQ), and substernal locations. DFT was defined using the critical mass hypothesis, in which threshold voltage is defined as the applied voltage required such that 95% of the ventricular myocardium has an electrical field strength of  $>5$  V/cm.<sup>27</sup> Modeling results showed that while the DFT using an SQ coil was double that of a transvenous RV coil, the substernal coil DFT was only 22% higher than the RV coil DFT (Figure 1).<sup>28</sup>

These modeling results were then corroborated by preclinical animal studies. A total of 11 swine ( $39.3 \pm 9.5$  kg) were implanted with three leads each: a transvenous lead with a 5.7 cm coil in the RV, a prototype lead with an 8 cm defibrillation coil positioned in the subcutaneous plane parasternally to the right side of the sternum, and the same prototype lead with 8 cm coil positioned within the substernal space near the sternal midline. An active can emulator was positioned on the left lateral thorax to form an appropriate vector for defibrillation. DFT was performed using a step-up/step-down protocol, with DFTs calculated via logistic regression. The average DFT for the substernal lead was shown to be  $22 \pm 6$  J, which was markedly lower than for the SQ coil ( $121 \pm 76$  J) and more comparable to the transvenous coil ( $15 \pm 6$  J). While DFTs in swine are greater than for humans for both SQ and TV leads, DFT testing of all three lead configurations within the same animal provided a relative comparison and indicated that substernal DFTs should be approximately 1.5 times that of transvenous systems. In humans, where the average transvenous DFT is approximately 10 J, the average substernal DFT would thus be expected to be approximately 15 J.<sup>29</sup>

Overall, preclinical animal studies and modeling showed that substernal defibrillation could be achieved at lower energies than those required by S-ICD and at energies more similar to TV-ICD.

## 4.3 | Anatomical characterization and implant procedure development

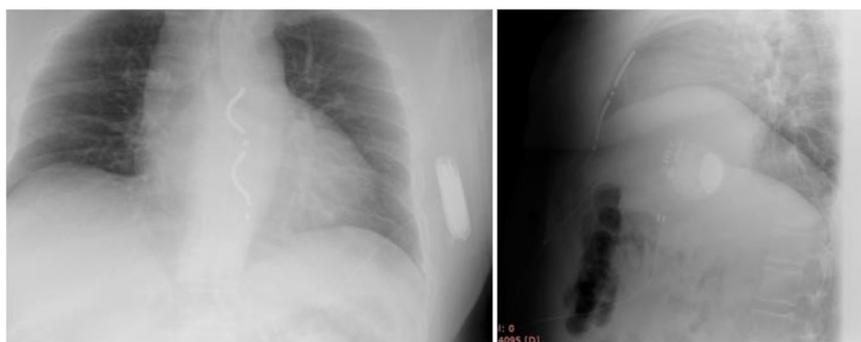
Human CT image analysis was conducted alongside preclinical modeling and animal studies to characterize relationships between the heart, lungs, and sternum, which helped to provide inputs to the lead design and the EV ICD lead implant procedure. Analysis of 68 segmented CT scans characterized the ventricular center of mass and found it to be left of the sternal midline in  $>92\%$  of subjects. In addition, the myocardium was found to be  $\leq 10$  mm posterior to the sternum in  $>92\%$  of subjects when measuring along a potential substernal lead path from the xiphisternal junction to the level of the fifth intercostal space. The lungs were shown to be  $\geq 5$  mm lateral to the sternum in the vast majority of subjects.<sup>30</sup>

The EV ICD implant procedure was developed from preclinical human cadaver and animal studies, as well as from CT image analysis, three-dimensional printed models, and other simulations. In brief, the substernal lead is implanted via a small incision near the xiphoid process and positioned within the substernal space via a blunt tunneling rod backloaded with a 9 French (Fr) introducer sheath. The proximal end of the lead is tunneled to a subcutaneous tissue pocket on the left midaxillary line and connected to the device to form an appropriate defibrillation vector. Fluoroscopic imaging in the anteroposterior (AP) and lateral projections, as well as electrical data obtained during the implant, contributed to the specific placement of the lead and device (Figure 2). Through clinical research experience, described subsequently, the EV ICD implant procedure has been further optimized.

## 5 | CLINICAL EVALUATION OF THE EXTRAVASCULAR ICD

Preclinical research evaluations provided the knowledge base to progress to human feasibility studies, and three acute human clinical studies were initiated sequentially to explore the potential development of the EV ICD system.

The first clinical feasibility evaluation of substernal therapy delivery was the Acute Substernal Defibrillation (ASD) study, conducted in 2015.<sup>31</sup> In the ASD study, 16 patients underwent substernal implantation of a commercially available defibrillation lead



**FIGURE 2** Implanted extravascular ICD (EV ICD) system. Representative X-ray images of the implanted EV ICD system from a patient in the supine position.

with 8 cm defibrillation coil (Model 6937) using a commercially available tunneling tool (Model 6996T; Medtronic). A cutaneous patch electrode was used to simulate a device on the patient's left midaxillary region. Among the 16 patients, 14 were induced successfully into VF, and per protocol, a single defibrillation shock of 35 J was delivered, followed by an external defibrillator shock if the substernal shock failed. Substernal defibrillation was successful in 13 of 14 patients (93%). The single instance of shock failure was associated with high and lateral shock coil placement, in which the tunneling path and lead placement occurred to the left of the sternal border by approximately  $\geq 1$  cm. The leftward placement of the lead had presumably truncated the available vector for defibrillation with the cutaneous patch electrode on the patient's left side, and in this patient's subsequent planned coronary artery bypass graft procedure, the left mammary artery bed was observed to be bruised from the leftward implant path, with no further sequelae.<sup>31</sup>

Overall, the ASD study demonstrated that substernal defibrillation was feasible using an 8 cm defibrillation coil and energies available in TV-ICDs. In addition, the ASD study revealed the importance of maintaining an implant trajectory beneath the sternum, both to avoid the internal thoracic vessels adjacent to the sternum<sup>32</sup> and to maximize the amount of cardiac tissue between the substernal coil and the electrode (or device) on the patient's left side.

The Substernal Pacing Acute Clinical Evaluation (SPACE), also conducted in 2015, was the second clinical feasibility study in the development course of the EV ICD, evaluating the feasibility of substernal pacing and sensing.<sup>33</sup> The SPACE study collected pacing and sensing data using a commercially available decapolar catheter (Marinr®; Medtronic) from a variety of electrode spacings, including bipolar and unipolar configurations, with a cutaneous patch electrode used as a surrogate for an implanted device. Among 26 patients who underwent catheter implantation and pacing evaluation, ventricular pacing capture was achieved in 18, and among the remainder, 3 patients had atrial instead of ventricular capture due to catheter placement too far superior, while 5 showed high or variable impedance indicative of air ingestion into the mediastinum. The average pacing threshold across all vectors was  $5.8 \pm 4.4$  volts (V) at 10 ms pulse width. Among patients with successful bipolar capture, widely spaced electrode pairs (19 or 10 mm) consistently resulted in the lowest pacing thresholds as opposed to a shorter bipolar spacing (3 mm). The mean R-wave amplitude ranged from 2.98 to 4.11 mV in the unipolar configuration and from 0.83 to 3.95 mV in the bipolar configuration. In one patient, bruising of the anterior pericardium without disruption of the pericardial sac was noted at the patient's subsequent planned sternotomy procedure and the resulting effusion was drained without sequelae. The presumptive cause of effusion occurred when the tunneling tool advanced abruptly through the diaphragmatic attachments when force was applied and the blunt tunneling tool contacted the heart.<sup>33</sup>

Overall, the SPACE study demonstrated the feasibility of substernal pacing and sensing and showed the benefit of wider bipolar electrode pairs on pacing performance. The SPACE study also showed the importance of controlled dissection through the

diaphragmatic attachments to facilitate safe entry into the substernal space.

Following the ASD and SPACE studies, the substernal lead implant procedure was revised to minimize future adverse events. Thereafter, surface landmarks were drawn on the skin to denote the sternal borders, sternal midline, xiphoid process, and top of the cardiac silhouette, helping to maintain the tunneling tool trajectory below the sternum (Figure 3); in addition, a hemostatic instrument was introduced to facilitate limited blunt dissection through the diaphragmatic attachments for initial entry to the substernal tissues.

The ASD and SPACE studies, along with the aforementioned preclinical modeling, animal studies, and CT image analysis, provided critical input to design a lead for substernal implantation and improved therapy delivery, including the coil length for defibrillation therapy, the electrode optimizations for pacing, and the shape of the lead to improve the lead for therapy effectiveness. From these inputs, the epsilon-shaped EV ICD lead was designed to preferentially orient the defibrillation coils toward the patient's right side, maximizing the amount of cardiac tissue located between the coils and the device while also positioning the pace/sense ring electrodes more leftward than the defibrillation coils and nearer the cardiac center of mass, improving defibrillation, pacing and sensing performance (Figure 4).

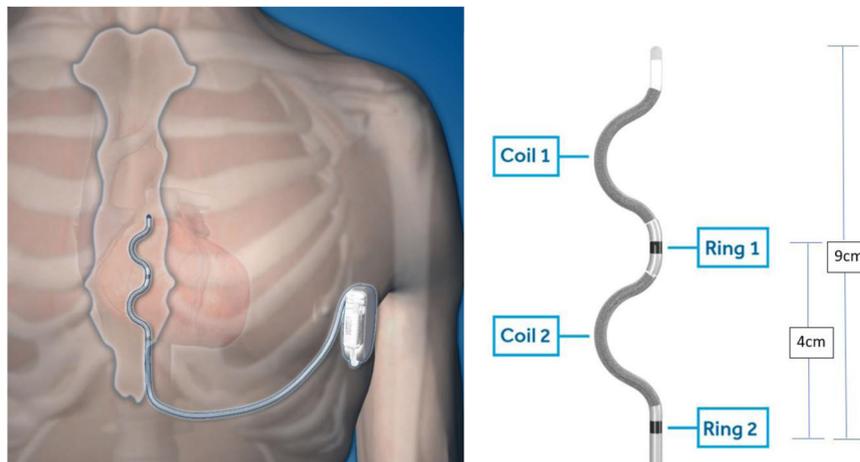
The third human clinical feasibility study was the Acute Extravascular Defibrillation, Pacing and Electrogram (ASD2) study. The ASD2 study was conducted from 2016 to 2017 to further assess pacing and defibrillation efficacy using the new epsilon-shaped substernal lead and to collect high-fidelity multivector substernal electrograms.<sup>34</sup>

Seventy-nine patients underwent implantation with the epsilon-shaped substernal lead, and a cutaneous patch electrode was used as a surrogate for an implanted device in nearly all patients (an implanted active can emulator was used in eight patients). Ventricular pacing was successful in at least 1 vector in 76 of 78 patients (97.4%), and a single 30-J shock successfully terminated 104 of 128 VF episodes (81.3%), demonstrating the ability to pace and defibrillate using a lead designed specifically for the substernal space.<sup>34</sup> The high-fidelity electrograms successfully collected during induced VT/



**FIGURE 3** Preprocedural chest markings. The lateral edges of the sternum (dotted lines) and sternal midline (solid line) are denoted. In this example, a cutaneous patch electrode is positioned on the left midaxillary line to emulate an ICD can.

**FIGURE 4** Extravascular ICD (EV ICD) system placement and lead design. EV ICD system with epsilon-shaped lead implanted within the substernal space and the device positioned on the patient's left midaxillary line (left image). The defibrillation coil segments (Coil 1 and Coil 2) are each 4 cm in length and oriented toward the patient's right; the ring electrodes (Ring 1 and Ring 2) are nearer the cardiac center of mass (right image).



VF and intrinsic rhythms were later used to develop and validate the sensing and detection algorithms specific to EV ICD.

As previously reported, there were five adverse events adjudicated as being causally related to the ASD2 procedure, four of which resulted in no lasting sequelae and one of which was a pericardial effusion with tamponade that resulted in patient death following an improper tunneling procedure.<sup>34</sup> Thereafter, a tunneling tool for substernal lead delivery, described in subsequent sections, was designed to enhance procedural safety, and blunt finger dissection was introduced as a means of gaining access to the substernal space through the diaphragmatic attachments.

Overall, acute feasibility data from >120 patients from the ASD, SPACE, and ASD2 studies, as well as the system and procedure improvements implemented throughout, provided the knowledge base to initiate a chronic study. The first-in-human pilot study was conducted in 2018 incorporating inputs from all predicate clinical studies. The entirety of the EV ICD system design was evaluated, including the epsilon-shaped lead, and for the first time, an ICD with sensing and detection algorithms specific to the substernal space as well as dedicated delivery tools designed for EV ICD implantation.

The EV ICD pilot study was a prospective, nonrandomized, chronic first-in-human study conducted in four sites in Australia and New Zealand characterizing the safety of the EV ICD system and implant procedure as well as the effectiveness of defibrillation, sensing, and pacing.<sup>35</sup>

The EV ICD system was implanted successfully in 20 patients who then proceeded to defibrillation testing. There were no intraprocedural complications. Fluoroscopic guidance and medical judgment were used to center the lead over the right ventricular cardiac silhouette, and the device was placed in a left midaxillary tissue pocket. Induced ventricular arrhythmias were terminated in 18 of 20 patients (90.0%) with  $\geq 10$ -J safety margin, consistent with prior clinical studies of existing ICDs,<sup>36–38</sup> and had a median lowest demonstrated energy for defibrillation of 15 J. Pacing capture was achieved in 19 of 20 patients (95%) at implant with a mean pacing threshold of  $5.4 \pm 2.2$  V and remained stable over time, including  $5.8 \pm 1.8$  V at 6 months and  $4.9 \pm 1.5$  V at 12 months among patients tested in the supine posture.<sup>35,39</sup>

One patient experienced five episodes of monomorphic VT outside the hospital setting, which were successfully detected and treated by the EV ICD system. In the first episode, intermittent pacing capture was observed; VT was terminated successfully with appropriate shock by the device. Pacing output was subsequently increased and among four later episodes of VT, two self-terminated and two showed ATP reset without termination, requiring appropriate and successful shocks.<sup>35,39</sup>

Mean R-wave amplitude in the ring-to-ring vector was  $3.4 \pm 2.0$  mV at implant and remained stable over time ( $3.5 \pm 2.0$  mV at 6 months and  $4.4 \pm 2.2$  mV at 12 months among patients evaluated in the supine posture).<sup>35,39</sup> Mean VF amplitude at implant was  $2.8 \pm 1.7$  mV, and VF was detected at a sensitivity of  $\geq 0.3$  mV in all patients tested clinically (representing a two-fold safety margin over nominal).<sup>35</sup>

Postural effects on sensing performance were robustly evaluated.<sup>40</sup> Patients were evaluated initially at implant in the supine posture and the sensing vector was programmed Ring 1-Ring 2 (primary vector) (Figure 4). Before discharge and at follow-up visits, sensing in sinus rhythm was evaluated in multiple postures. Overall, R-wave amplitude was  $1.9 \pm 0.9$  mV for Ring 1-Ring 2, averaged over all positions and post-implant times. R-wave amplitude for the primary sensing vector was found to be generally stable over time, but occasional fluctuations occurred—an observation that has also been reported for S-ICD systems.<sup>41</sup> Importantly, R-wave amplitudes obtained at implant testing in the supine posture were not markedly different from R-waves observed later in other postures in ambulatory patients. However, anticipating the possibility of variability in R-wave amplitude across postures, VF induction and termination were demonstrated at implant in the pilot study, and the device was programmed with a safety margin for VF sensing in all patients.<sup>40</sup>

The EV ICD pilot study provided information to improve device settings and additional recommendations for the implant procedure. In particular, computational torso models were developed for each of the pilot study patients using CT scans and intraoperative fluoroscopic imaging. For each finite element patient model, 150–200 combinations of electrode locations were studied, including the actual implant locations as determined by postimplant CT, to help

determine the best lead and device location to maximize defibrillation efficacy. From these analyses, the desired lead location was shown to be slightly left of the sternal midline with the proximal ring electrode located ~1 cm superior to the xiphisternal junction, while the desired device location was shown to be at the intersection of the leftmost projection of the heart and the most posterior margin of the heart as observed with fluoroscopic imaging.<sup>42</sup> These inputs were later used to inform system placement for the pivotal study of the EV ICD system.

In their totality, the acute feasibility and first-in-human clinical studies with >140 acute and chronic implants contributed to the advancement of the EV ICD system, including refinements of the lead, device, algorithms, implant procedure, and programming recommendations. The complete body of preclinical and clinical evidence provided the confidence to enter a large-scale pivotal study.<sup>43</sup>

## 6 | EV ICD SYSTEM DESIGN AND OPERATION

Due to the proximity of the substernal lead to the heart relative to the S-ICD, the EV ICD offers therapies currently unavailable in S-ICD systems, including ATP and asystole support pacing as well as lower DFTs. The full set of EV ICD system design features and their operation is currently under evaluation within the pivotal study.<sup>43</sup>

## 7 | EV ICD DEVICE CAPABILITIES

The current EV ICD device is an investigational single-chamber, MR-conditional, EV ICD (volume = 33 cm<sup>3</sup>) with ICD generator positioning in a subcutaneous or an intermuscular tissue pocket along the left midaxillary line. It is a multiprogrammable cardiac device that monitors and regulates the patient's heart rate, also providing diagnostic and monitoring features to assist with system evaluation and patient care. The EV ICD provides up to 40 J of delivered energy for defibrillation therapy.

### 7.1 | Sensing and detection

There are three sensing vectors available in the EV ICD system: a near-field vector via Ring 1-to-Ring 2 and two far-field vectors: Ring 1-to-Can and Ring 2-to-Can. Ring 1-to-Ring 2 is the primary sensing vector, and the two far-field vectors can serve as alternates if sensing is inadequate with the primary vector (Figure 4).

Because the EV ICD lead is near the heart but not in direct contact with the epicardium or myocardium, sensing and detection from the substernal space are different than for commercially available transvenous and subcutaneous systems and have required the development of unique algorithms.

The sensing and detection architecture of the EV ICD was developed by modifying an existing TV-ICD algorithm set (Visia AF MRI, Medtronic plc). To address the increased potential for oversensing noncardiac or unwanted cardiac signals from the wide far-field sensing vector and the increased potential for undersensing sinus rhythm or VF due to lower amplitude cardiac electrograms, the basic sensing method was changed, several new features were added, and other existing features from transvenous systems were modified to make them specific to a substernal application.

The nine new or modified algorithmic features of EV ICD have been described previously by Swerdlow et al,<sup>40</sup> but in general, the algorithms within EV ICD are aimed at three main purposes: to provide basic dynamic sensing capability, to reject oversensed signals, and to discriminate between SVT and VT.

Given the lower amplitude signals associated with the substernal lead design and placement, the EV ICD provides greater sensitivity and lower nominal setting for sensing than TV-ICDs, allowing for programming of sensitivity as low as 0.075 mV (range 0.075–1.2 mV), with a nominal setting of 0.15 mV.

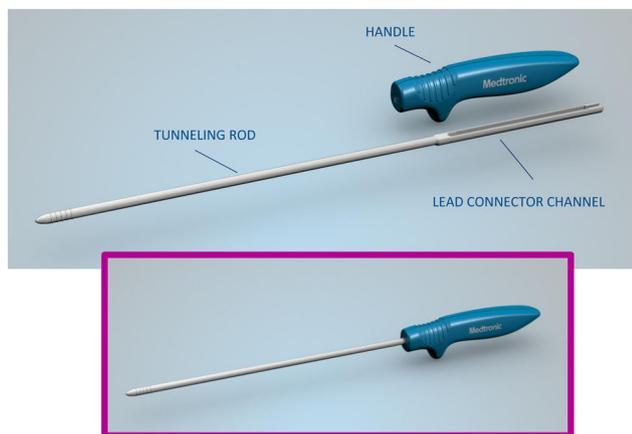
### 7.2 | Pacing capabilities

There are three pacing vectors available in the EV ICD system. Two are low-voltage (Ring 1-to-Ring 2 and Ring 1-to-Coil 2) with a programmable output voltage of 1–8 V and a maximum pulse width of 8 ms. The third vector is from Coil 1-to-Coil 2 and permits pacing from the high-voltage circuitry if a higher output is required (Figure 4). The output voltage is programmable from 10 to 30 V and has a maximum pulse width of 10 ms.

The EV ICD provides three pacing therapies: post-shock pacing to provide hemodynamic support during bradycardia following a shock, ventricular ATP to provide the opportunity for painless therapy for termination of monomorphic VT, and short-duration pause prevention pacing to prevent morbidity and mortality associated with asystole.



**FIGURE 5** Sternal tunneling tool. A 9-French introducer sheath is backloaded onto the malleable tunneling rod and introduced into the anterior mediastinum. Subsequently, the sternal tunneling tool is removed, and the lead is inserted through the retained introducer sheath.



**FIGURE 6** Transverse tunneling tool. The transverse tunneling tool is used to create a tunneling path from the xiphoid incision site to the left midaxillary tissue pocket. Once the tunnel is created, the handle is removed and the lead connector pin is inserted into the tunneling tool channel. The lead connector pin is pulled through the tunneling tract to the pocket for connection to the ICD generator.

### 7.3 | EV ICD lead

The EV ICD lead is a preshaped, MR-conditional lead with passive fixation, designed for sensing, cardioversion, defibrillation, and pacing therapies. The lead is implanted through a straight introducer sheath. After proper positioning over the cardiac silhouette and verification of electrical parameters, the sheath is removed and the distal portion of the lead relaxes to take its epsilon shape, providing passive fixation within the substernal tissues, and as previously described, optimizing therapy effectiveness in its preferred orientation (Figure 4). An anchoring sleeve near the xiphoid incision site where the lead is introduced is used for suturing to the surrounding fascia.

### 7.4 | EV ICD implant tools

The sternal tunneling tool (Medtronic plc) is designed to deliver an introducer and the distal portion of an extravascular lead into the substernal space. The tool (Figure 5) consists of a stainless-steel tunneling rod that delivers a 9-Fr introducer to the anterior mediastinum and which has a preformed bend to direct the tip of the tool toward the underside of the sternum. The tunneling rod is malleable to accommodate patient anatomy. The tool also contains an external guide that remains above the skin and indicates the distance and direction of the tunneling rod. The external guide is hinged and removable to accommodate physician preference and patient anatomy. A SafeSheath® II (Model SSCL9; Oscor) introducer is used with the sternal tunneling tool.

The transverse tunneling tool (Medtronic plc) is designed to deliver the proximal portion of an extravascular lead from the incision near the xiphisternum to the device pocket during implantation of the EV ICD system. The tunneling rod has a shaped tip to facilitate tunneling and the rod can be removed from the handle to expose a channel into which the connector of the EV ICD lead can be secured during tunneling (Figure 6).

The EV ICD system, including the device, lead, and both tunneling tools, is currently in worldwide pivotal evaluation. The pivotal study allowed enrollment of up to 400 patients at up to 60 sites worldwide to demonstrate the safety and efficacy of the EV ICD system. Enrollment was completed in late 2021 with the study conclusion expected in April 2022.<sup>43</sup>

## 8 | CONCLUSIONS

Extensive preclinical research evaluations and four human clinical studies with >140 combined implants have enabled the development and refinement of the EV ICD system, currently in a worldwide pivotal study. Compared to existing commercially available subcutaneous ICDs, the EV ICD system includes a smaller device that uses lower defibrillation energy, which may result in longer battery life, and is able to deliver pacing therapies such as ATP and backup asystole pacing from a single device. The extravascular ICD with substernal lead placement may represent a clinically meaningful solution for patients at risk of SCD while overcoming some of the limitations of commercially available systems.

### ACKNOWLEDGMENTS

The study authors would like to thank all the investigators of the EV ICD human clinical studies, the patients who consented to be enrolled, and the EV ICD scientific and engineering teams, with special appreciation for early leadership and support from Becky Dolan and Rick McVenes. All preclinical and clinical research studies detailed herein were funded in full by Medtronic plc.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

### ORCID

Amy E. Thompson  <http://orcid.org/0000-0002-7363-5870>

Ian Crozier  <http://orcid.org/0000-0003-4652-7791>

Paul Friedman  <http://orcid.org/0000-0001-5052-2948>

Juergen Kuschyk  <http://orcid.org/0000-0001-7827-4974>

### REFERENCES

1. Srinivasan NT, Schilling R. Sudden cardiac death and arrhythmias. *Arrhythm Electrophysiol Rev*. 2018;7(2):111-117. doi:10.15420/aer.2018:15:2
2. Schuder JC, Stoeckle H, Gold JH, West JA, Keskar PY. Experimental ventricular defibrillation with an automatic and completely implanted system. *Trans Am Soc Artif Intern Organs*. 1970;16:207-212.
3. Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AI. Standby automatic defibrillator. An approach to prevention of sudden coronary death. *Arch Intern Med*. 1970;126:158-161.
4. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35(18):1186-1194. doi:10.1093/eurheartj/ehf511
5. Zipes DP, Roberts D. Results of the international study of the implantable pacemaker cardioverter-defibrillator. A comparison

- of epicardial and endocardial lead systems. The Pacemaker-Cardioverter-Defibrillator Investigators. *Circulation*. 1995;92(1):59-65.
6. Arenal A, Proclemer A, Kloppe A, et al. Different impact of long detection interval and anti-tachycardia pacing in reducing unnecessary shocks: data from Advance III trial. *Europace*. 2016;18(11):1719-1725.
  7. Weiss R, Knight BP, Gold MR, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. *Circulation*. 2013;128:944-953.
  8. Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defect in implantable cardioverter-defibrillators over a period of >10 years. *Circulation*. 2007;115:2474-2480.
  9. Molina JE, Benditt DG. An epicardial subxiphoid implantable defibrillator lead: superior effectiveness after failure of standard implants. *Pacing Clin Electrophysiol*. 2004;27(11):1500-1506.
  10. Bauersfeld U, Tomaske M, Dodge-Khatami A, Rahn M, Kellenberger CJ, Prêtre RU. Initial experience with implantable cardioverter defibrillator systems using epicardial and pleural electrodes in pediatric patients. *Ann Thorac Surg*. 2007;84:303-305.
  11. Jacob S, Lieberman RA. Percutaneous epicardial defibrillation coil implantation: a viable technique to manage refractory defibrillation threshold. *Circ Arrhythm Electrophysiol*. 2010;3(2):214-217.
  12. Pae JY, Kim YN, Do MY, et al. The internal jugular vein as an alternative venous access for a revision of a fractured implantable cardioverter-defibrillator lead. *Korean J Intern Med*. 2017;32(2):360-362. doi:10.3904/kjim.2015.221
  13. Bardy GH, Smith WM, Hood MA, et al. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med*. 2010;363:36-44.
  14. Boersma L, Barr C, Knops R, et al. Implant and midterm outcomes of the subcutaneous implantable cardioverter-defibrillator registry: the EFFORTLESS study. *J Am Coll Cardiol*. 2017;70:830-841.
  15. Gold MR, Lambiase PD, El-Chami MF, et al. Primary results from the understanding outcomes with the S-ICD in primary prevention patients with low ejection fraction (UNTOUCHED) trial. *Circulation*. 2021;143(1):7-17.
  16. Stuijt W, Quast AF, Baalman S, Nordkamp L, Wilde A, Knops R. Improving the care for female subcutaneous ICD patients: a qualitative study of gender-specific issues. *IJCA*. 2020;317:91-95.
  17. Theuns DA, Crozier IG, Barr CS, et al. Longevity of the subcutaneous implantable defibrillator: long-term follow-up of the european regulatory trial cohort. *Circ Arrhythmia Electrophysiol*. 2015;8(5):1159-1163. doi:10.1161/CIRCEP.115.002953
  18. Do K, Lee C, Kiankhooy A, Chang P, Doshi R. Substernal subcutaneous implantable cardioverter-defibrillator lead placement for the management of inappropriate shocks. *Heart Rhythm*. 2019;5(8):407-410.
  19. Tung SK, Bennett M, Yeung-Lai-wah JA, Ling H. Minimal invasive extra cardiac placement of high voltage defibrillator leads. *Heart Rhythm*. 2007;4(5 Suppl.):S200.
  20. Guenther M, Kolschmann S, Knaut M. Letter to the editors: substernal lead implantation: a novel option to manage DFT failure in S-ICD patients. *Clin Res Cardiol*, 2015, 104, 189-191, doi:10.1007/s00392-014-0764-5.
  21. Boyle TA, Cohen J, Carrillo R. Substernal implantation of a subcutaneous implantable cardioverter-defibrillator in a patient with preexisting hemodialysis reliable outflow graft. *Heart Rhythm Case Rep*. 2016;2:412-414.
  22. Bhagwandien RE, Kik C, Yap SC, Szili-Torok T. Substernal ICD lead implantation in a patient not suitable for subcutaneous ICD implantation without venous access due to superior vena cava syndrome. *Heart Rhythm Case Rep*. 2017;3:97-99.
  23. Hata H, Sumitomo N, Nakai T, Amano A. Retrosternal implantation of the cardioverterdefibrillator lead in an infant. *Ann Thorac Surg*. 2017;103:e449-e451.
  24. Marshall M, Christie M, Zhang X, Nikolski V, Olson N. Pacing and sensing performance of non-contact electrodes in the substernal space in swine. *Heart Rhythm*. 2016;13(5S):S106.
  25. Swenson D, Nikolski V. Insilico testing of anti-tachycardia pacing from an extravascular defibrillator system with a lead in the mediastinal space. *Heart Rhythm*. 2018;15(5):S491-S589. doi:10.1016/j.hrthm.2018.03.028
  26. Nikolski V, Christie M, Vander Heyden J. First report on anti-tachycardia pacing from an extravascular defibrillator system with a lead in the mediastinal space. *Heart Rhythm*. 2017;14(5):S339.
  27. Zipes DP, Fischer J, King RM, Nicoll A, Jolly WW. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium. *Am J Cardiology*. 1975;36:37-44.
  28. Zhang P, Grinberg Y, Nikolski V, et al. Modeling of novel substernal defibrillation coil electrode location shows significant reduction in defibrillation threshold compared to a subcutaneous ICD system. *Heart Rhythm*. 2016;13(5S):S59.
  29. Thompson A, Cao J, Christie M, Nikolski V, DeGroot P. Comparison of defibrillation thresholds in swine for transvenous, subcutaneous and substernal electrode configurations. *Heart Rhythm*. 2016;13(5S):S59-S60.
  30. Lahm R, Bhatia V, Harris M. Anatomical inputs for the development of a novel extravascular ICD lead implant procedure. *EP Europace*. 2016;18(S1):i72. doi:10.1093/europace/18.suppl\_1.i72
  31. Chan JYS, Lelakowski J, Murgatroyd FD, et al. Novel Extravascular defibrillation configuration with a coil in the substernal space: the ASD clinical study. *J Am Coll Cardiol EP*. 2017;3:905-910.
  32. Glassberg R, Sussman S, Glickstein M. CT anatomy of the internal mammary vessels: importance in planning percutaneous trans-thoracic procedures. *Am J Roentgenol*. 1990;155(2):397-400.
  33. Sholevar DP, Tung S, Kuriachan V, et al. Feasibility of extravascular pacing with a novel substernal electrode configuration: the substernal pacing acute clinical evaluation study. *Heart Rhythm*. 2018;15:536-542.
  34. Boersma LVA, Merkely B, Neuzil P, et al. Therapy from a novel substernal lead: the ASD2 study. *JACC Clin Electrophysiol*. 2019;5(2):186-196.
  35. Crozier I, Haqqani H, Kotschet E, et al. First-in-human chronic implant experience of the substernal extravascular implantable cardioverter defibrillator. *J Am Coll Cardiol EP*. Nov 2020;6(12):1525-1536.
  36. Boersma LV, El-Chami MF, Bongiorno MG, et al. Understanding outcomes with the EMBLEM S-ICD in primary prevention patients with low EF study (UNTOUCHED): clinical characteristics and perioperative results. *Heart Rhythm*. 2019;16(11):1636-1644.
  37. Blatt JA, Poole JE, Johnson GW, et al. No benefit from defibrillation threshold testing in the SCD-HeFT (sudden cardiac death in heart failure trial). *J Am Coll Cardiol*. 2008;52(7):551-556.
  38. Neuzner J, Hohnloser SH, Kutiyfa V, et al. Effectiveness of single- vs. dual-coil implantable defibrillator leads: An observational analysis from the SIMPLE study. *J Cardiovasc Electrophysiol*. 2019;30(7):1078-1085. doi:10.1111/jce.13943
  39. Kotschet E, Crozier I, Haqqani H, et al. Chronic follow-up from the pilot study of a novel substernal extravascular implantable cardioverter-defibrillator. *Eur Heart J*. 2020;41(Suppl2):406.
  40. Swerdlow CD, Zhang X, Sawchuk R, et al. Design and preliminary results of sensing and detection for an extravascular implantable cardioverter-defibrillator. *JACC Clin Electrophysiol*. 2021;7(11):1387-1399. doi:10.1016/j.jacep.2021.03.00410.1016/j.jacep.2021.03.004
  41. Sharma D, Sharma PS, Miller MA, Singh SM, Kalahasty G, Ellenbogen KA. Position and sensing vector-related triple counting and inappropriate shocks in the subcutaneous

- implantable cardioverter-defibrillator system. *Heart Rhythm*. 2015;12:2458-2460.
42. Wilkinson J, Blauer J, Abeyratne A, et al. Defibrillation threshold modeling to refine implant recommendations for an extracardiac ICD system. *Eur Heart J*. 2020;41(S2), doi:10.1093/ehjci/ehaa946.0787
  43. Crozier I, O'Donnell D, Boersma L, et al. The extracardiac implantable cardioverter defibrillator: the pivotal study plan. *J Cardiovasc Electrophysiol*. 2021;32(9):2371-2378. doi:10.1111/jce.15190

**How to cite this article:** Thompson AE, Atwater B, Boersma L, et al. The development of the extracardiac defibrillator with substernal lead placement: A new Frontier for device-based treatment of sudden cardiac arrest. *J Cardiovasc Electrophysiol*. 2022;33:1085-1095. doi:10.1111/jce.15511