

Effectiveness of cardiac device envelopes in preventing infections among pacemaker patients: The REINFORCE Brady real-world project



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BACKGROUND Infections related to cardiac implantable electrical devices are among the most challenging and costly complications. Although the absorbable antibiotic-eluting envelope has shown efficacy in reducing infection risk, data on its use in pacemaker (PM) and cardiac resynchronization therapy PM (CRT-P) devices are limited.

OBJECTIVES This study aimed to assess the effectiveness of the TYRX envelope in preventing systemic and pocket infections in patients undergoing PM or CRT-P implantation or revision.

METHODS This retrospective, multicenter analysis included 896 patients undergoing PM or CRT-P implantation or revision between August 2020 and April 2024. Patients were categorized into 2 groups: the envelope group ($n = 350$), receiving the TYRX envelope, and the control group ($n = 546$).

RESULTS Over a mean follow-up of 2.2 ± 2.1 years, systemic or pocket infections occurred in 1.2% of patients, with significantly fewer infections in the envelope group (0.3%) than the control

group (1.8%) ($P = .05$). The envelope was associated with an 89% reduction in infection risk (incidence rate ratio 0.11, 95% confidence interval 0.05–0.23, $P < .001$). Kaplan-Meier analysis showed that, at 4 years, the cumulative incidence of infection was 0.4% in the envelope group vs 2.5% in the control group (hazard ratio 7.36, $P = .03$).

CONCLUSIONS In patients with PMs and CRT-Ps, the use of the TYRX envelope is associated with significantly lower occurrence of device-related infections. This benefit was sustained over long-term follow-up, supporting its effectiveness in routine clinical practice.

KEYWORDS Systemic infection; Pacemaker; Pocket infection; Antibiotic-eluting envelope; Device-related complications

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Introduction

Infections are among the most complex and costly complications for patients with cardiac implantable electrical devices (CIEDs).^{1–3} Infection predictors have been extensively investigated in literature,^{4–9} and the efficacy and safety of

the absorbable antibiotic-eluting envelope (TYRX, Medtronic, Minneapolis, MN) in preventing CIED infections have been proven in either observational studies or randomized trials.^{10–16} Moreover, real-world data from clinical practice have shown that TYRX use is associated with a lower risk

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KEY FINDINGS

- The antibacterial envelope was effective even in a lower-risk, pacemaker (PM)-based population: unlike previous studies mostly focused on implantable cardioverter-defibrillator or cardiac resynchronization therapy defibrillator recipients, this analysis included only PM and cardiac resynchronization therapy PM patients, 73.6% of whom underwent de novo implantation. Despite 67.2% being classified as low risk by the Prevention of Arrhythmia Device Infection Trial (PADIT) score, the antibacterial envelope still showed benefit.
- The antibacterial envelope use was associated with a significant reduction in infection rates: over a mean follow-up of 2.2 years, systemic or pocket infections occurred in 0.3% of patients in the TYRX group vs 1.8% in the control group ($P = .05$), with a 4-year incidence of 0.4% vs 2.5%, respectively. The antibacterial envelope remained an independent predictor of lower infection risk (hazard ratio [HR] 0.11, $P = .042$).
- The protective effect was evident despite worse baseline characteristics in the TYRX group: patients receiving the envelope had higher PADIT scores.
- The antibacterial envelope also showed benefit in single- and dual-chamber PM recipients: in this subgroup ($n = 752$), the 4-year infection rate was significantly lower in the TYRX group (0.6%) than the control group (3.1%, HR 7.34, $P = .033$), supporting its use even in standard low-voltage devices.

of the composite endpoint of systemic or pocket infection by more than 60%.¹¹ Nevertheless, most patients studied had an implantable cardioverter-defibrillator (ICD) or a cardiac resynchronization therapy defibrillator (CRT-D). Limited data are available regarding the efficacy of the envelope in patients with pacemakers (PMs) or CRT PMs (CRT-PMs), a population frequently older with a different clinical profile than ICD/CRT-D recipients. This analysis aimed to evaluate the efficacy of preventing infection-related events associated with PM or CRT-PM surgery in real-world clinical practice.

Methods

Project design

The analysis included consecutive patients who underwent a de novo PM or CRT-PM implant or repeated CIED surgery between April 2020 and April 2024 at 9 Italian centers participating in the One Hospital Clinical Service project. Repeated CIED surgery includes generator replacement; system revision (pocket revision and/or lead repositioning owing to dislodgement); and system upgrade if 1 or more leads were added, with or without previous lead extraction or removal. This project serves as both a clinical data repository and a medical care initiative aimed at describing and improving

the quality of diagnostic and therapeutic strategies using technologies and therapies in Italian clinical practice. It provides a shared platform for the prospective collection, management, analysis, and reporting of data from patients treated with Medtronic therapies.

In the REINFORCE (Reducing Infections and Pocket Hematoma Through Cardiac Device Envelope) project,¹¹ physicians prospectively collected data regarding CIED procedures and the use of the TYRX antibacterial envelope to evaluate the risk of infection and other outcomes associated with CIED surgery. This project received approval from each site's institutional review board and local ethics committees and adheres to the principles of the 1975 Declaration of Helsinki, as confirmed by the previous approval from each institution's human research committee. All patients enrolled in the One Hospital Clinical Service project provided an informed consent for data collection and analysis. The analysis reported in this paper adhered to Consolidated Standards of Reporting Trials guidelines. This investigation seeks to describe the population of patients with PM or CRT-PM who received the TYRX antibacterial envelope during CIED surgery for the prevention of device-related infections and assess the effectiveness of the TYRX in preventing CIED surgery-associated infections, including system infections and pocket infections.

The patient population was categorized into 2 groups: the envelope group, which included patients who received an absorbable antibiotic-eluting envelope (TYRX) during the initial procedure or a repeated system surgery, and the control group, comprising patients who underwent PM or CRT-PM surgery without the use of the envelope. The decision to use the TYRX envelope was made at the discretion of the individual implanter, based on clinical judgment. No center-level protocol or institutional mandate dictated its use, and practices varied within and across centers.

This analysis was conducted retrospectively on data that had been prospectively collected by the centers as part of their routine clinical workflow.

Population and procedural characteristics

During the baseline visit, several patients' clinical characteristics were collected, including age, sex, New York Heart Association class, CHA₂DS₂-VASc scores, presence of hypertension, diabetes, previous thromboembolic events, presence of structural heart disease (with the left ventricular ejection fraction measured by echocardiography), presence of renal insufficiency, and immunodeficiency. Moreover, the history of procedures on existing pockets was collected (de novo implant, generator replacement, or system revision or upgrade, including any lead procedure), device type (PM or CRT-PM), presence of active or abandoned leads, and presence of fever in the 48 hours prior to the procedure. Antibiotic prophylaxis was administered in all patients according to the clinical practice of each center; cephalosporins were the agent used most frequently. In particular, cefazolin or first-generation cephalosporins were given 1 hour before the

incision. In case of allergy to cefazolin, vancomycin (15 mg/kg) was administered 2 hours before the incision. All information about any infection-related adverse events or pocket hematoma occurring during the procedure or follow-up was recorded and collected.¹⁷ A pocket infection was defined as superficial cellulitis in the region of the CIED pocket, wound dehiscence, erosion, purulent drainage or a deep incisional (pocket) surgical-site infection, or persistent bacteremia, according to the definition used in the WRAP-IT (Worldwide Randomized Antibiotic Envelope Infection Prevention) trial.¹⁰ A CIED-related systemic infection was defined by the presence of clinical signs of bacteremia associated with positive blood cultures and/or positron emission tomography–computed tomography proving endovascular lead activity and/or lead vegetations or septic emboli or persistent bacteremia with no alternative source but CIED leads.

Follow-up and event collection

Follow-up visits were conducted in accordance with the clinical protocols established by each center, which included appointments for suture removal or wound assessment 10 to 15 days after surgery, followed by a subsequent evaluation at 12 months. During these scheduled visits, a comprehensive assessment of the patient's symptoms was performed, accompanied by an electrocardiogram, device interrogation, pocket examination, and review of the patient's medication regimen. In cases where patients did not attend their scheduled in-person follow-up visits, attempts were made to reach them or their relatives via telephone; if 2 attempts were unsuccessful, survival information was retrieved from the National Office of Vital Statistics.¹¹

Statistical analysis

Descriptive statistics were used to summarize all results. These include mean and standard deviation for continuous variables and counts and percentages for categorical variables. Summary statistics were reported with a maximum of 2 decimals, as appropriate. Continuous variables were compared between groups using the Wilcoxon test. Categorical variables were compared between groups using χ^2 test or Fisher's exact test, as appropriate. When analyzing the endpoints as time to first event, the Kaplan-Meier method was used to estimate survival rates, along with their 95% confidence intervals (CIs), and differences between groups were tested using the log-rank test.

Incidence rates (IRs) were calculated as the number of infection-related events per 100 patient-months. To compare the event rates between groups, Poisson regression models were used, with deviance scaling applied to account for potential over- or underdispersion. The resulting estimates were expressed as IR ratios with corresponding 95% CIs. To evaluate predictors of systemic or pocket infections, Cox proportional hazards regression models were used. Both univariable and multivariable analyses were performed, and the proportional hazards assumption was tested. The results were expressed as hazard ratios (HRs) with 95%

CIs. The multivariable Cox regression model used stepwise selection with entry of 0.10 and stay of 0.05 criteria, respectively, and infection event as the dependent variable. All statistical tests were based on a 2-sided significance level of .05. We calculated for each patient the raw Prevention of Arrhythmia Device Infection Trial (PADIT) risk scores.⁴ SAS software version 9.4 (SAS Institute Inc, Cary, NC) was used to perform statistical analyses.

Results

We analyzed data from 896 patients implanted with PM or CRT-P. Most patients (78.4%) received a Medtronic-manufactured CIED device, whereas the remaining patients received devices from other manufacturers. The population was divided into 2 groups based on whether or not the TYRX envelope was used. The envelope group comprised 350 patients (39%), whereas the control group comprised 546 patients (61%). De novo implants were 660 (73.6% of the studied population): 56.3% (197/350) in the envelope group vs 84.7% (463/546) in the control group ($P < .001$).

Baseline and procedural characteristics

The baseline characteristics of the entire population and the 2 patient groups are presented in Table 1. The 2 patient cohorts exhibited several differences. In particular, the envelope group included a higher proportion of females and patients with a history of heart failure and ischemic heart disease, previous syncope, valvular disease, diabetes, and renal disease. Overall, patients in the envelope group had more comorbidities and a higher CHA₂DS₂-VASc score. Even from an infection risk perspective, the 2 subpopulations differed. In general, the population with TYRX was at a higher infection risk based on literature reports. In fact, the percentage of high-risk patients is 22.9% (80/350) in the envelope group and 5.7% (31/547) in the control group ($P < .001$). The types of devices and the number of leads implanted per group are presented in Table 1. All patients had antibiotic prophylaxis during CIED surgery.

Systemic or pocket infection

During a mean follow-up time of 2.2 ± 2.1 years, a systemic or a pocket infection occurred in 11 patients (1.2%): 1 (0.3%) in the envelope group and 10 (1.8%) in the control group ($P = .05$), as presented in Table 2. Pocket infections occurred in 8 patients in the control group, whereas systemic infections occurred in 1 patient in the envelope group and 2 in the control group. All pocket infections resulted in CIED system removal (device and leads). Systemic infection occurred in 3 patients, 1 in the envelope group and 2 in the control group. One of these 2 patients resulted in death 10 months after the last CIED revision. The IR per 100 patient-months of systemic or pocket infections was 0.01 (95% CI 0.00–0.02) in the envelope group and 0.09 (95% CI 0.07–0.11) in the control group, corresponding to an IR ratio of 0.11 (95% CI 0.05–0.23, $P < .001$).

In the Kaplan-Meier analysis, at 4 years, the incidence of systemic infection or pocket infection was 2.5% (1.3%–

Table 1 Baseline characteristics of the total population and statistical comparisons between the 2 groups of patients: subjects in the envelope group vs the control group

Baseline characteristic	Total (N = 896)	Envelope (n = 350)	Control (n = 546)	P value
Demographics				
Median age (y)	81.0 (73.0–85.0)	80.0 (71.0–85.0)	81.0 (73.0–86.0)	.312
Sex (male)	60.8% (545)	55.7% (195)	64.1% (350)	.012*
BMI (kg/m ²)	26.3 ± 4.6	26.7 ± 4.9	26.0 ± 4.4	.130
Medical history				
History of HF	30.5% (273)	39.4% (138)	24.0% (135)	<.001*
NYHA class III/IV	33.7% (93/273)	32.4% (44/138)	34.5% (49/135)	.718
History of AT/AF	40.0% (358)	40.6% (142)	39.5% (216)	.744
Paroxysmal AF	21.1% (189)	19.3% (67)	22.3% (122)	.288
Persistent AF	4.7% (42)	4.7% (16)	4.7% (26)	.965
Permanent AF	14.2% (127)	16.7% (58)	12.5% (69)	.084
Ischemic heart disease	24.3% (217)	28.7% (100)	21.1% (117)	.014*
History of stroke/TIA	5.0% (45)	5.2% (18/343)	4.8% (27)	.786
Hypertension	78.7% (696)	80.8% (277)	77.4% (419)	.241
Diabetes	24.6% (220)	31.5% (110)	20.2% (110)	<.001*
Chronic kidney disease	26.9% (241)	41.4% (144)	16.3% (97)	<.001*
CHADS ₂ score of ≥2	73.1% (654)	79.3% (277)	68.8% (377)	.001*
CHA ₂ DS ₂ -VASc score of ≥4	54.6% (489)	64.7% (226)	47.7% (263)	<.001*
COPD	10.4% (93)	10.2% (35)	10.6% (58)	.854
LVEF (%)	53.2 ± 10.7	50.5 ± 9.9	55.7 ± 10.8	<.001*
Risk score				
PADIT risk score	2.8 ± 3.1	4.0 ± 3.5	2.0 ± 2.6	<.001*
Low (score 0–4)	67.2% (602)	48.6% (170)	79.1% (432)	<.001*†
Medium (score 5–6)	20.4% (183)	28.6% (100)	15.2% (83)	
High (score ≥7)	12.4% (111)	22.9% (80)	5.7% (31)	
Implantable device Type				
CRT-P	16.1% (144)	21.1% (74)	12.8% (70)	<.001*
Dual-chamber PM	62.4% (559)	67.1% (235)	59.3% (324)	<.001*
Single-chamber PM	21.5% (193)	11.7% (41)	27.8% (152)	<.001*
De novo CIED	73.7% (660)	56.3% (197)	84.7% (463)	<.001*
Previous devices	26.3% (236)	43.7% (153)	15.3% (83)	<.001*
Replacement	77.1% (182/236)	71.2% (109/153)	88.0% (73/83)	.028*
System Revision	0.8% (2/236)	1.3% (2/153)	0.0% (0/83)	
Upgrading	19.1% (45/236)	24.2% (37/153)	9.6% (8/83)	
Downgrading	3.0% (7/236)	3.3% (5/153)	2.4% (2/83)	
Antiplatelet and anticoagulant use				
Antiplatelets	30.6% (274)	23.8% (83)	35.2% (191)	<.001*
Anticoagulant	31.0% (277)	28.9% (101)	32.5% (176)	.272

AF = atrial fibrillation; AT = atrial tachycardia; BMI = body mass index; CIED = cardiac implantable electronic device; COPD = chronic obstructive pulmonary disease; CRT-P = cardiac resynchronization therapy pacemaker; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PADIT = Prevention of Arrhythmia Device Infection Trial; PM = pacemaker; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachyarrhythmias.

*Statistically significant.

†Statistical test conducted between the entire envelope cohort vs the control group on device distribution.

4.9%) in the control group and 0.4% (0.1%–3.1%) in the envelope group (HR 7.36, $P = .03$) (Figure 1). In the subpopulation who underwent de novo PM/CRT-P implant (660 patients, 73.7%), the incidence of systemic or pocket infection events was 0% in the envelope group and 1.7% (8/463) in the control group.

There was no significant difference in the incidence of hematoma events between the 2 populations studied: no events occurred in the envelope group (0%), whereas 4 events were recorded in the control group (0.7%, $P = .896$).

To identify predictors of infection events in the overall population, a univariate Cox regression analysis was conducted, considering key comorbidities, device type (number of leads), de novo implant, and the use of the TYRX antibac-

terial envelope. Age at implant was the only variable with a significant HR ($P = .039$). In the multivariate analysis, independent predictors of infection events, both systemic and pocket, were identified: diabetes, which significantly increased the risk of infection ($P = .012$), and the use of TYRX (HR 0.11, 95% CI 0.01–0.92, $P = .042$) and older age, which significantly reduced infection risk (Table 3). The characteristics of patients who experienced systemic or pocket infection events are presented in Table 4.

Subgroup of single- and dual-chamber PM

In the subpopulation of 752 patients with single- or dual-chamber PMs, the use of TYRX significantly reduced the

Table 2 Infection-related events or pocket hematoma of the total population and comparison between the 2 groups of patients: subjects in the envelope group vs the control group

Clinical event	Total (N = 896)	Envelope (n = 350)	Control (n = 546)	P value
At least 1 infection-related clinical event (systemic or pocket infection)	1.2% (11/896)	0.3% (1/350)	1.8% (10/546)	.050
Pocket infection	0.9% (8/896)	0.0% (0/350)	1.5% (8/546)	.020
Systemic infection	0.3% (3/896)	0.3% (1/350)	0.4% (2/546)	.997
Pocket hematoma	0.4% (4/896)	0.0% (0/350)	0.7% (4/546)	.163

risk of systemic or pocket infections. In particular, at 12 months, the incidence of infectious events was 0.6% (95% CI 0.1–4.0) in the TYRX group compared with 2.6% (1.3%–5.2%) in the control group. At 4 years, the respective risks were 0.6% (0.1%–4.0%) and 3.1% (1.6%–5.9%) in the TYRX group vs the control group (HR 7.34, 95% CI 1.00–60.00, $P = .033$) (Figure 2).

Discussion

Main results

To the best of our knowledge, this is the first large observational analysis specifically focusing on the preventative effect of TYRX in a contemporary population receiving low-voltage CIEDs. The main findings of this analysis are as follows: (1) in clinical practice, the TYRX antibacterial envelope is also used in patients with low-voltage devices (PM or CRT-P) who have a higher infection risk owing to multiple comorbidities; (2) the TYRX envelope seems to be effective in preventing infection events even in patients with PMs, including those with single- or dual-chamber devices; and

(3) TYRX remained an independent factor associated with lower infection risk even in a population typically considered at lower risk.

One of the most severe complications, with significant clinical and economic impact related to PM implantation, is device-related infections. In the population with CIEDs, the incidence of infections generally ranges from 1% to 15.0%.¹ This incidence can be attributed to various factors related to the patient's clinical characteristics, the complexity of the surgical procedure, and the number of re-interventions.^{1–4} Data on lower-risk patients and, in general, PM recipients are limited. A recent study from Denmark analyzed the effectiveness and cost-effectiveness of CRT-P and CRT-D reoperations, but did not consider PM implants.¹⁸

Our analysis was focused on patients who had undergone PM or CRT-P implantation or system revision surgery. Moreover, nearly 74% of the studied population underwent a de novo PM/CRT-P implantation procedure, whereas 336 (26 %) underwent a repeated procedure, thus being at a

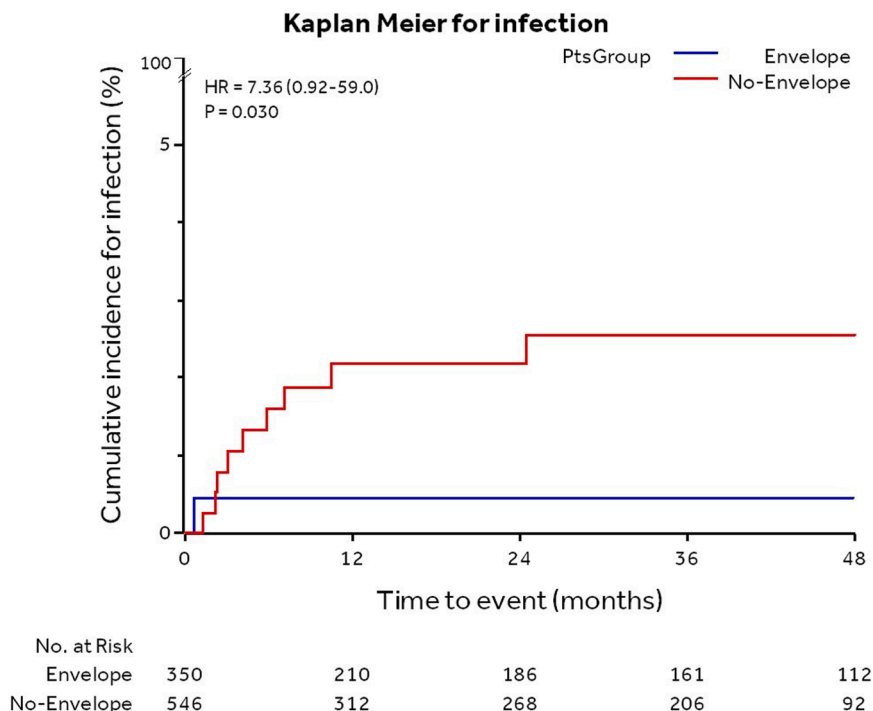
**Figure 1** Cumulative event rate of systemic or pocket infection in the envelope and control groups by Kaplan-Meier estimate. HR = hazard ratio; Pts = patients.

Table 3 Univariate and multivariate Cox regression analysis of predictors for systemic or pocket infection events

Univariate analysis			Multivariate analysis	
Variable	HR (95% CI)	P value	HR (95% CI)	P value
Age at implant	0.97 (0.95–1.00)	.039*	0.96 (0.93–0.99)	.004*
Sex (female)	0.60 (0.16–2.27)	.454		
History of HF	0.80 (0.15–4.15)	.789		
Diabetes	3.26 (0.94–11.33)	.064*	6.28 (1.51–26.17)	.012*
Chronic kidney disease	1.94 (0.46–8.13)	.364		
PM type (monochamber vs others)	1.63 (0.43–6.18)	.470		
PM type (dual-chamber vs others)	1.58 (0.42–5.96)	.498		
De novo devices	1.10 (0.29–4.22)	.893		
TYRX used	0.14 (0.02–1.09)	.060*	0.11 (0.01–0.92)	.042*

*indicates the variables evaluated in multivariate analysis.

The table summarizes the HRs and the corresponding 95% CIs for each predictor variable. The multivariate analysis was conducted using a stepwise approach.

CI = confidence interval; HF = heart failure; HR = hazard ratio; PM = pacemaker.

higher risk of infection according to clinicians' judgment¹⁷ and infection risk scores.^{5,9,19} The population is relatively elderly, with 30% having heart failure, 40% atrial fibrillation, and 30% diabetes. Overall, 62.5% of the patients had a CHA₂DS₂-VAsC score of >4. However, 70% of the population was classified as low infection risk based on the PADIT score. In contrast, the first large randomized WRAP-IT study, designed to evaluate the efficacy of TYRX in preventing infections, included less than 25% of patients with PMs. The overall WRAP-IT study population was considered at an elevated risk of CIED infection based on historical data from the literature and included patients with CRT-D devices and those undergoing CIED revisions, replacements, or upgrades.¹⁰ Chaudhry et al¹² confirmed the clinical efficacy of the antibacterial envelope TYRX in a population of CIED patients with mostly intermediate- to high-risk infection as defined by PADIT scores. At 12-month follow-up, no local infection occurred in the envelope group compared with 2.6% in the control group. Pranata et al¹³ in a systematic review and meta-analysis showed that the antibiotic envelope was safe and effective in reducing the risk of major infections in a high-risk patient receiving CIED implantation, especially in those receiving high-power devices (CRT-D

and ICD). In this analysis, even when excluding patients with biventricular PMs, the use of TYRX seems to reduce the risk of infection by a factor of 7. Furthermore, although the 2 study populations differed at baseline, the use of the antibacterial envelope remained an independent protective factor in reducing device-related infection risk. This analysis reflected real-world clinical practice in cardiology centers, where the TYRX group generally consisted of a sicker population with more comorbidities and a higher risk of infection. Importantly, this higher-risk profile often justifies the use of infection prevention strategies such as the antibacterial envelope, and the observed reduction in infection rates despite this disadvantageous clinical background further reinforces the potential protective effect of TYRX in real-world settings. The very low number of infections observed in this context strengthens the signal of a potential protective effect, even if causality cannot be formally established in this study design. Although larger and more robust studies are needed, our findings may offer useful exploratory insights for this patient population.

In line with the data from the WRAP-IT long-term study,²⁰ our analysis also showed an increasing incidence of infectious events in the control group over time. At 12

Table 4 Characteristics of patients with CIED infection

Patient	Envelope group (Y/N)	Systemic infection (Y/N)	Pocket infection (Y/N)	Type of device (PM/CRT)	De novo procedure (Y/N)	Replacement only (Y/N)	System revision (Y/N)	Diabetes (Y/N)	Kidney disease (Y/N)
1	Y	Y	Y	PM	N	Y	N	N	N
2	N	Y	Y	PM	Y	N	N	Y	Y
3	N	Y	N	PM	Y	N	N	Y	Y
4	N	N	Y	PM	Y	N	N	N	N
5	N	N	Y	PM	Y	N	N	N	N
6	N	N	Y	PM	Y	N	N	N	N
7	N	N	Y	PM	Y	N	N	N	N
8	N	N	Y	PM	N	Y	N	N	N
9	N	N	Y	PM	N	Y	N	Y	N
10	N	N	Y	PM	Y	N	N	Y	N
11	N	N	Y	PM	Y	N	N	Y	Y

CIED = cardiac implantable electrical device; CRT = cardiac resynchronization therapy; N = no; PM = pacemaker; Y = yes.

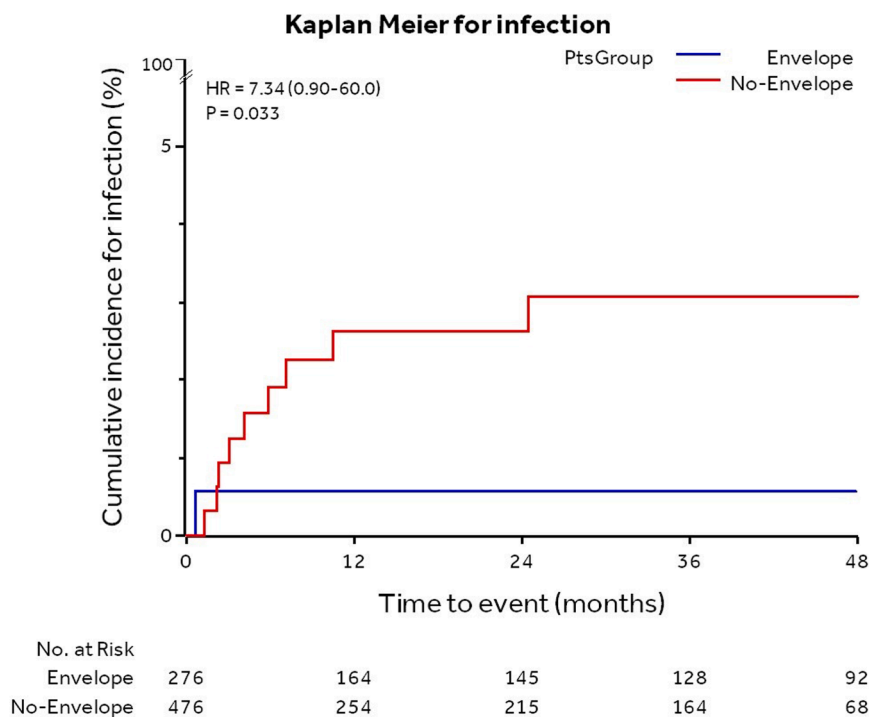


Figure 2 Cumulative event rate of systemic or pocket infection in the envelope and control groups by Kaplan-Meier estimate in the subcohort of PM patients only. HR = hazard ratio; PM = pacemaker; Pts = patients.

months, the incidence of events in the TYRX group was 0.4% and remained stable, whereas in the control group, it was 2.2% and increased to 2.5% at 4 years. These data seem to confirm that preventing bacterial seeding at any index procedure may prevent pocket infection at a later stage^{11,20} and suggest that the use of TYRX may lead to a sustained benefit in the long term.

The very low rate of systemic infections observed in this cohort was consistent throughout the follow-up period. It is important to note that the TYRX envelope primarily acts at the pocket level, eluting antibiotics locally to reduce early colonization and surgical-site infection.¹⁰ Consequently, the envelope is most effective in preventing pocket-related complications, which can serve as a source for systemic infection. Although the TYRX may reduce systemic infection risk indirectly—by avoiding bacterial spread from the pocket along the leads—it is unlikely to prevent systemic infections caused by hematogenous seeding in the absence of local involvement.

Cost-effectiveness considerations and number needed to treat

A cost/benefit consideration can be derived from the observed difference in infection rates between the 2 groups. In our analysis, the cumulative incidence of systemic or pocket infections at 4 years was 2.5% in the control group and 0.4% in the TYRX group, corresponding to an absolute risk reduction of 2.1%. This results in a number needed to treat of approximately 48 to prevent 1 infection. Although this value is within the range reported in previous cost-

effectiveness analyses (number needed to treat 35–185), it is slightly below the threshold of 2.7% infection risk identified in the WRAP-IT-based Italian economic model as necessary to justify the cost-effectiveness of the envelope.²¹ This difference likely reflects the lower baseline risk in our population, which is also supported by the PADIT score: 67.2% of patients in our cohort were classified as low risk.

Limitations

This analysis collects data from the clinical practice of participating centers. Therefore, the typical limitations of an observational study may apply. In particular, the 2 patient subgroups exhibited different clinical characteristics and infection risk profiles, given that treatment allocation was not randomized but driven by individual clinical judgment. However, this difference reflects real-world practice, in which the antibacterial envelope is more frequently used in patients considered at higher risk—even among those undergoing PM implantation, typically viewed as a low-risk group. Although this heterogeneity represents a limitation, it also underscores the relevance of our findings: the fact that infection rates were significantly lower in the envelope group—despite their higher baseline risk—supports the hypothesis of a protective effect.

It is important to underline that the limited number of infective events, although a constraint for statistical robustness, was anticipated owing to the generally low baseline risk in this population. This contributes to the scarcity of previous data focused specifically on de novo PM and CRT-P recipients, making our analysis an initial step to address

this evidence gap. Future larger-scale studies are needed to confirm these preliminary observations. Another limitation of this analysis is that most implanted devices (78.4%) were manufactured by Medtronic, which may affect the generalizability of the findings to CIEDs from other manufacturers.

Finally, infective events may also be underreported; hence, we considered only events that led to rehospitalization or an invasive procedure as endpoints. Some minor events, such as incidental fever, were not collected.

Conclusion

Our findings suggest that TYRX use is associated with a reduced incidence of pocket infections in PM and CRT-P recipients, with a sustained protective effect over 4 years, despite the higher baseline risk in the TYRX group.

Clinical perspective

From a clinical perspective, integrating the TYRX antibacterial envelope into PM and CRT procedures may offer an additional tool to reduce device-related infections. In this multicenter analysis, TYRX use was associated with fewer infections and a durable benefit over time, indicating potential for improved outcomes and resource use. Nonetheless, its application should be guided by careful clinical assessment.

Funding Sources: Open Access fees were supported by TRX Italy.

Disclosures: M.Z. received speaker's fees from Abbott, Biotronik, and Boston Scientific. G.B. reported small speaker fees from Bayer, Boehringer Ingelheim, Boston, Daiichi Sankyo, Janssen, and Sanofi, outside of the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients enrolled in the One Hospital Clinical Service project provided informed consent for data collection and analysis.

Ethics Statement: This project received approval from each site's institutional review board and local ethics committees and adheres to the principles of the 1975 Declaration of Helsinki, as confirmed by the previous approval from each institution's human research committee. The analysis reported in this paper adhered to Consolidated Standards of Reporting Trials guidelines.

Data Availability: The datasets generated during and/or analyzed during the current study are available on reasonable request.

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