DESIGN PAPER

Design of a post-market registry for the extravascular implantable cardioverter-defibrillator: The Enlighten Study

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BACKGROUND The extravascular implantable cardioverter-defibrillator (EV-ICD) with substernal lead placement has been shown to terminate ventricular arrhythmias safely and effectively while being outside the vasculature. The performance of the EV-ICD system with a novel inappropriate shock-reducing algorithm in a real-world setting has yet to be investigated.

OBJECTIVE The objective of the Enlighten Study: the EV-ICD Post-Approval Registry is to provide a comprehensive measure of the safety and performance of the EV-ICD system in real-world clinical practice over the lifetime of the device.

METHODS The Enlighten Study is a global, prospective, observational, multicenter, post-approval study utilizing the manufacturer's Product Surveillance Registry. Eligible patients implanted with an Aurora EV-ICD system at participating centers will be included. Follow-up clinical data will be collected approximately every 6 months throughout the lifetime of the device, enrolling a minimum of 500 patients.

RESULTS The primary endpoint of the study is major system-related complication-free survival at 5 years post-implantation, with a minimum threshold of >79%. The study will also characterize device performance that includes, but is not limited to, freedom from system- or procedure-related complications, performance of antitachycardia pacing, characterization of sensing and detection, inappropriate therapy, shock effectiveness, battery depletion, and system revisions.

CONCLUSION The Enlighten Study: the EV-ICD Post-Approval Registry will examine the real-world performance of the post-market EV-ICD system. Additionally, this study will allow for a robust assessment of EV-ICD–related complications, device revisions, and extractions over chronic (>5 years) implant durations.

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KEYWORDS Antitachycardia pacing; EV-ICD; Extravascular; Implantable cardioverter-defibrillator; Postapproval; Ventricular arrhythmias

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KEY FINDINGS

- Substernal placement of the extravascular implantable cardioverter-defibrillator (EV-ICD) has been shown to be effective and safe in pre-market studies, but the real-world performance with the post-market Aurora EV-ICD system with novel discriminators (Smart Sense) is unknown.
- The Enlighten Study will be the first assessment of the real-world safety and performance of the EV-ICD, utilizing Medtronic's global Product Surveillance Registry (PSR) platform to follow 500 or more patients for the lifetime of the device.
- The study's primary endpoint is freedom from major system- or procedure-related complications at 5 years post-implantation, with a goal of >79%.

Introduction

Implantable cardioverter-defibrillator (ICD) systems reduce mortality for patients at risk of sudden cardiac death.[1,2] Traditional placement of transvenous ICD leads in the vasculature is associated with several complications including systemic infection and injury to the vasculature.[3–5] The extravascular implantable cardioverter-defibrillator (EV-ICD) was developed as an alternative to transvenous systems with the goal of providing a suite of equivalent therapies including antitachycardia pacing (ATP) and post-shock and pause prevention pacing without the need for venous access.[6]

The first chronic human implantations of the EV-ICD system were reported in the EV-ICD Pilot Study, which showed the device to be safe and effective in a small cohort of patients across Australia and New Zealand.[7] More recently, the EV-ICD Pivotal Study confirmed the safety and performance of the EV-ICD system in a large, global cohort, leading to market approval of the device in several regions.[8] The performance of the EV-ICD system in the real-world over the lifetime of the device has yet to be investigated. Additionally, the post-market EV-ICD system differs from that used in the Pilot and Pivotal studies due to enhancements to sensing and detection to reduce inappropriate shocks and enhancements to lead manufacturing. Medtronic's Product Surveillance Registry (PSR) is designed to support prospective, multicenter post-market surveillance of approved devices. The Enlighten Study will utilize the PSR platform to report on the chronic, real-world performance of the post-market EV-ICD system. Herein, we describe the rationale and design for the Enlighten Study.

Methods

Study design

The Enlighten Study: the EV-ICD Post-Approval Registry (NCT06048731) is a global, prospective, observational, multicenter study. The study protocol was approved by ethics committees at each participating site, and written informed consent was provided by all study patients. Study objectives will be analyzed dynamically throughout the study period; the primary objective will be formally analyzed when 500 new patient enrollments have sufficient follow-up. Analysis will be conducted and reported based on local regulatory requirements. All patients enrolled and successfully implanted with an Aurora EV-ICD system (Medtronic) will be followed for as long as the device remains in use. If an Aurora EV-ICD system is not successfully implanted, patients will be exited from the registry after the implantation attempt unless a system- and/or implantation procedure–related adverse event (AE) is identified. If an Aurora EV-ICD system- and/or implantation procedure–related AE is identified, the patient will be followed until the event is resolved or there are no further actions. Successfully implanted patients are expected to have scheduled follow-up visits approximately every 6 months, but at least annually, or as prompted by reportable AEs. An independent clinical events committee will adjudicate all system-related AEs for relatedness to the device and classify each event as a major complication, minor complication, or an observation. A major complication is defined as a complication that results in death, permanent loss of device function due to mechanical or electrical dysfunction of the device, hospitalization, prolonged hospitalization by 48 hours or more, or system revision. A separate independent episode review committee (ERC) will adjudicate all treated episodes to determine therapy appropriateness.

Aurora EV-ICD system

The EV-ICD system has been previously described.[9] However, the post-market Aurora EV-ICD system used in the Enlighten Study will include Smart Sense Noise Discrimination, a novel feature designed to reduce inappropriate therapy resulting from P-wave oversensing.[10] If noise or P waves are identified, ventricular tachycardia (VT)/ventricular fibrillation (VF) detection and therapy are withheld. See Figure 1 for an image of the device and lead.

Study population and eligibility

The purpose of the Product Surveillance Registry (PSR) is to understand device usage in a real-world setting. Inclusion and exclusion criteria are outlined in Table 1. Patients planning to receive an Aurora EV-ICD system, based on the treating physician's medical discretion, are eligible for enrollment and must consent prior to implantation. Where applicable, active patients who participated in a pre-market EV-ICD clinical study and were successfully implanted are eligible to participate in the Enlighten Study if they are followed at a participating PSR study site and are consented into the Enlighten Study. Patients who were previously implanted in the pre-market studies who were reconsented for long-term follow-up in the Enlighten Study will not be included in the primary objective analysis; however, data collected from these patients may contribute to ancillary analyses where appropriate. Patients will be followed according to the expected routine care in the local geography.

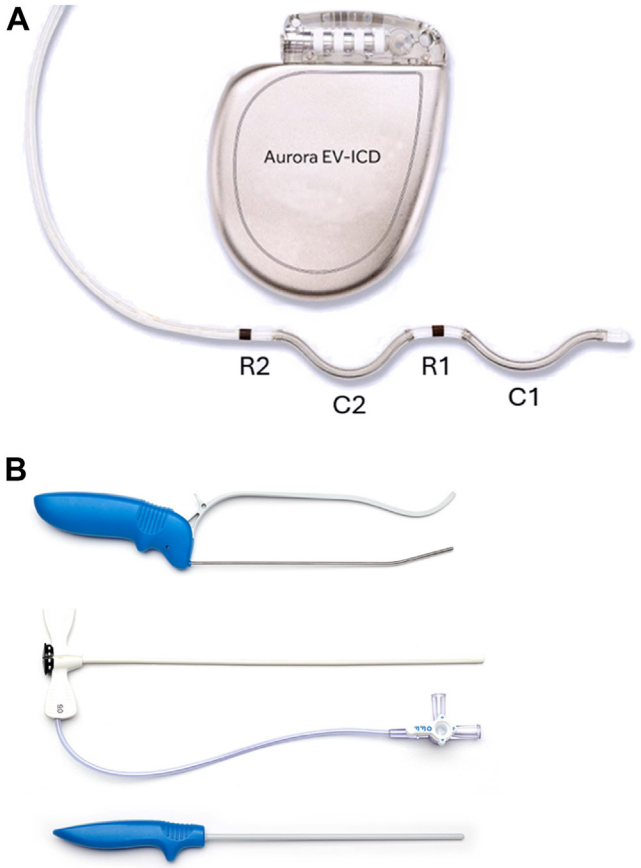

Figure 1 Aurora EV-ICD system and tools. A: The extravascular implantable cardioverter-defibrillator (EV-ICD) with epsilon-shaped quadripolar lead. (B) The sternal tunneling tool (top), hemostatic peel-away introducer system (middle), and transverse tunneling tool (bottom). C = coil; R = ring.

Any site that is part of the PSR can be an enrollment site after hands-on implementation training is completed and a principal investigator is chosen to assume responsibility for the PSR at the site. The PSR aims to be geographically diverse in order to reflect the wide range of patients who can benefit from the Enlighten Study. Sites are a strong combination of academic, community, urban, suburban, and rural centers spanning across the North America, Europe, the Middle East, and Asia Pacific regions.

Table 1 Product surveillance registry eligibility criteria.

Inclusion criteria
1. Patient or legally authorized representative provides authorization and/or consent per institution and geographical requirements
2. Patient is intended to receive or be treated with an EV-ICD device system and must be enrolled prior to the EV-ICD device implantation procedure
Exclusion criteria
1. Patient who is, or is expected to be, inaccessible for follow-up
2. Patient is excluded by local law
3. Patient is currently enrolled in or plan to enroll in concurrent drug/device studies that may confound the PSR results

EV-ICD = extravascular implantable cardioverter-defibrillator; PSR = product surveillance registry.

Table 2 Sample size estimates for chronic device-related complication-free survival.

Annual attrition	95% CI level	90% survival at 5 y	80% survival at 10 y
5%	±5	250	487
	±7	140	263
	±10	77	137
10%	±5	327	835
	±7	183	451
	±10	100	236
15%	±5	435	1479
	±7	244	798
	±10	133	417

CI = confidence interval.

Sample size

The sample size was determined by regulatory requirements to be the minimum effective sample size needed at the time point of interest and the expected patient attrition rate. Based on previous registry studies, the expected annual attrition including patient deaths, unsuccessful implantations, and patient dropouts is projected to be between 5% and 10%.

Due to the long-term nature of the study as well as the variability in attrition and system-related complication survival rates over time, a range of sample sizes is provided in Table 2 at various time points and is intended to give a general estimate of sample sizes needed to assess product performance. The actual enrollment size may vary due to factors such as implantation volumes, attrition rates, and manufacturing changes. Therefore, the study will target a minimum goal of 500 enrolled patients. Patients who previously participated in the pre-market studies do not contribute to the minimum required study sample size.

Study objectives

A complete list of Enlighten Study objectives is provided in Table 3. These objectives provide a comprehensive measure of product performance and patient safety for the Aurora EV-ICD system in real-world clinical practice. Primary objective 1 and ancillary objective 1 will provide sufficient data to demonstrate long-term safety and performance of the Aurora EV-ICD system. The remaining ancillary objectives will further characterize the Aurora EV-ICD system in real-world practice. A description of endpoints and statistical methods used for the objectives is provided subsequently. All analyses used for assessing survival-based objectives for the updated Aurora EV-ICD system are implemented through Kaplan-Meier methodology and are expressed in terms of system (device and lead) survival, with time 0 being the date of implantation with analysis limited to successfully implanted systems (primary objective 1 and ancillary objective 2) or including all implantation attempts (ancillary objective 1).

Primary objective 1: Demonstrate 5-year Aurora EV-ICD major system-related complication-free survival >79%

The primary objective of the Enlighten Study is to demonstrate that the freedom from major complications related to

Table 3 Enlighten Study: the EV-ICD Post-Approval Registry objectives.

Study **o**bjectives (full product life cycle)	
Primary objective 1	To demonstrate 5-y Aurora EV-ICD major system-related complication-free survival >79%
Ancillary objective 1	To estimate the Aurora EV-ICD major system- and/or procedure-related complication-free survival probability as a function of time post-implantation
Ancillary objective 2	Characterize the rate of abnormal battery depletion complications as a function of time post-implantation
Ancillary objective 3	Summarize all device system revisions (eg, reposition, replacement, explantation) including reasons for modification and action taken
Ancillary objective 4	Summarize patient deaths
Ancillary objective 5	Summarize patient demographics and baseline medical history
Ancillary objective 6	Characterize extracardiac pacing sensation
Ancillary objective 7	Summarize ATP with spontaneous arrhythmias
Ancillary objective 8	Characterize asystole pacing
Ancillary objective 9	Characterize sensing and detection
Ancillary objective 10	Characterize defibrillation shock effectiveness for terminating spontaneous VT/VF arrhythmia
Ancillary objective 11	Characterize lead location and lead motion at implantation

ATP = antitachycardia pacing; EV-ICD = extravascular implantable cardioverter-defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

the Aurora EV-ICD system at 5 years exceeds 79%. This benchmark was set to be consistent with Food and Drug Administration expectations. The prospective global EV-ICD Pivotal Study confirmed the safety of the EV-ICD, as demonstrated by the estimated major system- and procedure-related complication-free rate of 92.6% at 6 months, with a lower confidence bound of 89.0% of the 2-sided 95% confidence interval.[8]

All system-related events occurring within the chronic time frame (>30 days from implantation), which are determined to be major complications, will be included in this survival analysis, with the exception of infection complications. The 2-sided 95% confidence interval will be calculated using the log-log transformation. The primary objective will be formally assessed when the initial 500 new patient enrollments either have been followed for 60 months (ie, completed 60-month visit or visit window has closed) or have exited the study.

Ancillary objective 1: Estimate the Aurora EV-ICD major system- and/or procedure-related complication-free survival probability as a function of time post-implantation

Ancillary objective 1 will assess all major complications regardless of when they occur (ie, those that occur at the time of implantation or anytime during follow-up). All AEs adjudicated as being a major complication related to the Aurora EV-ICD system and/or procedure will be included in the analysis.

Ancillary objective 2: Characterize the rate of abnormal battery depletion complications as a function of time post-implantation

An abnormal battery depletion endpoint is defined as an investigator-reported event with a battery-related primary diagnosis. At each patient assessment, sites are required to actively confirm via case report form whether the device had an abnormal battery depletion. If the device did have abnormal battery depletion, as determined at the discretion of the clinician, sites are required to report this as an event which is reviewed by the clinical events committee. Subsequently, additional data related to the abnormal battery depletion are collected including the primary diagnosis, relevant symptoms and clinical findings, diagnostic testing, actions taken, and outcome. If confirmation of a battery depletion event is reported and corresponding data are missing, ongoing attempts will be made to obtain information needed to adequately review the reported event.

Ancillary objectives 3, 4, 5 6, 7, and 8

Ancillary objectives 3 through 8 are intended to be descriptive in nature to gain additional information about the safety and performance of the EV-ICD system. Summary statistics, including minimum, maximum, median, mean, and standard deviation, will be used for patient demographics, as appropriate. For ancillary objective 3, any system modifications that are not related to an event will be described including the date, reasons, and clinical action taken. Ancillary objective 4 will examine patient deaths, which will be classified by the clinical events committee and determined if it is related to the EV-ICD system or procedure. Ancillary objective 5 will report patient baseline characteristics as available. Ancillary objectives 6 through 8 will continue to investigate EV-ICD ATP and pacing capabilities. The Pivotal Study showed EV-ICD to be comparable to transvenous systems at providing effective ATP.[8]

Ancillary objective 9: Characterize the sensing and detection performance of the EV-ICD

Sensing performance will be partially characterized by providing the minimum, maximum, median, mean, and standard deviation for electrical parameters, as needed. Device-treated episodes (eg, ATP-treated episodes, episodes resulting in shock) will be adjudicated by an ERC, comprising predominantly independent physicians, and will contribute towards the analysis of this objective. Appropriate and inappropriate shocks will be characterized as a part of the sensing and detection analysis with all episodes adjudicated by the ERC. Results will be summarized in aggregate using descriptive statistics. Shocks delivered

by the device for spontaneous arrhythmias will be partitioned by whether the treated rhythm was a VT/VF episode, and by the specific rhythm of the episode. Both the number of episodes and the number of subjects experiencing such episodes will be reported, as well as the energy delivered. Kaplan-Meier curves for time to first appropriate shock and time to first inappropriate shock will be created to demonstrate shock incidence.

Ancillary objective 10: Characterize defibrillation shock effectiveness for terminating spontaneous VT/VF arrhythmias

Shock effectiveness will be analyzed by summarizing episodes and assessing whether each shocked arrhythmia was converted by the first programmed therapy and whether each episode was converted by the full set of programmed therapies.

Ancillary objective 11: Characterize lead location and lead motion at implantation

The lead location, relative to anatomical markers, and any lead movement will be characterized at implantation. Any repositioning of the lead or retunneling performed at implantation will also be collected.

Ethical conduct

This study is being conducted in compliance with international ethical and scientific quality standards, known as good clinical practice. Good clinical practice includes review and approval by an independent institutional review board and/or ethics committee prior to study initiation as applicable, continuing review by the institutional review board/ethics committee, and obtaining and documenting the freely given informed consent of a patient before initiating the study.

Significance of the study

The Enlighten Study is clinically impactful for several reasons. It is the first assessment of the performance and safety of the EV-ICD in the real world. The study will provide insight on the procedure, post-implantation modifications, and device programming from a larger and more diverse pool of implanters. Furthermore, the Enlighten Study allows for examination of the device over its entire lifespan, which is important for characterizing chronic lead extraction, battery life, and any late-term complications that may arise. The Enlighten Study will also deliver the first assessment of the novel Smart Sense Noise Discrimination algorithm and its performance at reducing inappropriate shock. Last, this study will provide data to assess the benefit of ICD therapy in a diverse cohort of contemporary patients, as well as ICD utilization in specific indicated populations, on both a regional and global scale.

The Enlighten Study is designed to robustly assess the safety and performance of the Aurora EV-ICD system throughout the lifetime of the device in a large, global population.

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Patient Consent: Written informed consent was provided by all study patients.

Ethics Statement: The study protocol was approved by ethics committees at each participating site and conducted in compliance with international ethical and scientific quality standards, known as good clinical practice.

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