The World-wide Randomized Antibiotic Envelope Infection Prevention (WRAP-IT) trial: Long-term follow-up

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BACKGROUND The World-wide Randomized Antibiotic Envelope Infection Prevention trial reported a 40% reduction in major cardiac implantable electronic device (CIED) infections within 12 months of the procedure with the use of an antibacterial-eluting envelope (TYRX Absorbable Antibacterial Envelope, Medtronic, Mounds View, MN).

OBJECTIVE The purpose of this report was to describe the longer-term (>12 months) envelope effects on infection reduction and complications.

METHODS All trial patients who underwent CIED replacement, upgrade, revision, or initial cardiac resynchronization therapy – defibrillator implantation received standard-of-care infection prophylaxis and were randomized in a 1:1 ratio to receive the envelope or not. CIED infection incidence and procedure and system-related complications were characterized through all follow-up (36 months) by using Cox proportional hazards regression modeling.

RESULTS In total, 6800 patients received their intended randomized treatment (3371 envelope; 3429 control; mean follow-up period 21.0 ± 8.3 months). Major CIED-related infections occurred in 32 envelope patients and 51 control patients (Kaplan-Meier [KM] estimate 1.3% vs 1.9%; hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.41–0.99; $P = .046$). Any CIED-related infection

This work was supported by Medtronic. Dr Mittal has received honoraria/consultant fees from Abbott, Boston Scientific, and Medtronic. Dr Wilkoff has received honoraria/consultant fees from Abbott, Medtronic, and Philips. Dr Kennergren has received honoraria/consultant fees from Biotronik, Boston Scientific, Medtronic, and Philips. Dr Poole has received honoraria/consultant fees from Boston Scientific, EBR Solutions, Kestra, and Medtronic. Dr Corey has received honoraria/consultant fees from Arsanis, Basilea, Bayer, Contrafect, Medtronic, Melinta, Motif, Paratek, Pfizer, Quintiles, Tetraphase, The Medicines Company, Theravance, Bio2 Medical, Cempra, Meiji Seika Pharm Co., Novella, Regeneron, and SC Pharma. Dr Addo has received honoraria/consultant fees from Abbott. Dr Issa has received honoraria/consultant fees from Boston Scientific and royalty from Elsevier. Dr Redpath has received research grant from Medtronic. Dr Boersma has received consultant fees from Medtronic. Dr Korantzopoulos has received honoraria/consultant fees from Bayer, Boehringer Ingelheim, Elpen, Medtronic, Merck, Sharp & Dohme, and Pfizer. Ms Krueger, Dr Lande, Ms Morss, and Dr Seshadri are employees of Medtronic; Dr Tarakji has received honoraria/consultant fees from Medtronic and AliveCor. The rest of the authors report no conflicts of interest. ClinicalTrials.gov identifier: NCT02277990. **Address reprint requests and correspondence:** Dr Suneet Mittal, Valley Health System, 970 Linwood Avenue, Paramus, NJ 07652. E-mail address: MITTSU@Valleyhealth.com.

1547-5271/

https://doi.org/10.1016/j.hrthm.2020.02.011

occurred in 57 envelope patients and 84 control patients (KM estimate 2.1% vs 2.8%; HR 0.69; 95% CI 0.49–0.97; $P = .030$). System- or procedure-related complications occurred in 235 envelope patients and 252 control patients (KM estimate 8.0% vs 8.2%; HR 0.95; 95% CI 0.79–1.13; $P < .001$ for noninferiority); the most common were lead dislodgment (1.1%), device lead damage (0.5%), and implant site hematoma (0.4%). Implant site pain occurred less frequently in the envelope group (0.1% vs 0.4%; $P = .067$). There were no (0.0%) reports of allergic reactions to the components of the envelope (mesh, polymer, or antibiotics).

CONCLUSION The effects of the TYRX envelope on the reduction of the risk of CIED infection are sustained beyond the first year postprocedure, without an increased risk of complications.

KEYWORDS Cardiac resynchronization therapy; Complication; Generator replacement; Infection; Implantable cardioverter-defibrillator; Pacemaker; Replacement

(Heart Rhythm 2020;17:1115–1122)

Introduction

Cardiac implantable electronic device (CIED) infection is a rare but serious complication that can lead to significant morbidity, mortality, and cost.[1–5] Management typically involves extraction of the implanted system (device and lead[s]), which can result in the need for prolonged hospitalization. Other than the use of a sterile, adequate surgical technique and the administration of intravenous preoperative antibiotics,[6] there has been a lack of evidence on other prophylactic strategies to prevent CIED infections. Recently, the World-wide Randomized Antibiotic Envelope Infection Prevention (WRAP-IT) trial,[7,8] a large global randomized CIED trial, reported a 40% reduction in major CIED infections and 61% reduction in pocket infections within 12 months of the procedure with the use of an absorbable antibiotic-eluting envelope. There is still a lack of understanding of the lifetime risk of CIED infection, beyond first year postprocedure that may still be attributed to the procedure. The longer-term impact of the envelope on outcomes has also not yet been quantified, which is the aim of the present analysis.

Methods

Study design

The design of the WRAP-IT trial has previously been described.[7] Briefly, the aim of this prospective, randomized, multicenter, single-blinded, postmarket, interventional clinical trial was to compare the incidence of major CIED infections through 12 months postprocedure in patients who received the envelope (TYRX Absorbable Antibacterial Envelope, Medtronic, Mounds View, MN) during their procedure vs patients who did not receive the envelope (ClinicalTrials.gov identifier: NCT02277990). All patients received standard-of-care infection prevention strategies and were randomly assigned in a 1:1 ratio, stratified by study site and device type (pacemaker/cardiac resynchronization therapy – pacemaker [CRT-P] or implantable cardioverter-defibrillator/cardiac resynchronization therapy – defibrillator [CRT-D]), to receive the envelope during their procedure (envelope group) or not (control group). The study protocol was approved by the ethics committee at each participating institution, and all patients provided written informed consent. All deaths and adverse events potentially related to the procedure or implanted system were adjudicated by a Clinical Events Committee. Safety oversight was provided by an independent data monitoring committee managed by the Cleveland Clinic Coordinating Center for Clinical Research.

Patients and intervention

Detailed study inclusion and exclusion criteria have been described previously.[7,8] Patients undergoing CIED generator replacement or system upgrade with or without new leads, patients undergoing pocket/lead revision, or patients undergoing an initial CRT-D implantation procedure were enrolled in study. As per the study protocol, pacemaker (including CRT-P) enrollment and randomizations were capped at 25% of the target sample size.

The TYRX envelope is an absorbable single-use prosthesis designed to hold a CIED when implanted in the body. The envelope is constructed from a multifilament knitted mesh and coated with an absorbable polymer mixed with minocycline and rifampin. The antibiotics are eluted into the local tissue for a minimum of 7 days, and the envelope is fully absorbed in 9 weeks.

End points and definition of CIED infection

The WRAP-IT trial had 1 primary end point—incidence of major CIED infections through 12 months postprocedure—and 3 secondary end points—CIED procedure–related or system-related complications through 12 months postprocedure, major or minor CIED infections within 12 months of the procedure, and major CIED infections >12 months postprocedure—as reported previously.[7,8] In this report, we extend the analysis of the secondary end point to confirm that the TYRX envelope does not increase CIED procedure–related or system-related complications beyond 12 months postprocedure. *CIED infection* was defined as superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion, or purulent drainage; deep incisional or space (pocket) surgical-site infection that met the Centers for Disease Control and Prevention criteria, independent of time from surgery; persistent bacteremia; or endocarditis. *Major CIED infections* were defined as those that

resulted in CIED system removal, an invasive CIED procedure (eg, pocket revision without removal), treatment with long-term antibiotic therapy (if the patient was not a candidate for system removal) with infection recurrence after discontinuation of antibiotic therapy, or death. *All other CIED infections* including superficial incisional surgical-site infections that met the Centers for Disease Control and Prevention criteria, independent of the time from surgery, were defined as minor CIED infections unless they met the major CIED infection criteria.

System- and procedure-related complications

All serious adverse events were collected and those suspected to be related to the procedure or system were adjudicated as complications or observations by the Clinical Events Committee. For the purpose of this analysis, we focused on adverse events that could have a clinical impact. *Complications* were defined as adverse events resulting in death, involving termination of significant device function or requiring invasive intervention. Each complication was adjudicated to be related to the CIED procedure (replacement/upgrade/new implant/revision or system modification including the TYRX envelope if applicable) or one of the CIED system components (device, right ventricular lead, right atrial lead, left ventricular lead, other lead, or the TYRX envelope). Procedure- or system-related complications were categorized as those occurring within $\leq$30 days (acute) of the procedure vs those occurring $>$30 days from the procedure (chronic). Complications that were adjudicated as infections were not included in the procedure-related and system-related complication classifications. Complication classification was mutually exclusive such that procedure-related complications were not included in the system-related groups.

Statistical analysis

For the purpose of this report, the incidence of CIED infection and the procedure- and system-related complication rates through all follow-up were evaluated in the WRAP-IT trial patients receiving their randomized treatment (per protocol) using Cox proportional hazards regression modeling. CIED procedure- or system-related complications were compared using a noninferiority margin for the hazard ratio (HR) of 1.33 (ie, envelope vs control HR for complications must be significantly $<$1.33). Patients who did not receive their intended randomized treatment were excluded from this analysis. Generalized linear modeling with a logarithmic link function was used to determine and compare annualized system revision rates. All analyses were performed using the R statistical package (R Project for Statistical Computing) or SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients and procedures

Patient recruitment occurred from January 2015 through July 2017, with 7075 patients enrolled and 6983 randomized at 181 centers in 25 countries within North America, Europe, Asia, and South America. Enrollment, randomization, and follow-up of the trial patients are reported previously.[8]

The envelope was successfully implanted in 99.7% of patients. A total of 6903 patients underwent CIED generator replacement or revision, upgrade, or de novo CRT-D implantation. Of these patients, 3396 received an envelope and 3507 did not receive an envelope during their initial procedure. There were 25 and 78 patients who crossed over from the control and treatment arms, respectively, such that 3371 patients were randomized to receive and actually received the envelope and 3429 patients were randomized to not receive and did not receive the envelope. Thus, 6800 patients were included in this analysis. Reasons for crossover were primarily attributed to physician discretion or inadvertent oversight. In the envelope group, the envelope was not successfully implanted in 10 procedures owing to limited pocket space. Notably, none of the patients who crossed over at the initial procedure to either arm experienced any major CIED infection. Device types included CRT-D (49%), CRT-P (4%), implantable cardioverter-defibrillator (26%), and implantable pulse generator (20%). Patients were followed for a mean duration of 21.0 $\pm$ 8.3 months; the duration of follow-up did not differ significantly between groups.

Patient characteristics at baseline (Table 1) were balanced between the 2 groups except for a higher percentage of low-dose (prednisone $\leq$20 mg/d) immunosuppressive use in the control group (P = .001); however, the standardized difference for immunosuppressive use does not suggest imbalance since the absolute value did not exceed 0.1. The mean age was 70.1 $\pm$ 12.4 years; 28.2% of patients were women.

During the entire follow-up period, 231 system revisions occurred in 191 envelope patients and 284 in 230 control patients (annualized rate 0.039 for envelope vs 0.047 for control; P = .030; 95% confidence interval [CI] 0.034–0.045 for envelope and 0.042–0.053 for control); excluding system modifications related to major infections or that occurred on or after major infections for a patient, 179 system revisions occurred in 161 envelope patients and 204 in 192 control patients (annualized rate 0.030 for envelope vs 0.034 for control; P = .257; 95% CI 0.026–0.035 for envelope and 0.030–0.039 for control).

Long-term major and minor CIED infections

Throughout the follow-up period, major CIED infections occurred in 32 envelope patients and 51 control patients (36-month Kaplan-Meier [KM] estimated event rate 1.3% and 1.9%, respectively; HR 0.64; 95% CI 0.41–0.99; P = .046) (Figure 1). Major or minor CIED infections occurred in 57 envelope patients and 84 control patients (36-month KM estimated event rate 2.1% and 2.8%, respectively; HR 0.69; 95% CI 0.49–0.97; P = .030) (Table 2). The envelope effect was driven by the significant reduction in major pocket infections (HR 0.41; 95% CI 0.23–0.72; P = .002) (Figure 2). The long-term incidence of bacteremia/endocarditis in the envelope group remained low (36-month KM estimated event rate 0.7%; HR 1.53; 95% CI 0.69–3.41) and was

Table 1 Baseline and procedural characteristics of patients who received their randomized treatment

Characteristic	Envelope (n = 3371)	Control (n = 3429)
Age (y)	70.0 ± 12.5	70.1 ± 12.4
Sex: female	959 (28.4)	957 (27.9)
Body mass index*	29.1 ± 6.1	29.2 ± 6.3
Medical history		
Cardiomyopathy	2294 (68.1)	2339 (68.2)
Coronary artery disease	1407 (41.7)	1455 (42.4)
Myocardial infarction	955 (28.3)	923 (26.9)
COPD	442 13.1)	412 (12.0)
Diabetes	1043 (30.9)	1066 (31.1)
Renal dysfunction	562 (16.7)	544 (15.9)
Cardiovascular surgical history		
CABG	704 (20.9)	750 (21.9)
Valve surgery	306 (9.1)	297 (8.7)
Number of prior CIEDs	1.2 ± 0.9	1.2 ± 1.0
Years since first CIED	9.0 ± 4.9	9.1 ± 5.0
Previous CIED infection†	43 (1.3)	50 (1.5)
Baseline medications		
Antiplatelets	1950 (57.8)	1942 (56.6)
Anticoagulants	1323 (39.2)	1366 (39.8)
Antibiotics	36 (1.1)	32 (0.9)
Immunosuppressive	46 (1.4)	84 (2.4)
Insulin	336 (10.0)	365 (10.6)
Oral antidiabetic	598 (17.7)	612 (17.8)
Infection management strategy‡		
Periprocedure antibiotic	3323 (98.6)	3386 (98.7)
Preprocedure antibiotic	3175 (94.2)	3264 (95.2)
Antibiotic during procedure	672 (19.9)	677 (19.7)
Postprocedure antibiotic	962 (28.5)	1045 (30.5)
Pocket wash	2482 (73.6)	2587 (75.4)
CIED type received		
Low power		
Pacemaker	703 (20.9)	691 (20.2)
CRT-P	126 (3.7)	167 (4.9)
High power		
ICD	889 (26.4)	872 (25.4)
CRT-D	1653 (49.0)	1699 (49.5)

Values are presented as mean ± SD or as n (%).

There were no significant differences between the 2 groups, except for the use of immunosuppressive agents ($P = .001$), with values not adjusted for multiple testing; the standardized difference for immunosuppressive agents does not suggest imbalance, since the absolute value does not exceed 0.1.

CABG = coronary-artery bypass grafting; CIED = cardiac implantable electronic device; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy – defibrillator; CRT-P = cardiac resynchronization therapy – pacemaker; ICD = implantable cardioverter-defibrillator.

*The body mass index is the weight in kilograms divided by the square of the height in meters.

†Shown are patients with CIED infection >12 mo before trial enrollment.

‡Counts and percentages indicate patients with procedure attempts.

not different between groups ($P = .295$). In 15 patients who experienced a major bacteremia/endocarditis CIED infection in the envelope group, 4 of these infections were initially onset after 12 months compared with 3/10 major bacteremia/endocarditis infections in the control group occurring in the same time frame. However, no statistically significant difference in the number of major bacteremia/endocarditis infections across treatment occurs either within the first 12 months ($P = .328$) or through all follow-up ($P = .295$).

Safety and system- and procedure-related complications

Complications that occurred throughout the follow-up period after the index CIED procedure and that were related to the CIED system or procedure occurred in 235 patients in the envelope group and 252 patients in the control group. There was no increased risk of procedure- or system-related complications between groups (36-month KM estimated event rate 8.0% and 8.2%, respectively; HR 0.95; 95% CI 0.79–1.13; $P < .001$ for noninferiority and $P = .546$ for superiority) (Figure 3). Excluding the primary end point of major infections, the KM 36-month non–infection-related complication event rate was 7.1% in both groups (HR 0.98; 95% CI 0.81–1.18; $P = .0007$ for noninferiority and $P = .824$ for superiority) (Supplemental Figure S1).

Neither acute (127 events in 115 patients, 3.4% vs 131 events in 119, 3.5%) nor chronic (120 in 102, 3.0% vs 128 in 108, 3.2%) system- and procedure-related complications were increased in the envelope group (Table 3). Other than infections, the most common complications were lead dislodgment (91 in 74 patients, 1.1%), device lead damage (37 in 37, 0.5%), and implant site hematoma (31 in 31, 0.4%). Implant site pain occurred less frequently in the envelope group (5 in 5, 0.1% vs 13 in 13, 0.4%; $P = .068$). There were no (0.0%) reports of allergic reactions to the components of the envelope (mesh, polymer, or antibiotics).

Discussion

In the 6800 patients in the WRAP-IT trial who received their randomized allocated treatment, the effects of the TYRX absorbable antibacterial envelope on the reduction of the risk of CIED infection were sustained beyond the first year postprocedure. WRAP-IT was a randomized controlled CIED trial designed to evaluate the safety and efficacy of the TYRX absorbable antibacterial-eluting envelope and, to our knowledge, currently the largest randomized global CIED trial. As previously reported,[8] the primary objective of the trial was met; adjunctive use of the antibacterial envelope resulted in a 40% reduction in the incidence of major CIED infections within 12 months of the initial procedure in comparison to standard-of-care infection prevention strategies alone. In this analysis, the longer-term effects of the envelope were evaluated beyond the first year postprocedure and a reduction in major CIED infections through study follow-up (36 months) and without an increased risk of system- or procedure-related complications was observed. These results add to the existing body of literature, confirming the safety and efficacy of the envelope in reducing the risk of CIED infection[9–13] and further our understanding of envelope effects that are sustained beyond the first year postprocedure.

In WRAP-IT trial patients who received standard-of-care infection prevention strategies alone, the rate of major CIED infections continued to rise at 12 months postprocedure and

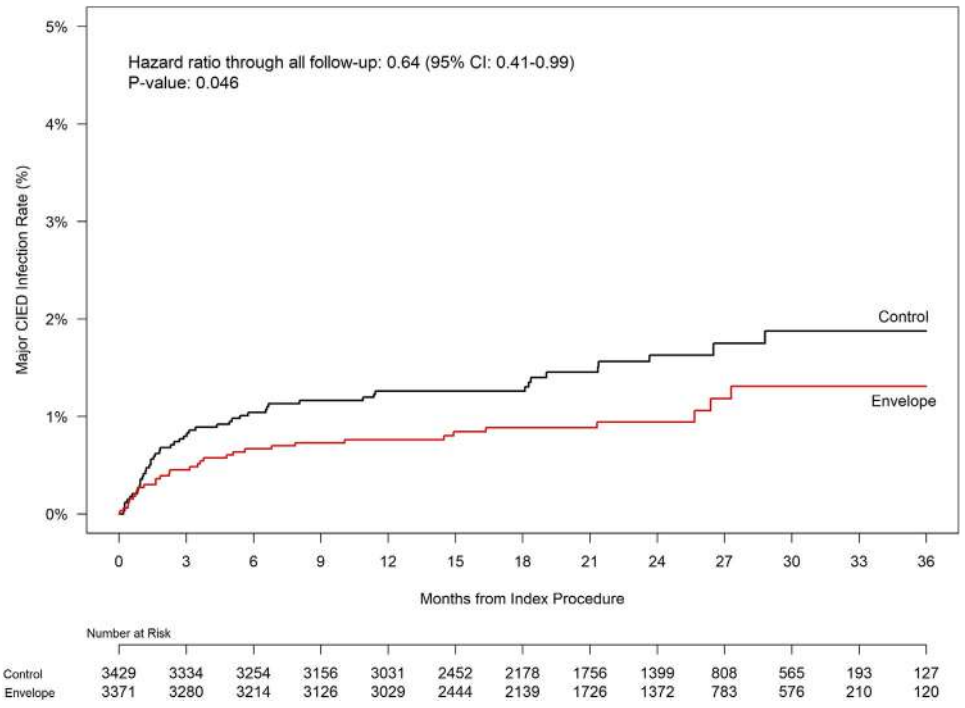

Figure 1 Major cardiac implantable electronic device (CIED) infection rate through all follow-up. CI = confidence interval.

was 1.9% at 3 years follow-up and the rate of initial major infections occurring more than a year postprocedure was >20% higher than that of the envelope group. The major value of this study comes from longer-term follow-up, as device-related infections are time dependent and not confined to the 12 months after the implantation procedure. This sustained benefit of the envelope is well illustrated when one considers that the major CIED infection rate rises in both arms (envelope 0.7%–1.3%; control 1.2%–1.9%) but the difference attributable to the envelope is sustained (HR 0.60–0.64). As such, these results confirm that the effects of the envelope were not limited to short-term follow-up and further underscore the longer-term benefits of TYRX adjunctive to standard-of-care infection prevention strategies alone. Although a number of studies support the use of local antibiotic delivery,[9–14] there is limited evidence of infection prophylaxis other than the use of preoperative antibiotics and the efficacy of postoperative antibiotics is yet to be established. The recent Prevention of Arrhythmia Device Infection Trial (PADIT) trial[15] found no additional benefit of incremental antibiotics and prolonged antibiotic prophylaxis has been correlated with an increased risk of acquired antibiotic resistance.[16] Notably, the sustained effect of the envelope observed in this study was driven by a significant 59% reduction in the incidence of major pocket infection, which typically accounts for up to 60% of all CIED infections and is mainly attributed to bacterial seeding of the operative site (incision, device pocket, capsule, and/or CIED components) at the time of device implantation.[6] The localized treatment benefit of the envelope appears to be site- and infection-type specific, which speaks to the "biological plausibility" of the trial results being attributed to the use of the envelope since we did not observe any significant differences in systemic infections long-term.

Table 2 Major and minor infection types through all follow-up

	Envelope (n = 3371)		Control (n = 3429)			
CIED infection status	No. of events (no. of patients, % of patients)	KM estimate	No. of events (no. of patients, % of patients)	KM estimate	Total (N = 6800)	Hazard ratio (95% CI)
Total CIED infections	65 (57, 1.7%)	2.1%	91 (84, 2.4%)	2.8%	156 (141, 2.1%)	0.69 (0.49–0.97)
Major infections within 36 mo[†]	38 (32, 0.9%)	1.3%	56 (51, 1.5%)	1.9%	94 (83, 1.2%)	0.64 (0.41–0.99)
Pocket	18 (17, 0.5%)	0.6%	45 (42, 1.2%)	1.5%	63 (59, 0.9%)	0.41 (0.23–0.72)
Bacteremia/endocarditis	20 (15, 0.4%)	0.7%	11 (10, 0.3%)	0.4%	31 (25, 0.4%)	1.53 (0.69–3.41)
Minor infections within 36 mo	27 (27, 0.8%)	0.8%	35 (35, 1.0%)	1.1%	62 (62, 0.9%)	0.79 (0.48–1.30)

CI = confidence interval; CIED = cardiac implantable electronic device.
[†]Major CIED infections may meet >1 criterion.

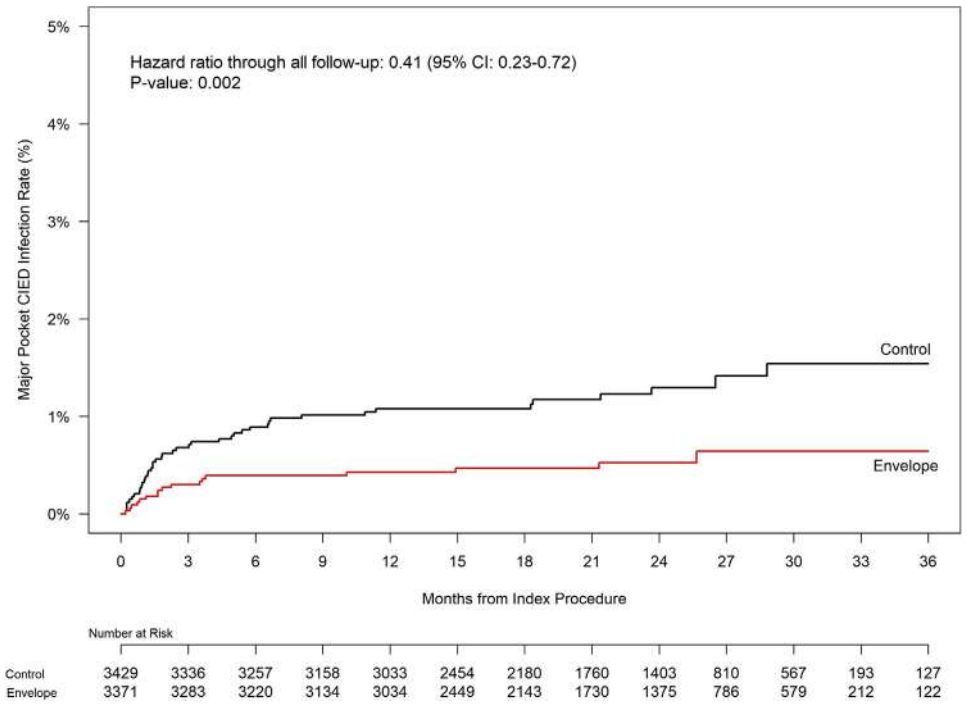

Figure 2 Major cardiac implantable electronic device (CIED) pocket infection rate through all follow-up. CI = confidence interval.

The risk of developing a pocket infection soon after a CIED procedure is considerable and may vary depending on the procedure, device type, and duration of follow-up. Data from previous reports, however, suggest that there is a lifetime risk associated with CIED infections that can extend beyond the first year postprocedure.[17,18] In the WRAP-IT trial data, a majority of the major CIED infections that occurred beyond the first year postprocedure were pocket infections in patients who received standard-of-care infection prevention strategies alone. The significant reduction in the incidence of pocket infections observed in the TYRX arm throughout the follow-up duration signals a sustained effect of the envelope even though the antibiotics are eluted over the course of 7 days. Minocycline and rifampin

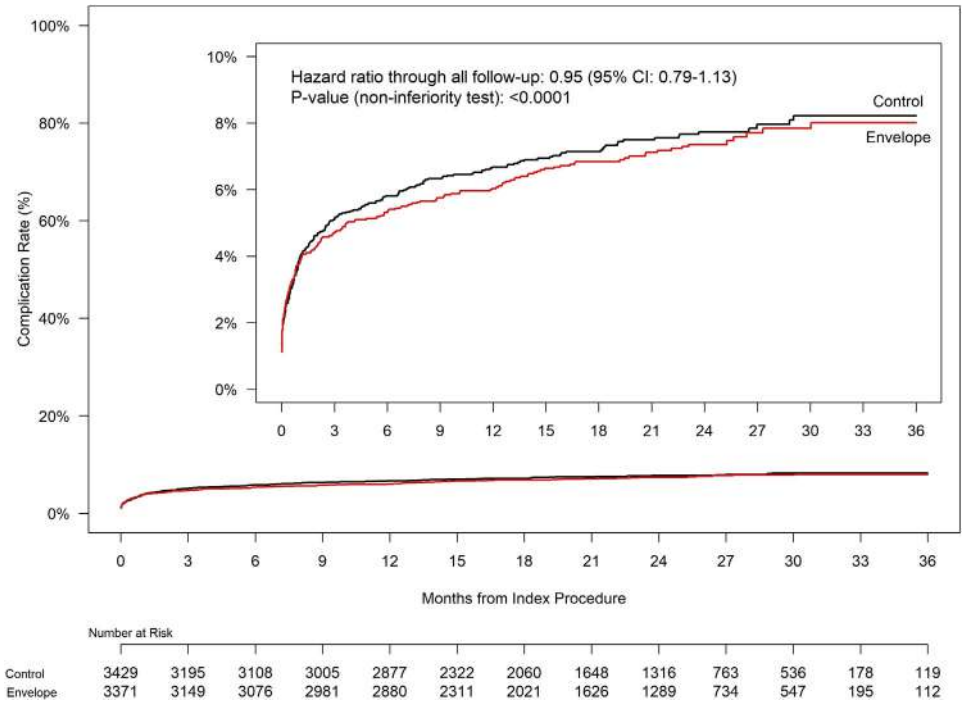

Figure 3 System- or procedure-related complication rate through all follow-up. CI = confidence interval.

Table 3 Acute and chronic complications, excluding infections

	Acute complications (≤30 d)		Chronic complications (>30 d)		All complications	
Complication classification	Envelope (n = 3371)	Control (n = 3429)	Envelope (n = 3371)	Control (n = 3429)	Envelope (n = 3371)	Control (n = 3429)
Procedure related	121 (109, 3.23%)	125 (114, 3.32%)	61 (53, 1.57%)	76 (67, 1.95%)	182 (156, 4.63%)	201 (169, 4.93%)
Lead related	5 (5, 0.15%)	6 (6, 0.17%)	47 (45, 1.33%)	43 (41, 1.20%)	52 (50, 1.48%)	49 (47, 1.37%)
Generator related	1 (1, 0.03%)	0 (0, 0.00%)	12 (11, 0.33%)	9 (8, 0.23%)	13 (12, 0.36%)	9 (8, 0.23%)
Total	127 (115, 3.41%)	131 (119, 3.47%)	120 (102, 3.03%)	128 (108, 3.15%)	247 (207, 6.14%)	259 (214, 6.24%)

The results are provided as number of events (number of patients, percenatge of patients).

are broad-spectrum antibiotics that may inhibit the growth of indolent bacteria that could colonize a device pocket after the procedure without clinical manifestation and lead to late onset infections.

Although the use of the envelope may require a slightly larger CIED device pocket, no increase in the risk of system- or procedure-related complications throughout study follow-up was observed. Excluding CIED-related infections, the non–infection-related complication event rate was comparable between the envelope and control groups. These data confirm that this advantage is observed early during follow-up and is sustained in the longer-term in light of the well-balanced baseline and procedural characteristics between groups. Neither acute (3.4% vs 3.5%) nor chronic (3.0% vs 3.2%) system- and procedure-related complications were increased in the envelope group. The most commonly reported complications were lead dislodgment, device lead damage, and implant site hematoma, which are expected in a population that is largely composed of patients undergoing replacement procedures and are consistent with the findings from the REPLACE Registry.[19]

In particular, there were fewer reports of implant site pain in the envelope group (0.1% vs 0.4%; $P = .068$). While the exact mechanism of this effect remains to be explored, there are plausible mechanisms. The formation of a slightly larger device pocket to accommodate the envelope may be an attributable factor. The antibiotics minocycline and rifampin have also been reported to exert a variety of biological actions independent of their antimicrobial activity, including effects on nociception.[20,21] More importantly, there were no reports of allergic reactions to any of the components of the envelope (mesh, polymer, or antibiotics) given the relatively large sample size of the study population, further highlighting the long-term safety of the envelope.

Limitations

While the results of this analysis add to the existing body of literature confirming the safety and efficacy of the antibacterial envelope, it is important that they are interpreted with caution. Owing to factors inherent to the nature of the trial design, the patient population was limited to those receiving generators from 1 device manufacturer. The envelope was also commercially available during the trial, which may have influenced participation in the trial. Baseline characteristics were well balanced between groups, with the exception of the use of immunosuppressives; however, there was only 1 major infection that occurred in this group within the first 12 months and is therefore unlikely to impact the interpretation of the results.

Conclusion

This analysis confirms that the beneficial effects of the envelope are sustained beyond the first year postprocedure as driven by a significant reduction in pocket infection. Envelope use does not increase the risk of complications and is associated with a reduced risk of implant site pain. The WRAP-IT trial provides strong evidence for the use of TYRX for infection prevention in this patient population.

Acknowledgments

We thank all the WRAP-IT sites and investigators who have contributed to the trial and this data set. We also thank Sarah Willey, MPH, for her management of the trial.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.02.011.

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