Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT)

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Background Cardiac implantable electronic device (CIED) infection is a major complication that is associated with significant morbidity and mortality. The aim of this study is to determine whether Medtronic TYRX absorbable envelope reduces the risk of CIED infection through 12 months of follow-up post procedure.

Methods WRAP-IT is a randomized, prospective, multi center, international, single-blinded study. Up to 7,764 subjects who are undergoing CIED generator replacement, upgrade, or revision, or a de novo CRT-D implant, will be enrolled and randomized (1:1) to receive the TYRX envelope or not. The primary endpoint is major CIED infection throughout 12 months of follow up after the procedure. Data will be analyzed with an intention to treat approach. WRAP-IT will also assess the performance of Medtronic's lead monitoring algorithms in subjects whose CIED includes a transvenous right ventricular defibrillation system.

Conclusions WRAP-IT is a large randomized clinical trial that will assess the efficacy of TYRX absorbable envelope in reducing CIED infection, define its cost effectiveness, and will also provide a unique opportunity to better understand the pathophysiology and risk factors for CIED infection. (Am Heart J 2016;180:12-21.)

Background

Over the last few decades, there has been growing evidence of the importance of Cardiac Implantable Electronic Devices (CIEDs) in improving both quality of life and survival among patients with heart disease.[1–4] With growing indications for CIED implantation, the incidence of these procedures continues to increase as the population ages and the density of comorbidities rises.[5–7] In addition, patients with CIEDs are undergoing several device-related procedures due to battery depletion, evolving indications requiring upgrades, and device or lead advisories and recalls.[8–10] This surge in CIED procedures has led to rising awareness of associated complications including CIED infections and lead complications. Many recent studies have indicated that the rate of newly diagnosed CIED infection is rising out of proportion to the rate of newly implanted devices,[7,11,12] and a large body of evidence from both tertiary centers and national databases has indicated that CIED infection is associated with significant morbidity and mortality, and represents a major financial burden.[7,13–20] The precise incidence of CIED infection is dependent upon the duration of follow-up, poorly characterized by the literature and lacks a prospective trial validation.

Improving strategies to reduce infection will be largely dependent on understanding the contributing factors to CIED infections. Currently, there are a number of risk factors that have been associated with infection that can be categorized as either procedure or patient related. The most frequently cited procedure related risks include device type, foregoing the use of IV prophylaxis, early reintervention (typically to manage a pocket hematomas and/or reposition or replace a lead), and most commonly secondary procedures for device replacements or upgrades.[21,22] A recent study demonstrated that CRT devices carried the highest risk for infection and that replacements increased the risk for all devices.[22] Patient characteristics commonly associated with CIED infection include, but are not limited to, diabetes, renal insufficiency, chronic steroid use, anticoagulation use, heart failure, previous open heart surgery.[23–25] To date, the use of

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pre-procedural intravenous cefazolin is the only proven therapy to significantly reduce CIED infection through a randomized control trial design.[26] Future randomized studies are warranted to evaluate new infection reduction strategies and therapies.

The Medtronic TYRX absorbable antibacterial envelope (TYRX envelope) is an absorbable sterile prosthesis designed to hold a pacemaker or defibrillator pulse generator and create a stable environment when implanted in the body. The TYRX envelope is constructed from multifilament knitted mesh (polymer made of glycolide, caprolactone, and trimethylene carbonate) that is coated with an absorbable polyarylate polymer. The purpose of the absorbable coating is to act as a carrier for the 2 antimicrobial agents at concentrations of 8.0 mg rifampin and 5.1 mg minocycline (medium size, permanent pacemaker [PPM]), and 11.9 mg rifampin and 7.6 mg minocycline (large size, implantable cardioverter defibrillator [ICD]). The TYRX Envelope releases the antimicrobial agents, rifampin and minocycline, for a minimum of 7 days to reduce the risk of infection of the implanted CIED following surgery and after approximately 9 weeks, the envelope is completely absorbed. Current published efficacy data demonstrate low infection rates with the use of the first-generation TYRX non-absorbable antibacterial envelope; however, the efficacy of the absorbable envelope is unknown.

In addition to infection, another major complication following CIED replacement is lead fractures and malfunctions.[27] Medtronic ICDs contain a suite of lead monitoring features, including Lead Integrity Alert (LIA), lead noise alert (LNA), and defibrillation impedance alerts, designed to detect ICD lead issues. Previous research has demonstrated the ability of these algorithms to improve electrogram (EGM) signal discrimination, detect pace/sense conductor failures, and prevent inappropriate shocks for ventricular tachycardia (VT)/ventricular fibrillation (VF).[28,29] While the ability of the LIA algorithm to detect pace/sense conductor failures has been established from retrospective data, the ability of this set of lead monitoring features to detect other lead system events (including insulation breaches connector issues, dislodgements, perforations, and lead to lead interaction) in ICD leads has not been prospectively evaluated.

Although infection and lead system events have been studied in the past, they are still not well understood or completely addressed with current technology. Therefore, WRAP-IT was designed as a randomized, prospective, multi-center, international, single-blinded study to define the incidence of major CIED infections and evaluate the ability of the TYRX absorbable antibacterial envelope to reduce major CIED infections for a minimum of 12 months after CIED generator replacement, upgrade, or revision, or a de novo cardiac resynchronization therapy – defibrillator (CRT-D) implant. Additionally, WRAP-IT will characterize the performance of Medtronic's suite of lead monitoring features in patients whose CIED system includes a transvenous right ventricular (RV) defibrillation system.

Methods

Study design

The study is expected to be conducted at up to 225 sites worldwide with up to 7,764 subjects enrolled in order to randomize approximately 6,988 subjects. Relative to patients receiving ICDs with or without CRT, patients receiving pacemakers may have a reduced risk of a major CIED infection. Thus, to ensure an adequate CIED infection event rate for the trial, the enrollment of subjects receiving a replacement of a pacemaker (including cardiac resynchronization therapy – pacemaker [CRT-P]) will be capped at approximately 25% of the total randomized study population (ie, approximately 1,746 subjects). This strategy will provide us with sufficient number of pacemakers to evaluate the effectiveness of the TYRX Absorbable Envelope in both pacemaker and defibrillation systems. The first subject was enrolled on January 6, 2015, and the enrollment period is expected to take approximately 24 months. As of March 16, 2016, a total of 2,809 patients have been enrolled in the study. Patients will be followed up for a minimum of 12 months until all randomized patients have the opportunity to complete the 12-month visit.

Expected participating geographies may include, but are not limited to, North America, Central America, South America, Europe, Middle East, Africa, and Asia.

To ensure a widespread distribution of data, minimize site bias in study results and ensure that sites will be able to adequately manage and follow subjects enrolled in the study, the maximum number of randomized subjects allowed at a single site is 100 subjects. Sites are encouraged to enroll as many consecutive eligible subjects as appropriate.

Subject population

Patients meeting one or more of the following criteria may be enrolled: (1) an ACC/AHA/HRS or ESC guideline-recommended need for a de novo CRT-D and subject has a geography approved indication for a CRT-D, (2) an existing PPM, CRT-P, ICD, or CRT-D undergoing generator replacement or generator upgrade with or without the addition of new leads, or (3) an existing PPM, CRT-P, ICD, or CRT-D (without the pocket being opened in the last 365 days) and is undergoing a CIED system revision, are eligible for the enrollment in the study. Subjects who enroll in the study and proceed with a device procedure must be implanted with a Medtronic single, dual, or CRT pacemaker or defibrillator that has received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the procedure will take place. Subjects with an existing non-Medtronic device are eligible but a